Ilse van Beusekom

Healthcare consumption and health-related quality of life of intensive care survivors

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Healthcare consumption and health-related quality of life of intensive care survivors

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Chapter 1

General introduction

Annually, there are over 80,000 intensive care unit (ICU) admissions in the Netherlands and an increasing number of ICU patients is fortunately surviving their ICU admission [1]. Six decades ago, at the onset of ICU care, up to 33% of the patients did not survive their ICU admission [2, 3]. As a result of improved medical technology, knowledge and treatment, the in-hospital mortality rates dropped to 10-15% during the last decade [4-7]. Due to this increased survival-rate, the focus on ICU outcome measures shifted from solely ICU and in-hospital mortality to long-term survival, morbidity and quality of life (QoL) after discharge.

The terms QoL, health-related quality of life (HRQoL), and health status are used interchangeably in the literature. These terms are often ambiguously defined and most definitions do not sufficiently differentiate them [8]. However, there are some important differences to mention. QoL is a broad multidimensional concept covering all aspects of life, and health is only one aspect of QoL. HRQoL is an aspect of QoL that relates specifically to a person's health [9]. HRQoL is defined by the Centers for Disease Control and Prevention as an individual's or a group's perceived physical and mental health over time [10]. Health status is more narrow in scope and it omits the evaluation by the patient, the consumer of health-care services [11, 12]. In this thesis we will focus on the health status, in terms of healthcare consumption, and the HRQoL. However, for readability we will use the term HRQoL from here on.

POST-INTENSIVE CARE SYNDROME

After hospital discharge many ICU survivors suffer severe and long-term complaints, all leading to restrictions in societal participation and a decreased HRQoL [13-16]. Some ICU survivors even speak of '*a life before and a life after their ICU admission*' [17].

The term post-intensive care syndrome (PICS) was introduced in 2012 by the Society of Critical Care Medicine and is defined as '*new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization*' [15]. Since 2012, numerous studies about the prevalence and risk factors of PICS have been published, as well as research about follow-up care for ICU survivors.

Many ICU patients will suffer from some component of PICS after ICU discharge, however its exact prevalence remains unknown. ICU acquired weakness is the most common form of physical impairment and it is estimated that around 40% of the ICU survivors will suffer ICU acquired weakness [18, 19]. Other forms of physical impairments are loss of muscle mass, neuromuscular weakness, sensory and nociceptive changes, impaired lung function and fatigue. Known risk factors for physical impairments are prolonged mechanical ventilation (>7 days), sepsis and multi-system organ failure [19, 20].

Attention or concentration, memory, mental processing speed, and executive function are areas of cognition that are commonly affected and cognitive impairment is reported in 25% to 78% of the ICU survivors [21]. Pre-existing cognitive impairment, older age and delirium are reported risk factors for cognitive impairment [21, 22]. Frequently described mental health problems are anxiety [23], depression [24] and post-traumatic stress disorder (PTSD) [25]. It is estimated that around 30% of the ICU survivors will suffer anxiety, 30% depression and 25% PTSD. Although a number of single-centre studies identified female gender, age <50 years, lower education level, pre-existing disability/unemployment, and ICU sedative- and analgesia use as risk factors for mental health problems, recently published systematic reviews and meta-analyses did not confirm a significant association between these risk factors and the development of mental health problems after ICU discharge [23-25].

Post-intensive care syndrome - family

PICS and other problems faced after ICU discharge do not only affect the patient, but also reduce the physical, mental, social, and financial position of patients' informal caregivers, often family members, as well. The combination of problems affecting informal caregivers is known as PICS-Family (PICS-F) [15, 26]. Major risk factors for PICS-F are female gender, lower educational level, having a loved one who died or was close to death, low social support and poor communication with ICU staff members [26].

Even though there is an increasing number of studies published about PICS and PICS-F, most studies are relatively small, have a short follow-up time, lack comparison with a control group, do not include preadmission (baseline) measurements, have low response rates, and are focussing on specific ICU sub-populations and their informal caregivers. Therefore the pooled outcomes can be conflicting [16]. Furthermore, the number of studies performed in the Netherlands is small and are lacking the ability to draw general and generalizable conclusions. Therefore there is still need for more insight into the complete scope of burdens ICU survivors and their informal caregivers suffer after ICU discharge.

ICU FOLLOW-UP CARE

ICU follow-up care has been recommended to address the long-term and severe complains ICU patients suffer after discharge [15]. ICU follow-up care aims to detect PICS in an early stage so that the ICU survivors will be referred to the appropriate health professional(s) during consultation and can be treated to reduce the symptoms of PICS. In some ICU guidelines, it is recommended to have an ICU follow-up clinic for ICU survivors and their informal caregivers [27]. However, there is no evidence for the (cost-) effectiveness of ICU follow-up care.

A study conducted in the Netherlands, to create an overview of the state of follow-up care in 2012, showed that 23 (40%) of the responding hospitals had follow-up care for ICU patients [28]. However, the organization of the follow-up care varied greatly, as well as the timing, the type and frequency of care, and the selection of ICU patients. To standardise the ICU follow-up care in the Netherlands, recommendations regarding the design and setting of post-ICU clinics were formulated based on a survey among Dutch ICUs and the available literature. Research about the follow-up care in other countries, such as the United Kingdom, Denmark, Sweden and Norway [29-31] showed similar results; less than half of the ICUs offer follow-up care and the follow-up care varied greatly in organization and timing.

Even though a large part of the ICUs provide follow-up care, it is still not clear which ICU survivors do need which care at which moment. Therefore more research is necessary to improve the (cost-) effectiveness of ICU follow-up care.

HEALTHCARE CONSUMPTION IN RELATION TO HEALTH-RELATED QUALITY OF LIFE

Many ICU survivors suffer from some components of PICS after discharge, all leading to a decreased HRQoL. However, there is a gap in knowledge with respect to the HRQoL of ICU patients before their ICU admission and its change over time. By comparing the HRQoL of ICU patients before ICU admission with the HRQoL after ICU admission, we can gain insight in the impact of the critical illness and the effect of the ICU admission on the HRQoL. Moreover, by comparing the HRQoL of ICU patients with the HRQoL of people form the general population and we can justify the need for follow-up care.

A few studies reported that the HRQoL before ICU admission is associated with mortality and the HRQoL after ICU discharge [16, 32-34]. However, measuring the HRQoL before ICU admission is rather difficult. Most ICU patients are not able to complete questionnaires at the time of ICU admission and proxies tend to underestimate the patient's HRQoL [32]. Moreover, outcomes can be influenced by recall bias and due to the methodological properties of the underlying questionnaires, e.g. with the SF-36 the HRQoL can only be queried up to four weeks before ICU admission [16, 35].

High use of healthcare resources is associated with an impaired health status and a reduced HRQoL [36, 37]. By studying the healthcare consumption of ICU patients we can make assumptions about and make comparisons between the HRQoL of ICU patients before and after ICU admission. At the same time, it gives insight into the different types and quantities of healthcare consumed by ICU patients and can be used to identify the gap between the need for healthcare and the consumed healthcare. The ICU population is a very heterogeneous

population and it is likely that the need for healthcare and the healthcare consumption varies largely between subgroups of ICU patients. Therefore, in this thesis healthcare consumption of several common patient groups will be investigated.

To study the healthcare consumption of ICU patients in the Netherlands, two databases were merged: the national health insurance claims database of Vektis [38] and the database of the National Intensive Care Evaluation (NICE) registry, a national quality registry database for ICUs [1]. By merging these two databases, we were able to gain insight in the healthcare consumption of ICU patients during the year before ICU admission and the year after ICU discharge and to compare these outcomes with the healthcare consumption of a population based control group. To this end, we focused on 1) the total healthcare costs, 2) the types and prevalence of chronic conditions for which patients receive treatment and the association of clinical variables with chronic conditions and 3) the frequency of general practitioner (GP) consultations during the year before and the year after hospital discharge.

Total healthcare costs

The total costs of all healthcare consumed can be seen as a proxy of the HRQoL. By studying the total healthcare costs, subgroups of ICU patients which consume significant healthcare resources can be identified. Healthcare costs can also be used to compare healthcare consumption between the ICU population and the general population and results can be compared to international studies on healthcare consumption.

Chronic conditions

Factors present before ICU admission, such as chronic conditions, are strong predictors of hospital resource use [39]. Moreover, chronic conditions play an important role in the HRQoL and are important predictors for mortality [4, 40, 41]. Therefore, generally applied ICU scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) IV and SAPS II include several chronic conditions to quantify severity of illness and to predict mortality [42, 43]. After determining which types of chronic conditions are most frequent within the Dutch ICU population, the association between clinical variables and the development of these chronic conditions can be studied.

GP consultations

As in many other North-western European countries, in the Dutch healthcare system the GP plays a key role in the healthcare trajectory of all patients and acts like a gatekeeper between the patient and other healthcare providers. If the patient experiences problems that are typically non-life-threatening, the GP will be the first healthcare professional they consult. If needed, the GP refers the patients to the right healthcare provider. This raises the question of whether this is also the case when ICU survivors consult their GP about complaints

experienced as part of PICS. A first step is to gain insight in the current situation. Up to date, it is unknown if ICU survivors contact their GP more often after ICU discharge than before, and if the number of visits changes over time.

The NICE registry

The NICE registry was established by intensivists, to facilitate quality-monitoring and quality-improvement initiatives and to benchmark the performance of single ICUs to national values and to outcomes of comparable ICUs [1]. In 1996, at the start of the registry, only a small proportion of Dutch ICUs participated. Over the years the NICE registry has expanded and, currently, all Dutch ICUs are participating.

All ICUs are collecting demographic data, physiological data and clinical data of all patients admitted to their ICU, such as, age, gender, primary reason for ICU admission, comorbidities, admission and discharge data (date and location), ICU and in-hospital mortality, ventilator status and all variables required to quantify severity of illness and to calculate mortality risks according to, among others, the prognostic model APACHE IV [42].

Twice a year, the NICE registry generates feedback reports for every participating ICU. These reports can help to optimise the healthcare process and can be used for benchmarking purposes [44]. Throughout the years, the content of the reports broadened from only ICU mortality and in-hospital mortality to also long-term survival. Up to date there is no information about the HRQoL, the functional status, or the healthcare consumption available within the NICE registry.

Vektis

Healthcare insurance is compulsory for Dutch citizens and essentially all (99%) of the Dutch inhabitants have private healthcare insurance [45]. The Vektis databases [38] contain reimbursement data on all medical treatments paid for by Dutch insurance companies, as well as demographic information, such as gender, date of birth, socio-economic status (SES) and a proxy for date of death, for all registered residents of the Netherlands. Information about the healthcare consumption of ICU patients was derived from the Vektis database as well as information about the healthcare consumption of a population based control group.

The total healthcare costs are based on all reimbursement data available from health insurance companies and available as a total sum per calendar-year. Among others, the Vektis database contains claims for pharmaceutical care, including information on provided drugs, the Anatomical Therapeutic Chemical (ATC) code, the date the drug was supplied, and the quantity supplied. To determine the chronic conditions, Vektis uses Pharmaceutical Cost Groups (PCGs) as a proxy. PCGs are based on the idea that a patient with a certain chronic

condition can be identified by claims for specific prescribed drugs [46, 47]. The validity of pharmacy based claims data for the assessment of chronic conditions and prevalence estimates has been demonstrated before in different countries [47-51]. Vektis also includes all claims of GP contacts in the GP Information System.

Since the Vektis databases contain information about all registered residents of the Netherlands, outcomes with respect to the healthcare consumption of ICU patients could be compared to the healthcare consumption of a population based control group.

AIM AND OUTLINE OF THIS THESIS

The general aims of this thesis are 1) to gain insight in the burden ICU patients and their informal caregivers suffer after hospital discharge and their need for healthcare after discharge and 2) to gain insight into the healthcare consumption of ICU survivors during the year before and the year after ICU admission. Furthermore, we will identify subgroups of ICU survivors with high healthcare consumption which are likely to benefit from ICU follow-up care.

In the first part of this thesis we focus on the burden ICU survivors and their informal caregivers face and the healthcare they need. In Chapter 2 we describe the implementation and evaluation of the feasibility of a web-based triage tool in the ICU follow-up clinic, developed to collect patient-reported HRQoL data. Additionally, outcomes gained by the web-based triage tool are compared with those from conventional paper-based questionnaires to assess the differences between these two groups. In Chapter 3 we assess which burdens for informal caregivers of adult ICU survivors have been documented and describe which assessment tools are used. Furthermore we make recommendations on which burden should be assessed, which tools could be used and how screening of the informal caregiver can be integrated in the post-ICU care of ICU survivors.

In the second part we gain insight into the healthcare consumption of ICU survivors during the year before ICU admission and during the year after ICU discharge. Chapter 4 provides information with respect to the healthcare costs for the general ICU population in comparison to a population based control group. Chapter 5 and Chapter 6 provide information on two subgroups of the ICU population. Chapter 5 focusses on elderly patients for which care providers debate whether these patients might be too expensive to admit to an ICU. Chapter 6 focusses on intoxicated ICU patients for whom the ICU admissions are questionable due to the low risk of mortality. In Chapter 7 we describe the types and prevalence of chronic conditions in an ICU population and compare these with a population based control group during the year before ICU admission and we quantify the risk of developing new chronic

conditions in ICU patients compared to the control group. Chapter 8 focusses on the association of clinical variables, measured during the first 24 hours of ICU admission, and the newly developed chronic conditions within a population of ICU survivors in the year after ICU admission. In Chapter 9 we gain insight in the frequency of GP consultations during the year before and the year after hospital discharge, and the change over time for ICU survivors as opposed to a matched control group from the general population.

Chapter 10 summarizes the main findings and provides an overall discussion of the work in this thesis. In this chapter we compare the healthcare ICU survivors receive as opposed to the healthcare they need and we discuss the implications for clinical practice. The strengths and limitations of the different studies are addressed and recommendations for further research are presented.

REFERENCES

1. Dutch National Intensive Care Evaluation (NICE) registry http://www.stichting-nice.nl Accessed 08.11.2016.
2. Baskett PJ. Is an intensive care unit really necessary? Bristol Med Chir J. 1965;80:298.
3. Pearce DJ. Experiences in a small respiratory unit of a general hospital with special reference to the treatment of tetanus. Anaesthesia. 1961;16.
4. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. Crit Care Med. 2013;41:5.
5. Wunsch H, Angus DC, Harrison DA, Collange O, Fowler R, Hoste EA et al. Variation in critical care services across North America and Western Europe. Crit Care Med. 2008;36:10.
6. Australian and New Zealand Intensive Care Society: ANZICS Centre for Outcome and Resource Evaluation Annual Report 2014-2015. Melbourne: ANZICS2016. http://www.anzics.com.au/www.anzics.com.au/pages/CORE/CORE-Reports.html.
7. Canadian Institute for Health Information: Care in Canadian ICUs. Ottawa, ON: CIHI2016. https://secure.cihi.ca/free_products/ICU_Report_EN.pdf.
8. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? Pharmacoeconomics. 2016;34:7.
9. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273:1.
10. Health-Related Quality of life (HRQOL). Centers for Disease Control and Prevention. https://www.cdc.gov/hrqol/index.htm. Accessed 18.01.2019.
11. Guyatt G, Feeny D, Patrick D. Issues in quality-of-life measurement in clinical trials. Control Clin Trials. 1991;12:4 Suppl.
12. Guyatt G, Feeny D, Patrick D. Postscript. Control Clin Trials. 1991;12:4 Suppl.
13. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med. 2009;41:13.
14. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009;41:5.
15. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:2.
16. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38:12.
17. Blank L. Speciale fysio voor IC-patiënt. Noord Hollands Dagblad. 2019 February 27.
18. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: A systematic review. J Intensive Care Soc. 2015;16:2.
19. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med. 2007;33:11.
20. Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007;131:5.
21. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. Chest. 2006;130:3.
22. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:14.

23. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2016;43.
24. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. Crit Care Med. 2016;44:9.
25. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med. 2015;43:5.
26. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. Crit Care Med. 2012;40:2.
27. Tan T, Brett SJ, Stokes T, Guideline Development G. Rehabilitation after critical illness: summary of NICE guidance. BMJ. 2009;338.
28. van der Schaaf M, Bakhshi-Raiez F, Van der Steen M, Dongelmans DA, De Keizer NF. Recommendations for the organization of intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol. 2015;81:2.
29. Griffiths JA, Barber VS, Cuthbertson BH, Young JD. A national survey of intensive care follow-up clinics. Anaesthesia. 2006;61:10.
30. Kjer CKW, Estrup S, Poulsen LM, Mathiesen O. Follow-up after intensive care treatment: a questionnaire survey of intensive care aftercare in Denmark. Acta Anaesthesiol Scand. 2017;61:8.
31. Egerod I, Risom SS, Thomsen T, Storli SL, Eskerud RS, Holme AN et al. ICU-recovery in Scandinavia: a comparative study of intensive care follow-up in Denmark, Norway and Sweden. Intensive Crit Care Nurs. 2013;29:2.
32. Hofhuis JG, Spronk PE, van Stel HF, Schrijvers AJ, Bakker J. Quality of life before intensive care unit admission is a predictor of survival. Crit Care. 2007;11:4.
33. Wehler M, Martus P, Geise A, Bost A, Mueller A, Hahn EG et al. Changes in quality of life after medical intensive care. Intensive Care Med. 2001;27:1.
34. Iribarren-Diarasarri S, Aizpuru-Barandiaran F, Munoz-Martinez T, Loma-Osorio A, Hernandez-Lopez M, Ruiz-Zorrilla JM et al. Health-related quality of life as a prognostic factor of survival in critically ill patients. Intensive Care Med. 2009;35:5.
35. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:6.
36. Ruhl AP, Huang M, Colantuoni E, Karmarkar T, Dinglas VD, Hopkins RO et al. Healthcare utilization and costs in ARDS survivors: a 1-year longitudinal national US multicenter study. Intensive Care Med. 2017;43:7.
37. Wammes JJG, van der Wees PJ, Tanke MAC, Westert GP, Jeurissen PPT. Systematic review of high-cost patients' characteristics and healthcare utilisation. BMJ Open. 2018;8:9.
38. Vektis. http://www.vektis.nl. Accessed 08.11.2016.
39. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH et al. Five Year Mortality and Hospital Costs Associated With Surviving Intensive Care. Am J Respir Crit Care Med. 2016;194:2.
40. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, de Jonge E, de Keizer NF. Determinants of mortality after hospital discharge in ICU patients: literature review and Dutch cohort study. Crit Care Med. 2013;41:5.
41. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes. 2004;2.
42. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34:5.

43. Le Gall J, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA. 1993;270:24.
44. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015;44:6.
45. Centraal Bureau voor de Statistiek (CBS). Statline. http://statline.cbs.nl/Statweb/dome/default.aspx. Accessed 17.01.2019.
46. Lamers LM. Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. Med Care. 1999;37:8.
47. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy. 2004;68:1.
48. Huber CA, Szucs TD, Rapold R, Reich O. Identifying patients with chronic conditions using pharmacy data in Switzerland: an updated mapping approach to the classification of medications. BMC Public Health. 2013;13.
49. Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. J Health Serv Res Policy. 2005;10:4.
50. Chini F, Pezzotti P, Orzella L, Borgia P, Guasticchi G. Can we use the pharmacy data to estimate the prevalence of chronic conditions? a comparison of multiple data sources. BMC Public Health. 2011;11.
51. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995;48:8.

Chapter 2

Lessons learnt during the implementation of a web-based triage tool for Dutch intensive care follow-up clinics

Ilse van Beusekom, Ferishta Bakhshi-Raiez, Nicolette F. de Keizer, Dave A. Dongelmans and Marike van der Schaaf

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ABSTRACT

Objectives: Screening for symptoms of post-intensive care syndrome is based on a long list of questionnaires, filled out by the intensive care unit (ICU) survivor and manually reviewed by the health professional. This is an inefficient and time-consuming process. The aim of this study was to evaluate the feasibility of a web-based triage tool and to compare the outcomes from web-based questionnaires to those from paper-based questionnaires.

Design: A mixed-methods study.

Setting: Nine Dutch ICU follow-up clinics.

Participants: 221 ICU survivors and 14 health professionals.

Interventions: A web-based triage tool was implemented by nine ICU follow-up clinics. End users, that is, health professionals were interviewed in order to evaluate the feasibility of the triage tool. ICU survivors were invited to fill out web-based questionnaires 3 months after hospital discharge.

Primary outcomes: Outcomes of the questionnaires were merged with clinical data from a national quality registry to assess the differences in outcomes between paper-based and web-based questionnaires.

Results: 221 ICU survivors received an invitation to fill out questionnaires, 93 (42.1%) survivors did not respond to the invitation. Respondents to the web-based questionnaires (n=54) were significantly younger and had a significantly longer ICU stay than those who preferred the paper-based questionnaires (n=74). The prevalence of mental, physical and nutritional problems was high, although comparable between the groups. Health professionals' interviews revealed that the software was complex to use (n=8) and although emailing survivors is very convenient, not all survivors have an email address (n=7).

Conclusions: Web-based screening software has major benefits compared with paper-based screening. However, implementation has shown to be rather difficult and there are important barriers to consider. Although different in age, the health status is comparable between the users of the web-based questionnaire and paper-based questionnaire.

INTRODUCTION

Intensive care unit (ICU) survivors frequently suffer long-term and severe complaints after ICU discharge [1, 2] and a single term is used to identify the presence of one or more impairments after critical illness: post-intensive care syndrome (PICS) [3].

Because of the complexity and magnitude of the complaints, multidisciplinary care after ICU discharge is required [4]. ICU follow-up care aims to detect PICS in an early stage and the ICU survivors will be referred to the appropriate health professional(s) during consultation. In some ICU guidelines, it is recommended to have an ICU follow-up clinic [5].

Generally, screening for symptoms of PICS is based on a long list of paper-based questionnaires, filled out manually by the survivor and reviewed by the health professional before or during consultation. This is an inefficient and time-consuming process. Moreover, there is a high rate of non-responders due to the age and medical conditions of survivors and because survivors cannot always be traced on their home address [6, 7].

We created a web-based triage tool to collect patient-reported screening data. The tool supports automatic processing of the data before presenting it to the health professional. Web-based screening has major benefits compared with paper-based screening, for example, more complete data, less entry errors and easy storage of data [8], leading to enhanced integrity and accuracy of outcome data [9]. In previous literature, the benefits of web-based screening software have been pointed out in clinical trial settings [10]. However, research on the implementation of software in clinical care and the use of web-based screening in ICU survivors and ICU personnel is scarce.

The aim of this study was to evaluate the feasibility of our web-based triage tool in the ICU follow-up clinic and to assess the outcomes gained by web-based questionnaires compared with those from conventional paper-based questionnaires.

MATERIALS AND METHODS

Setting

Based on the recommendations of Van der Schaaf et al. [11], (box 1), a new web-based triage tool was created and tested during a pilot study. The tool supports automatic collection and processing of data for ICU follow-up care. The study was conducted between 1 June 2014 and 30 June 2015. All ICUs participating in the Dutch National Intensive Care Evaluation (NICE) registry that had an ICU follow-up clinic were invited to participate in this pilot study. The NICE registry is a quality registry which contains demographic data, physiological

data and clinical data for all ICU patients in the Netherlands [12, 13]. We aimed to include 10 ICU's in this pilot study.

Box 1. Recommendations for eligibility of intensive care unit (ICU) survivors for ICU follow-up clinics [11]
- Invite all survivors who received > 48 hours mechanical ventilation.
- Invite the partners of survivors.
- Plan the first visit to the ICU follow-up clinic 12 weeks after hospital discharge with the possibility for a follow-up at indication.
- Screen survivors with respect to their needs and ICU-related sequelae.
- Use electronic patient-reported screening instruments to identify survivors in the need for ICU follow-up care.
- Have an ICU nurse, whether or not with an intensivist, carrying out the ICU follow-up clinic.
- Involve a physiotherapist to perform a comprehensive physical screening. Integrate follow-up care data into a national quality registry for ICU to monitor and improve quality of life and functional status of survivors.

Web-based triage tool

The triage tool includes a module for health professionals to be used in the follow-up clinic and a web-based questionnaire module for ICU survivors.

During the development of the triage tool, both modules were tested for usability. The module for health professionals was evaluated with four health professionals by means of semi structured interviews [14]. The usability of the web-based questionnaire module was evaluated with four ICU survivors using the think aloud method [14, 15]. Outcomes of the semi structured interviews and the think aloud sessions resulted in minor adjustments of the triage tool prior to implementation of the triage tool in this pilot study [14].

The triage tool automatically extracted data of eligible survivors from the hospital information system (HIS). Nine weeks after hospital discharge, the health professionals received a prompt to send the survivor an invitation by email to fill out a set of online questionnaires and to invite the survivor to visit the ICU follow-up clinic 3 months after hospital discharge. If there was no response from the survivor within the next week, the health professional received a prompt to call the survivor. During this phone call, the health professional would ask for the reason of the non-response and explain the importance of screening for PICS and a visit to the ICU follow-up clinic. If survivors stated that they were unable to fill out the online questionnaires, paper-based questionnaires were issued. The paper-based questionnaires were entered in the system manually by the health professional or the secretary.

The pilot study included the questionnaires described in Table 2.1. Besides these validated questionnaires, work and income-related questions, common problems after ICU admission and visits to health professionals after ICU admission were queried (Appendix 2.1 to 2.3).

The results of the questionnaires were automatically processed by the triage tool and compared with the cut-off points. During the follow-up consultation, the health professional and the survivor discussed the outcomes of the questionnaires and the survivor was referred to a specialist if necessary. This was similar to the process before the implementation of the triage tool except for the fact that the outcomes of the questionnaires were calculated and present before the start of the consultation. Health professionals were trained to use the software before the start of the study. The 3-hour training was given by the developers of the tool and a researcher (IvB or FBR). During the pilot study, the health professionals were contacted regularly and offered assistance when necessary.

Table 2.1 Validated questionnaires used during this study

Name	Description	Cut-off point
Hospital Anxiety and Depression Scale [27]	A 14-items screening tool consisting of two subscales which evaluate symptoms of depression (seven items) and symptoms of anxiety (seven items).	Scores of >= 8 to identify patients prone to develop depression or anxiety.
Short From 36 [28]	A 36-item screening-tool comprising two components; a physical- and a mental component score. Component scores range from 0 to 100, with higher scores indicating better health status [29].	Scores of < 40 to identify decreased physical or mental health.
Trauma Screening Questionnaire [30]	A 10-item screening tool used to identify post-traumatic stress disorder (PTSD).	Scores of >= 6 to identify possible PTSD.
Malnutrition Universal Screening Tool [31]	A 3-item screening tool to obtain the risk of malnutrition.	Scores >= 1 to identify patients with a risk of malnutrition

Evaluation of the feasibility of the triage tool

After finishing the pilot study, semi structured interviews were conducted with health professionals who used the tool, to gain insight in the feasibility of the triage tool. The semi structured interviews were hold from July 2015 until September 2015 and conducted by one researcher (IvB). All health professionals were interviewed in their own working environment and an informed consent was verbally issued and recorded before the interview started.

All interviews were recorded digitally and transcribed verbatim. The thematic content analysis method was used to analyse the qualitative data.16 All interviews were coded individually by two researches (IvB and FBR). Both researchers extracted the statements from the transcripts and grouped the statements by themes. The themes and statements were discussed until 100% agreement was achieved on the coding. The statements of the health professionals were compared with the characteristics of the survivors and the outcomes of the questionnaires in order to relate the qualitative data to the quantitative data.

Finally, the health professionals were requested to fill out the System Usability Scale (SUS) [17]. The SUS is a tool to evaluate software tools. Scores range from 0 to 100 and a SUS score above 68 is indicating an above average usability [17].

Questionnaire outcomes of the ICU survivors

The outcomes of the questionnaires were used to evaluate the type and severity of symptoms of PICS present in survivors. The anonymised data of the questionnaires were linked with clinical data from the NICE registry to gain insight in the demographics and clinical differences between survivors who filled out the web-based questionnaires compared with those who filled out the paper-based questionnaires. Data linking was based on a unique identifying number available in both databases.

Categorical data were presented as numbers and percentages, continuous data as medians and IQR. Differences between the web-based questionnaire group and the paper-based questionnaire group for non-normally distributed data were calculated using the Mann-Whitney U test. Differences between the two groups for normally distributed data were calculated using the t-test. For categorical data, the χ^2 test was used to assess the differences between the study groups. All analyses were performed using IBM SPSS Statistics V.24 [18].

Patient and public involvement

No patients were directly involved in the development of the research question, design of the study or interpretation of the results. However, the usability of the web-based questionnaire module was evaluated with ICU survivors. Outcomes of the evaluation resulted in minor adjustments of the module prior to the implementation of the triage tool in this pilot study.

RESULTS

Of the 23 Dutch ICUs with an ICU follow-up clinic, nine ICUs (39.1%) participated in the pilot study. One ICU withdrew due to reorganisation 8 months after the start of the study. Of the eight participating ICUs, one (12.5%) was located in a university hospital, one (12.5%) in a teaching hospital and six (75.0%) in community hospitals.

Evaluation of the feasibility of the triage tool

During this pilot study, 531 survivors were eligible for follow-up care and were extracted from the HIS. Before sending out the invitations, the health professional would check if the survivor was still alive and 42 (7.9%) survivors were reported as 'deceased after hospital discharge'. Of the remaining survivors, 221 (45.2%) received an invitation to fill out the questionnaires and to attend follow-up care. Other reasons for not inviting the survivor,

besides death, were not collected. There were no significant differences in characteristics between survivors who were invited or not.

Ninety-three (42.1%) survivors did not respond to the invitation. Of the non-responders, 28 (30.1%) were phoned by the health professional to ask for the reason for non-response; three (10.7%) could not be reached on their phone number, 8 (28.6%) said they were well and did not need follow-up care, three (10.7%) said they were unable to fill out questionnaires and to attend follow-up care due to their poor health status, two (7.1%) had no recollection of the ICU admission, six (21.4%) were already involved in a rehabilitation programme, one (3.6%) had no computer and five (17.9%) gave other reasons. It is unknown whether the other 65 non-responders were not contacted or that the phone calls were not registered. There were no significant differences in characteristics between non-responders and responders.

Fourteen health professionals worked with the system and were interviewed; five intensivists, six ICU nurses, one physical therapist and two medical secretaries. The duration of the interviews ranged from 21 to 39 min. Ten health professionals filled out the SUS with an average score of 56.

Table 2.2 shows the main barriers to using the tool for survivors, according to the health professionals. The email addresses of survivors or family members were not always routinely collected before the start of the study. During the study, this was implemented in the regular workflow in the HIS.

Health professionals were surprised to find out that a large part of survivors mentioned not to have an email address, even the 'younger' survivors of 40-50 years old. Over 70% of the health professionals said that the ICU population in general is older, and that survivors are not ready to use web-based questionnaires because of their age, that survivors were too sick to fill out the questionnaires or that survivors did not want to be confronted with the ICU admission.

According to the health professionals, if follow-up care is offered on a voluntary basis, some survivors will reject it (28.6%). Lack of interest, avoidance as part of post-traumatic stress disorder (PTSD), distance to hospital, burden to ask caregivers for support are frequently stated reasons by the health professionals for survivors to reject ICU follow-up care. Most health professionals (85.7%) would like to see follow-up care as part of the routine care, only few health professionals think of the follow-up care as an extra service to the survivor.

Table 2.2 Themes exemplifying the statements of the 14 health professionals

Themes	Statements
Personal themes	E-mailing the patient is very convenient, especially during night shifts (n=7).
	I did not think about e-mailing the patient, I like to call patients (n=2).
Software-related themes	The software was complex (n=8).
	Patients' e-mail addresses were not available in the HIS at the start of the pilot, calling the patient to collect the e-mail address was very time consuming (n=8).
	Since we used so little, I forgot how to send an e-mail with it (n=5).
Patient-related themes	Patients did not have an e-mail address, even not the patients of 40 to 50 years old (n=10).
	Patients are not ready to use the web-based questionnaires, in 10 years this will be different (n=10).
	Some patients are not interested in follow-up care, sometimes they are too sick and sometimes they already have support (n=10).
Organization-related themes	There are no resources available for follow-up care, we arranged it in our own time (n=4).
	A follow-up consultation is not part of the 'routine care process', patients perceive it as optional and might not come (n=4).

Questionnaire outcomes of the ICU survivors

In total, 54 survivors filled out the web-based questionnaires and 74 survivors used the paper-based version. Eighty-seven survivors attended ICU follow-up care. Table 2.3 gives an overview of characteristics of survivors, grouped by paper-based or web-based data collection. Survivors who preferred web-based questionnaires were significantly younger compared with survivors who filled out the paper-based questionnaires ($p<0.05$) and had a longer ICU stay ($p<0.05$). Survivors who filled out the web-based questionnaires had a significant higher prevalence of PTSD, measured with the Trauma Screening Questionnaire. For all other patient-reported outcomes, there were no significant differences between survivors who filled out the web-based questionnaires as opposed to survivors who filled out paper-based questionnaires.

In the paper-based group, less questionnaire outcomes could be calculated due to missing items, that is, in the paper-based group 13.2% of the results were missing, in the web-based questionnaire group this was 2.8%.

Within both questionnaire groups, there was a large prevalence of possible mental problems, physical problems and nutritional problems (Table 2.3 and Figure 2.1). Not all survivors with possible problems had contact with the appropriate health professionals during the time of filling out the questionnaires.

Table 2.3 Characteristics of ICU survivors who returned the questionnaires

	Web-based questionnaire (n=54)	Paper-based questionnaire (n=74)	*p*-values*
Male n (%)	29 (53.7%)	35 (47.3%)	0.59
Age	60.5 (52.3; 67.5)	69.5 (54.5; 75.1)	<0.05
Type of ICU admission			
• Medical n (%)	46 (85.2%)	58 (78.4%)	0.43
• Surgical n (%)	4 (7.4%)	5 (6.8%)	
• Emergency surgery n (%)	4 (7.4%)	11 (14.9%)	
ICU length of stay	11.8 (6.5; 20.7)	9.6 (5.9; 16.9)	<0.05
Hospital length of stay	21.0 (14.5; 37.5)	22.0 (14.0; 31.0)	0.45
Mechanical ventilation days	5.6 (4.0; 12.1)	4.9 (3.4; 8.5)	0.08
APACHE IV score¥	70.0 (56.5; 82.0)	73.5 (60.5; 88.8)	0.13
Questionnaires			
HADS	0 missing	5 missing	
• Anxiety n (%) >= 8	20 (37.0%)	17 (24.6%)	0.14
• Depression n (%) >= 8	15 (27.8%)	22 (31.9%)	0.66
TSQ	2 missing	4 missing	
• n (%) >= 6	15 (28.8%)	10 (14.3%)	<0.05
SF-36	0 missing	8 missing	
• Mental Component	48.4 (36.5; 53.6)	47.9 (39.8; 53.8)	0.44
• Physical component	34.6 (25.1; 42.1)	37.6 (30.2; 44.4)	0.21
MUST	4 missing	22 missing	
• n (%) >= 1	27 (50.0%)	24 (32.4%)	0.43

¥ Only calculated for the ICU survivors which met the APACHE IV inclusion criteria.
* Mann-Whitney-U test for non-normally distributed data, T-test for normally distributed data, and χ^2 test for categorical data.
APACHE IV, Acute Physiology and Chronic Health Evaluation; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; MUST, Malnutrition Universal Screening Tool; SF-36, Short From 36; TSQ, Trauma Screening Questionnaire.

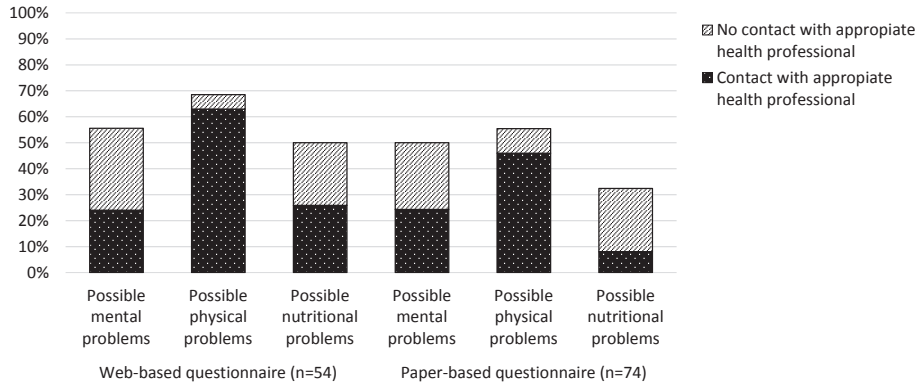

Figure 2.1 Prevalence of possible mental problems, physical problems and nutritional problems

DISCUSSION

We implemented a web-based triage tool to evaluate its feasibility and to assess the outcomes of web-based questionnaires compared with paper-based questionnaires. In previous literature, the benefits of web-based screening software have been pointed out in clinical trial settings [10]. However, our study showed that the implementation in daily practice might be difficult and we identified important barriers to consider. Survivors who responded to the web-based questionnaires were significantly younger and had a significantly longer ICU stay than those who preferred the paper-based questionnaires. Health status at the time of filing out the questionnaire did not differ between the two groups. Strikingly, the prevalence of mental, physical and nutritional problems was equally high in both groups and the majority did not receive care for these complaints before they visited the ICU follow-up clinic.

Though the tool was evaluated and adjusted before implementation, eight (57.1%) health professionals found the software too complex to use. The average SUS score was 56, indicating a less than average usability and necessitating improvement of the software. A point of interest is the time between the training and the start of the pilot study. Not all ICU follow-up clinics started the pilot study at the same time, while the training was given on three dates during two consecutive weeks. Moreover, during the evaluation the pilot study, five health professionals mentioned that they used the software so little, they forgot how to send an email with it. For future research, it is advised to plan the training shortly before the start of the study and to use the new software on a regular basis.

Over 40% of the respondents filled out the web-based questionnaires. Health professionals stated that many survivors did not have an email address and expressed that survivors in general are not ready yet to use the web-based triage tool because of their age. This was not in line with the results of the telephone calls where only one (3.6%) survivor stated that they did not had an email address. Moreover, as our society is focussing and relying more and more on digital systems, survivors not having an email address will be no barrier in the future. Already in 2013, 95% of all Dutch households had access to a computer with an internet connection [19].

Digitally issued questionnaires have major benefits compared with paper-based questionnaires, such as more complete data, less entry errors and easy storage of data [8]. Our study confirmed this finding as we found that in the paper-based questionnaire group, there was more information missing. A possible explanation can be the use of checks and prompts in the web-based questionnaires when items were not filled out. Another major benefit is that by using web-based screening software, survivors with possible health problems can be identified without visiting the hospital. The outcomes of the questionnaires can be used in clinical decision-making and tailored care. This will improve the effectiveness of the treatments.

The prevalence of possible mental, physical and nutritional problems was high among the respondents. However, not all survivors received the appropriate care after hospital discharge. Even though there is no consensus on the (cost-) effectiveness of intensive care follow-up programmes [20-22], we believe that our triage tool is a step in the right direction. Follow-up care should be offered as stepped care, so it can be tailored to the needs of survivors. The triage tool makes it possible to highlight the problem areas so they can be addressed during consultation. Furthermore, the triage tool can be used to reach large groups of survivors as the data collection and processing is less labour intensive.

People choosing to fill out questionnaires online were significantly younger compared with those preferring paper-based questionnaires [23]. According to previous published studies, younger age has been found to be a risk factor for PTSD [24] and a prolonged hospital stay is associated with lower mental or physical quality of life [25]. In our study, survivors who used the web-based questionnaires were also younger compared with survivors in the paper-based group and had a longer ICU stay. This can be a possible explanation for the finding that survivors in the web-based questionnaire group had a significantly higher risk of developing PTSD compared with survivors in the paper-based group.

A strength of this study was the use of mixed methods, that is, qualitative and quantitative methods. By using mixed methods, we were able to verify the statements of health professionals with the clinical data and questionnaire outcomes of survivors. For example, health professionals stated that a large part of survivors did not have an email address and that survivors were sometimes not able to fill out questionnaires due to their health status. However, these concerns were not validated with the phone calls. A possible explanation can be that survivors that could not been reached had the worst health status [26].

Though 531 survivors were eligible for follow-up care, eventually only 128 survivors responded to the questionnaires. This is first due to the fact that only 221 of the 531 eligible survivors received an invitation to fill in the questionnaire and visit the follow-up clinic. A limitation of this study is that we have little information on why certain survivors were, and others were not, invited. During the interviews, the health professionals mentioned the absence of financial support from the department as a major problem. Some health professionals provide follow-up care in their own time, this makes it difficult to offer ICU follow-up care customarily. Second, of the 221 ICU survivors invited to fill out the questionnaires, 93 did not respond resulting in a response rate of 57.9%. A review conducted on the quality of life after ICU admission described that three (6%) of their included studies had a response rate of < 50% and 24 studies (45%) had a response rate between 50% and 79% [2]. In sight of this review, we consider the response rate of our study average.

During the interviews, all health professionals repeatedly stressed the importance of follow-up care for survivors, to address the burden these survivors suffer after their ICU admission. They all endorse the necessity and the benefits of ICU follow-up care, however, these ideas are not yet supported by scientific research. Filling out web-based questionnaires will have added value due to digitalising society. Questionnaire outcomes are present during consultation and can be discussed with survivors and their families. The results of these web-based questionnaires can be used to gain insight in the efficiency of the ICU follow-up care, if stored in a national database with options to benchmark the long-term outcomes of survivors.

CONCLUSIONS

Web-based screening software has major benefits compared with paper-based screening, however, the implementation has shown to be difficult and there are important barriers to consider. In order to successfully implement a new web-based triage tool, health professionals need time and support to use it. The email addresses should be queried at hospital admission so that it will not be necessary to collect the email address after hospital discharge. In both web-based and paper-based population, there was a large prevalence of survivors with possible mental, physical and nutritional problems and we suggest ICU follow-up care in order to address these problems. We think that our software is a starting point of making ICU follow-up care feasible and effective.

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APPENDICES

Appendix 2.1 Work-related questions

1. Describe the job you had before your ICU admission
2. Which situation reflects your situation best: before my ICU admission I was/I had:
   a. employed
   b. self-employed
   c. partially incapacitated
   d. (early) retired
   e. unemployed / looking for employment
   f. fully incapacitated
   g. social assistance
   h. fulltime 'man around the house'/'woman around the house'
   i. student
3. What were your main tasks in the job you had before your ICU admission?
   a. mostly physically demanding tasks
   b. mostly mentally demanding tasks
   c. a mixture of physically and mentally demanding tasks
   d. no physically or mentally demanding tasks
4. According to you contract, how many hours did you work before your ICU admission?
5. How many hours did you work before your ICU admission?
6. Describe your current job
7. Which situation reflects your current situation best: after my ICU admission I was/I had:
   a. employed
   b. self-employed
   c. partially incapacitated
   d. (early) retired
   e. unemployed / looking for employment
   f. fully incapacitated
   g. social assistance
   h. fulltime 'man around the house'/'woman around the house'
   i. student
8. What are your main tasks in your current job?
   a. mostly physically demanding tasks
   b. mostly mentally demanding tasks
   c. a mixture of physically and mentally demanding tasks
   d. no physically or mentally demanding tasks
9. According to your current contract, how many hours do you work?
10. How many hours do you work after your ICU admission?
11. Are you disturbed by your health status within your current job?
    a. no
    b. a bit
    c. strongly
12. Did your financial situation decline compared to the situation before your ICU admission?

Appendix 2.2 Common problems after an ICU admission

Do you experience decreased vision compared to the situation before ICU admission?	Yes	No
Do you experience decreased hearing compared to the situation before ICU admission?	Yes	No
Do you experience decreased taste compared to the situation before ICU admission?	Yes	No
Do you experience decreased voice compared to the situation before ICU admission?	Yes	No
Do you have more problems with your balance compared to your situation before ICU admission?	Yes	No
Do you experience a change in defecation (consistency, frequency) compared to your situation before ICU admission?	Yes	No
Do you experience more problems urinating compared to the situation before ICU admission?	Yes	No
Do you experience decreased sexual functions compared to the situation before ICU admission?	Yes	No
Do you experience a change menstruation compared to the situation before ICU admission?	Yes	No
Do you experience more stiffness of your joints compared to the situation before ICU admission?	Yes	No
Do you experience more muscle weakness compared to the situation before ICU admission?	Yes	No
Do you experience more hair loss compared to the situation before ICU admission?	Yes	No
Do you experience more itching or exfoliation of your skin compared to the situation before ICU admission?	Yes	No

Appendix 2.3 Visits to healthcare professionals after ICU admission

Did you visit a general practitioner within the last 3 months?	Yes	No
Did you visit a district nurse or did you receive professional home care within the last 3 months?	Yes	No
Did you visit a physical therapist within the last 3 months?	Yes	No
Did you visit an occupational therapist within the last 3 months?	Yes	No
Did you visit a speech therapist within the last 3 months?	Yes	No
Did you visit a dietician within the last 3 months?	Yes	No
Did you visit a social worker within the last 3 months?	Yes	No
Did you visit a psychologist within the last 3 months?	Yes	No
Did you visit a psychiatrist within the last 3 months?	Yes	No
Did you visit a rehabilitation specialist within the last 3 months?	Yes	No
Did you visit a pulmonologist within the last 3 months?	Yes	No
Did you visit a dermatologist within the last 3 months?	Yes	No
Did you visit a neurologist within the last 3 months?	Yes	No
Did you visit an orthopaedist within the last 3 months?	Yes	No
Did you visit another healthcare professional within the last 3 months?		
If yes, which healthcare professional?		

REFERENCES

1. Angus DC, Carlet J. 2002 Brussels Roundtable Participants. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med 2003;29:368–77.
2. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010;38:2386–400.
3. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012;40:2.
4. van der Schaaf M, Beelen A, Dongelmans DA, et al. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med 2009;41:360–6.
5. Tan T, Brett SJ, Stokes T. Guideline Development Group. Rehabilitation after critical illness: summary of NICE guidance. BMJ 2009;338:b822.
6. Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. Eur J Epidemiol 2001;17:991–9.
7. van der Schaaf M, Beelen A, Dongelmans DA, et al. Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med 2009;41:1041–8.
8. van Gelder MMHJ, Bretveld RW, Roeleveld N. Web-based Questionnaires: The Future in Epidemiology? Am J Epidemiol 2010;172:1292–8.
9. Coons SJ, Eremenco S, Lundy JJ, et al. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. Patient 2015;8:4.
10. Cox CE, Wysham NG, Kamal AH, et al. Usability Testing of an Electronic Patient-Reported Outcome System for Survivors of Critical Illness. Am J Crit Care 2016;25:340–9.
11. van der Schaaf M, Bakhshi-Raiez F, Van der Steen M, et al. Recommendations for the organization of intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol 2015;81:2.
12. van de Klundert N, Holman R, Dongelmans DA, et al. Data resource profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol 2015;44:1850.
13. NICE. Dutch National Intensive Care Evaluation (NICE) registry. http://www. stichting-nice.nl (accessed 08 Nov 2016).
14. Mahieu GR. Follow-up system for intensive care patients: preliminary evaluation of workflow and usability. Amsterdam: University of Amsterdam, 2014.
15. Boren T, Ramey J. Thinking aloud: reconciling theory and practice. IEEE Trans Prof Commun 2000;43–261–78.
16. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci 2013;15:398–405.
17. Brooke J. SUS: A Quick and Dirty Usability Scale. In: Usability evaluation in industry. London: Taylor & Francis, 1996:189–94.
18. IBM Corp. IBM SPSS Statistics for Windows. Version 24.0. Armonk, NY: IBM Corp.
19. Centraal Bureau voor de Statistiek (CBS). Statline, 2017. (accessed 01 Feb 2017).
20. Cuthbertson BH, Rattray J, Campbell MK, et al. The practical study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ 2009;339:b3723.
21. Jones C, Skirrow P, Griffiths RD, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med 2003;31:2456–61.

22. Elliott D, McKinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. Crit Care 2011;15:R142.
23. Zuidgeest M, Hendriks M, Koopman L, et al. A comparison of a postal survey and mixed-mode survey using a questionnaire on patients' experiences with breast care. J Med Internet Res 2011;13:e68.
24. Brewin CR, Andrews B, Valentine JD. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J Consult Clin Psychol 2000;68:748–66.
25. Baldwin FJ, Hinge D, Dorsett J, et al. Quality of life and persisting symptoms in intensive care unit survivors: implications for care after discharge. BMC Res Notes 2009;2:160.
26. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med 2010;153.167.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
28. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:6.
29. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055–68.
30. Brewin CR, Rose S, Andrews B, et al. Brief screening instrument for post-traumatic stress disorder. Br J Psychiatry 2002;181:158–62.
31. Elia M. Screening for malnutrition: a multidisciplinary responsibility. Development and use of the Malnutrition Universal Screening Tool ('MUST') for Adults. Redditch: BAPEN, 2003.

Chapter 3

Reported burden on informal caregivers of ICU survivors: a literature review

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ABSTRACT

Background: Critical illness and the problems faced after ICU discharge do not only affect the patient, it also negatively impacts patients' informal caregivers. There is no review which summarizes all types of burden reported in informal caregivers of ICU survivors. It is important that the burdens these informal caregivers suffer are systematically assessed so the informal caregivers can receive the professional care they need. We aimed to provide a complete overview of the types of burdens reported in informal caregivers of adult ICU survivors, to make recommendations on which burdens should be assessed in this population, and which tools should be used to assess them.

Method: We performed a systematic search in PubMed and CINAHL from database inception until June 2014. All articles reporting on burdens in informal caregivers of adult ICU survivors were included. Two independent reviewers used a standardized form to extract characteristics of informal caregivers, types of burdens and instruments used to assess these burdens. The quality of the included studies was assessed using the Newcastle-Ottawa and the PEDro scales.

Results: The search yielded 2,704 articles, of which we included 28 in our review. The most commonly reported outcomes were psychosocial burden. Six months after ICU discharge, the prevalence of anxiety was between 15% and 24%, depression between 4.7% and 36.4% and post-traumatic stress disorder (PTSD) between 35% and 57.1%. Loss of employment, financial burden, lifestyle interference and low health-related quality of life (HRQoL) were also frequently reported. The most commonly used tools were the Hospital Anxiety and Depression Scale (HADS), Centre for Epidemiological Studies-Depression questionnaire, and Impact of Event Scale (IES). The quality of observational studies was low and of randomized studies moderate to fair.

Conclusions: Informal caregivers of ICU survivors suffer a substantial variety of burdens. Although the quality of the included studies was poor, there is evidence that burden in the psychosocial field is most prevalent. We suggest screening informal caregivers of ICU survivors for anxiety, depression, PTSD, and HRQoL using respectively the HADS, IES and Short Form 36 and recommend a follow-up period of at least 6 months.

BACKGROUND

Since 1992, the in-hospital mortality of intensive care unit (ICU) patients declined from 32% [1, 2] to 15-20% [3, 4]. ICU survivors frequently suffer from psychological distress, reduced social well-being and long-term physical limitations which may result in a reduced quality of life [5]. This combination of complaints has been defined as post-intensive care syndrome (PICS).

PICS and other problems faced after ICU discharge do not only affect the patient, but also reduce the physical, mental, social, and financial position of patients' informal caregivers, often family members. The combination of psychological problems affecting informal caregivers is known as PICS-family (PICS-F) [6, 7], though there is disagreement on what the term 'caregiver burden' entails and how it should be utilized [8].

Systematic reviews have been published on the burden on informal caregivers of ICU patients, but all have different definitions of caregiver burden. Some reviews only include quantitative literature [9], some only focus on the needs and satisfaction of informal caregivers [10, 11] and others focus on specific burdens, such as PICS-F [7], post-traumatic stress disorder (PTSD) [12] or psychosocial burdens [13, 14]. There is no review which summarizes all reported burdens informal caregivers of ICU survivors can suffer after discharge, and no clear overview of tools to asses these burdens. It is important that the burdens on these informal caregivers, in addition to PICS-F symptoms, are systematically assessed so the informal caregivers can receive professional care if necessary.

We performed a literature review to: (1) assess which burdens on informal caregivers of adult ICU survivors have been documented; (2) assess which assessment tools are used; and (3) make recommendations on which burden should be assessed and which tools could be used.

MATERIALS AND METHODS

We searched for articles describing burden on informal caregivers of adult ICU survivors, using PubMed and CINAHL from database inception to June 2014. The search strategy is presented in Table 3.1. Only English and Dutch articles were included.

Two authors (IvB and FBR) independently assessed the titles and abstracts of 50 randomly selected articles to ensure that the inclusion criteria were not ambiguous. For 47 (94%) of these articles the inclusion criteria were applied identically. After discussing the differences, consensus was reached. We considered the consistency between the two authors sufficient and made no alterations to the inclusion criteria. We included original studies if: the subject of the study was an informal caregiver of an adult ICU patient; the ICU patient was dis-

charged from hospital alive; at least one of the measurements of the burden took place after hospital discharge; and the burden on the informal caregiver was a main outcome of the study. We excluded studies on deceased ICU patients, studies on the needs or satisfaction of the informal caregiver, presence during cardiopulmonary resuscitation, and involvement in end-of-life decisions, because we hypothesized that informal caregivers of these groups would suffer different burdens.

One author (IvB) evaluated the titles and abstracts of all articles. The abstracts were either included, excluded or marked as doubtful. Another author (FBR) read the title and abstract of articles marked as doubtful and both authors discussed these articles to reach consensus on inclusion. We supplemented our searches by scanning the reference lists of previously included articles. The full text of all eligible articles was read by two authors (IvB and one of FBR, NdK, MvdS, or DAD). Both authors extracted data on the study type, characteristics of the informal caregivers, hospital and setting, type of burden and instruments used to assess the burden. If information could not be extracted from the article or online appendices, we e-mailed the corresponding author for additional information. We assessed the quality of the quantitative articles, using the Newcastle-Ottawa scale (NOS) [15] for observational studies and the PEDro scale [16] for randomized trials.

RESULTS

We retrieved 2,704 articles using the search strategy described in Table 3.1. After removing duplicates, we assessed the title and abstract of 2,311 articles and excluded 2,264 articles based on title and abstract. Figure 3.1 summarizes the inclusion process and provides the reasons for exclusion. We assessed the full text of 47 articles and excluded another 21 articles. We hand searched the references of the 26 included articles and included two additional studies. Nine authors were contacted to complete the data for 12 articles and six authors responded.

Table 3.1 Search strategy

Database		Search terms	
PubMed	Participant	Mesh	Caregivers; family; spouses; family health; proxy
	ICU	Mesh	Critical care; critical illness; intensive care units; intensive care
	Exclusion	Mesh	Intensive care, neonatal; intensive care units, pediatric; intensive care units, neonatal; child; infant; infant, newborn; child, preschool
CINAHL	Participant	Mesh	Family; caregiver burden; caregivers; spouses; family health
	ICU	Mesh	Critical care; critical illness; intensive care units
	Exclusion	Mesh	Intensive care, neonatal; intensive care units, pediatric; intensive care units, neonatal; neonatal Intensive care nursing; pediatric critical care nursing; child; infant; infant, newborn; child, preschool

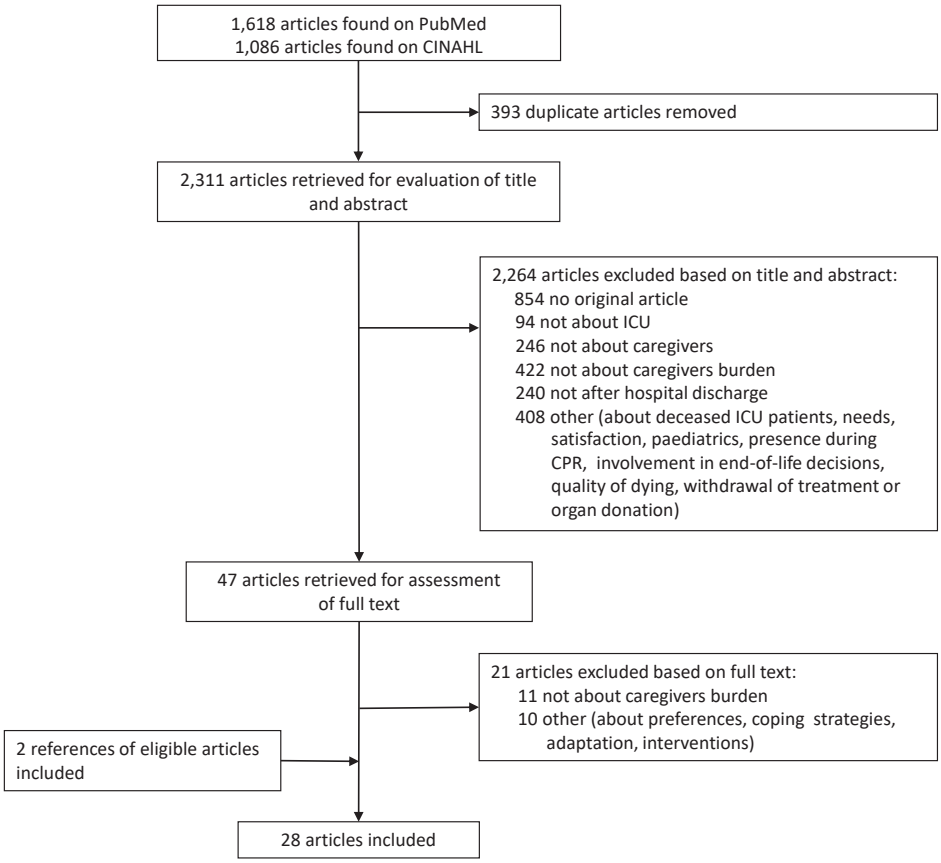

Figure 3.1 Flow diagram of literature search results, the inclusion process and the reason for exclusion

Study characteristics and quality

There is a wide variety in study and informal caregiver characteristics (Appendix 3.1). Fourteen studies were conducted in northern America [17-30], 12 in Europe [31-42], one in Australia [43] and one in Botswana [44]. The follow-up period ranged from 2 weeks after hospital discharge to 4 years after ICU discharge. Most of the informal caregivers were female (47-100%) and most of them were the partner/spouse of the ICU survivor (24-100%).

We present the results of the quality assessment of the included articles in Table 3.2. The NOS scores for the 24 observational studies ranged from two to three on a scale of zero to nine, indicating low quality. The PEDro scale score for the three randomized controlled trials ranged from four to seven on a scale of zero to ten, indicating moderate to fair quality.

Table 3.2 Quality of included studies

Non-randomized studies assessed with the Newcastle-Ottawa Scale				
Author, year	Selection	Comparability	Outcome	Total score
Ågård, 2014 [31]	1	0	2	3
Anderson, 2008 [17]	1	0	2	3
Azoulay, 2005 [32]	1	0	2	3
Bayen, 2013 [33]	1	0	2	3
Cameron, 2006 [18]	1	0	2	3
Choi, 2011 [19]	1	0	1	2
Choi, 2012 [20]	1	0	2	3
Dithole, 2013 [44]	1	0	1	2
Douglas, 2003 [22]	1	0	2	3
Douglas, 2010 [24]	1	0	2	3
Foster, 2003 [43]	1	0	2	3
Garrouste-Orgeas, 2012 [34]	1	0	2	3
Im, 2004 [25]	1	0	2	3
Lemiale, 2010 [37]	1	0	1	2
De Miranda, 2011 [38]	1	0	2	3
McAdam, 2012 [26]	1	0	2	3
Myhren, 2004 [39]	1	0	1	2
Van Pelt, 2007 [27]	1	0	2	3
Van Pelt, 2010 [28]	1	0	1	2
Rodríguez, 2005 [41]	1	0	1	2
Rodríguez, 2005 [40]	1	0	1	2
Swoboda, 2002 [29]	1	0	2	3
Wartella, 2009 [30]	1	0	1	2
Young, 2005 [42]	1	0	2	3

Randomized controlled trails assessed with the PEDro Scale	
Author, year	Total score
Douglas, 2005 [23]	4/10
Jones, 2004 [36]	7/10
Jones, 2012 [35]	5/10

Burden

We found a large diversity in types of burden reported. Table 3.3 shows a summary of the main findings. A complete overview of all types of burden is presented in Appendix 3.2.

Nineteen studies (68%) assessed depression (Appendix 3.3), of these eight used the Hospital Anxiety and Depression Scale (HADS) subscale [17, 26, 32, 34, 36-38, 42], seven the Centre for Epidemiological Studies-Depression (CES-D) questionnaire [18, 22-25, 27, 28, 31],

Table 3.3 Summary of main findings of the reported burden

Type of burden	Time of measurement	Reported outcomes
Anxiety*	During admission	42%-80%
	3 months	24%-63%
	6 months	15%-24%
Depression	During admission	16%-90%
	3 months	12%-26%
	6 months	5%-36%
	12 months	23%-44%
Post-traumatic stress disorder	During admission	57%
	3 months	30%-42%
	6 months	35%-57%
	12 months	32%-80%
Employment status	Up to 50% of the informal caregivers reduced their work hours, quit their job or were fired in order to provide informal care	
Health-related quality of life	Major decreases in mental health, limited changes in physical health	
Use of medication	Between 8% and 32% of informal caregivers started to use medications after the ICU admittance of their relative	
Lifestyle interference	Up to 12 months after discharge, almost 50% of informal caregivers had to quit activities in order to take care of the patient	

one the short version of the CESD [20], one the Zarit Burden Inventory [33], one the Brief Symptom Inventory (BSI) [30] and one a self-developed questionnaire [39]. The prevalence was between 16% and 90% during ICU or hospital stay and between 12.2% and 26.2% 3 months, 4.7% and 36.4% 6 months, and 22.8% and 44% 12 months after ICU discharge. The cross-sectional study reported a prevalence of 31.9%.

Ten studies assessed anxiety (36%) (Appendix 3.4), of these eight used the HADS [17, 26, 32, 34, 36-38, 42], one the BSI [30] and one a self-developed questionnaire [39]. The prevalence was between 42% and 79.7% during ICU or hospital stay and between 24.4% and 62.5% 3 months and 15% and 24% 6 months after ICU discharge.

Post-traumatic stress was assessed in eight studies (29%) (Appendix 3.5), of these three used the Impact of Event Scale (IES) [17, 32, 36], three the IES-Revised (IES-R) [26, 34, 38], one the PTSD Checklist-specific scale [44] and one the Post-Traumatic Stress Syndrome-14 screening tool [35]. The prevalence was 56.8% during ICU stay and between 29.8% and 42% 3 months, 35% and 57.1% 6 months and 31.7% to 80% 12 months after ICU discharge.

Thirteen studies described informal caregivers' employment status [18-20, 22-25, 27, 29, 31, 32, 43, 44] and at study enrolment between 25.4% and 72.3% were in paid employment.

Four studies reported a reduction in employment around 2 months after enrolment [24, 25, 27, 29] and two reported that almost 50% of informal caregivers, who had been employed at enrolment, reduced their work hours, quit their job or were fired in order to provide informal care [24, 29]. Of the informal caregivers, who were employed prior to the ICU admission, 84.6% had returned to their previous work 12 months after enrolment [31]. Their mean sick leave was 11 days (range 4-42) for full-time employees and 9 days (range 0-44) for part-time employees during the patient's ICU stay and 17 days (range 0-124) for full-time employees and 21 days (range 0-106) for part-time employees during the 12 months after ICU discharge [31]. Thirty-eight percent of the informal caregivers reported that it was somewhat difficult to pay for basic needs such as food, housing, medical care and heating. Some of them even moved to a less expensive home, delayed educational plans or medical care for themselves or another family member, or filed for bankruptcy due to the financial burdens [29].

Of the seven studies which described health-related quality of life (HRQoL), four used the Short Form 36 (SF-36) [18, 32, 33, 37], one used the Short Form 8 (SF-8) [23] and two used a single-measure item [22, 24] (Appendix 3.6). Two found no change in physical health scores [33, 37], one reported that 36% of informal caregivers experienced negative changes in their physical health [22], and one reported no statistically significant differences in changes in physical health between informal caregivers and controls over time [23]. Three studies reported major decreases in the mental health of informal caregivers [32, 33, 37], one reported that informal caregivers scored lower on all domains of the SF-36 than an age- and gender-matched population [18], and one reported a slight decrease in general health [32].

Six studies reported on informal caregivers' use of antidepressant, anxiolytic, hypnotic and psychotropic medication [24, 32, 37-39, 44]. Between 8.4% and 32% of informal caregivers started to use these medications after ICU admittance [32, 37, 38] and 14% used more hypnotics and 4% more anxiolytics after the ICU stay than before [39]. Between 8.4% [32] and 17% [38] of informal caregivers received psychiatric or psychological support after their relative's ICU admission, 40% saw a healthcare professional for emotional problems [20]. Six months after ICU admission, 21.1% had delayed obtaining care for themselves because of the patient's illness [29].

Eight studies assessed the lifestyle interference of informal caregivers (Appendix 3.7). Two used the Activity Restriction Scale [27, 28], two the Changes in Role Function scale [19, 25], one the Caregiving Impact Scale [18], one the 'objective indicator' portion of the 'objective and subjective burden' tool [22], one the Family Impact Survey [29] and one qualitative methods [42]. Lifestyle interference was high [19, 27, 28], the percentage of informal caregivers who had quit other activities in order to care for the ICU survivor was 84.5% 1

month and 45.8% 12 months after ICU admission [29]. One month after ICU discharge, 75% had moderate or great restrictions in visiting friends and 48% in practicing hobbies and recreation [19]. They provided about 5 hours of care a day [22, 25, 27, 43] between hospital discharge [22] and 12 months after initiation of mechanical ventilation [27].

Qualitative research

Five studies had qualitative elements. One relied entirely on semi-structured interviews [21] and four had some qualitative components [31, 38, 42, 44]. They mainly reported psychosocial burdens, such as sleep disorders, nightmares, sadness, distress, anxiety, exhaustion, crying for no apparent reason and keeping a distance from family and friends. Parents described it as 'emotionally draining' to explain the situation to the children [21] or were scared of leaving children alone with the ICU survivor at home. Children's involvement made it more complicated to balance the logistics of home life and work [21, 31]. An ICU admission can also impact the relationship between the ICU survivor and the informal caregiver. Informal caregivers and ICU survivors can feel more irritated with each other, experience less freedom than before [42], experience a sense of increased distance in their relationship [21] or even attribute the end of their relationship to the ICU admission [31]. However, one couple stated that they showed each other more tenderness and respect and another reported that their life was more positive following the ICU admission [42].

DISCUSSION

We performed a literature review to assess the burdens experienced by informal caregivers of adult ICU survivors have been documented, how they are assessed and to make recommendations on which burdens should be assessed. We have shown that informal caregivers of ICU survivors have extensive burdens following the patient's ICU admission. This is reflected in psychosocial status, quality of life, lifestyle, employment and financial status. The most frequently used assessment tools were the HADS, the CES-D, the IES and the SF-36.

Psychosocial burdens are most commonly reported and, in this review, we described these in depth. Generally, the prevalence was highest during and shortly after the ICU admission, decreased over time, but remained higher compared to control groups. In contrast, the prevalence of PTSD increased over time. Although different measurement tools were used, the prevalence of depression among informal caregivers of ICU survivors was higher than among informal caregivers of patients with colorectal cancer [45] and following coronary bypass surgery [46], stroke, hip fracture, congestive heart failure and myocardial infarction [46]. We found that, 3 months after ICU discharge, between a quarter and two-thirds of informal caregivers reported anxiety. This is similar to the prevalence reported in a systematic review on anxiety in informal caregivers of people with dementia [47]. Burdens such as

insomnia, concentration problems, fear of death and spiritual problems were only described by few authors in low-quality, observational studies. However, these burdens can influence informal caregivers substantially. Further research on the scope of these problems and the appropriated assessment tools is necessary.

A range of assessment tools can be used to quantify the burdens on informal caregivers. However, these tools use different cut-off points to quantify the burden. For example, the HADS uses two different cut-off points. Scores of eight to ten on the anxiety or depression subscale potentially indicate pathology and scores of 11 or more are considered more definite [48]. However, these tools can be used as screening instruments, but are not valid methods for obtaining a clinical diagnosis and cannot predict which informal caregivers will need professional treatment to recover.

Correct use of the questionnaires is crucial, but not always found. For example in the article by McAdam [26] the IER-R is used for informal caregivers during ICU admission of their relative and refers to the outcome as PTSD. However, according to the definition of PTSD, PTSD cannot be evaluated during the event. Symptoms have to be present for at least 1 month after the event of interest in order to be diagnosed as PTSD [49].

Possible benefits of post-ICU clinics for ICU survivors are mentioned before [50]. However, we did not find any recommendations on screening informal caregivers in post-ICU care, though there are recommendations on inviting the informal caregiver to the patient's post-ICU care [51]. Considering the high prevalence of a wide range of burdens in informal caregivers, we highly recommend assessing the informal caregiver as part of the post-ICU care so they can be referred to the appropriate healthcare provider(s) if necessary.

There is a large resemblance between a recently published systematic review about the psychosocial outcomes informal caregivers of ICU patients can suffer [13] and our study, as 11 articles were included in both studies. However, a strength of our study is that we did not restrict our literature search to psychosocial outcomes and could include 17 additional articles [17, 26, 29-34, 36-44]. Consequently, we also report on other burdens such as anxiety, loss of employment, financial problems and healthcare consumption. Recognition of these additional types of burden is important for referral to the appropriated healthcare provider. Another strength of our review is that we included both quantitative and qualitative studies describing burdens informal caregivers can suffer. This means that we could identify additional burdens such as sleeping disorders and negative impacts on social life and relationships [21, 31, 38, 42, 44].

Our study also has some limitations. Two pairs of articles describe the same data from samples of 57 [40, 41] and 284 [32, 37] informal caregivers. Both pairs of articles report on results obtained using the same instruments at the same time points. Since we did not perform a meta-analysis, we believe that the influence of these duplicate data is limited. In addition, the methodological quality of the 24 observational studies was low and the three randomized studies moderate to fair. Although all of the studies report similar results, more high-quality studies are needed to obtain accurate assessments of the prevalence and severity of burdens informal caregivers suffer.

CONCLUSIONS

Our findings suggest that critical illness and problems faced after ICU discharge have long-term effects on informal caregivers of ICU survivors. Psychosocial symptoms of PICS-F, such as depression, anxiety and post-traumatic stress symptoms, and decreased health-related quality of life are the most commonly reported burden.

We recommend screening for these burdens and recommend a follow-up period of at least 6 months. Screening could be done by the ICU department or rehabilitation department of the hospital where the patient was admitted. Screening on symptoms of PICS-F could be integrated in the post-ICU care, if offered, for ICU patients. The screening could be performed with a telephone consultation, or as part of a visit to a post-ICU clinic by the ICU survivor [51]; thus combining aftercare for patients and their informal caregivers. In the absence of an ICU aftercare programme, it is important that the family physician should be aware of the risk for PICS-F symptoms in informal caregivers of former ICU patients. Informal caregivers can be screened using validated tools such as the HADS, IES, CES-D and SF-36.

ACKNOWLEDGEMENTS

We would like to thank Rebecca Holman for editing this manuscript.

APPENDICES

Appendix 3.1 Characteristics of informal caregivers

Author, year	Location	Design	n	Subgroup	Age Mean ± SD	Female (%)	Relationship to ICU patient (%)
Ågård, 2014 [31]	Denmark	Longitudinal observational descriptive	18		57 (30-73)[a]	61.1%	Partner 100%
Anderson, 2008 [17]	USA	Prospective longitudinal cohort	50		54 (26-76)[b]	84%	Spouse 36% Parent 26% Child 12% Sibling/niece/nephew 6% Unknown 20%
Azoulay, 2005 [32]	France	Longitudinal	284		51 (41-61)[c]	67.6%	Spouse 48.2% Children 13.2% Parents 23.9% Other family 14.6%
Bayen, 2013 [33]	France	Prospective inception cohort	66[d]		50.3 ± 13.1	73%	Parent 48% Spouse 38% Brother/sister 3% Other family 8% Other 3%
Cameron, 2006 [18]	Canada	Cross-sectional	47		52.9 ± 13.6	68.1%	Spouse 66.0% Parent 23.4% Other 6.4%
Cox, 2009 [21]	USA	Semi-structured interviews	24		53 (38-64)[c]	83%	Spouse or partner 63% Child 8% Other family 25% Friend 4%
Choi, 2011 [19]	USA	Longitudinal	69[e]		< 30 year 23% 31-50 year 32% 51-70 year 46% > 70 year 13% Unknown 6%	52%	Spouse 55% Adult child 22% Parent/guardian 9% Sibling 6% Other 9%
Choi, 2012 [20]	USA	Longitudinal descriptive	50		52.3 ± 11.8	74.0%	Spouse 58.0% Adult child 24.0% Parent/sibling 17.9%
Dithole, 2013 [44]	Botswana	-	28		35.0 (26-54)[c]	60.7%	Spouse 100%
Douglas, 2003 [22]	USA	Prospective longitudinal descriptive	135		54.1 ± 15.3	73.3%	Spouse 43.7% Son/daughter 30.4% Sibling 8.9% Other relative 8.1% Other 8.9%
Douglas, 2005 [23]	USA	Prospective experimental	211	Experimental	53.1 ± 14.5	73.9%	Spouse 39.8% Son/daughter 31.3% Sibling 9.0% Other relative 14.7% Other 5.2%

	Education (%)	Employment (%)	Ethnicity (%)	Key inclusion ICU patient
	-	Full-time 55.6% Part-time 16.7% Unemployed 5.6% Retired 22.2%	-	ICU survivor Age 25-70 year Intubated > 96 h
	Attended college 34%	-	White 84% African American 16%	ICU stay > 2 days
	-	Unemployed 28.3%	Not of European descent 13%	ICU stay > 2 days
	-	-	-	Age > 15 year, severe TBI (i.e. GCS < 8 before hospital admission)
	≤ college 55.3% ≥ university 36.2%	Working 40.4% Caregiver/Home-maker 36.2% Other 21.3%	-	Age ≥ 16 years, ARDS survivors
	-	-	White 79% African-American 17% Native American 4%	Required MV, diagnosed with ARDS
	-	Employed 59% Unemployed/ retired 36% Unknown 4%	White 91% African- American 9%	Age ≥ 18 years, MV > 7 consecutive days
	Years of education 14.5 ± 3.3	Employed 54.0%	White 92.0%	Age ≥ 21 years, MV ≥ 4 consecutive days
	None 14.3% Primary 28.6% HS 21.4% Tertiary 35.7%	Working/Student 71.4% No formal employment 28.6%	-	Received MV
	-	Full-time 54.8% Part-time 8.1% Retired 18.5% Not working/ not retired 18.5%	White 74.1%	Age ≥ 18 year, MV > 4 days
	-	Employed 53.5% Retired 25.0% Not employed 21.5%	White 65.9%	Age ≥ 18 year MV > 72 hours

Appendix 3.1 Characteristics of informal caregivers (continued)

Author, year	Location	Design	n	Subgroup	Age Mean ± SD	Female (%)	Relationship to ICU patient (%)
			79	Control	52.6 ± 17.7	68.4%	Spouse 46.8% Son/daughter 34.2% Sibling 12.7% Other relative 5.1% Other 1.3%
Douglas, 2010 [24]	USA	Prospective study	252	White	49.4 ± 14.5	78.0%	Spouse 24.6% Son/daughter 34.7% Sibling 11.9% Parent 27.1% Other 1.7%
			118	Non-white	54.3 ± 14.3	67.0%	Spouse 44.4% Son/daughter 23.0% Sibling 8.3% Parent 18.7% Other 5.6%
Foster, 2003 [43]	Australia	Descriptive and correlational	71		51.8 ± 14.3	71.8%	Spouse 62.0% Parent 11.3% Adult child 23.9% Other 2.8%
Garrouste-Orgeas, 2012 [34]	France	Prospective single-center study	48	Pre-diary	-	-	Spouses 27.0% Grown children 33.3% Siblings 18.7% Parents 12.5% Other family 2.0% Friends 6.2%
			49	Diary	-	-	Spouses 44.9% Grown children 28.5% Siblings 8.1% Parents 8.1% Other family 10.2% Friends 0%
			46	Post-diary	-	-	Spouses 39.1% Grown children 15.2% Siblings 15.2% Parents 21.7% Other family 8.7% Friends 0%
Im, 2004 [25]	USA	Prospective cohort	115		52.9 ± 14.2	76.5%	Spouse 52.2% Adult child 18.3% Parent/guardian 19.1% Friend 0.9% Others 9.6%
Jones, 2004 [36]	UK	RCT	58	Rehabilitation	62 ± 17	63%	Spouse/partner 50.0% Adult child 20.7% Parent 17.2% Sibling 6.9% Grandchild/niece 5.2%
			46	Control	60 ± 15.4	55%	Spouse/partner 54.3% Adult child 17.4% Parent 19.6% Sibling 6.5% Grandchild/niece 2.2%

	Education (%)	Employment (%)	Ethnicity (%)	Key inclusion ICU patient
	-	Employed 43.4% Retired 27.6% Not employed 28.9%	White 63.3%	
	< HS 6.1% ≥ HS < college 75.6% ≥ college 18.2%	Employed 59.8%	White 100%	MV > 72 hours, GCS < 6
	< HS 8.4% ≥ HS < college 65.9% ≥ college 24.7%	Employed 58.7%	African-American 82.2% Hispanic 10.2% Asian 4.2% Other 3.4%	
	-	Full time 16.9% Part time 8.5% Casual 9.9% Unpaid 38% Unemployed 26.8%	-	ICU stay ≥ 5 days, admitted with a neurological condition
	-	-	France 81.2% Africa 10.4% European countries ≠ France 4.1% Other 4.1%	ICU stay ≥ 4 days
	-	-	France 83.6% Africa 4.0% European countries ≠ France 10.2% Other 2.0%	
	-	-	France 69.5% Africa 17.3% European countries ≠ France 2.1% Other 10.8%	
	≤ HS 55.7% > HS 44.3%	Employed 28.6% Homemaker 28.6% Retired 21.7% Other 20.8%	White 90.4% Black 8.7% Other 0.9%	Age ≥ 18 year MV > 48 h
	-	-	British 100%	ICU stay > 48 h, emergency admission and had been ventilated.
	-	-	British 100%	

Appendix 3.1 Characteristics of informal caregivers (continued)

Author, year	Location	Design	n	Subgroup	Age Mean ± SD	Female (%)	Relationship to ICU patient (%)
Jones, 2012 [35]	Sweden and UK	RCT	15 15	Intervention Control	- -	73.3% 80.0%	Spouse/partner 56.7% Child/child-in-law 26.7% parent 10% Siblings 6.7%
Lemiale, 2010 [37]	France	Longitudinal Observational	284		51 (41-61)[c]	67.6%	Spouse 48.2%
De Miranda, 2011 [38]	France	Prospective study	102		-	-	Spouse 53.9%
McAdam, 2012 [26]	USA	Longitudinal descriptive	74 [f]	-	51.3 ± 13.1	58.1%	Spouse/partner 43.2% Adult child 33.8% Parent 10.8% Sibling 10.8% Other 1.4%
Myhren, 2004 [39]	Norway	Prospective study	50		-	32%	Spouses/cohabitant 40% Child 30% Parents 14% Siblings 6% Other 10%
Van Pelt, 2007 [27]	USA	Prospective parallel cohort	169		54.6 ± 14.7	75.7%	Spouse 52.7% Other family 35.5% Not family 11.8%
Van Pelt, 2010 [28]	USA	prospective, longitudinal observational	48[e]		52.8 ± 12.8	81.2%	Spouse 47.9% Other family 37.5% Not family 14.6%
Rodríguez, 2005 [41]	Spain	-	57		40.47[g]	47.4%	Parents 49.1%
Rodríguez, 2005 [40]	Spain	-	57		40.47[g]	47.4%	Parents 49.1% Husband/wife 19.3% Brother/sister 17.5% Son/daughter 8.8% Others 5.3%
Swoboda, 2002 [29]	USA	-	102		-	52%	Husband 22.7% Wife 35.6% Child 19.8% Sibling 5% Significant other 6%
Wartella, 2009 [30]	USA	-	51		43.7 (19-84)[b]	66%	-
Young, 2005 [42]	UK	Single measure-ment point	20		53.30 ± 13.94	75%	-

[a] Median (range)
[b] Mean (range)
[c] Median (IQR)
[d] n baseline measured during (first) follow-up period
[e] n informal caregivers who completed all follow-up points
[f] n baseline measured during ICU stay
[g] Mean

	Education (%)	Employment (%)	Ethnicity (%)	Key inclusion ICU patient
	-	-	-	ICU stay ≥ 72 h and received MV ≥ 24 h
	-	-	-	
	-	-	-	ICU stay of >48 h
	-	-	-	History of COPD, ICU stay > 24 hrs for COPD exacerbation
	≥ college 71.6%	-	White 59.5% Asian/Pacific Islander 20.3% Hispanic 13.5% Black 6.8%	Age ≥ 18 year ICU stay ≥ 72 h received MV, and an APACHE II ≥ 20 in the first 24 hours
	-	-	-	Age ≥ 18 year ICU stay ≥ 6 days Receiving MV Trachea intubated or tracheotomy
	≥ 12th grade 88.8%	Employed 28.7%	White 91.1% Black 8.3% Other 0.6%	Age ≥ 18 year Received MV ≥ 48 h
	≥ 12th grade 87.5%	-	White 91.7% Black 8.3%	Age ≥ 18 year Received MV ≥ 48 h Survived ≤ 12 months after initiation MV
	-	-	-	Age ≥ 14 year Survived ICU admission
	Completed primary studies 54.4%	-	-	head and brain trauma, poly-traumatized or traumatic quadri-plegics as an result of an unexpected accident
	-	Employed 74%	-	Admitted to a surgical ICU ICU stay > 6 days
	-	-	Caucasian 52% African American 42%	Diagnosed with TBI in the emergency department admitted to a neuroscience ICU
	-	-	-	Age ≥ 18 year ICU stay ≥ 24

TBI: Traumatic brain injury
ICU: Intensive Care Unit
COPD: Chronic obstructive pulmonary disease
USA: United States of America
UK: United Kingdom
RCT: Randomised controlled trial
MV: Mechanical ventilation
GCS: Glasgow Coma Scale
ARDS: Acute respiratory distress syndrome
HS: High school
APACHE II: Acute Physiology and Chronic Health Evaluation II

Appendix 3.2 Overview of all burden reported in the included articles

Themes	Burden
Psychological	PTSD [17, 26, 32, 34-36, 38, 44] Anxiety [17, 26, 30, 32, 34, 36-39, 42, 44] Depression [17, 20, 22-28, 30, 32-34, 36-39, 42, 44] Suicidal depression [40, 41], anxious depression [40, 41] Emotional distress [18, 30], emotional problems [20], emotional instability [44], emotional burden [43] Distress [19, 21] Feeling overloaded as a result of caregiving activities [22] Hopelessness [21] Overwhelmed [21, 23] Insomnia [39], sleep disorders [38], sleep disturbances [44], poor sleep patterns, including nightmares, waking up at odd hours, and struggling to fall asleep [44], "I would keep myself awake to check he was still breathing" [42], restriction in sleeping habits [19] Concentration problems [39, 44] Intrusion [26, 34, 44] Fear [44], Fear of down death [40, 41] Crying for no apparent reason [44] Startle reactions [44] Feeling cut off from people [44] Re-experiencing the event [44], Avoidance [26, 34, 44] Hyper arousal symptoms [26, 34, 44] Peritraumatic dissociation [34] Sadness [38] Somatization [30] Hostility [30], Agitation [40, 41] Denial [30] Hypochondriasis [40, 41] Low Energy Level [40, 41] Guilt-resentment [40, 41] Boredom-withdrawal [40, 41] Paranoia [40, 41] Psychopathic deviation [40, 41] Schizophrenia [40, 41] Psychasthenia [40, 41] Psychological Inadequacy [40, 41]
Physical	Physical problems such as pain and arthritis [31] Poor physical health [22], physical burden [43] Exhaustion [21], having little less energy [22] Physical reactions such as sweating or palpations [44] Health problems [23]
HRQoL	Physical problems such as pain and arthritis [31] Poor physical health [22], physical burden [43] Exhaustion [21], having little less energy [22] Physical reactions such as sweating or palpations [44] Health problems [23]
Spiritual	Fear related to supernatural phenomena [44] Fear that ICU patient had been "bewitched" [44]

Appendix 3.2 Overview of all burden reported in the included articles (continued)

Themes	Burden
Social	Complicated logistics of home life [31] Social problems [31], social burden [43] "Now we are in all the time" [42], "not able to go out as much as before" [42], "I have lost interest in everything. I do not go to the saloon, do not visit my friends. I am afraid of life" [44] Lack of support [21, 23] Strain of balancing child care and work [21] Keeping distant from family and friends [44], generalised dissociation from people [44] Restrictions in visiting friends, hobbies, sport and recreation, shopping for self, doing household chores, caring for self, caring for others, eating habits, and maintaining friendship [19]
Relationship	Separation [31] "Freedom in relationship has lessened" [42] "More irritable with each other" [42] increased distance in relationship [21] "I do not think we have a real normal marriage now"[21] Feeling of irritation with the ICU patient [21] Feeling of anger with the ICU patient [21] "It was hard living with him [the ICU patient]" [21] "Our relationship will never be the same. It is all gone . . . different" [21] "we are sinking" [21]
Financial	Difficulties to pay for basics such as food, housing, medical care, and heating [25] Most of savings lost [29] Major source of family income lost [29] Moved to a less expensive home because of the cost of the illness [29] Delayed medical care for themselves because of the cost of the illness [29] Altered educational plans because of the cost of the illness [29] Financial pressures to return to work [21] Having little less money [22]
Employment	Los of employment [31] Reduction in employment [27], restrictions in work [19] Early retirement to become an informal caregiver [31] Sick leave from work [31] Often taking a day off from work to drive the patient to clinic visits [31] Reduced work hours for caregiving role [24, 25] Quit work for caregiving role [24, 25, 29] Fired as a result of the caregiving role [24] "When I came back, I did not have that [multimillion-dollar] project anymore. They seem to have forgotten they promoted me" [21]
Other	Long commutes to rehabilitation facility [31] Burden [23, 33], Caregiver burden [20] Lifestyle interference [18], lifestyle restriction [27], lifestyle disruption [28], restriction of activities [25], disrupted schedule [23] Lower levels of mastery [18] Having little less time [22], time-dependent burden [43] Having little less privacy [22], having little less personal freedom [22] Developmental burden [43] "Did not have any back up at home" [42] A lingering feeling of regret [21] "Doing a lot more jobs now"[42]

HRQoL: Health-related quality of life

Appendix 3.3 Depression: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Anderson, 2008 [17]	HADS	0-21	≥ 11	50	-	During ICU stay	16%	7 ± 4
				39		1 month after enrolment	8%	4 ± 4
				34		6 months after enrolment	6%	4 ± 3
Azoulay, 2005 [32]	HADS	0-21	≥ 11	284	-	3 months after ICU discharge or death	20.1%	-
Bayen, 2013 [33]	ZBI	0-88	> 24	66	-	1 year after injury	44%	25.1 ± 17.2
Cameron, 2006 [18]	CES-D	0-60	≥ 16	47	-	On average 23 months after hospital discharge	31.9%	12 (4; 23)[a]
Choi, 2012 [20]	shortened CES-D	0-30	≥ 8	50	-	During ICU admission	90%	16.4 ± 7.1
				41	-	At ICU discharge	73%	10.5 ± 5.9
				31	-	2 months after ICU discharge.	61%	10.3 ± 5.9
de Miranda, 2011 [38]	HADS	0-21	≥ 8	102	-	At ICU discharge	25.7%	-
				47		3 months after ICU discharge	14.9%	-
Douglas, 2003 [22]	CES-D	0-60	≥ 16	135	-	At hospital discharge	51.2%	15.5 ± 11.8
				77	-	6 months after hospital discharge	36.4%	13.9 ± 12.8
Douglas, 2005 [23]	CES-D	0-60	≥ 16	206	Experimental	At hospital discharge	52.9%	17.8 ± 12.3
				79	Control		41.0%	15.8 ± 10.9
				166	Experimental	2 months after hospital discharge	31.3%	12.3 ± 11.5
				56	Control		29.2%	12.2 ± 11.4
Douglas, 2010 [24]	CES-D	0-60	≥ 16	252	white	ICU admission	75.2%	23.7 ± 10.9
				118	Non-white		72.0%	23.4 ± 11.2
				193	White	2 months after hospital discharge	45.4%	15.7 ± 12.8
				84	Non-white		50.5%	16.8 ± 13.2

Appendix 3.3 Depression: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies (continued)

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Garrouste-Orgeas, 2012 [34]	HADS	0-21	≥ 8	48	Pre-diary	ICU discharge	25%	5.1 ± 4.1
				49	Diary		30.6%	6.6 ± 4.6
				46	Post-diary		41.3%	7.5 ± 3.9
				48	Pre-diary	3 months after ICU discharge	18.8%	4.7 ± 5.0
				46	Diary		21.7%	4.1 ± 4.4
				42	Post-diary		26.2%	5.1 ± 4.5
Im, 2004 [25]	CES-D	0-60	≥ 16	115	-	2 months following the onset of prolonged MV	33.9%	13.2 ± 11
Jones, 2004 [36]	HADS	0-21	≥ 11	58	Rehabilitation	On the general ward	22%	6.5 ± 4.38
				46	Control		31%	7 ± 4.52
				50	Rehabilitation	2 months after ICU discharge	7.8%	3.8 ± 3.42
				40	Control		7%	4.6 ± 4
				47	Rehabilitation	6 months after ICU discharge	4.7%	3.7 ± 3.51
				37	Control		5.6%	4.6 ± 4.1
Lemiale, 2010 [37]	HADS	0-21	-	284	-	3 months ICU discharge or death	20.1%	-
McAdam, 2012 [26]	HADS	0-21	≥ 8	74	-	During ICU stay	70.3%	9.62 ± 4.2
			≥ 11				43.2%	
			≥ 8	41	-	3 months after ICU discharge or death	26.8%	5.6 ± 4.6
			≥ 11				12.2%	
Myhren, 2004 [39]	Self-developed questionnaire	-	-	50	-	During ICU stay	-	-
				50	-	1 month after the ICU stay	-	-

Appendix 3.3 Depression: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies (continued)

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Van Pelt, 2007 [27]	CES-D	0-60	≥ 16	115	-	2 months after MV initiation	33.9%	13.2 ± 11.0
				107	-	6 months after MV initiation	30.8%	12.7 ± 11.2
				92	-	12 months after MV initiation	22.8%	10.6 ± 10.7
Van Pelt, 2010 [28]	CES-D	0-60	≥ 16	48	-	2 months after MV initiation	37.5%	13.4 ± 12.4
				48	-	6 months after MV initiation	29.2%	12.3 ± 12.0
				48	-	12 months after MV initiation	29.2%	11.8 ± 12.1
Wartella, 2009 [30]	BSI - Depression	-	-	51	-	At ICU admission	-	0.36 ± 0.62
				51	-	At ICU discharge	-	0.27 ± 0.50
				51	-	1 month after ICU discharge	-	0.16 ± 0.33
Young, 2005 [42]	HADS	0-21	≥ 8	20	-	3 months after ICU discharge	25%	-
			≥ 11				15%	-

CES-D: Centre for Epidemiological Studies-Depression
HADS: Hospital Anxiety and Depression Scale
ICU: Intensive care unit
MV: Mechanical ventilation
ZBI: Zarit Burden Inventory
BSI: Brief Symptom Inventory
[a] Median (IQR)

Appendix 3.4 Anxiety: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Anderson, 2008 [17]	HADS	0-21	≥ 11	50	-	During ICU stay	42%	10 ± 4
				39	-	1 month after enrolment	21%	7 ± 5
				34	-	6 months after enrolment	15%	6 ± 5
Azoulay, 2005 [32]	HADS	0-21	≥ 11	284	-	3 months after ICU discharge or death	49.3%	-
De Miranda, 2011 [38]	HADS	0-21	≥ 8	102	-	At ICU discharge	72.2%	-
				47	-	3 months after ICU discharge	40.4%	-
Garrouste-Orgeas, 2012 [34]	HADS	0-21	≥ 8	48	Pre-diary	At ICU discharge	47.9%	7.9 ± 3.3
				49	Diary		50.0%	7.9 ± 3.0
				46	Post-diary		59.5%	8.7 ± 2.7
				48	Pre-diary	3 months after ICU discharge	62.5%	10.4 ± 4.8
				46	Diary		39.1%	7.6 ± 4.8
				42	Post-diary		61.9%	8.8 ± 4.3
Jones, 2004 [36]	HADS	0-21	≥ 11	58	Rehabilitation	On the general ward	58%	11 ± 4.85
				46	Control		62%	12 ± 4.43
				50	Rehabilitation	2 months after ICU discharge	27%	6.9 ± 4.84
				40	Control		35%	7.8 ± 4.71
				47	Rehabilitation	6 months after ICU discharge	22%	6.8 ± 5.03
				37	Control		24%	3.7 ± 4.61
Lemiale, 2010 [37]	HADS	0-21	-	284	-	3 months after ICU discharge or death	49.3%	-
McAdam, 2012 [26]	HADS	0-21	≥ 8	74	-	During ICU stay	79.7%	11.80 ± 4.7
			≥ 11				59.5%	
			≥ 8	41	-	3 months after ICU discharge or death	43.9%	7.3 ± 3.9
			≥ 11				24.4%	

Appendix 3.4 Anxiety: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies (continued)

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Myhren, 2004 [39]	Self-developed questionnaire	-	-	50	-	During ICU stay	-	-
				50	-	1 month after the ICU stay	-	3.0 ± 1.0
Wartella, 2009 [30]	BSI - Anxiety	-	-	51	-	At ICU admission	-	1.31 ± 0.75
				51	-	At ICU discharge	-	0.74 ± 0.54
				51	-	1 month after ICU discharge	-	0.5 ± 0.38
Young, 2005 [42]	HADS	0-21	≥ 8	20	-	3 months after ICU discharge	50%	-
			≥ 11				35%	-

HADS: Hospital Anxiety and Depression Scale
ICU: Intensive care unit
BSI: Brief Symptom Inventory

Appendix 3.5 Post-traumatic stress: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Anderson, 2008 [17]	IES	0-75	> 30	34	-	6 months after enrolment	35%	25 ± 19
Azoulay, 2005 [32]	IES	0-75	> 30	284	-	3 months after ICU discharge or death	33.1%	22 (11; 34)[a]
De Miranda, 2011 [38]	IES-R	0-88	≥ 22	47	-	3 months after ICU discharge	29.8%	-
Dithole, 2013 [44]	PCL-S	17-85	> 44	28	-	6 months after ICU discharge	57.1%	-
Garrouste-Orgeas, 2012 [34]	IES-R	0-88	≥ 22	40	Pre-diary	12 months after ICU discharge	80%	32.7 ± 12.9
				41	Diary		31.7%	21.6 ± 10.7
				34	Post-diary		67.6%	29.8 ± 14.5
Jones, 2004 [36]	IES	0-75	> 19	50	Rehabilitation	2 months after ICU discharge	53%	23.6 ± 19
				40	Control		63%	25 ± 18.2
				47	Rehabilitation	6 months after ICU discharge	38%	21.8 ± 18.5
				37	Control		55%	27 ± 20.86
Jones, 2012 [35]	PTSS-14	14-98	-	15	Intervention	1 month after ICU discharge	-	31.2 ± 15.3
				15	Control		-	32.1 ± 15.9
				15	Intervention	3 months after ICU discharge	-	21.7 ± 8.3
				15	Control		-	30.9 ± 15.2
McAdam, 2012 [26]	IES-R	0-88	Mean score ≥ 1.5	74	-	During ICU stay	56.8%	1.74 ± 0.88
				41	-	3 months after ICU discharge or death	42%	1.27 ± 0.86

ICU: Intensive care unit
IES: Impact of Event Scale
IES-R: Impact of Event Scale-Revised
PCL-S: PTSD Checklist-Specific scale
PTSS-14: Post-Traumatic Stress Syndrome-14 scale
[a] Median (IQR)

Appendix 3.6 Health-related quality of life: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Azoulay, 2005 [32]	SF-36	0-100	-	284	-	3 months after ICU discharge or death	-	-
Bayen, 2013 [33]	SF-36 - PCS	0-100	-	66	-	1 year after injury	-	48.3 ± 8.9
	SF-36 - MCS	0-100	-	66	-		-	36.7 ± 11.7
Cameron, 2006 [18]	SF-36 - Physical functioning	0-100	-	47	-	On average 23 months after hospital discharge		55 (28; 80)[a]
	SF-36 - Role physical	0-100	-					67 (0; 100)[a]
	SF-36 - Bodily pain	0-100	-					62 (32; 100)[a]
	SF-36 - General health	0-100	-					52 (35; 72)[a]
	SF-36 - Vitality	0-100	-					50 (30; 70)[a]
	SF-36 - Social functioning	0-100	-					75 (38; 100)[a]
	SF-36 - Role emotional	0-100	-					67 (0; 100)[a]
	SF-36 - Mental health	0-100	-					76 (47; 88)[a]
Douglas, 2003 [22]	5-point Likert scale	1-5	≤ 2	135	-	At hospital discharge	19.0%	3.74 ± 1.0
				77	-	6 months after hospital discharge	26.8%	3.29 ± 1.1
Douglas, 2005 [23]	SF-8 - PCS	0-100	-	211	Experimental	At hospital discharge	-	52.9 ± 7.7
				79	Control		-	51.9 ± 8.2
				163	Experimental	2 months after hospital discharge	-	51.3 ± 9.4
				48	Control		-	51.5 ± 10.2
	SF-8 - MCS	0-100	-	163	Experimental	At hospital discharge	-	45.2 ± 12.0
				48	Control		-	45.9 ± 11.8
				163	Experimental	2 months after hospital discharge	-	44.4 ± 12.7
				48	Control		-	46.3 ± 11.2
Douglas, 2010 [24]	5-point Likert scale	1-5	≤ 2	252	White	ICU admission	47.6%	3.8 ± 1.4
				118	Nonwhite		59.5%	3.4 ± 1.5
				193	White	2 months after hospital discharge	66.1%	3.3 ± 1.4
				84	Nonwhite		86.0%	2.9 ± 1.4

Appendix 3.6 Health-related quality of life: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies (continued)

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Time of measurement	Prevalence %	Mean ± SD
Lemiale, 2010 [37]	SF-36 - PCS SF-36 - MCS • role emotional • social functioning • vitality • mental health	0-100 0-100	-	284	-	3 months after ICU discharge or death	-	89 (66; 94)[a] - 66 (50; 80)[a] 70 (60; 90)[a] 60 (45; 70)[a] 64.6 (53.2; 77.7)[a]

CU: Intensive care unit
MCS: Mental component summary
PCS: Physical component summary
SF-36: Short Form-36
SF-8: Short Form-8
[a] Median (IQR)

Appendix 3.7 Lifestyle interference: Assessment tools, time points and outcomes measures for informal caregivers for quantitative studies

Author, year	Assessment tool	Score range	Cut-off score	n	Subgroup	Follow-up	Prevalence %	Mean ± SD
Cameron, 2006 [18]	CIS	0-84	-	47	-	On average 23 months after hospital discharge	-	20.3 ± 24.0
Choi, 2011 [19]	CRF	11-44	-	69	-	1 month after ICU discharge	-	23 ± 8.3
				69	-	6 months after ICU discharge	-	19.4 ± 8.6
Douglas, 2003 [22]	'objective indicator' portion of the 'objective and subjective burden' tool	9-45	-	135	-	At hospital discharge	-	32.97 ± 4.98
				77	-	6 months after hospital discharge	-	31.1 ± 6.5
Im, 2004 [25]	CRF	11-44	-	115	-	2 months following the onset of prolonged MV	-	22.1 ± 8.5
Swoboda, 2002 [29]	FIS - Quit other activities to care for family	Yes/no	Yes	95	-	Situation 2 weeks before ICU admission	44.2%	-
				69	-	1 month after ICU admission	84.5%	-
				61	-	3 months after ICU admission	63.9%	-
				53	-	6 months after ICU admission	50.9%	-
				52	-	12 months after ICU admission	45.8%	-
Van Pelt, 2007 [27]	ARS	11-44	-	115	-	2 months after MV initiation	-	22.1 ± 8.5
				107	-	6 months after MV initiation	-	20.5 ± 8.4
				92	-	12 months after MV initiation	-	20.0 ± 8.4
Van Pelt, 2010 [28]	ARS	11-44	-	48	-	2 months after MV initiation	-	22.3 ± 8.7
				48		6 months after MV initiation	-	19.7 ± 8.1
				48		12 months after MV initiation	-	19.4 ± 8.0

ARS: Activity Restriction Scale
CIS: Caregiving Impact Scale
CRF: Changes in Role Function scale
FIS: Family Impact Survey
ICU: Intensive Care Unit
MV: Mechanical ventilation

REFERENCES

1. Goldhill DR, Sumner A. Outcome of intensive care patients in a group of British intensive care units. Crit Care Med. 1998;26:1337-45.
2. Moreno R, Morais P. Outcome prediction in intensive care: results of a prospective, multicentre. Portuguese study. Intensive Care Med. 1997;23:177-86.
3. Kasza J, Moran JL, Solomon PJ. Outcome AN-ANZICSCf, Resource Evaluation C. Evaluating the performance of Australian and New Zealand intensive care units in 2009 and 2010. Stat Med. 2013;32:3720-36. doi:10.1002/sim.5779.
4. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. Crit Care Med. 2013;41:1229-36. doi:10.1097/CCM.0b013e31827ca4e1.
5. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009;41:360-6. doi:10.2340/16501977-0333.
6. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:502-9. doi:10. 1097/CCM.0b013e318232da75.
7. Davidson JE, Jones C, Bienvenu OJ. Family response to critical illness: postintensive care syndrome-family. Crit Care Med. 2012;40:618-24. doi:10.1097/CCM.0b013e318236ebf9.
8. Bastawrous M. Caregiver burden-a critical discussion. Int J Nurs Stud. 2013;50:431-41. doi:10.1016/j.ijnurstu.2012.10.005.
9. Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. Crit Care Med. 2009;37 (10 Suppl): S448-56. doi:10.1097/CCM.0b013e3181b6e145.
10. Paul F, Rattray J. Short- and long-term impact of critical illness on relatives: literature review. J Adv Nurs. 2008;62:276-92. doi:10.1111/j.1365-2648.2007.04568.x.
11. Verhaeghe S, Defloor T, Van Zuuren F, Duijnstee M, Grypdonck M. The needs and experiences of family members of adult patients in an intensive care unit: a review of the literature. J Clin Nurs. 2005;14:501-9. doi:10.1111/j.1365-2702.2004.01081.x.
12. Kross EK, Gries CJ, Curtis JR. Posttraumatic stress disorder following critical illness. Crit Care Clin. 2008;24:875-87. doi:10.1016/j.ccc.2008.06.002.ix-x.
13. Haines KJ, Denehy L, Skinner EH, Warrillow S, Berney S. Psychosocial outcomes in informal caregivers of the critically ill: a systematic review. Crit Care Med. 2015;43:1112-20. doi:10.1097/CCM.0000000000000865.
14. McAdam JL, Puntillo K. Symptoms experienced by family members of patients in intensive care units. Am J Crit Care. 2009;18:200-9. doi:10.4037/ajcc2009252.
15. Wells G OCD, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 22 January 2015.
16. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83:713-21.
17. Anderson WG, Arnold RM, Angus DC, Bryce CL. Posttraumatic stress and complicated grief in family members of patients in the intensive care unit. J Gen Intern Med. 2008;23:1871-6. doi:10.1007/s11606-008-0770-2.

18. Cameron JI, Herridge MS, Tansey CM, McAndrews MP, Cheung AM. Wellbeing in informal caregivers of survivors of acute respiratory distress syndrome. Crit Care Med. 2006;34:81-6.
19. Choi J, Donahoe MP, Zullo TG, Hoffman LA. Caregivers of the chronically critically ill after discharge from the intensive care unit: six months' experience. Am J Crit Care. 2011;20:12-22. doi:10.4037/ajcc2011243. quiz 3.
20. Choi J, Sherwood PR, Schulz R, Ren D, Donahoe MP, Given B, et al. Patterns of depressive symptoms in caregivers of mechanically ventilated critically ill adults from intensive care unit admission to 2 months postintensive care unit discharge: a pilot study. Crit Care Med. 2012;40:1546-53. doi:10.1097/CCM.0b013e3182451c58.
21. Cox CE, Docherty SL, Brandon DH, Whaley C, Attix DK, Clay AS, et al. Surviving critical illness: acute respiratory distress syndrome as experienced by patients and their caregivers. Crit Care Med. 2009;37:2702-8. doi:10.1097/CCM.0b013e3181b6f64a.
22. Douglas SL, Daly BJ. Caregivers of long-term ventilator patients: physical and psychological outcomes. Chest. 2003;123:1073-81.
23. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Impact of a disease management program upon caregivers of chronically critically ill patients. Chest. 2005;128:3925-36. doi:10.1378/chest.128.6.3925.
24. Douglas SL, Daly BJ, O'Toole E, Hickman Jr RL. Depression among white and nonwhite caregivers of the chronically critically ill. J Crit Care. 2010;25:364 e11-9.
25. Im K, Belle SH, Schulz R, Mendelsohn AB, Chelluri L, Investigators Q-M. Prevalence and outcomes of caregiving after prolonged (> or =48 hours) mechanical ventilation in the ICU. Chest. 2004;125:597-606.
26. McAdam JL, Fontaine DK, White DB, Dracup KA, Puntillo KA. Psychological symptoms of family members of high-risk intensive care unit patients. Am J Crit Care. 2012;21:386-93. doi:10.4037/ajcc2012582. quiz 94.
27. Van Pelt DC, Milbrandt EB, Qin L, Weissfeld LA, Rotondi AJ, Schulz R, et al. Informal caregiver burden among survivors of prolonged mechanical ventilation. Am J Respir Crit Care Med. 2007;175:167-73. doi:10.1164/rccm.200604-493OC.
28. Van Pelt DC, Schulz R, Chelluri L, Pinsky MR. Patient-specific, time-varying predictors of post-ICU informal caregiver burden: the caregiver outcomes after ICU discharge project. Chest. 2010;137:88-94. doi:10.1378/chest.09-0795.
29. Swoboda SM, Lipsett PA. Impact of a prolonged surgical critical illness on patients' families. Am J Crit Care. 2002;11:459-66.
30. Wartella JE, Auerbach SM, Ward KR. Emotional distress, coping and adjustment in family members of neuroscience intensive care unit patients. J Psychosom Res. 2009;66:503-9. doi:10.1016/j.jpsychores.2008.12.005.
31. Agard AS, Lomborg K, Tonnesen E, Egerod I. Rehabilitation activities, out-patient visits and employment in patients and partners the first year after ICU: a descriptive study. Intensive Crit Care Nurs. 2014;30:101-10. doi:10.1016/j.iccn.2013.11.001.
32. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med. 2005;171:987-94. doi:10.1164/rccm.200409-1295OC.
33. Bayen E, Pradat-Diehl P, Jourdan C, Ghout I, Bosserelle V, Azerad S, et al. Predictors of informal care burden 1 year after a severe traumatic brain injury: results from the PariS-TBI study. J Head Trauma Rehabil. 2013;28:408-18. doi:10.1097/HTR.0b013e31825413cf.

34. Garrouste-Orgeas M, Coquet I, Perier A, Timsit JF, Pochard F, Lancrin F, et al. Impact of an intensive care unit diary on psychological distress in patients and relatives*. Crit Care Med. 2012;40:2033-40. doi:10.1097/CCM.0b013e31824e1b43.
35. Jones C, Backman C, Griffiths RD. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: a pilot study. Am J Crit Care. 2012;21:172-6. doi:10.4037/ajcc2012569.
36. Jones C, Skirrow P, Griffiths RD, Humphris G, Ingleby S, Eddleston J, et al. Post-traumatic stress disorder-related symptoms in relatives of patients following intensive care. Intensive Care Med. 2004;30:456-60. doi:10.1007/s00134-003-2149-5.
37. Lemiale V, Kentish-Barnes N, Chaize M, Aboab J, Adrie C, Annane D, et al. Health-related quality of life in family members of intensive care unit patients. J Palliat Med. 2010;13:1131-7. doi:10.1089/jpm.2010.0109.
38. de Miranda S, Pochard F, Chaize M, Megarbane B, Cuvelier A, Bele N, et al. Postintensive care unit psychological burden in patients with chronic obstructive pulmonary disease and informal caregivers: a multicenter study. Crit Care Med. 2011;39:112-8. doi:10.1097/CCM.0b013e3181feb824.
39. Myhren H, Ekeberg O, Langen I, Stokland O. Emotional strain, communication, and satisfaction of family members in the intensive care unit compared with expectations of the medical staff: experiences from a Norwegian University Hospital. Intensive Care Med. 2004;30:1791-8. doi:10.1007/s00134-004-2375-5.
40. Rodríguez AM. Psychosocial adaptation in relatives of critically injured patients admitted to an intensive care unit. Span J Psychol. 2005;8:1138-7416. 41. Rodríguez AM, Gregorio MA, Rodriguez AG. Psychological repercussions in family members of hospitalised critical condition patients. J Psychosom Res. 2005;58:447-51. doi:10.1016/j.jpsychores.2004.11.011.
42. Young E, Eddleston J, Ingleby S, Streets J, McJanet L, Wang M, et al. Returning home after intensive care: a comparison of symptoms of anxiety and depression in ICU and elective cardiac surgery patients and their relatives. Intensive Care Med. 2005;31:86-91. doi:10.1007/s00134-004-2495-y.
43. Foster M, Chaboyer W. Family carers of ICU survivors: a survey of the burden they experience. Scand J Caring Sci. 2003;17:205-14.
44. Dithole K, Thupayagale-Tshweneagae G, Mgutshini T. Posttraumatic stress disorder among spouses of patients discharged from the intensive care unit after six months. Issues Ment Health Nurs. 2013;34:30-5. doi:10.3109/01612840.2012.715235.
45. Kim Y, Carver CS, Rocha-Lima C, Shaffer KM. Depressive symptoms among caregivers of colorectal cancer patients during the first year since diagnosis: a longitudinal investigation. Psychooncology. 2013;22:362-7. doi:10.1002/pon.2100.
46. Nieboer AP, Schulz R, Matthews KA, Scheier MF, Ormel J, Lindenberg SM. Spousal caregivers' activity restriction and depression: a model for changes over time. Soc Sci Med. 1998;47:1361-71.
47. Cooper C, Balamurali TB, Livingston G. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. International Psychogeriatrics/IPA. 2007;19:175-95. doi:10.1017/S1041610206004297.
48. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.
49. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington, DC: American Psychiatric Association; 1994.

50. Jones C, Skirrow P, Griffiths RD, Humphris GH, Ingleby S, Eddleston J, et al. Rehabilitation after critical illness: a randomized, controlled trial. Crit Care Med. 2003;31:2456-61. doi:10.1097/01.CCM.0000089938.56725.33.
51. Van der Schaaf M, Bakhshi-Raiez F, Van der Steen M, Dongelmans DA, De Keizer NF. Recommendations for the organization of intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol. 2014;81:135-44.

Chapter 4

Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: A descriptive study combining healthcare insurance data and data from a Dutch national quality registry

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ABSTRACT

Purpose: To identify subgroups of ICU patients with high healthcare utilization for healthcare expenditure management purposes such as prevention and targeted care.

Materials and methods: We conducted a descriptive cohort study, combining a national health insurance claims database and a national quality registry database for ICUs. Claims data in the timeframe 2012-2014 were combined with the clinical data of ICU patients admitted to an ICU during 2013. A population based control group was created based on the ICU population.

Results: 56,760 ICU patients and 75,232 controls from the general population were included. Median healthcare costs per day alive for the ICU population were significantly higher during the year before (€8.9 (IQR €2.4; €32.1)) and the year after ICU admission (€15.4 (IQR €5.4; €51.2)) compared to the control group ((€2.8 (IQR €0.7; €8.8) and €3.1 (IQR €0.8; €10.1)). ICU patients with more chronic conditions had significantly higher healthcare costs before and after ICU admission compared to ICU patients with less chronic conditions.

Conclusions: ICU patients have three to five times higher healthcare costs per day alive compared to a control population. Our findings can be used to optimize the healthcare trajectories of ICU patients with high healthcare utilization after discharge.

INTRODUCTION

In 2013, the total healthcare costs in the Netherlands were 93.3 billion euro, which amounts to 14.5% of the gross domestic product and is on average 5551 euro per inhabitant [1]. The hospital costs are the highest expenses of the total healthcare costs. They accounted for 25.4 billion euro in 2013, i.e. 27.2% of the total healthcare costs [1]. Worldwide, the intensive care unit (ICU) is one of the most expensive departments in a hospital. It is estimated that the ICU costs account for over 13% of the total hospital costs [2] and have increased by 16% during the timeframe of 1985-2000 [3].

High use of healthcare resources is associated with a complex health status and a reduced quality of life [4,5]. It is known that not only during the ICU admission the use of healthcare resources are high, also after discharge ICU survivors consume significant healthcare resources [6]. Previous research on the use of healthcare resources focused on small and specific ICU patient groups, such as recipients of prolonged mechanical ventilation, patients with acute respiratory distress syndrome, patients with severe sepsis, survivors of cardiac arrest, stroke patients, and traumatic brain injury survivors [7-12] and comparisons were made with only other ICU patients or only a hospitalized population.

It is unknown what the healthcare resource use is for large, general groups of ICU patients and how this relates to the general population. Furthermore, it is unknown whether the use of healthcare resources was already high in the year before ICU admission. More insight into use of healthcare resources is relevant for healthcare expenditure management. But most of all, identifying subgroups of patients with high healthcare costs is important for prevention and targeted care such as ICU follow-up care.

Through a unique collaboration we were able to merge data of a national health insurance claims database and a national quality registry database for ICUs to gain insight in the healthcare consumption of ICU patients and a population based control group. The aim of this study was to: a) describe the difference in healthcare costs between ICU patients and a population based control group in the year before ICU admission and the year after ICU admission in order to inform policy makers on healthcare expenditure management, and b) describe the healthcare costs of ICU patients for specified subgroups to motivate the set-up of follow-up clinics to monitor and lead the use of healthcare resource into the right direction.

METHODS

For this descriptive cohort study, we combined data of the Dutch National Intensive Care Evaluation (NICE) registry [13] with the data of the insurance claims database of Vektis [14].

Data sources

Vektis insurance claims database

Health insurance is obligatory for all Dutch citizens and essentially all (99%) Dutch inhabitants have private healthcare insurance [1]. The Vektis databases [14] contain reimbursement data on all medical treatments paid for by Dutch insurance companies, as well as demographic information, such as date of birth, gender and a proxy for date of death for all registered inhabitants of the Netherlands.

The socio-economic status (SES) was derived from the postcode of the person and the SES score for that postcode as determined by the Netherlands Institute for Social Research [15]. The SES score is based on the mean income of a postcode where a person lives, the fraction of people with a low income, the fraction of people with low education and the fraction of unemployed people. The SES score is ranked and the national mean is 0 (range -6.65; 3.02). A lower score indicates a lower SES and a higher scores indicates a higher SES.

All patients in the Vektis database who had a claim for an ICU day in the year 2013 and were 18 years or older during the year of ICU admission were included in the ICU-subset of the Vektis database. Based on this ICU-subset, a population based control group was extracted from the registered inhabitants of the Netherlands in the Vektis database. The population based control group was frequency matched based on the combination of the age, gender, and SES of patients from the ICU subset from the Vektis database, and had no claims for ICU care during 2013. Only ICU patients with no missing data for gender, age and SES were used in the frequency matching process which was undertaken before the linking process. From here on 'control population' will be used to refer to the population based control group.

Dutch National Intensive Care Evaluation database

The NICE registry is a national quality registry in which 90% of all the Dutch ICUs participated during the study period [16]. All ICUs are collecting demographic, physiologic, and clinical data of all patients admitted to their ICUs, including all variables required to quantify the severity of illness and to calculate case-mix adjusted mortality risks according to the Acute Physiology and Chronic Health Evaluation (APACHE) IV model [17].

All patients from the NICE registry aged ≥ 18 years during the year of ICU admission, admitted to an ICU during 2013, and discharged from the ICU before January 1st 2014 were included in the NICE registry subset.

Linking process

The ICU dataset extracted from the Vektis database and the NICE registry subset were linked anonymously using a deterministic linkage algorithm [18] and were linked in three steps.

First, records were linked if gender, date of birth, hospital of admission, ICU admission date, and ICU discharge date were identical in both datasets. Records which could not be linked during the first step, proceeded to the second step. In the second step, records were linked if gender, date of birth, hospital of admission and ICU admission date were identical. Records which could not be linked during the second step, proceeded to the third step. In the third step, records were linked if gender, date of birth, hospital of admission and ICU discharge date were identical in both databases.

Statistical analysis

The primary outcomes of this study are the healthcare costs per day alive during the year before and the year after ICU admission for the ICU population and the control group and a description of the differences between those two groups.

The year before ICU admission is defined as January 1st 2012 until December 31st 2012 and the year after ICU admission is defined as January 1st 2014 until December 31st 2014.

The total healthcare costs are based on all reimbursement data available from health insurance companies and only available as a total sum per calendar-year. The total healthcare costs were converted into healthcare costs per day alive by dividing the total healthcare costs per patient by the number of days alive during a calendar year. The healthcare costs per day alive are stated in euros and we will present the median and inter-quartile range (IQR), unless stated otherwise.

ICU patients who did not survive their hospital admission were excluded from all analyses as these patients have by definition no (costs per) day alive in the year after IC admission. Demographic data used for analyses, such as age and gender, were primary retrieved from the Vektis database. All clinical data was derived from the NICE registry and all data items are explained in Appendix 4.1. Descriptive statistics were used to characterize the demographic data of both study populations.

To estimate the cohort effect on the healthcare costs per day alive during the year before ICU admission and on the healthcare costs per day alive during the year after ICU admission, general linear modelling was used. The healthcare costs per day alive were skewed to the right and therefore the natural logarithm of the healthcare costs per day alive was used. Quartiles of age, gender and quartiles of SES were created and taken into account as confounders and as possible effect modifiers. A p-value of<0.05 was considered to indicate a statistically significant difference.

The ICU population was divided into subgroups based on the APACHE IV predicted mortality [17]; i.e. low-risk (predicted mortality ≥ 0% b 30%), medium-risk (predicted mortality ≥ 30% < 70%) and high-risk (predicted mortality ≥ 70%). Analyses regarding the APACHE IV predicted mortality were only preformed for ICU admissions which met the APACHE IV inclusion criteria [17]. Additionally, we grouped the ICU population by chronic conditions, acute conditions, type of ICU admission and by number of ICU (re-)admissions in 2013 and we performed sub-analyses for these subgroups.

Previous research has shown that healthcare costs are higher in the last 120 days prior to death [19]. A survival curve was constructed as secondary outcome to gain insight in the long-term mortality of both populations. For the survival analyses, the period at risk starts at the first of January 2013. Because of the increased healthcare costs around the time of death, all analyses were performed for the following three subgroups; i.e. people who died during 2013, people who died during 2014, and people who survived the entire study period.

RESULTS

We included 56,760 individual ICU patients, with a total of 61,174 ICU admissions in 2013, in the final dataset. The control population consists of 75,232 persons. Figure 4.1 gives an overview of the data linkage process. ICU patients who could not be linked between the two registries (6.2%) or who did not survive the hospital admission (13.9%) were excluded from all analyses. The median age of the ICU patients which could not be linked was 64 (IQR 51; 75) year, 58.5% was male and the median length of ICU stay was 0.9 (IQR 0.7; 1.9) days. The differences between the study population and the ICU patients who could not be linked were statistically significant.

Table 4.1 gives an overview of the characteristics of both study populations. In Appendix 4.2 we present the survival curve of the ICU population and the control population.

During the year before ICU admission, the crude healthcare costs of ICU survivors were mean: €31.3 (SD €65.1) and median: €8.9 (IQR €2.4; €32.1). During the year after ICU admission this was mean: €46.9 (SD €79.2), and median: €15.4 (IQR €5.4; €51.2). For the survivors of the control population this was mean: €12.1 (SD €31.0) and median: €2.8 (IQR €0.7; €8.8), and mean: €16.0 (SD €40.2), median: €3.1 (IQR €0.8; €10.1) respectively. The healthcare costs per day alive for the ICU population and the control population are reported in Figure 4.2. A detailed description of the crude healthcare costs per day alive of both study populations for all three subgroups is given in Appendix 4.3.

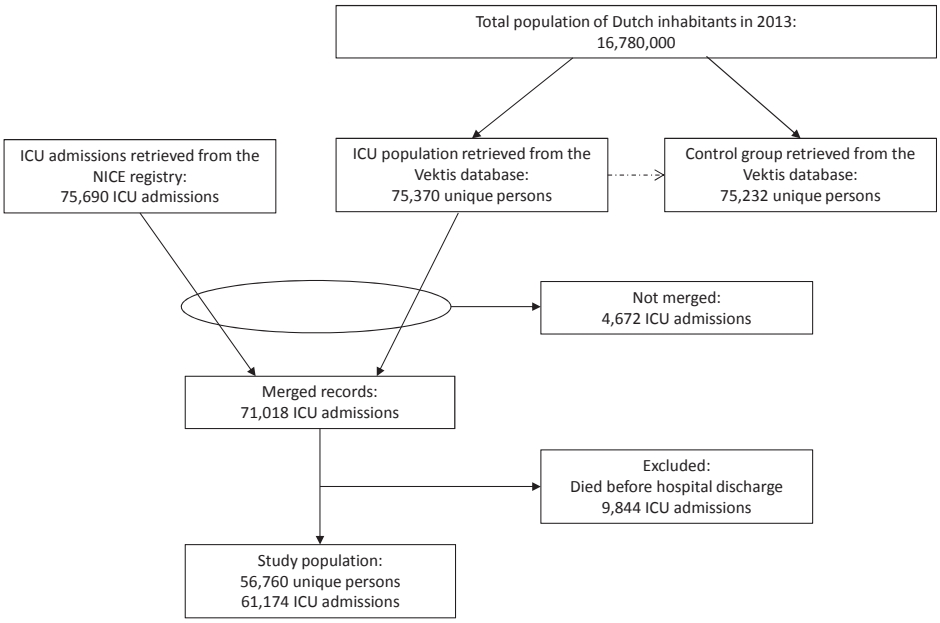

Figure 4.1 Flow chart of the linking process

Through general linear modelling we estimated that the healthcare costs of survivors of the ICU population was significantly higher during the year before ICU admission compared to the healthcare costs of the survivors of the control population. After correction for age, gender and SES, the difference in healthcare costs per day alive during the year before admission was €3.04 (CI €2.99; €3.10). During the year after admission the difference was €5.11 (CI €5.02; €5.21).

We estimated that, among the survivors of the ICU population, the healthcare costs per day alive of women were higher compared to the healthcare costs per day alive of men, during the year before and during the year after ICU admission ((€1.44 (CI €1.39; €1.48) and €1.33 (CI €1.29; €1.37) respectively). Within the control population women had significantly higher healthcare costs compared to men as well. During the year before ICU admission, the difference in healthcare costs between women of the ICU population and women of the control population was greater compared to the difference in healthcare costs between men of the ICU population and men of the control population (€1.16 (CI €1.12; €1.21) (*p*-value for interaction: $p<0.001$). During the year after ICU admission, this difference was €1.12 (CI €1.08; €1.16) (*p*-value for interaction: $p<0.001$).

Among survivors of the ICU population, we estimated that the oldest patients had significantly higher healthcare costs per day alive compared to the youngest patients during the

Table 4.1 Characteristics of the ICU population and the control group during the year of ICU admission

Socio-demographic characteristics	ICU population (n=56,760)	Control group (n=75,232)
Male†	34,111 (60.1%)	44,742 (59.5%)
Age‡	66 (54; 74)	66 (56; 75)
SES‡	0.2 (-0.6; 0.8)	0.2 (-0.6; 0.8)
Died during 2013†	3,465 (6.1%)	1,659 (2.2%)
Died during 2014†	4,291 (8.1%)	1,685 (2.3%)
Characteristics of the first ICU admission		
Admission type†		
• Medical	22,806 (40.2%)	
• Planned surgery	26,838 (47.3%)	
• Emergency surgery	6,932 (12.2%)	
• Missing	184 (0.3%)	
Conditions diagnosed before current ICU admission†		
• Chronic renal insufficiency or renal dialyses	2,508 (4.4%)	
• COPD or respiratory insufficiency	8,125 (14.3%)	
• Chronic cardiovascular insufficiency	3,325 (5.9%)	
• Haematological malignancy or metastatic neoplasm	2,750 (4.8%)	
• AIDS	74 (0.1%)	
• Immunological deficiency	3,604 (6.3%)	
• Diabetes	8,915 (15.7%)	
• Cirrhosis	519 (0.9%)	
Acute diagnosis†		
• CPR	1,611 (2.8%)	
• Burns	76 (0.1%)	
• Cardiac dysrhythmia	3,826 (6.7%)	
• GI bleeding	1,021 (1.8%)	
• CVA	1,746 (3.1%)	
• Intracranial mass effect	1,480 (2.6%)	
• CAP	2,569 (4.5%)	
• Sepsis	3,871 (6.8%)	
• OHCA	1,051 (1.9%)	
• SAH	548 (1.0%)	
• Trauma	2,785 (4.9%)	
Mechanical ventilation during the first 24 hrs of ICU admission†	27,012 (47.6%)	
Length of ICU stay‡	1.0 (0.8; 2.5)	
Length of hospital stay‡	9.0 (5.5; 16.0)	
APACHE IV score*[17]	49 (36; 65)	

† Number and percentage (%) ‡ Median and IQR

* Median and IQR. Only calculated for ICU admissions which met the APACHE IV inclusion criteria (n=54,074)

COPD: Chronic Obstructive Pulmonary Disease, CPR: Cardio Pulmonary Resuscitation, GI: Gastro Intestinal, CVA: Cerebrovascular Accident, CAP: Community Acquired Pneumonia, OHCA: Out of Hospital Cardiac Arrest, SAH: Subarachnoid Haemorrhage

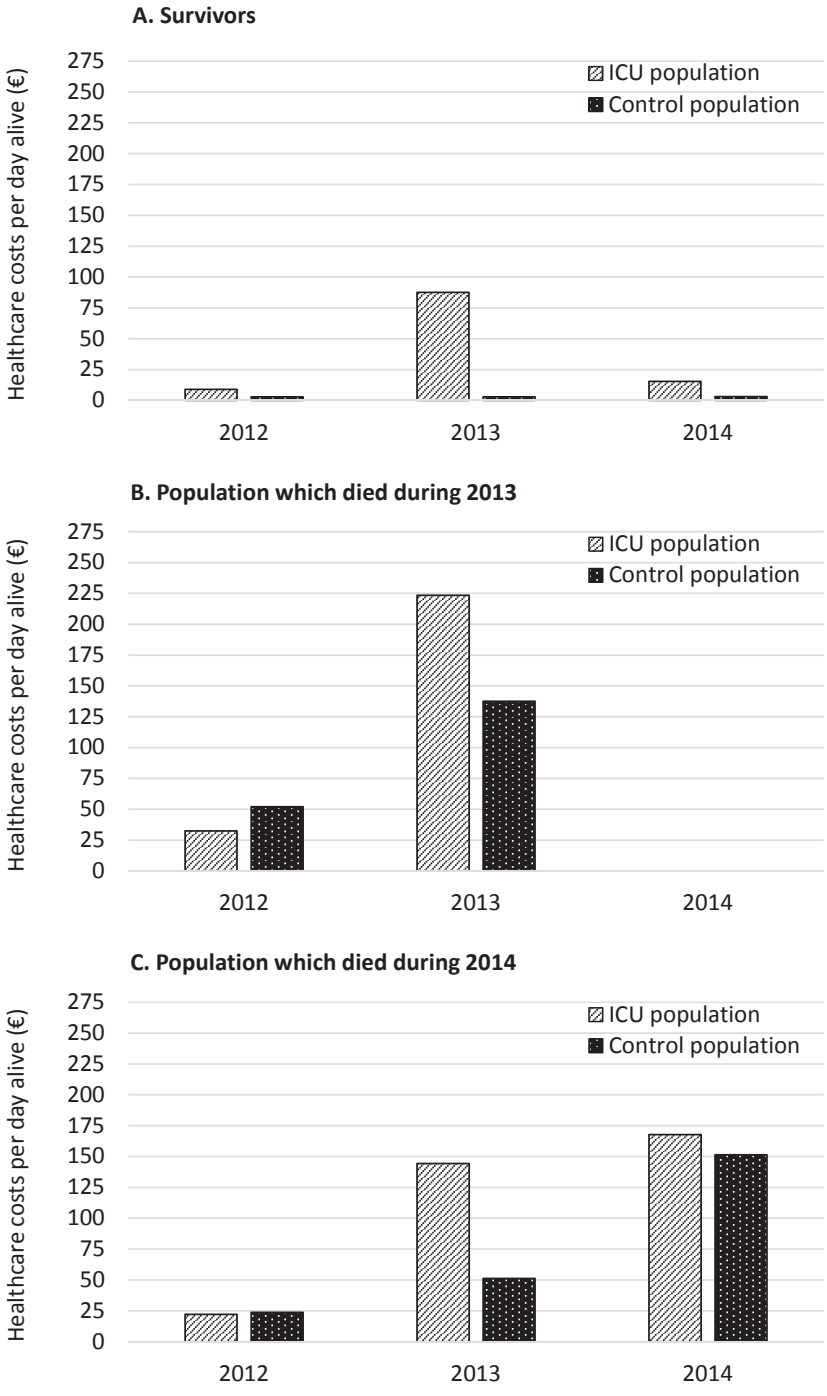

Figure 4.2 Healthcare costs per day alive for A. Survivors, B. Population which died during 2013, C. Population which died during 2014

year before and after ICU admission (€2.04 (CI €1.95; €2.12) and €2.16 (CI €2.08; €2.25) respectively). Within the control population similar significant results were found. During the year before ICU admission, the differences in healthcare costs between the ICU population and the control population are greater within the youngest people compared to the differences in healthcare costs between the ICU population and the control population in the oldest people (€0.33 (CI €0.32; €0.35) (p-value for interaction $p<0.001$). During the year after ICU admission, this difference was €0.28 (CI €0.27; €0.29) (p-value for interaction: $p<0.001$). Of the ICU patients who died during 2013, the youngest patients had significantly higher healthcare costs per day alive during the year before ICU admission compared to the oldest ICU patients who died ($p<0.05$). Within the control population a reversed result was found ($p<0.05$).

People with a high SES had significantly lower healthcare costs per day alive compared to people with a low SES during the year before and after ICU admission (€0.79 (CI €0.76; €0.81) and €0.80 (CI €0.77; €0.83) respectively). SES was no effect modifier (p-value for interaction: $p=0.13$ and $p=0.13$ respectively), thus the effect of SES on the healthcare costs are similar in both study populations.

Of the total ICU population, 3732 (6.6%) patients were admitted to the ICU more than once, with the number of readmissions ranging from 1 to 11 times. 3210 (86.0%) were admitted twice. ICU survivors who had over two ICU admissions, had significantly higher healthcare costs per day alive during the year before and after ICU admission (mean: €72.6 (SD €134.0) median: €22.3 (IQR €4.7; €82.2) and mean: €119.1 (SD €136.5), median: €62.3 (IQR €19.6; €186.8) respectively) compared to ICU patients who had one ICU admission (mean: €30.0 (SD €62.5), median: €8.7 (IQR €2.4; €30.7), and mean: €44.4 (SD €75.1), median: €14.6 (IQR €5.2; €48.0)) (Figure 4.3 A, Appendix 4.4) ($p<0.0001$ and $p<0.0001$ respectively).

Of all ICU patients, 22,282 (39.3%) had one or more chronic conditions diagnosed before the current ICU admission. ICU survivors with more than one chronic condition had significantly higher healthcare cost per day alive during the year before and after ICU admission ($p<0.0001$ and $p<0.0001$ respectively) (Figure 4.3 B, Appendix 4.5). Stratifying the healthcare costs per day alive by the five most prevalent chronic conditions shows that patients with renal insufficiency, haematological malignancies and immunological deficiency in particular had higher healthcare costs per day alive (Figure 4.3 D, Appendix 4.6).

Among ICU survivors, patients in the highest APACHE IV risk group had significantly lower healthcare costs per day alive during the year before ICU admission (i.e. mean: €29.0 (SD €83.6), median: €6.3 (IQR €1.9; €22.4)), compared to the low-risk group (i.e. mean: €30.7 (SD €63.7), median: €8.9 (IQR €2.4; €31.7)) ($p<0.0019$). During the year after ICU admission,

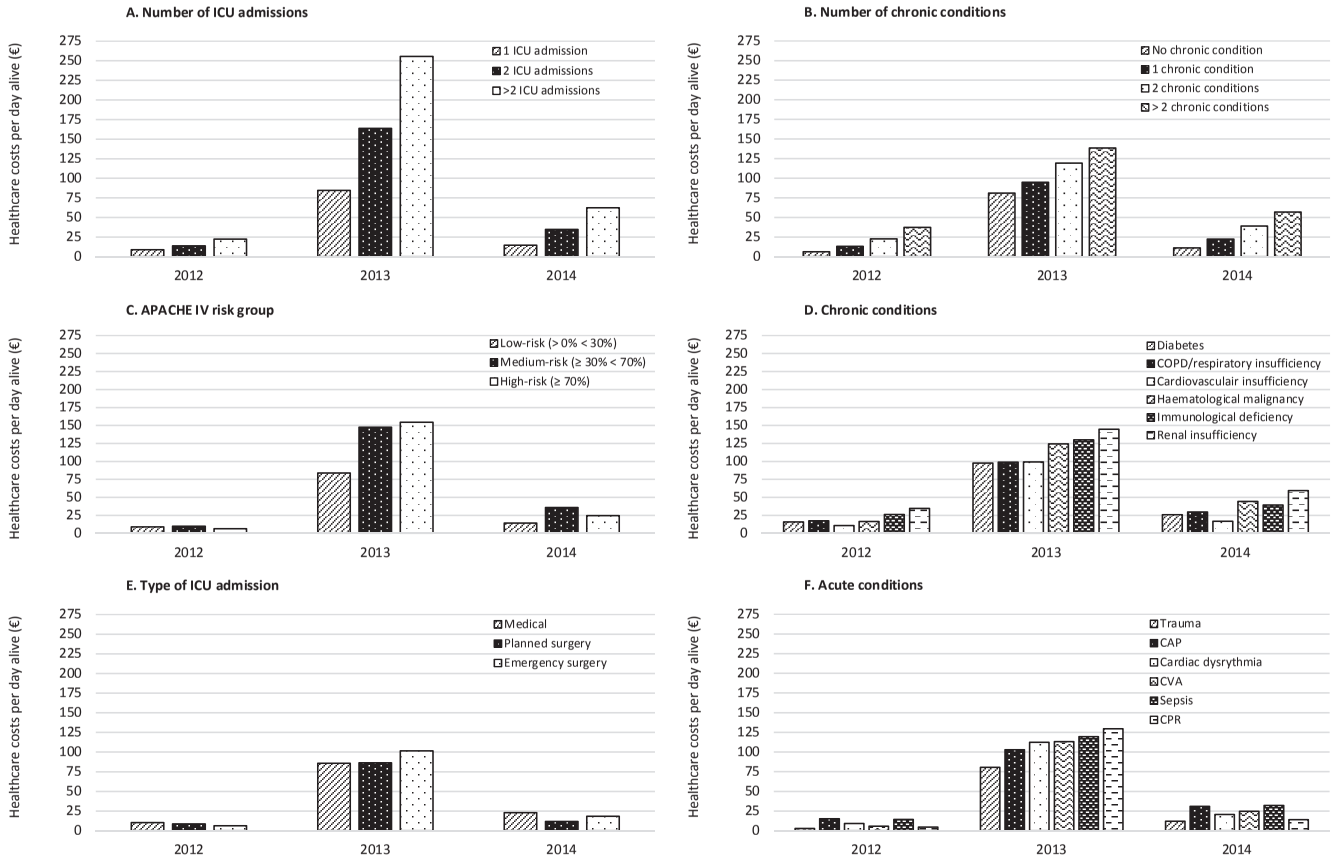

Figure 4.3 Healthcare costs per day alive, stratified by: A. number of ICU admissions, B. chronic conditions, C. APACHE IV risk group, D. number of chronic conditions, E. type of ICU admission and F. acute conditions

patients in the low-risk group had significantly the lowest healthcare costs per day alive (i.e. mean: €43.5 (SD €75.5), median: €14.2 (IQR €5.1; €46.1)) compared to the medium- and high-risk groups (i.e. medium-risk mean: €78.1 (SD €104.3), median: €36.0 (IQR €10.9; €110.7), high-risk mean: €65.3 (SD €93.6), median: €24.5 (IQR €7.2; €88.1)), low-risk) (p<0.0001) (Figure 4.3 C, Appendix 4.7).

Stratifying the ICU population by the six most prevalent acute diagnoses or by type of ICU admission, the healthcare costs per day alive shows less extreme deviation from the median healthcare costs per day alive of the total ICU population (Figure 4.3 E and 4.3 F).

DISCUSSION

This study showed that healthcare costs of ICU patients per day alive, for survivors of the entire study period, were five times higher during the year after ICU admission compared to the population based control group. During the year before ICU admission, the healthcare costs of ICU survivors were three times higher compared to survivors of the general Dutch population.

Stratifying the healthcare costs per day alive by number of ICU admissions or by chronic conditions showed great deviation from the median healthcare costs per day alive, indicating that those factors largely contribute to the healthcare costs. Lone et al. reported similar findings, stating that factors present before ICU admission, such as comorbidities and pre-ICU hospitalizations, were stronger predictors of hospital resource use than acute severity of illness [20]. Lone et al. used the Simplified Acute Physiology Score II (SAPS II) [18] to quantify the severity of illness while we used the APACHE IV severity of illness score. The APACHE IV model includes more chronic conditions compared to SAPS II model, and for this reason we would expect that ICU patients within the highest mortality risk group would consume the most healthcare resources during the year before and the year after ICU admission. However, the medium-risk patients have the highest healthcare costs per day alive during the year before and the year after ICU admission. A possible explanation for this result can be the exclusion of ICU patients who did not survive their hospital admission. The healthcare costs in the last 120days of life are known to be high[19] and more people are excluded for analyses from high mortality risk group compared to the medium and low-mortality risk groups.

Studies have shown that women experience more morbidity, higher medical service utilization and higher associated charges compared to men [21, 22]. Our results are in line with those studies as we found that women had higher healthcare costs per day alive compared to men within both study populations after correction for age and SES. The differences between

men and woman in healthcare should be a focus of healthcare expenditure management, and more research about this topic is necessary.

It is known that healthcare costs for older people, for people with a lower SES, and in the last 120 days prior to death tend to be higher [6,19]. We found that, among the survivors of the ICU population, older patients had higher healthcare costs compared to younger patients after correction for age, gender and SES. However, among ICU patients that died during 2013 younger patients had higher healthcare costs per day alive compared to older ICU patients who died. This difference in healthcare costs can be due to the fact that older patients are less likely to undergo major surgery or dialysis [23]. Though, after discharge older people are more likely to be readmitted and are more dependent of long-term care facilities, nursing homes or rehabilitation centres compared to younger people [24-26].

ICU patients in our study had a high prevalence of chronic conditions compared to the total Dutch population [1]. Although there are differences in definition of chronic conditions and data collection between these two data sources, we believe the differences are significant enough to influence the healthcare costs. Since factors present before ICU admission are predictors of hospital resource use [20], future research should provide more insight in the differences in prevalence of chronic conditions between ICU patients and the general population and should aim to identify its influence on healthcare utilization.

High healthcare costs before hospital or ICU admission may imply a greater need for healthcare services or factors such as health awareness, vigilance or better health utility. In light of the universal and pervasive health insurance coverage for the Dutch healthcare system we believe that our data shows that high healthcare costs are a marker for acuity and ICU care. Moreover, high healthcare resource use has been found a predictor for subsequent hospital cost by Lone et al. They reported that prior illness/resource use factors were the strongest predictors of the number of hospital admissions over a 5-year follow-up period [20].

The finding that ICU patients have high healthcare costs after discharge is in agreement with previous reported results [6,20]. After hospital discharge, ICU survivors suffer long-term and severe complaints such as cognitive and physical problems, a decreased quality of life, social problems, and restrictions in return to home because of their health status [27, 28]. The term post-intensive care syndrome (PICS) was introduced to identify the presence of one or more impairments after critical illness [29]. More coordination of healthcare after hospital discharge is necessary. Since the general practitioner does not always recognise the symptoms of PICS, ICU follow-up care has been suggested to address the problems ICU patients face after discharge [28, 30, 31]. In sight of the results of our study we suggest that ICU follow-up

care should, especially, be offered to ICU survivors with more chronic conditions, more ICU admissions, a higher age and a lower SES.

Our study has some limitations. The control population was created based on the total Dutch ICU population. Since this study focussed on the healthcare costs after ICU admission, ICU patients who did not survive their hospital admission were excluded from the analyses afterwards. This caused minor differences between the ICU population and the population based control group, as can be seen in Table 4.1. Because of the large population sizes, these differences are statistically significant; however we do not believe that they are clinically relevant. Furthermore, the total costs per patient were only known per calendar year. It is unclear which aspects of healthcare were most utilized or which aspects were most expensive and further research on this topic is necessary. Additionally, only costs reimbursed by health insurance companies under the compulsory insurance were taken into account. The total amount of healthcare costs does not include services paid for out of pocket or reimbursements via voluntary additional insurance. It is estimated that these costs are around €2 per person, per day [32]. Although we included the most important aspects of the healthcare costs, this might have affected our results. Other studies about the healthcare costs of ICU patients compared their results with hospitalized patients. Based on the available information in our study, we were not able to identify hospital admissions within our control group. Though this would have been an interesting addition, we think our study fills important gaps in knowledge since only 12% of the general population is annually hospitalized [1].

These limitations notwithstanding, the linkage between the national health insurance claims database and the national clinical ICU registry provides valuable insight in the healthcare utilization of ICU patients and a control population. The linkage rate between the two databases was high, resulting in a population that covers almost an entire country. As we focused on the differences between the two study populations, we suggest that future research should focus on factors causing the high healthcare costs of ICU patients before, during and after ICU admission. Knowledge on the healthcare trajectory of the ICU patient can be used for targeted care, such as ICU follow-up care, in order to manage healthcare costs.

CONCLUSION

We showed that people who were admitted to an ICU had approximately three to five times higher healthcare costs per day alive compared to a control population. The differences in healthcare costs are even present during the year before ICU admission and increases during the year after discharge. The healthcare costs before and after ICU admission are greatly influenced by the chronic conditions, ICU readmissions, age and SES of patients. The results

of our study can be used to optimize the healthcare trajectories of ICU patients with high healthcare utilization after discharge.

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APPENDICES

Appendix 4.1 Variables based on data of the NICE registry

General		
Variable name		Description
Admission type		There are 3 types of admission: 1. Medical: all the ICU admissions which are not directly transferred from the operation room or the recovery department to the ICU 2. Emergency surgery: immediate surgery where resuscitation, stabilization and physiological support occurs preceding or simultaneous with the surgery 3. Planned surgical: surgery planned on a date and time convenient for both patient and doctor or early surgery planned within 24h after surgery indication.
Conditions diagnosed before current ICU admission		
Variable name		Description
AIDS		Dichotomous variable. HIV positive with clinical complications (such as pneumocystis carinii pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis or toxoplasma infection), or HIV positive with a CD4 count < 200.
Cirrhosis		Dichotomous variable. The variable cirrhosis will be scored if one of the following options is true, prior to the ICU admission: There was a positive biopsy in combination with a documented portal hypertension or The patient had periods with high GI bleeding as a result of portal hypertension or The patient had periods with liver failure, coma or encephalopathy
Chronic renal insufficiency	• Chronic renal insufficiency	Dichotomous variable. If the patient has an increased level of serum creatinine (> 177 umol/L (2.0 mg/dL)) and in the medical history (before the present ICU admission) it is mentioned as 'chronic'.
	• Renal dialyses	Dichotomous variable. The patient received haemodialysis or peritoneal dialyses before the present ICU admission.
Respiratory insufficiency	• COPD	Dichotomous variable. The variable COPD will be scored if the patient used bronchodilators or steroids for Chronical Pulmonary Obstructive Diseases > 6 months before the present ICU admission.
	• Respiratory insufficiency	Dichotomous variable. Chronic restrictive obstructive or vascular diseases of the lungs, resulting in chronic need of mechanical ventilation.
Chronic cardiovascular insufficiency		Dichotomous variable. Angina or symptoms during rest of at minimal effort (New York Heart Association class IV).
Haematological malignancy	• Haematological malignancy	Dichotomous variable. Includes maligned lymphoma, acute leukaemia or multiple myeloma.
	• Metastatic neoplasm	Dichotomous variable. Metastatic neoplasm confirmed by clinic research or confirmed by a pathology rapport or Stage IV cancer

Appendix 4.1 Variables based on data of the NICE registry (continued)

Immunological deficiency	Dichotomous variable. Positive in case before the present ICU admission: Patient received long-term immunosuppressive therapy or, Patient used corticosteroids (shot term a high dose or longer-term a low dose, for example over 5 days 1mg/kg Prednison or over 20 days over 0.1mg/kg) or, Patient had active chemotherapy or radiotherapy during the past year or, Patient received chemotherapy or radiotherapy for Hodgkin or non-Hodgkin lymphoma before the present ICU admission or, Patient had documented humeral or cellular deficiencies
Diabetes	Dichotomous variable. The patient has a medication-dependent type of diabetes mellitus and was diagnosed a such before the present ICU admission.
Acute conditions	
Variable name	Description
Burns	Dichotomous variable. Burns, including inhalation trauma, is the cause of the ICU admission. If there are multiple causes for the ICU admission, the burns have to be so severe that, without the other causes, an ICU admission is necessary.
CAP	Dichotomous variable. A patient is considered a CAP patient if he meets the following criteria: One of the following APACHE IV diagnosis: • APACHE IV diagnosis 'Sepsis, pulmonary' • APACHE IV diagnosis 'Pneumonia, bacterial' • APACHE IV diagnosis 'Pneumonia, viral' • APACHE IV diagnosis 'Pneumonia, other' In combination with a length of hospital stay < 2 days before ICU admission, no long term dialysis before ICU admission and admission source is home or the same hospital.
CPR	Dichotomous variable. Patient received CPR in the 24 h preceding the ICU admission. Defibrillation and cardioversion without chest compression are not considered as CPR.
CVA	Dichotomous variable. Cerebral emboli, occlusion, haemorrhage or infarct evident at ICU admission or within the first hour of ICU admission.
Cardiac dysrhythmia	Dichotomous variable. Cardiac dysrhythmia is true if the patient has hemodynamic instabilities in the 24 hours preceding the ICU admission in combination with one of the following diagnosis: a) Arrhythmia b) Paroxysmal tachycardia c) Atrium fibrillation with a quick (>=120/min) ventricle response d) 2e/3e class AV Block
GI bleeding	Dichotomous variable. The patient had gastro-intestinal haemorrhage in the 24 hours preceding the ICU admission, identified during a endoscopy or by 'coffee grounds' in the nasogastric feeding tube.

Appendix 4.1 Variables based on data of the NICE registry (continued)

Intracranial mass effect	Dichotomous variable. Intracranial mass effect (abscess, tumour, haemorrhage, subdural, contusion) identified by a CT scan, MRI or other scan and consistent with one of the following: • Midline shift • Obliteration or distortion of the cerebral ventricle • Haemorrhage in the cerebral ventricles or subarachnoid spaces • Visible mass > 4cm or every mass which colours with contract media
OHCA	Dichotomous variable. A patient is considered a OHCA patient if the APACHE IV reason for admission is 'Cardiac arrest (with or without respiratory arrest)' or the variable 'CPR' in combination with an admission to the ICU directly from home or an emergency room is recorded.
SAH	Dichotomous variable. A patient is considered a SAH patient when he has one of the following APACHE IV diagnosis: • APACHE IV diagnosis 'Subarachnoid haemorrhage/arteriovenous malformation' • APACHE IV diagnosis 'Subarachnoid haemorrhage/intracranial aneurysm' • APACHE IV diagnosis 'Subarachnoid haemorrhage/intracranial aneurysm, surgery for'
Sepsis	Dichotomous variable. A patient is considered a sepsis patient when he has one of the following APACHE IV diagnosis: • APACHE IV diagnosis 'Sepsis, cutaneous/soft tissue' • APACHE IV diagnosis 'Sepsis, GI' • APACHE IV diagnosis 'Sepsis, gynaecologic' • APACHE IV diagnosis 'Sepsis, other' • APACHE IV diagnosis 'Sepsis, pulmonary' • APACHE IV diagnosis 'Sepsis, renal/UTI (including bladder)' • APACHE IV diagnosis 'Sepsis, unknown'
Trauma	Dichotomous variable. A patient is considered a sepsis patient when he has one of the following APACHE IV diagnosis: • APACHE IV diagnosis 'Abdomen only trauma' • APACHE IV diagnosis 'Abdomen/extremity trauma' • APACHE IV diagnosis 'Abdomen/face trauma' • APACHE IV diagnosis 'Abdomen/multiple trauma' • APACHE IV diagnosis 'Abdomen/pelvis trauma' • APACHE IV diagnosis 'Abdomen only trauma, surgery for' • APACHE IV diagnosis 'Abdomen/extremity trauma, surgery for' • APACHE IV diagnosis 'Abdomen/face trauma, surgery for' • APACHE IV diagnosis 'Abdomen/multiple trauma, surgery for' • APACHE IV diagnosis 'Abdomen/pelvis trauma, surgery for'

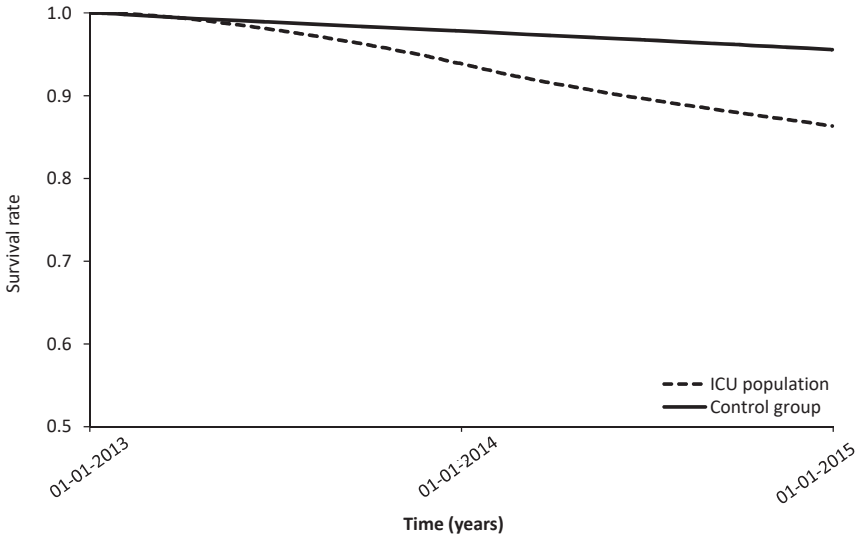
Appendix 4.1 Variables based on data of the NICE registry (continued)

	• APACHE IV diagnosis 'Abdomen/spinal trauma'	• APACHE IV diagnosis 'Abdomen/spinal trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ abdomen trauma'	• APACHE IV diagnosis 'Chest/ abdomen trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ extremity trauma'	• APACHE IV diagnosis 'Chest/ extremity trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ face trauma'	• APACHE IV diagnosis 'Chest/ face trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ multiple trauma'	• APACHE IV diagnosis 'Chest/ multiple trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ pelvis trauma'	• APACHE IV diagnosis 'Chest/ pelvis trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ spinal trauma'	• APACHE IV diagnosis 'Chest/ spinal trauma, surgery for'
	• APACHE IV diagnosis 'Chest/ thorax only trauma'	• APACHE IV diagnosis 'Chest/ thorax only trauma, surgery for'
	• APACHE IV diagnosis 'Extremity only trauma'	• APACHE IV diagnosis 'Extremity only trauma, surgery for'
	• APACHE IV diagnosis 'Extremity/face trauma'	• APACHE IV diagnosis 'Extremity/face trauma, surgery for'
	• APACHE IV diagnosis 'Extremity/multiple trauma'	• APACHE IV diagnosis 'Extremity/multiple trauma, surgery for'
	• APACHE IV diagnosis 'Face only trauma'	• APACHE IV diagnosis 'Face only trauma, surgery for'
	• APACHE IV diagnosis 'Face/ multiple trauma'	• APACHE IV diagnosis 'Face/ multiple trauma, surgery for'
	• APACHE IV diagnosis 'Head (CNS) only trauma'	• APACHE IV diagnosis 'Head (CNS) only trauma, surgery for'
	• APACHE IV diagnosis 'Head/ abdomen trauma'	• APACHE IV diagnosis 'Head/ abdomen trauma, surgery for'
	• APACHE IV diagnosis 'Head/ chest trauma'	• APACHE IV diagnosis 'Head/ chest trauma, surgery for'
	• APACHE IV diagnosis 'Head/ extremity trauma'	• APACHE IV diagnosis 'Head/ extremity trauma, surgery for'
	• APACHE IV diagnosis 'Head/ face trauma'	• APACHE IV diagnosis 'Head/ face trauma, surgery for'
	• APACHE IV diagnosis 'Head/ multiple trauma'	• APACHE IV diagnosis 'Head/ multiple trauma, surgery for'
	• APACHE IV diagnosis 'Head/ pelvis trauma'	• APACHE IV diagnosis 'Head/ pelvis trauma, surgery for'

Appendix 4.1 Variables based on data of the NICE registry (continued)

	• APACHE IV diagnosis 'Head/ spinal trauma'	• APACHE IV diagnosis 'Head/ spinal trauma, surgery for'
	• APACHE IV diagnosis 'Pelvis/ extremity trauma'	• APACHE IV diagnosis 'Pelvis/ extremity trauma, surgery for'
	• APACHE IV diagnosis 'Pelvis/ face trauma'	• APACHE IV diagnosis 'Pelvis/ face trauma, surgery for'
	• APACHE IV diagnosis 'Pelvis/hip only trauma'	• APACHE IV diagnosis 'Pelvis/ hip only trauma,surgery for'
	• APACHE IV diagnosis 'Pelvis/ multiple trauma'	• APACHE IV diagnosis 'Pelvis/ multiple trauma, surgery for'
	• APACHE IV diagnosis 'Pelvis/ spinal trauma'	• APACHE IV diagnosis 'Pelvis/ spinal trauma, surgery for'
	• APACHE IV diagnosis 'Spinal cord only trauma'	• APACHE IV diagnosis 'Spinal cord only trauma, surgery for'
	• APACHE IV diagnosis 'Spinal/ extremity trauma'	• APACHE IV diagnosis 'Spinal/ extremity trauma, surgery for'
	• APACHE IV diagnosis 'Spinal/ face trauma'	• APACHE IV diagnosis 'Spinal/ face trauma, surgery for'
	• APACHE IV diagnosis 'Spinal/ multiple trauma'	• APACHE IV diagnosis 'Spinal/ multiple trauma, surgery for'
	• APACHE IV diagnosis 'Trauma medical, other'	• APACHE IV diagnosis 'Trauma surgery, other'

AIDS - Acquired immune deficiency syndrome
APACHE - Acute Physiology and Chronic Health Evaluation
CABG - Coronary Artery Bypass Surgery
CAP - Community acquired pneumonia
COPD - Chronic obstructive pulmonary disease
CPR - Cardio Pulmonary Resuscitation
CT scan - Computed Tomography scan
CVA - Cerebrovascular Accident
GI - Gastro Intestinal
HIV - Human immunodeficiency virus
MI - Myocardial Infarct
MRI - Magnetic Resonance Imaging
OHCA - Out of Hospital Cardiac Arrest
SAH - Subarachnoid Haemorrhage
UTI - Urinary Tract Infection



Appendix 4.2 Kaplan Meier survival curve of the ICU population and control group

Appendix 4.3 Median (IQR) healthcare cost per day alive for the ICU population and the control group, expressed in euros (€)

	ICU population				Control group			
	n	2012	2013	2014	n	2012	2013	2014
Survivors								
Total subgroup	49,004	8.9 (2.4; 32.1)	87.5 (55.3; 141.4)	15.4 (5.4; 51.2)	71,888	2.8 (0.7; 8.8)	2.8 (0.7; 9.0)	3.1 (0.8; 10.1)
Male	29,525	7.7 (2.0; 27.8)	86.1 (56.1; 136.2)	13.5 (4.9; 43.8)	42,663	2.6 (0.6; 8.2)	2.6 (0.6; 8.4)	2.9 (0.7; 9.5)
Female	19,479	11.1 (3.2; 38.2)	90.2 (54.1; 149.2)	18.9 (6.5; 62.4)	29,225	3.1 (0.9; 9.7)	3.2 (0.9; 10.1)	3.4 (1.0; 11.0)
Age								
• Q1 (18-55)	14,261	6.3 (1.0; 30.9)	74.6 (39.3; 134.5)	11.2 (3.1; 43.6)	18,738	0.9 (0.3; 3.4)	0.8 (0.3; 3.4)	0.9 (0.3; 3.6)
• Q2 (56-65)	11,468	7.9 (2.0; 29.6)	86.8 (57.0; 137.1)	13.6 (5.0; 44.1)	16,472	2.0 (0.5; 6.1)	2.0 (0.6; 6.2)	2.1 (0.6; 6.5)
• Q3 (66-74)	12,470	9.7 (3.3; 31.2)	91.1 (62.3; 140.1)	15.4 (6.2; 48.1)	18,921	3.6 (1.2; 9.2)	3.6 (1.2; 9.3)	3.9 (1.4; 10.4)
• Q4 (75-103)	10,805	12.0 (4.7; 35.8)	99.7 (65.9; 150.8)	24.2 (8.9; 72.2)	17,757	6.7 (2.7; 19.5)	7.2 (2.8; 22.8)	8.4 (3.2; 31.0)
SES								
• Q1 (low)	11,919	10.1 (2.9; 34.8)	88.3 (55.0; 144.1)	17.6 (6.0; 58.6)	17,890	3.3 (0.9; 10.2)	3.3 (0.9; 10.3)	3.6 (0.9; 11.5)
• Q2	11,990	9.2 (2.4; 33.0)	87.1 (55.8; 141.1)	15.7 (5.6; 51.5)	17,899	2.9 (0.8; 9.0)	2.9 (0.8; 9.5)	3.2 (0.8; 10.6)
• Q3	12,381	8.5 (2.3; 31.5)	88.3 (55.7; 141.8)	14.8 (5.3; 49.7)	18,023	2.7 (0.7; 8.5)	2.7 (0.7; 8.7)	3.0 (0.8; 9.8)
• Q4 (high)	12,613	8.1 (2.2; 29.4)	86.7 (54.9; 139.3)	13.8 (5.0; 45.9)	18,076	2.4 (0.6; 7.6)	2.5 (0.7; 7.8)	2.7 (0.7; 8.7)
Population which died during 2013								
Total subgroup	3,465	32.5 (7.9; 94.1)	223.5 (142.8; 333.0)	-	1,659	52.1 (13.0; 137.9)	137.5 (55.6; 204.3)	-
Male	2,047	31.8 (8.1; 86.6)	222.6 (139.5; 339.8)	-	1,046	43.2 (10.5; 121.6)	126.9 (46.3; 200.4)	-
Female	1,418	33.4 (7.7; 101.3)	227.3 (149.9; 326.6)	-	613	76.0 (19.1; 160.7)	159.3 (76.7; 205.8)	-
Age								
• Q1 (18-55)	366	45.1 (7.1; 132.4)	251.8 (139.4; 399.7)	-	35	26.5 (1.3; 76.4)	102.0 (17.2; 185.1)	-
• Q2 (56-65)	593	31.8 (6.2; 99.7)	226.0 (142.0; 352.3)	-	96	29.6 (5.2; 83.7)	105.2 (31.0; 225.6)	-
• Q3 (66-74)	886	32.1 (7.5; 88.7)	229.9 (143.4; 341.3)	-	310	41.5 (9.4; 115.5)	116.6 (35.9; 223.5)	-
• Q4 (75-103)	1,620	30.9 (9.1; 84.2)	215.6 (143.8; 311.7)	-	1,218	57.3 (14.9; 146.5)	148.0 (67.5; 200.0)	-

Appendix 4.3 Median (IQR) healthcare cost per day alive for the ICU population and the control group, expressed in euros (€) (continued)

	ICU population				Control group			
	n	2012	2013	2014	n	2012	2013	2014
SES								
• Q1 (low)	973	30.7 (7.8; 93.5)	222.8 (139.3; 343.6)	-	453	52.2 (15.4; 131.3)	138.6 (64.3; 199.4)	-
• Q2	834	34.7 (8.9; 90.1)	227.6 (144.7; 323.0)	-	413	54.7 (12.9; 145.3)	142.3 (48.6; 205.1)	-
• Q3	823	29.4 (7.3; 82.9)	218.4 (141.3; 333.0)	-	410	51.8 (12.4; 123.3)	134.3 (64.8; 206.0)	-
• Q4 (high)	832	36.7 (8.3; 102.0)	227.6 (145.8; 339.9)	-	383	48.8 (9.6; 148.6)	134.1 (52.4; 200.4)	-
Population which died during 2014								
Total subgroup	4,291	22.1 (5.5; 71.0)	144.3 (91.5; 219.9)	167.7 (83.6; 275.1)	1,685	23.6 (6.1; 89.3)	51.2 (11.8; 134.7)	151.3 (67.5; 220.9)
Male	2,539	18.7 (5.2; 62.0)	139.5 (89.0; 214.2)	157.1 (77.5; 266.1)	1,033	18.2 (5.4; 67.8)	39.7 (9.5; 104.8)	134.1 (57.1; 209.0)
Female	1,752	27.3 (6.1; 85.8)	152.0 (96.0; 225.1)	186.5 (95.3; 284.9)	652	33.4 (7.8; 119.6)	84.8 (18.2; 173.2)	180.5 (86.7; 228.5)
Age								
• Q1 (18-55)	547	24.8 (3.4; 101.7)	143.4 (85.6; 244.7)	164.4 (76.7; 295.5)	28	5.4 (0.8; 16.8)	26.8 (1.5; 124.6)	106.5 (13.5; 192.8)
• Q2 (56-65)	897	20.4 (3.5; 73.0)	151.1 (96.2; 243.8)	153.5 (78.1; 285.6)	129	5.8 (1.2; 28.0)	24.8 (5.8; 79.1)	109.3 (50.0; 212.7)
• Q3 (66-74)	1,240	19.4 (5.0; 64.0)	142.0 (93.1; 219.5)	165.2 (79.8; 284.6)	316	15.0 (3.3; 51.1)	32.2 (6.3; 96.4)	124.3 (53.5; 220.1)
• Q4 (75-103)	1,607	23.7 (7.5; 67.6)	141.2 (90.4; 202.8)	182.0 (92.3; 256.0)	1,212	30.2 (8.7; 105.5)	61.4 (14.4; 155.0)	165.2 (75.8; 221.9)
SES								
• Q1 (low)	1,089	23.0 (6.5; 72.8)	148.8 (95.7; 221.6)	173.2 (87.0; 284.9)	486	20.1 (6.7; 88.7)	53.6 (11.7; 136.6)	145.2 (65.1; 221.0)
• Q2	1,085	20.9 (5.0; 73.4)	144.0 (90.4; 212.2)	185.8 (85.6; 288.8)	440	25.5 (6.3; 77.7)	49.0 (13.9; 121.4)	139.7 (58.0; 205.7)
• Q3	1,073	20.2 (5.1; 63.5)	142.3 (91.7; 220.5)	153.2 (78.6; 258.5)	385	20.5 (5.6; 85.4)	50.6 (10.2; 132.6)	157.7 (74.3; 223.2)
• Q4 (high)	1,042	23.7 (5.9; 75.2)	143.1 (89.8; 223.2)	164.1 (84.0; 263.4)	374	25.5 (6.0; 99.5)	52.4 (10.2; 148.1)	170.1 (74.2; 233.3)

Appendix 4.4 Median (IQR) healthcare cost per day alive grouped by number of ICU admissions, expressed in euros (€)

	Number of ICU admissions = 1				Number of ICU admissions = 2	
	n	2012	2013	2014	n	2012
Survivors						
Total subgroup	46,000	8.7 (2.4; 30.7)	84.6 (53.4; 133.1)	14.6 (5.2; 48.0)	2,583	13.7 (3.0; 53.9)
Male	27,730	7.6 (2.0; 26.5)	83.4 (54.3; 128.2)	12.8 (4.7; 41.1)	1,551	11.0 (2.7; 47.5)
Female	18,270	10.8 (3.2; 36.5)	87.0 (52.1; 141.2)	17.9 (6.3; 58.6)	1,032	17.2 (3.8; 64.5)
Age						
• Q1 (18-55)	13,224	5.9 (1.0; 29.0)	70.6 (37.4; 123.3)	10.4 (3.0; 39.3)	869	10.6 (1.5; 75.1)
• Q2 (56-65)	10,763	7.7 (2.0; 28.3)	84.0 (55.4; 129.0)	12.9 (4.9; 40.4)	594	14.4 (2.7; 56.4)
• Q3 (66-74)	11,728	9.5 (3.2; 30.1)	88.3 (60.9; 132.9)	14.9 (6.1; 45.8)	650	13.7 (3.4; 48.6)
• Q4 (75-103)	10,285	11.9 (4.6; 35.4)	97.1 (64.4; 146.1)	23.4 (8.7; 70.0)	470	15.8 (6.0; 44.2)
SES						
• Q1 (low)	11,155	9.8 (2.8; 33.2)	85.1 (53.1; 136.0)	16.6 (5.8; 54.7)	646	15.5 (3.7; 58.5)
• Q2	11,241	8.9 (2.4; 31.8)	84.0 (54.1; 133.5)	15.1 (5.4; 48.7)	652	14.1 (3.0; 52.5)
• Q3	11,624	8.3 (2.3; 30.1)	85.3 (53.6; 133.2)	14.0 (5.1; 46.4)	657	13.4 (2.7; 54.7)
• Q4 (high)	11,888	8.0 (2.1; 28.5)	84.3 (53.4; 130.8)	13.2 (4.9; 42.9)	622	11.8 (2.8; 47.3)
Population which died during 2013						
Total subgroup	3,179	32.8 (8.2; 94.1)	217.9 (139.8; 322.6)	-	246	31.6 (6.5; 98.3)
Male	1,871	32.7 (8.4; 87.6)	214.3 (135.6; 325.7)	-	156	27.0 (6.2; 76.5)
Female	1,308	32.9 (7.9; 100.9)	221.7 (146.2; 320.0)	-	90	35.6 (6.5; 110.7)
Age						
• Q1 (18-55)	325	47.2 (7.1; 132.1)	237.8 (137.0; 376.2)	-	36	42.8 (5.4; 181.5)
• Q2 (56-65)	529	31.2 (6.3; 98.2)	217.9 (138.5; 342.9)	-	47	34.2 (5.2; 111.6)
• Q3 (66-74)	785	32.2 (7.6; 88.7)	220.6 (140.5; 319.5)	-	86	32.4 (6.2; 90.5)
• Q4 (75-103)	1,530	31.6 (9.3; 86.1)	212.4 (141.3; 307.8)	-	77	26.7 (7.4; 59.4)
SES						
• Q1 (low)	902	30.1 (7.6; 93.5)	214.8 (135.7; 326.9)	-	63	31.2 (11.1; 86.6)
• Q2	759	35.1 (9.4; 92.3)	218.5 (141.9; 314.2)	-	59	30.8 (4.2; 120.9)
• Q3	748	29.9 (7.4; 83.2)	213.0 (138.2; 317.8)	-	68	21.6 (5.1; 60.7)
• Q4 (high)	768	36.7 (8.5; 99.7)	223.7 (143.9; 334.1)	-	55	39.4 (7.8; 129.2)
Population which died during 2014						
Total subgroup	3,849	21.7 (5.4; 68.3)	137.9 (87.8; 206.5)	165.1 (81.6; 264.6)	381	23.6 (6.3; 82.1)
Male	2,260	18.5 (5.1; 60.3)	132.8 (85.5; 201.4)	152.8 (76.1; 258.7)	239	23.0 (6.1; 76.5)
Female	1,589	26.6 (6.0; 83.0)	146.7 (92.8; 213.4)	183.0 (93.8; 279.8)	142	28.8 (6.5; 98.5)
Age						
• Q1 (18-55)	473	21.6 (2.8; 83.0)	134.3 (80.4; 225.0)	154.9 (74.4; 285.0)	61	60.9 (18.5; 168.9)
• Q2 (56-65)	786	19.2 (3.3; 67.4)	146.6 (91.5; 226.7)	150.8 (76.9; 279.3)	91	30.3 (4.6; 86.1)
• Q3 (66-74)	1,099	20.1 (5.0; 64.2)	136.3 (88.5; 206.5)	164.0 (78.2; 282.9)	124	14.7 (4.4; 52.9)
• Q4 (75-103)	1,491	24.2 (7.5; 67.0)	136.5 (88.2; 196.8)	180.3 (90.9; 250.7)	105	16.0 (7.6; 73.1)
SES						
• Q1 (low)	973	22.2 (5.9; 69.8)	144.6 (92.0; 209.5)	170.7 (84.0; 282.7)	99	28.0 (10.3; 75.1)
• Q2	975	20.7 (4.9; 72.3)	135.7 (87.4; 200.7)	182.3 (84.6; 285.6)	95	25.7 (5.3; 86.1)
• Q3	961	19.3 (5.1; 62.6)	135.6 (87.8; 206.1)	149.0 (76.9; 250.0)	95	20.8 (4.1; 81.1)
• Q4 (high)	938	23.4 (5.7; 71.9)	137.7 (87.4; 211.9)	160.5 (83.0; 256.4)	92	29.6 (6.4; 87.8)

Number of ICU admissions = 2			Number of ICU admissions > 2		
2013	2014	n	2012	2013	2014
163.6 (107.7; 254.6)	34.8 (10.2; 106.2)	421	22.3 (4.7; 82.2)	255.6 (158.0; 402.6)	62.3 (19.6; 186.8)
162.8 (108.5; 247.6)	29.2 (9.1; 94.1)	244	16.9 (3.6; 68.8)	247.4 (151.8; 398.6)	45.8 (13.4; 156.5)
164.1 (105.4; 264.9)	44.7 (12.1; 127.7)	177	27.7 (7.6; 111.7)	266.9 (175.6; 424.0)	92.8 (36.2; 202.7)
164.8 (95.1; 287.9)	35.9 (7.3; 127.8)	168	28.0 (3.9; 111.3)	273.8 (152.7; 422.7)	67.2 (17.5; 202.2)
162.3 (109.2; 262.2)	33.4 (10.4; 104.7)	111	17.6 (4.1; 77.6)	260.8 (160.7; 455.4)	63.5 (28.3; 177.4)
163.7 (110.3; 238.0)	30.6 (10.7; 83.0)	92	25.4 (8.1; 59.2)	242.1 (190.7; 431.8)	50.3 (18.9; 167.6)
165.4 (118.9; 234.6)	40.2 (14.8; 108.7)	50	16.2 (4.3; 53.0)	215.1 (146.0; 284.9)	62.6 (19.2; 145.9)
162.2 (105.4; 245.0)	38.9 (10.5; 126.2)	118	25.0 (4.8; 86.7)	238.2 (148.4; 424.0)	74.7 (19.6; 177.4)
160.0 (101.7; 253.9)	33.0 (9.9; 103.3)	97	27.0 (7.5; 82.2)	267.0 (198.0; 398.4)	62.1 (21.1; 177.4)
169.0 (114.4; 265.3)	35.0 (11.0; 98.3)	100	18.5 (4.6; 82.3)	188.0 (150.0; 326.1)	48.0 (19.2; 148.7)
167.6 (107.8; 257.0)	33.9 (9.9; 96.9)	103	16.4 (3.4; 81.0)	275.3 (207.9; 452.1)	67.1 (20.6; 208.4)
301.9 (200.2; 457.5)	-	40	18.6 (7.3; 67.0)	311.8 (229.3; 480.1)	-
302.3 (195.7; 463.3)	-	20	16.9 (8.4; 74.9)	339.8 (242.9; 504.3)	-
301.8 (200.2; 422.6)	-	20	32.9 (6.5; 67.0)	274.4 (229.3; 480.1)	-
369.4 (232.8; 519.7)	-	5	18.7 (7.6; 32.2)	371.7 (267.7; 843.5)	-
300.3 (179.7; 434.2)	-	7	95.4 (22.8; 136.7)	427.1 (265.1; 485.7)	-
313.7 (201.1; 477.4)	-	15	18.5 (5.5; 57.5)	281.8 (186.7; 442.3)	-
257.8 (185.8; 374.9)	-	13	9.5 (7.3; 35.7)	279.4 (222.9; 421.0)	-
284.9 (212.7; 515.8)	-	8	41.8 (19.0; 100.7)	407.4 (250.5; 458.3)	-
332.4 (183.3; 429.0)	-	16	16.9 (5.0; 40.9)	264.0 (195.9; 311.8)	-
271.8 (185.4; 436.6)	-	7	14.2 (1.9; 136.7)	485.7 (418.7; 676.4)	-
303.9 (190.3; 477.4)	-	9	9.5 (7.6; 95.4)	279.4 (220.8; 371.7)	-
216.0 (138.8; 312.2)	196.4 (98.3; 321.3)	61	61.0 (10.5; 157.6)	353.0 (209.1; 479.0)	235.5 (137.1; 409.8)
204.0 (138.5; 301.7)	186.5 (90.1; 331.1)	40	30.0 (5.6; 155.6)	305.7 (171.5; 415.8)	231.1 (122.7; 392.1)
232.7 (143.5; 337.0)	215.0 (111.8; 309.3)	21	75.6 (33.2; 157.6)	451.4 (266.4; 570.2)	273.3 (160.9; 445.8)
255.1 (146.9; 396.6)	232.6 (99.4; 379.1)	13	139.9 (34.8; 184.7)	288.3 (162.6; 479.0)	282.5 (179.4; 466.0)
200.2 (138.8; 310.8)	160.6 (92.3; 331.1)	20	62.5 (8.1; 126.0)	350.5 (173.2; 444.4)	296.0 (181.6; 422.2)
216.4 (134.3; 303.3)	181.0 (85.5; 316.4)	17	40.0 (6.9; 81.9)	446.6 (266.4; 587.1)	210.1 (115.9; 306.0)
209.8 (148.5; 287.0)	207.9 (107.3; 297.0)	11	24.0 (10.1; 157.6)	363.0 (181.9; 451.4)	186.5 (117.5; 395.8)
211.4 (126.1; 289.2)	190.8 (100.7; 311.4)	17	104.2 (61.0; 171.9)	306.7 (161.2; 385.0)	230.7 (146.0; 409.8)
199.8 (154.5; 323.0)	216.0 (94.6; 352.5)	15	6.9 (5.0; 33.2)	360.9 (219.7; 479.0)	231.7 (84.2; 388.4)
233.7 (143.5; 318.5)	197.0 (99.7; 297.0)	17	67.9 (24.0; 202.3)	470.3 (363.0; 556.4)	314.9 (137.1; 434.6)
229.9 (143.1; 353.9)	172.5 (85.2; 326.2)	12	56.9 (10.3; 120.7)	278.4 (151.9; 367.0)	226.3 (183.9; 411.4)

Appendix 4.5 Median (IQR) healthcare cost per day alive grouped by number of chronic conditions, expressed in euros (€)

	No chronic conditions				One chronic condition	
	n	2012	2013	2014	n	2012
Survivors						
Total subgroup	31,245	6.2 (1.5; 23.3)	80.9 (49.3; 128.3)	11.1 (3.9; 37.3)	13,243	13.1 (4.7; 40.8)
Male	18,785	5.2 (1.2; 19.2)	80.3 (50.5; 124.2)	9.6 (3.5; 31.2)	8,025	11.6 (4.2; 37.3)
Female	12,460	7.9 (2.1; 29.4)	82.2 (47.5; 135.8)	13.9 (4.7; 47.5)	5,218	15.7 (5.8; 46.8)
Age						
• Q1 (18-55)	10,835	4.1 (0.7; 22.2)	67.8 (35.9; 120.5)	8.3 (2.4; 32.6)	2,684	14.5 (3.5; 53.4)
• Q2 (56-65)	7,029	5.2 (1.2; 19.6)	81.4 (52.8; 125.1)	9.6 (3.7; 30.0)	3,297	11.6 (3.9; 39.4)
• Q3 (66-74)	7,166	6.9 (2.2; 22.1)	85.9 (57.5; 128.1)	11.2 (4.8; 34.5)	3,889	12.4 (5.0; 36.4)
• Q4 (75-103)	6,215	9.5 (3.5; 29.3)	94.2 (62.2; 141.7)	18.6 (7.1; 60.4)	3,373	14.7 (6.0; 39.8)
SES						
• Q1 (low)	7,147	7.1 (1.8; 25.9)	80.6 (48.1; 130.2)	12.5 (4.2; 42.7)	3,502	13.5 (5.1; 39.7)
• Q2	7,594	6.2 (1.5; 24.3)	79.8 (49.4; 127.8)	11.3 (4.1; 38.6)	3,239	13.7 (4.6; 42.2)
• Q3	8,023	6.1 (1.5; 23.1)	82.3 (49.9; 128.6)	11.0 (3.9; 37.2)	3,320	12.9 (4.6; 41.0)
• Q4 (high)	8,395	5.6 (1.4; 20.3)	81.0 (49.9; 127.4)	9.9 (3.7; 32.8)	3,169	12.5 (4.6; 40.5)
Population which died during 2013						
Total subgroup	1,439	23.9 (4.6; 76.5)	211.4 (132.9; 316.8)	-	1,247	32.0 (9.3; 95.0)
Male	839	24.1 (4.8; 71.0)	206.8 (129.0; 321.6)	-	732	32.0 (9.3; 90.9)
Female	600	23.6 (4.4; 88.0)	216.2 (140.5; 311.3)	-	515	32.0 (9.2; 100.9)
Age						
• Q1 (18-55)	179	28.1 (3.2; 101.2)	231.4 (120.1; 360.8)	-	119	48.6 (13.5; 135.2)
• Q2 (56-65)	209	13.3 (2.4; 73.0)	211.3 (140.3; 328.1)	-	229	33.8 (7.6; 98.2)
• Q3 (66-74)	321	20.6 (4.3; 74.0)	224.1 (136.9; 343.6)	-	328	31.7 (7.3; 82.3)
• Q4 (75-103)	730	27.5 (5.9; 74.7)	208.3 (133.2; 298.0)	-	571	29.0 (10.1; 88.0)
SES						
• Q1 (low)	379	24.1 (4.6; 68.1)	191.1 (131.3; 316.7)	-	366	31.4 (8.4; 100.4)
• Q2	350	29.7 (5.8; 93.2)	222.9 (144.1; 317.4)	-	286	27.4 (9.2; 80.6)
• Q3	354	16.7 (4.3; 66.0)	213.0 (131.5; 324.0)	-	296	29.4 (8.5; 80.7)
• Q4 (high)	355	24.6 (4.3; 80.9)	214.1 (125.2; 310.8)	-	297	41.3 (10.4; 108.0)
Population which died during 2014						
Total subgroup	1,794	12.2 (3.1; 52.9)	136.5 (86.9; 206.1)	152.0 (74.3; 250.7)	1,558	23.9 (6.8; 68.6)
Male	1,072	11.5 (3.2; 45.2)	132.7 (83.7; 198.5)	143.1 (65.2; 250.0)	900	20.6 (5.7; 58.8)
Female	722	15.0 (3.1; 68.3)	143.1 (91.1; 214.6)	175.2 (84.3; 252.3)	658	27.6 (8.2; 84.8)
Age						
• Q1 (18-55)	267	9.3 (1.3; 58.0)	131.0 (73.4; 228.0)	131.8 (49.9; 251.5)	182	35.3 (6.7; 108.2)
• Q2 (56-65)	325	9.5 (1.7; 52.5)	136.3 (85.9; 214.6)	133.3 (69.9; 261.0)	332	20.4 (3.6; 65.4)
• Q3 (66-74)	484	7.6 (2.5; 38.7)	139.0 (93.2; 213.3)	151.6 (74.1; 260.8)	468	23.7 (6.0; 66.2)
• Q4 (75-103)	718	17.4 (5.2; 59.6)	136.8 (89.7; 194.4)	177.9 (84.0; 246.5)	576	23.7 (8.4; 64.0)
SES						
• Q1 (low)	440	13.8 (3.4; 58.6)	137.1 (85.5; 213.3)	157.4 (74.4; 278.6)	406	24.9 (8.4; 67.4)
• Q2	450	12.1 (3.6; 48.6)	132.8 (83.1; 193.8)	169.4 (75.6; 262.8)	402	20.8 (4.8; 65.4)
• Q3	483	11.4 (2.7; 55.4)	139.0 (93.4; 206.6)	146.3 (71.4; 240.4)	364	24.4 (6.9; 63.8)
• Q4 (high)	421	12.0 (3.2; 52.1)	134.3 (84.6; 206.5)	151.8 (75.5; 244.2)	384	27.1 (7.2; 79.0)

One chronic condition			Two chronic conditions		
2013	2014	n	2012	2013	2014
94.8 (63.5; 152.2)	22.3 (8.6; 65.6)	3,779	22.7 (8.1; 66.0)	119.3 (77.8; 196.9)	38.9 (14.6; 101.1)
92.3 (63.0; 147.8)	19.5 (7.8; 58.1)	2,238	20.6 (7.4; 58.4)	115.0 (76.6; 186.7)	33.5 (13.4; 91.5)
99.2 (64.1; 159.2)	27.7 (10.0; 76.7)	1,541	26.5 (9.3; 77.1)	125.6 (80.1; 206.4)	46.5 (16.7; 119.6)
88.9 (50.9; 166.1)	22.8 (7.6; 70.5)	640	33.4 (8.1; 99.7)	144.1 (78.9; 248.0)	47.6 (16.1; 130.5)
91.5 (60.8; 143.1)	18.8 (7.7; 56.7)	972	24.8 (7.8; 75.1)	117.3 (75.8; 204.8)	35.1 (13.0; 98.8)
94.3 (66.5; 147.1)	20.2 (8.4; 59.3)	1,173	20.5 (7.9; 54.6)	115.7 (78.8; 176.4)	35.7 (14.3; 85.3)
104.4 (69.8; 157.8)	28.4 (10.9; 80.0)	994	20.4 (9.1; 54.5)	117.8 (78.8; 177.6)	42.7 (16.4; 103.1)
95.3 (61.6; 152.7)	23.8 (9.0; 68.9)	1,043	24.0 (8.9; 69.7)	118.5 (79.4; 187.1)	40.9 (14.6; 105.7)
93.6 (64.9; 151.8)	22.7 (8.8; 64.6)	977	21.6 (7.7; 65.1)	120.4 (80.4; 195.4)	37.7 (15.0; 94.7)
95.3 (63.9; 151.9)	21.7 (8.1; 65.0)	866	19.9 (7.9; 57.1)	117.5 (75.3; 196.9)	35.3 (13.7; 97.1)
95.2 (63.6; 153.0)	21.2 (8.2; 64.1)	891	26.3 (8.4; 71.0)	120.1 (76.1; 203.3)	41.4 (14.9; 106.1)
223.9 (148.2; 340.0)	-	602	48.6 (16.9; 114.0)	249.1 (159.5; 361.3)	-
224.5 (143.3; 347.3)	-	367	50.8 (17.0; 113.3)	240.2 (150.4; 358.0)	-
223.7 (153.2; 331.8)	-	235	46.8 (16.2; 114.1)	256.2 (174.9; 378.0)	-
251.1 (162.8; 387.9)	-	59	88.5 (25.3; 156.6)	352.9 (211.0; 523.5)	-
219.8 (139.5; 374.0)	-	124	65.1 (16.2; 132.7)	250.1 (158.4; 363.4)	-
226.9 (144.3; 331.1)	-	169	40.6 (16.4; 97.5)	231.6 (153.0; 319.5)	-
220.8 (150.8; 320.2)	-	250	43.5 (16.0; 108.7)	241.7 (154.4; 346.1)	-
230.9 (143.4; 353.5)	-	162	41.4 (16.9; 108.7)	252.5 (156.7; 368.4)	-
228.0 (139.6; 323.1)	-	158	51.7 (20.1; 105.4)	244.2 (153.3; 346.1)	-
204.7 (148.6; 315.2)	-	140	50.3 (16.0; 123.7)	250.2 (154.2; 365.4)	-
235.4 (157.1; 354.2)	-	142	52.0 (12.7; 117.2)	236.2 (171.8; 365.1)	-
141.1 (88.2; 214.0)	166.7 (84.5; 271.0)	732	43.3 (11.9; 99.1)	169.6 (111.4; 252.8)	186.1 (101.2; 318.6)
138.0 (87.1; 209.2)	154.2 (77.5; 258.9)	431	37.9 (11.5; 88.8)	163.0 (104.8; 250.1)	174.2 (99.6; 320.7)
148.0 (91.5; 221.8)	186.1 (98.1; 288.5)	301	50.4 (12.4; 108.8)	175.4 (116.1; 253.8)	192.6 (103.6; 315.2)
146.0 (87.8; 244.7)	183.9 (100.3; 316.8)	80	58.7 (14.1; 129.4)	204.9 (133.2; 340.7)	213.3 (115.4; 387.1)
146.7 (88.6; 226.5)	146.2 (74.9; 263.8)	197	40.7 (9.3; 103.1)	183.8 (133.9; 306.7)	182.3 (105.7; 325.3)
135.1 (87.4; 209.2)	160.4 (75.8; 271.7)	219	39.0 (10.2; 88.8)	162.9 (108.3; 240.3)	177.3 (97.7; 331.2)
140.6 (90.7; 201.9)	181.9 (99.0; 262.8)	236	41.5 (13.7; 91.3)	150.5 (93.7; 217.5)	192.5 (97.5; 272.1)
149.4 (88.2; 217.0)	171.0 (90.5; 283.0)	192	44.2 (11.8; 101.1)	170.9 (118.7; 246.0)	198.9 (118.8; 328.5)
142.5 (91.1; 210.4)	184.4 (88.0; 283.3)	172	53.9 (13.5; 111.1)	167.4 (108.8; 243.9)	196.3 (100.1; 342.0)
130.7 (85.2; 206.3)	148.2 (78.3; 260.5)	185	35.6 (8.8; 72.7)	174.3 (109.5; 282.0)	165.7 (92.4; 294.5)
140.8 (89.1; 223.0)	156.3 (86.5; 258.2)	183	43.9 (14.5; 104.3)	162.9 (103.9; 242.0)	172.0 (92.6; 286.8)

Appendix 4.5 Continued: Median (IQR) healthcare cost per day alive grouped by number of chronic conditions, expressed in euros (€)

	More than two chronic conditions			
	n	2012	2013	2014
Survivors				
Total subgroup	737	37.3 (13.8; 93.0)	138.4 (83.9; 225.8)	56.7 (21.1; 134.7)
Male	477	38.2 (12.7; 90.5)	134.5 (83.9; 218.9)	51.6 (18.6; 123.0)
Female	260	36.6 (14.5; 98.1)	146.4 (83.5; 240.2)	69.2 (27.8; 158.6)
Age				
• Q1 (18-55)	102	55.6 (20.2; 130.7)	175.4 (100.9; 345.3)	69.5 (28.2; 209.2)
• Q2 (56-65)	170	40.6 (13.8; 102.6)	146.2 (83.0; 244.1)	52.6 (22.6; 116.6)
• Q3 (66-74)	242	32.9 (11.3; 87.9)	135.2 (83.5; 214.1)	52.8 (19.7; 132.9)
• Q4 (75-103)	223	30.7 (14.8; 80.2)	126.3 (79.5; 193.8)	62.1 (18.5; 128.7)
SES				
• Q1 (low)	227	40.5 (13.9; 94.2)	131.2 (79.5; 230.2)	60.5 (20.9; 163.2)
• Q2	180	35.6 (15.7; 91.2)	134.5 (84.2; 206.2)	61.1 (27.0; 123.9)
• Q3	172	38.6 (12.1; 93.0)	141.5 (86.4; 234.5)	57.0 (19.8; 135.0)
• Q4 (high)	158	37.6 (13.6; 94.3)	147.8 (88.2; 247.2)	41.6 (19.2; 119.8)
Population which Died during 2013				
Total subgroup	177	61.5 (25.0; 112.2)	230.3 (138.5; 342.5)	-
Male	109	61.5 (20.5; 97.2)	232.6 (143.8; 342.5)	-
Female	68	62.3 (28.7; 142.9)	222.8 (138.0; 348.5)	-
Age				
• Q1 (18-55)	9	61.5 (25.7; 191.6)	248.0 (178.2; 342.5)	-
• Q2 (56-65)	31	53.8 (20.5; 112.2)	230.9 (131.2; 578.2)	-
• Q3 (66-74)	68	75.3 (36.1; 125.5)	257.8 (158.9; 392.4)	-
• Q4 (75-103)	69	50.5 (19.7; 94.3)	182.5 (114.6; 276.4)	-
SES				
• Q1 (low)	66	57.2 (24.7; 109.9)	236.0 (140.1; 331.9)	-
• Q2	40	46.2 (19.4; 97.2)	220.7 (155.9; 302.3)	-
• Q3	33	62.6 (34.4; 115.9)	242.1 (127.5; 383.4)	-
• Q4 (high)	38	91.3 (26.4; 134.0)	222.8 (143.8; 338.2)	-
Population which died during 2014				
Total subgroup	207	56.4 (20.5; 123.4)	165.0 (104.8; 260.6)	229.3 (123.3; 355.3)
Male	136	50.7 (22.3; 106.7)	148.5 (97.2; 244.2)	218.0 (110.3; 341.1)
Female	71	74.5 (18.3; 147.1)	196.7 (132.4; 308.4)	253.8 (145.3; 368.2)
Age				
• Q1 (18-55)	18	120.6 (53.1; 177.4)	156.7 (119.1; 332.8)	322.0 (218.2; 482.3)
• Q2 (56-65)	43	58.7 (19.1; 136.2)	187.6 (127.2; 330.1)	251.1 (124.4; 408.5)
• Q3 (66-74)	69	55.9 (20.8; 125.2)	156.8 (105.7; 256.6)	241.1 (126.8; 345.5)
• Q4 (75-103)	77	45.7 (18.3; 110.6)	155.9 (85.4; 243.6)	200.8 (111.5; 281.0)
SES				
• Q1 (low)	51	50.8 (18.3; 120.8)	145.0 (98.5; 220.0)	193.9 (108.9; 268.0)
• Q2	61	63.9 (25.7; 127.6)	200.2 (107.7; 292.1)	237.8 (135.1; 365.0)
• Q3	41	52.7 (12.8; 128.7)	163.8 (84.1; 253.5)	252.3 (152.9; 368.2)
• Q4 (high)	54	58.1 (20.1; 112.0)	172.2 (112.2; 291.7)	218.9 (138.4; 410.2)

Appendix 4.6 Median (IQR) healthcare cost per day alive grouped by chronic condition, expressed in euros (€)

	Chronic renal insufficiency or renal dialyses				COPD or respiratory insufficiency	
	n	2012	2013	2014	n	2012
Survivors						
Total subgroup	1,792	34.5 (10.5; 112.6)	144.6 (83.0; 252.4)	59.3 (18.6; 196.9)	6,446	17.4 (6.7; 51.6)
Male	1,168	32.0 (9.8; 102.7)	136.8 (80.1; 250.7)	52.5 (16.4; 183.5)	3,698	15.7 (6.3; 47.8)
Female	624	40.7 (12.5; 133.9)	152.6 (89.7; 257.1)	72.6 (22.6; 217.4)	2,748	20.3 (7.5; 56.6)
Age						
• Q1 (18-55)	301	61.6 (15.6; 205.6)	201.4 (93.3; 334.7)	110.9 (30.7; 246.7)	1,143	19.9 (5.3; 72.7)
• Q2 (56-65)	323	49.5 (11.5; 176.5)	179.5 (86.7; 301.0)	68.0 (19.2; 220.3)	1,715	16.6 (6.0; 49.7)
• Q3 (66-74)	526	33.5 (10.4; 94.3)	138.7 (82.8; 241.7)	55.5 (19.3; 207.7)	1,858	16.6 (6.6; 44.8)
• Q4 (75-103)	642	23.7 (9.4; 74.5)	115.4 (79.4; 205.0)	44.0 (14.6; 137.3)	1,730	18.3 (8.3; 49.3)
SES						
• Q1 (low)	502	34.8 (11.5; 123.4)	145.4 (86.6; 260.0)	72.4 (21.6; 215.4)	1,850	17.6 (6.8; 52.4)
• Q2	461	38.0 (11.3; 112.3)	144.0 (84.5; 252.3)	65.7 (19.7; 204.3)	1,648	17.9 (6.8; 52.4)
• Q3	405	33.6 (9.4; 100.3)	133.2 (78.1; 240.0)	52.0 (15.9; 186.5)	1,561	16.8 (6.4; 47.5)
• Q4 (high)	424	30.7 (9.8; 116.6)	149.3 (84.9; 251.9)	49.9 (17.5; 173.4)	1,386	17.4 (6.5; 53.9)
Population which died during 2013						
Total subgroup	336	68.2 (22.2; 144.4)	265.9 (162.6; 393.8)	-	721	43.3 (16.2; 100.2)
Male	227	68.9 (20.3; 140.0)	267.6 (158.0; 387.4)	-	426	40.9 (15.1; 94.4)
Female	109	68.0 (25.9; 153.6)	262.7 (179.3; 428.1)	-	295	48.1 (18.5; 117.2)
Age						
• Q1 (18-55)	18	220.9 (85.6; 319.2)	439.0 (319.1; 565.3)	-	46	70.6 (25.7; 154.7)
• Q2 (56-65)	38	79.3 (17.0; 153.6)	260.6 (156.7; 492.1)	-	134	45.5 (16.3; 114.0)
• Q3 (66-74)	90	67.0 (26.8; 129.0)	280.9 (171.2; 457.5)	-	211	46.4 (18.5; 100.2)
• Q4 (75-103)	190	61.0 (18.4; 129.0)	247.5 (159.5; 356.2)	-	330	38.9 (14.3; 87.6)
SES						
• Q1 (low)	108	66.2 (24.4; 151.6)	263.8 (158.2; 383.3)	-	241	40.9 (14.4; 103.1)
• Q2	84	61.8 (25.0; 137.3)	256.5 (158.1; 381.3)	-	173	45.8 (19.8; 83.8)
• Q3	68	56.3 (15.1; 148.6)	272.8 (160.8; 395.9)	-	161	42.6 (16.0; 108.8)
• Q4 (high)	76	85.7 (23.9; 169.1)	269.5 (188.2; 470.3)	-	145	44.4 (15.1; 104.6)
Population which died during 2014						
Total subgroup	380	56.1 (21.0; 149.3)	184.4 (109.9; 305.9)	238.5 (123.1; 409.0)	958	35.9 (11.9; 87.1)
Male	256	49.4 (21.0; 126.5)	170.9 (99.5; 284.2)	237.6 (116.9; 408.0)	555	31.0 (10.1; 79.2)
Female	124	67.1 (21.8; 167.5)	209.9 (126.9; 335.1)	241.2 (128.3; 409.2)	403	40.7 (14.5; 96.6)
Age						
• Q1 (18-55)	25	86.6 (46.0; 190.3)	332.8 (171.0; 417.7)	371.4 (198.8; 575.7)	79	54.2 (17.9; 122.6)
• Q2 (56-65)	57	85.2 (33.1; 262.7)	244.8 (115.4; 346.5)	287.3 (144.5; 485.0)	208	38.4 (12.6; 101.8)
• Q3 (66-74)	118	61.1 (22.2; 160.5)	214.6 (126.4; 334.7)	328.3 (162.7; 453.9)	318	30.5 (9.6; 76.6)
• Q4 (75-103)	180	42.9 (13.6; 108.1)	155.8 (92.3; 245.7)	203.1 (107.8; 318.1)	353	31.5 (13.1; 79.2)
SES						
• Q1 (low)	94	62.3 (22.2; 137.3)	177.0 (114.0; 270.3)	216.3 (122.9; 386.3)	266	40.2 (14.3; 92.6)
• Q2	107	62.4 (22.2; 165.3)	196.3 (111.6; 293.8)	237.4 (132.4; 388.0)	250	36.2 (10.4; 94.0)
• Q3	93	47.3 (13.7; 184.2)	181.9 (86.9; 326.9)	261.5 (122.6; 406.7)	217	29.2 (10.7; 64.5)
• Q4 (high)	85	54.9 (22.3; 133.8)	197.4 (115.4; 291.7)	251.3 (115.9; 452.6)	224	37.5 (12.1; 93.6)

COPD or respiratory insufficiency			Chronic cardiovascular insufficiency		
2013	2014	n	2012	2013	2014
98.8 (63.3; 161.4)	29.5 (11.5; 80.5)	2,785	10.9 (3.5; 36.9)	99.3 (72.4; 151.7)	16.8 (6.5; 53.5)
98.4 (63.1; 156.5)	26.2 (10.7; 73.3)	1,920	9.3 (2.8; 32.5)	95.8 (71.2; 144.8)	14.4 (5.7; 44.2)
99.5 (63.4; 167.2)	35.8 (12.8; 93.4)	865	14.5 (4.9; 45.7)	108.4 (76.8; 167.8)	25.1 (8.8; 73.9)
94.6 (52.4; 192.2)	32.0 (9.8; 101.5)	394	9.0 (1.6; 38.3)	96.6 (71.9; 163.0)	14.9 (5.7; 49.1)
93.6 (58.9; 151.3)	24.3 (9.8; 67.9)	620	7.3 (2.1; 32.5)	92.1 (71.9; 142.9)	11.4 (4.9; 38.8)
98.2 (66.5; 153.0)	27.8 (11.1; 72.4)	868	10.6 (3.9; 31.0)	97.1 (71.7; 145.4)	14.6 (6.2; 44.7)
107.4 (71.1; 161.3)	37.0 (14.8; 95.4)	903	14.9 (5.5; 41.7)	110.3 (74.3; 157.4)	27.6 (9.5; 75.0)
99.4 (62.2; 154.1)	29.9 (11.8; 79.1)	741	11.4 (3.8; 34.9)	98.6 (72.5; 152.4)	17.9 (7.0; 59.3)
100.6 (65.2; 162.4)	32.4 (12.3; 84.5)	714	9.7 (3.4; 33.1)	97.9 (72.2; 148.6)	16.9 (6.7; 51.0)
97.8 (63.6; 161.5)	26.6 (10.5; 74.9)	674	11.2 (3.5; 42.4)	99.7 (72.7; 157.4)	15.7 (6.1; 54.4)
96.1 (61.3; 167.0)	29.1 (11.4; 83.8)	653	11.1 (3.3; 38.3)	101.0 (72.4; 150.5)	16.6 (6.3; 52.8)
230.6 (138.3; 343.8)	-	261	48.1 (14.8; 104.3)	232.5 (153.2; 368.3)	-
218.8 (129.9; 320.8)	-	165	54.6 (18.2; 104.7)	235.2 (150.8; 389.0)	-
240.2 (153.2; 367.3)	-	96	36.9 (12.7; 88.2)	227.9 (153.3; 327.1)	-
274.7 (166.4; 477.8)	-	9	40.9 (10.1; 137.3)	182.0 (146.7; 262.2)	-
221.9 (120.0; 366.3)	-	29	53.8 (18.4; 145.7)	277.5 (195.3; 579.2)	-
239.9 (147.5; 363.7)	-	63	75.6 (18.8; 129.6)	262.1 (154.2; 511.1)	-
216.6 (138.3; 321.1)	-	160	41.9 (13.1; 88.6)	216.3 (148.2; 320.1)	-
231.6 (135.6; 357.6)	-	90	44.9 (14.3; 101.6)	235.7 (149.8; 360.3)	-
219.6 (137.7; 319.7)	-	64	36.3 (13.3; 94.7)	250.8 (144.9; 344.5)	-
230.9 (138.3; 325.5)	-	53	51.0 (13.5; 131.8)	222.8 (140.8; 325.5)	-
233.6 (149.4; 365.1)	-	54	56.4 (18.8; 104.6)	222.8 (170.2; 511.1)	-
143.6 (93.0; 216.0)	173.8 (91.4; 280.1)	279	33.1 (9.6; 73.1)	156.5 (107.8; 223.7)	185.8 (97.7; 282.9)
137.9 (91.2; 209.5)	161.4 (87.7; 252.9)	177	32.2 (9.4; 66.3)	140.6 (98.7; 211.5)	163.1 (89.5; 265.0)
155.4 (95.4; 224.9)	189.5 (98.1; 322.1)	102	35.3 (10.1; 84.8)	175.6 (142.9; 246.5)	198.9 (121.4; 284.9)
162.6 (99.9; 272.6)	186.1 (95.8; 290.4)	10	28.5 (6.3; 94.2)	216.3 (113.5; 264.1)	219.6 (152.6; 575.7)
154.4 (101.2; 240.0)	177.9 (83.3; 326.4)	49	34.2 (9.4; 64.7)	151.1 (114.0; 257.1)	163.7 (105.2; 363.6)
136.8 (91.1; 215.3)	166.2 (81.3; 260.8)	67	34.9 (7.2; 67.5)	152.1 (99.8; 230.4)	187.7 (99.1; 341.8)
141.8 (90.1; 199.6)	182.2 (103.4; 264.5)	153	32.6 (11.0; 75.8)	162.3 (108.7; 213.8)	191.8 (92.6; 234.6)
149.3 (96.5; 220.0)	176.0 (94.8; 260.8)	72	33.0 (10.0; 98.8)	153.7 (113.7; 201.1)	194.7 (114.2; 276.8)
138.7 (90.5; 202.7)	185.7 (94.6; 289.4)	74	36.5 (13.4; 73.3)	156.1 (107.4; 244.8)	208.2 (83.4; 304.1)
144.2 (89.8; 216.0)	160.0 (89.2; 262.8)	62	33.6 (7.7; 62.1)	143.5 (91.9; 223.0)	155.3 (92.4; 251.1)
143.8 (94.8; 226.4)	179.1 (86.2; 285.8)	71	25.9 (8.1; 64.7)	169.5 (115.4; 235.8)	172.8 (99.1; 283.2)

Appendix 4.6 Continued: Median (IQR) healthcare cost per day alive grouped by chronic condition, expressed in euros (€)

	Haematological malignancy or metastatic neoplasm				Immunological deficiency	
	n	2012	2013	2014	n	2012
Survivors						
Total subgroup	1,581	16.4 (3.8; 58.9)	124.5 (79.6; 189.4)	44.5 (14.0; 104.2)	2,621	26.0 (6.8; 72.6)
Male	890	16.8 (3.7; 61.8)	118.0 (78.0; 192.2)	46.0 (14.5; 110.7)	1,480	6.5 (69.4;)
Female	691	16.0 (3.9; 55.9)	128.3 (82.5; 188.4)	42.3 (13.0; 97.5)	1,141	7.7 (75.4;)
Age						
• Q1 (18-55)	358	13.6 (1.6; 74.2)	129.7 (81.9; 216.3)	43.8 (10.7; 115.3)	722	31.1 (6.4; 89.8)
• Q2 (56-65)	437	16.5 (3.4; 59.3)	132.0 (86.3; 209.1)	46.2 (14.6; 116.6)	742	27.4 (5.9; 83.1)
• Q3 (66-74)	475	16.3 (5.2; 54.8)	123.8 (79.0; 181.5)	44.2 (15.1; 95.5)	691	23.6 (6.7; 57.7)
• Q4 (75-103)	311	19.5 (6.3; 53.6)	111.8 (71.0; 156.5)	40.5 (14.0; 97.8)	466	23.7 (8.5; 57.2)
SES						
• Q1 (low)	329	17.2 (4.9; 55.0)	117.7 (77.8; 188.5)	43.4 (13.1; 102.0)	643	26.1 (7.5; 74.0)
• Q2	352	16.0 (3.8; 61.0)	128.2 (79.7; 183.2)	42.7 (15.5; 107.4)	657	25.5 (6.7; 70.1)
• Q3	429	13.5 (3.2; 57.1)	121.4 (79.3; 188.4)	38.2 (13.6; 100.5)	631	23.7 (5.5; 70.2)
• Q4 (high)	469	21.0 (3.8; 65.2)	125.9 (80.8; 196.4)	49.1 (14.1; 110.8)	689	29.6 (7.2; 73.7)
Population which died during 2013						
Total subgroup	579	32.0 (6.7; 91.7)	217.9 (149.1; 316.3)	-	405	51.0 (16.3; 118.2)
Male	319	39.0 (6.9; 90.1)	223.8 (148.1; 327.5)	-	243	50.4 (14.6; 112.8)
Female	260	29.3 (6.0; 98.9)	215.1 (150.8; 305.8)	-	162	54.6 (20.9; 123.3)
Age						
• Q1 (18-55)	90	48.8 (10.2; 129.2)	251.8 (173.2; 424.8)	-	59	65.2 (15.6; 131.2)
• Q2 (56-65)	153	40.1 (6.7; 95.2)	226.0 (148.1; 320.5)	-	102	64.4 (16.9; 138.2)
• Q3 (66-74)	183	37.6 (6.2; 83.5)	213.1 (153.0; 296.5)	-	135	57.5 (23.1; 114.4)
• Q4 (75-103)	153	20.6 (5.8; 64.9)	201.9 (141.9; 306.1)	-	109	36.3 (11.7; 79.1)
SES						
• Q1 (low)	130	24.3 (6.2; 85.8)	220.9 (148.2; 313.1)	-	94	64.5 (17.9; 142.5)
• Q2	144	28.8 (5.6; 79.9)	201.0 (139.5; 318.0)	-	104	45.1 (16.9; 98.2)
• Q3	138	36.8 (8.2; 84.4)	215.7 (155.6; 337.2)	-	103	50.8 (16.0; 114.4)
• Q4 (high)	166	40.6 (7.2; 109.6)	228.1 (152.0; 308.6)	-	104	62.6 (14.3; 130.2)
Population which died during 2014						
Total subgroup	590	21.6 (5.1; 78.0)	151.4 (95.1; 225.2)	166.5 (87.0; 282.4)	578	45.0 (9.2; 101.4)
Male	335	21.4 (4.8; 71.2)	157.0 (92.5; 232.1)	160.5 (88.1; 269.4)	327	7.6 (87.7;)
Female	255	22.0 (5.4; 84.9)	147.1 (95.6; 219.8)	172.1 (85.3; 287.7)	251	11.1 (115.3;)
Age						
• Q1 (18-55)	98	41.0 (6.1; 136.0)	169.4 (104.4; 270.1)	218.5 (121.2; 346.8)	116	53.3 (15.3; 129.6)
• Q2 (56-65)	188	20.2 (3.1; 69.2)	168.9 (116.5; 249.2)	166.6 (85.2; 293.7)	165	27.9 (3.6; 78.1)
• Q3 (66-74)	171	20.8 (5.5; 79.4)	146.5 (95.4; 222.4)	157.4 (84.1; 257.5)	180	51.5 (11.0; 101.5)
• Q4 (75-103)	133	20.2 (7.2; 54.0)	110.8 (74.7; 177.8)	156.7 (85.6; 229.2)	117	28.8 (10.3; 99.3)
SES						
• Q1 (low)	134	19.4 (3.7; 60.3)	154.6 (95.1; 203.7)	167.3 (90.5; 286.8)	134	32.2 (8.8; 93.2)
• Q2	124	15.8 (5.4; 79.9)	152.1 (92.0; 233.6)	200.2 (99.1; 303.9)	149	48.5 (8.8; 109.2)
• Q3	150	18.3 (4.8; 67.5)	154.6 (95.6; 225.1)	153.9 (79.7; 263.1)	139	29.4 (7.1; 72.7)
• Q4 (high)	182	36.2 (7.3; 87.9)	149.4 (96.0; 228.3)	162.9 (88.7; 260.6)	156	58.1 (17.3; 115.0)

Immunological deficiency			Diabetes		
2013	2014	n	2012	2013	2014
129.9 (82.6; 206.2)	39.2 (14.0; 91.6)	7,446	15.8 (6.5; 45.1)	97.8 (65.3; 156.3)	25.8 (10.4; 75.0)
129.4 (83.4; 204.1)	37.6 (13.3; 87.6)	4,556	13.9 (5.8; 39.6)	93.3 (64.3; 148.1)	22.4 (9.6; 63.5)
130.7 (80.6; 211.2)	42.2 (15.1; 98.2)	2,890	19.1 (7.8; 53.3)	104.9 (67.6; 168.9)	32.7 (12.3; 93.7)
135.6 (83.0; 227.0)	39.0 (13.4; 92.8)	1,158	17.3 (5.9; 56.5)	82.3 (46.5; 154.2)	22.7 (8.8; 75.4)
130.5 (85.8; 213.6)	40.1 (13.4; 91.6)	1,799	14.9 (5.8; 42.5)	92.5 (63.3; 147.0)	21.8 (9.6; 63.2)
130.9 (85.2; 199.6)	37.8 (14.7; 88.0)	2,494	15.2 (6.8; 43.2)	98.5 (68.4; 151.7)	24.8 (10.2; 68.7)
120.9 (76.4; 172.4)	40.2 (14.7; 94.7)	1,995	16.4 (7.0; 44.2)	111.4 (73.2; 168.8)	33.2 (13.1; 95.0)
125.3 (78.9; 204.3)	43.4 (13.9; 102.3)	2,122	17.1 (6.9; 48.1)	103.1 (66.6; 165.4)	29.0 (11.1; 85.3)
126.4 (83.3; 190.9)	36.4 (13.2; 84.7)	1,807	16.8 (6.6; 44.8)	95.9 (66.6; 154.9)	25.4 (10.9; 73.3)
131.7 (82.8; 209.1)	36.4 (13.6; 83.6)	1,777	14.4 (6.3; 43.4)	96.8 (64.8; 153.7)	25.4 (10.3; 70.5)
136.4 (85.8; 216.4)	40.5 (15.3; 98.9)	1,730	15.1 (6.3; 44.0)	94.8 (63.9; 151.7)	23.3 (9.5; 67.5)
252.3 (160.8; 349.0)	-	645	38.9 (13.0; 101.1)	229.1 (152.3; 343.8)	-
251.0 (151.8; 352.9)	-	384	38.4 (13.2; 94.0)	226.3 (152.4; 340.2)	-
252.4 (168.6; 338.2)	-	261	40.6 (12.3; 110.4)	240.2 (152.3; 359.9)	-
329.5 (178.2; 492.0)	-	28	99.4 (32.9; 181.8)	288.3 (189.8; 448.0)	-
252.5 (150.0; 369.1)	-	97	38.2 (10.9; 100.8)	241.4 (146.6; 450.5)	-
240.7 (161.0; 309.8)	-	178	38.8 (12.0; 94.0)	225.3 (149.1; 363.3)	-
230.3 (157.2; 323.7)	-	342	37.6 (13.0; 98.1)	226.9 (157.0; 323.2)	-
258.1 (164.0; 362.8)	-	208	37.1 (14.4; 97.5)	238.7 (153.1; 350.0)	-
240.5 (155.9; 308.7)	-	150	40.3 (13.3; 102.3)	231.8 (160.3; 347.1)	-
250.5 (152.4; 406.8)	-	139	34.2 (11.6; 91.8)	218.9 (137.7; 332.5)	-
240.3 (166.4; 339.1)	-	148	50.4 (12.1; 111.7)	226.3 (158.6; 348.6)	-
176.0 (122.5; 264.3)	179.0 (92.7; 301.7)	824	35.2 (10.5; 92.7)	151.4 (94.0; 236.4)	196.1 (98.1; 309.5)
170.9 (119.1; 258.7)	167.8 (87.9; 289.0)	497	33.1 (9.7; 77.8)	142.6 (91.5; 228.2)	174.2 (86.0; 314.3)
180.8 (130.2; 272.1)	196.6 (100.1; 316.8)	327	40.7 (12.5; 110.9)	165.0 (108.7; 248.1)	208.8 (126.2; 307.6)
177.0 (130.3; 316.9)	225.6 (114.2; 380.0)	52	70.2 (13.0; 168.0)	134.3 (86.5; 231.5)	178.0 (104.1; 337.4)
178.2 (137.7; 284.2)	158.1 (79.2; 310.4)	169	40.5 (11.8; 94.5)	175.6 (102.7; 304.0)	185.8 (96.1; 333.9)
176.7 (113.3; 239.6)	177.3 (75.2; 265.0)	252	28.3 (9.5; 84.0)	143.9 (94.5; 216.7)	181.7 (88.1; 314.3)
169.0 (111.4; 242.3)	182.7 (111.0; 281.0)	351	32.8 (11.3; 87.7)	150.6 (92.1; 224.2)	200.0 (104.4; 283.3)
179.7 (132.4; 253.3)	191.1 (103.8; 321.2)	239	33.7 (11.1; 91.7)	151.5 (99.6; 224.8)	197.5 (103.4; 307.2)
186.2 (137.6; 285.0)	201.7 (88.7; 320.4)	224	44.5 (11.4; 113.7)	159.1 (103.6; 249.1)	204.4 (104.5; 335.9)
169.3 (113.8; 270.1)	161.1 (76.9; 281.0)	181	31.5 (10.0; 84.9)	149.1 (81.9; 237.6)	188.0 (90.5; 320.6)
169.5 (107.7; 242.1)	161.2 (92.9; 294.4)	180	34.7 (11.4; 83.9)	146.3 (93.3; 246.5)	187.7 (88.2; 280.2)

Appendix 4.7 Median (IQR) healthcare cost per day alive grouped by APACHE IV predicted mortality, expressed in euros (€)

	Low predicted mortality				Median predicted mortality	
	n	2012	2013	2014	n	2012
Survivors						
Total subgroup	42,468	8.9 (2.4; 31.7)	83.9 (52.9; 130.1)	14.2 (5.1; 46.1)	3,274	9.8 (2.5; 38.1)
Male	25,651	7.7 (2.0; 27.5)	82.8 (53.8; 125.6)	12.4 (4.6; 39.2)	1,900	8.3 (2.1; 34.2)
Female	16,817	11.1 (3.3; 37.9)	85.9 (51.5; 137.6)	17.2 (6.1; 56.9)	1,374	12.1 (3.2; 42.1)
Age						
• Q1 (18-55)	12,578	6.4 (1.1; 31.1)	71.1 (37.6; 122.8)	10.6 (3.0; 40.7)	699	3.8 (0.6; 28.2)
• Q2 (56-65)	10,067	7.8 (2.0; 28.9)	83.2 (55.1; 125.6)	12.7 (4.8; 39.1)	646	9.6 (1.9; 46.5)
• Q3 (66-74)	10,821	9.7 (3.3; 30.9)	87.4 (60.4; 129.6)	14.4 (5.9; 43.2)	872	10.4 (3.3; 37.4)
• Q4 (75-103)	9,002	11.9 (4.6; 35.5)	96.0 (63.8; 142.9)	21.7 (8.3; 65.3)	1,057	12.1 (5.0; 38.4)
SES						
• Q1 (low)	10,280	10.1 (2.9; 34.6)	84.3 (52.1; 131.9)	16.1 (5.6; 52.1)	814	11.1 (3.2; 41.3)
• Q2	10,404	9.1 (2.4; 32.8)	83.3 (53.5; 130.6)	14.5 (5.2; 46.6)	823	10.1 (2.5; 34.9)
• Q3	10,766	8.5 (2.3; 31.0)	84.8 (53.5; 129.9)	13.6 (5.0; 44.9)	785	9.5 (2.5; 38.1)
• Q4 (high)	10,938	8.2 (2.2; 29.1)	83.3 (52.6; 128.2)	12.9 (4.8; 41.1)	845	8.8 (2.0; 36.6)
Population which died during 2013						
Total subgroup	2,326	34.5 (9.1; 96.5)	214.4 (139.3; 312.2)	-	713	29.8 (7.0; 88.9)
Male	1,377	34.2 (9.0; 88.4)	212.4 (136.4; 316.7)	-	413	31.1 (7.4; 81.9)
Female	949	35.0 (9.1; 104.6)	217.9 (146.3; 309.4)	-	300	29.4 (6.2; 100.1)
Age						
• Q1 (18-55)	258	46.9 (9.8; 134.4)	231.5 (133.9; 360.8)	-	54	45.3 (3.9; 129.1)
• Q2 (56-65)	413	32.3 (7.4; 99.4)	207.1 (139.3; 308.6)	-	94	35.1 (3.7; 101.9)
• Q3 (66-74)	595	32.8 (8.4; 87.4)	222.6 (138.8; 313.2)	-	172	37.4 (7.7; 96.5)
• Q4 (75-103)	1,060	34.2 (9.9; 90.3)	211.1 (141.6; 302.4)	-	393	26.2 (7.7; 79.0)
SES						
• Q1 (low)	650	31.9 (9.6; 96.4)	213.3 (138.1; 319.1)	-	200	27.4 (5.4; 88.0)
• Q2	564	38.3 (9.7; 91.0)	218.2 (142.3; 306.8)	-	173	27.2 (7.4; 81.7)
• Q3	563	29.9 (7.7; 87.4)	209.7 (137.7; 317.4)	-	166	30.8 (7.3; 80.6)
• Q4 (high)	547	39.6 (9.1; 104.3)	219.3 (140.3; 310.8)	-	173	33.7 (7.7; 99.1)
Population which died during 2014						
Total subgroup	3,339	21.3 (5.2; 67.3)	136.5 (87.9; 204.6)	154.5 (79.2; 259.3)	621	26.0 (6.5; 83.1)
Male	1,983	18.0 (4.9; 61.0)	131.6 (85.5; 198.8)	145.6 (75.2; 252.4)	378	24.0 (6.4; 78.7)
Female	1,356	26.7 (6.0; 82.4)	145.2 (91.8; 212.7)	174.1 (89.6; 268.2)	243	29.7 (6.5; 91.5)
Age						
• Q1 (18-55)	455	22.1 (2.9; 92.8)	133.2 (83.1; 228.0)	153.2 (72.2; 275.4)	49	46.4 (15.9; 124.8)
• Q2 (56-65)	699	21.3 (3.9; 73.0)	142.4 (91.5; 210.4)	144.1 (75.6; 266.2)	120	14.6 (2.5; 60.5)
• Q3 (66-74)	972	17.9 (4.7; 57.6)	134.8 (89.2; 205.1)	155.4 (77.4; 259.2)	179	39.0 (6.9; 106.1)
• Q4 (75-103)	1,213	23.8 (7.8; 67.4)	135.2 (87.2; 195.5)	173.0 (88.0; 251.4)	273	25.8 (7.4; 73.3)
SES						
• Q1 (low)	849	23.1 (6.9; 72.1)	140.9 (88.6; 204.4)	163.5 (81.8; 274.1)	150	28.0 (6.0; 80.5)
• Q2	847	20.1 (4.8; 67.2)	134.7 (87.4; 200.2)	174.2 (83.4; 282.4)	156	26.3 (6.3; 93.1)
• Q3	844	19.2 (4.7; 63.0)	134.8 (88.0; 204.4)	143.9 (75.6; 246.6)	150	23.4 (7.0; 74.1)
• Q4 (high)	797	22.3 (5.5; 66.4)	136.2 (88.4; 211.2)	150.4 (78.0; 242.5)	165	28.8 (6.3; 87.6)

Median predicted mortality			High predicted mortality		
2013	2014	n	2012	2013	2014
147.6 (87.8; 239.2)	36.0 (10.9; 110.7)	1,020	6.3 (1.9; 22.4)	154.5 (101.9; 254.2)	24.5 (7.2; 88.1)
145.6 (87.1; 235.8)	30.7 (9.7; 97.2)	683	5.6 (1.5; 18.0)	150.3 (98.8; 242.8)	18.9 (6.4; 70.9)
151.9 (89.4; 243.0)	45.1 (13.3; 126.2)	337	8.5 (2.6; 28.0)	168.6 (105.3; 285.9)	34.2 (9.3; 124.5)
166.6 (87.0; 300.1)	22.6 (5.5; 78.2)	204	3.0 (0.5; 18.0)	146.4 (85.0; 290.7)	20.4 (5.6; 88.5)
167.4 (94.2; 281.8)	32.3 (9.1; 113.4)	236	4.7 (0.7; 21.2)	159.1 (108.2; 250.4)	19.0 (6.0; 59.5)
150.1 (94.0; 230.3)	38.4 (11.9; 99.3)	299	6.9 (2.5; 25.0)	153.7 (109.3; 257.0)	27.0 (7.9; 89.3)
131.5 (81.2; 202.5)	48.8 (15.3; 128.4)	281	8.9 (4.4; 22.8)	156.0 (97.6; 242.9)	29.3 (8.6; 116.4)
158.6 (90.5; 245.2)	47.1 (13.3; 135.4)	236	6.7 (1.9; 24.5)	164.2 (112.1; 262.8)	23.1 (6.9; 94.1)
143.8 (90.3; 228.5)	35.8 (11.3; 99.5)	250	7.5 (1.8; 22.6)	154.3 (96.6; 252.5)	29.6 (7.7; 104.5)
148.4 (86.2; 246.9)	33.4 (10.9; 96.4)	256	6.1 (1.8; 24.3)	154.7 (105.8; 265.1)	27.1 (8.4; 92.7)
142.7 (84.9; 237.1)	31.0 (9.5; 104.2)	275	5.9 (1.9; 17.7)	147.9 (89.8; 242.8)	16.6 (6.6; 61.9)
251.9 (162.2; 368.9)	-	190	19.1 (4.0; 50.7)	264.1 (157.2; 415.4)	-
254.1 (161.0; 367.0)	-	112	20.0 (5.9; 46.9)	276.2 (173.4; 417.0)	-
250.3 (162.5; 382.4)	-	78	17.7 (3.1; 63.2)	243.5 (155.9; 410.7)	-
354.7 (246.5; 522.3)	-	19	25.3 (8.5; 64.2)	331.3 (190.5; 652.4)	-
284.1 (178.4; 434.2)	-	34	11.4 (3.9; 83.0)	276.3 (204.2; 574.7)	-
247.1 (145.4; 364.3)	-	56	23.2 (4.6; 57.9)	272.3 (182.5; 463.0)	-
234.0 (161.8; 332.3)	-	81	15.9 (4.0; 37.1)	227.7 (132.1; 343.4)	-
247.8 (148.7; 354.9)	-	49	19.4 (4.2; 45.1)	281.6 (146.5; 431.4)	-
265.1 (164.7; 368.0)	-	45	14.9 (2.0; 36.0)	234.4 (155.9; 331.3)	-
250.0 (159.5; 368.9)	-	41	19.9 (1.9; 68.2)	240.4 (174.3; 415.4)	-
245.1 (174.1; 386.2)	-	55	28.2 (6.4; 64.2)	273.4 (203.1; 432.5)	-
181.0 (112.2; 269.9)	205.6 (101.4; 316.2)	123	14.7 (4.4; 74.1)	202.1 (130.6; 334.7)	192.2 (100.7; 266.5)
174.5 (112.2; 280.9)	194.9 (93.6; 305.0)	64	10.3 (3.2; 46.1)	208.2 (123.3; 300.0)	192.1 (91.5; 287.1)
193.2 (111.5; 266.7)	222.2 (111.0; 344.6)	59	18.5 (4.9; 118.3)	193.2 (134.0; 371.9)	192.2 (111.3; 247.9)
268.4 (144.2; 349.9)	302.9 (179.4; 520.8)	16	56.5 (8.5; 215.2)	452.4 (270.6; 907.4)	240.3 (126.6; 287.1)
213.4 (147.6; 346.8)	208.9 (100.6; 312.1)	26	22.3 (4.6; 119.4)	237.7 (87.9; 342.9)	189.1 (102.4; 283.4)
184.7 (113.1; 297.4)	212.9 (88.7; 372.7)	39	5.4 (3.9; 27.8)	209.5 (130.6; 297.2)	192.2 (69.6; 266.5)
163.0 (100.6; 231.5)	195.0 (106.6; 281.0)	42	14.6 (5.6; 72.3)	177.8 (121.9; 224.5)	188.4 (111.5; 210.5)
199.4 (116.6; 270.3)	212.5 (108.9; 320.1)	36	13.8 (3.4; 74.3)	177.2 (123.3; 314.7)	184.6 (109.3; 229.9)
163.3 (110.0; 258.1)	207.2 (92.3; 320.5)	23	9.0 (3.3; 154.9)	230.4 (187.2; 340.2)	231.7 (160.9; 291.7)
185.5 (110.9; 272.8)	194.8 (98.3; 302.9)	33	14.5 (4.1; 35.0)	206.9 (119.9; 311.8)	151.4 (75.7; 247.3)
184.1 (116.3; 269.9)	215.5 (107.2; 319.8)	31	27.8 (5.0; 82.5)	180.2 (114.6; 378.3)	192.2 (103.1; 324.0)

REFERENCES

1. Centraal Bureau voor de Statistiek (CBS), et al. http://statline.cbs.nl/Statweb/dome/ default.aspx. [accessed 10.09.2016].
2. Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 2010; 38:1.
3. Halpern NA, Pastores SM, Greenstein RJ. Critical care medicine in the United States 1985–2000: an analysis of bed numbers, use, and costs. Crit Care Med 2004;32:6.
4. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2004;2.
5. Librero J, Peiro S, Ordinana R. Chronic comorbidity and outcomes of hospital care: length of stay, mortality, and readmission at 30 and 365 days. J Clin Epidemiol 1999;52:3.
6. Lone NI, Seretny M, Wild SH, Rowan KM, Murray GD,Walsh TS. Surviving intensive care: a systematic review of healthcare resource use after hospital discharge. Crit Care Med 2013;41:8.
7. Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;174:5.
8. van Eeden M, van Heugten C, van Mastrigt GA, van Mierlo M, Visser-Meily JM, Evers SM. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke. BMJ Open 2015;5:11.
9. Graf J, Muhlhoff C, Doig GS, Reinartz S, Bode K, Dujardin R, et al. Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest. Crit Care 2008;12:4.
10. Yang CC, Shih NC, Chang WC, Huang SK, Chien CW. Long-term medical utilization following ventilator-associated pneumonia in acute stroke and traumatic brain injury patients: a case-control study. BMC Health Serv Res 2011;11.
11. Dick A, Liu H, Zwanziger J, Perencevich E, Furuya EY, Larson E, et al. Long-term survival and healthcare utilization outcomes attributable to sepsis and pneumonia. BMC Health Serv Res 2012;12.
12. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med 2010;153:3.
13. Dutch National Intensive Care Evaluation (NICE) registry. http://www.stichtingnice. nl. [accessed 08.11.2016].
14. Vektis. http://www.vektis.nl. [accessed 08.11.2016].
15. Knol F. Van hoog naar laag; van laag naar hoog. Den Haag: Sociaal en Cultureel Planbureau/ Elsevier Bedrijfsinformatie; 1998.
16. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data resource profile: the Dutch National Intensive Care Evaluation (NICE) registry of admissions to adult intensive care units. Int J Epidemiol 2015;44:6.
17. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34:5.
18. Roos LL,Wajda A. Record linkage strategies. Part I: estimating information and evaluating approaches. Methods Inf Med 1991;30:2.

19. Tanuseputro P, Wodchis WP, Fowler R, Walker P, Bai YQ, Bronskill SE, et al. The health care cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. PLoS One 2015;10:3.
20. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH, et al. Five year mortality and hospital costs associated with surviving intensive care. Am J Respir Crit Care Med 2016;194:2.
21. Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. J Fam Pract 2000;49:2.
22. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. BMC Public Health 2006;6.
23. Hamel MB, Phillips RS, Teno JM, Lynn J, Galanos AN, Davis RB, et al. Seriously ill hospitalized adults: do we spend less on older patients? Support investigators. Study to understand prognoses and preference for outcomes and risks of treatments. J Am Geriatr Soc 1996;44:9.
24. Conti M, Friolet R, Eckert P, Merlani P. Home return 6 months after an intensive care unit admission for elderly patients. Acta Anaesthesiol Scand 2011;55:4.
25. Rady MY, Johnson DJ. Hospital discharge to care facility: a patient-centered outcome for the evaluation of intensive care for octogenarians. Chest 2004;126:5.
26. Feng Y, Amoateng-Adjepong Y, Kaufman D, Gheorghe C, Manthous CA. Age, duration of mechanical ventilation, and outcomes of patients who are critically ill. Chest 2009;136:3.
27. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med 2009;41:13.
28. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med 2009;41:5.
29. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012;40:2.
30. Angus DC, Carlet J. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med 2003;29:3.
31. Griffiths JA, Barber VS, Cuthbertson BH, Young JD. A national survey of intensive care follow-up clinics. Anaesthesia 2006;61:10.
32. Centraal Bureau voor de Statistiek (CBS). Ruim 700 euro eigen betalingen aan zorg in 2015. https://www.cbs.nl/nl-nl/nieuws/2017/07/ruim-700-euro-eigen-betalingenaan-zorg-in-2015. [accessed 10.10.2017].

Chapter 5

Healthcare-related costs in very elderly intensive care patients

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ABSTRACT

Introduction: The long-term outcome of 'very old intensive care unit patients' (VOPs; ≥ 80 years) is often disappointing. Little is known about the healthcare costs of these VOPs in comparison to younger ICU patients and the very elderly in the general population not admitted to the ICU.

Methods: Data from a national health insurance claims database and a national quality registry for ICUs were combined. Costs of VOPs admitted to the ICU in 2013 were compared with costs of younger ICU patients (two groups, respectively 18-65 and 65-80 years old) and a matched control group of very elderly subjects who were not admitted to the ICU. We compared median costs and median costs per day alive in the year before ICU admission (2012), the year of ICU admission (2013) and the year after ICU admission (2014).

Results: A total of 9,272 VOPs were included and compared to three equally sized study groups. Median costs for VOPs in 2012, 2013 and 2014 (€5,944, €35,653 and €12,565) are higher compared to the ICU 18-65 population (€3,022, €30,223 and €5,052, all $p<0.001$) and the very elderly control population (€3,590, €4,238 and €4,723, all $p<0.001$). Compared to the ICU 65-80 population, costs of VOPs are higher in the year before and after ICU admission (€4,323 and €6,750, both $p<0.001$), but not in the year of ICU admission (€34,448, $p=0.950$). The median healthcare costs per day alive in the year before, the year of and the year after ICU admission are all higher for VOPs than for the other groups ($p<0.001$).

Conclusions: VOPs required more healthcare resources in the year before, the year of and the year after ICU admission compared to younger ICU patients and the very elderly control population, except compared to the ICU 65-80 population in the year of ICU admission. Healthcare costs per day alive, however, are substantially higher for VOPs than for all other study groups in all three studied years.

INTRODUCTION

The intensive care unit (ICU) is one of the most expensive departments of a hospital, consuming almost 15% of hospital budget and 1-2% of the gross domestic product (GDP) in Western countries [1-4]. After discharge, ICU survivors continue to consume significant healthcare resources [5].

'Very old intensive care unit patients' (VOPs; ≥ 80 years old) are responsible for a substantial proportion of ICU admissions, and as a result of ageing of the general population, they are a rapidly expanding subgroup of ICU patients in most Western countries [6-9].

Since both short- and long-term outcome of VOPs are worse than in younger patients [7, 10-15], the cost-effectiveness of ICU treatment in VOPs has been questioned. Although several studies about the outcome of ICU treatment of VOPs have been published in the last decade, little is known about the healthcare costs of VOPs in the period surrounding the ICU admission and how these costs compare to those of younger ICU patients or of the very elderly not admitted to the ICU. Information about healthcare utilization among VOPs before, during and after ICU treatment in relation to outcome is relevant to ethical and political discussions and decision making in times of increasing healthcare costs.

The aim of this study is to describe the healthcare costs of VOPs in the year before, the year of and the year after their ICU admission and compare them to younger ICU patients, and to a population-based control group of very elderly subjects not treated in the ICU.

METHODS

Study design

This is a retrospective cohort study combining clinical data of the Dutch national quality registry for ICUs [16] with data from the Dutch insurance claims database [17].

Data sources

Dutch National Intensive Care Evaluation registry

The Dutch National Intensive Care Evaluation (NICE) registry [16] is a national quality registry in which currently all Dutch ICUs participate [18]. These ICUs collect demographic, physiologic and clinical data of all admitted patients, including variables required to quantify the severity of illness (acute physiology score (APS) and acute physiology and chronic health evaluation (APACHE) III score [19]). APACHE III score is a covariate in the APACHE IV mortality prediction model [19].

Vektis insurance claims database

Health insurance is obligatory for all Dutch citizens. The Vektis databases [17] contain reimbursement data of essentially all (99%) Dutch inhabitants on all medical treatments paid for by Dutch insurance companies, as well as demographic information for all registered inhabitants of the Netherlands, such as date of birth, gender and a proxy for date of death (health insurance unregister date) and socioeconomic status (SES). The SES is derived from the zip code of the person and the SES score for that zip code, as determined by the Netherlands Institute for Social Research [20]. The SES score is based on the mean income of a zip code area where a person lives, the fraction of people with a low income, the fraction of people with low education and the fraction of unemployed people. The SES score is ranked and the national mean is 0 (range -6.65 to 3.02). A lower score indicates a lower SES and a higher score indicates a higher SES. Vektis also collects claims for pharmaceutical care. This information was used to determine the chronic conditions (Appendix 5.1).

Patient selection

For this study, all patients from the NICE registry aged 18 years or older during the year of ICU admission, admitted to an ICU in 2013 and discharged from the hospital before 1 January 2014 were included. From the Vektis database, an ICU subset and a control group were extracted. The ICU subset included all patients who had a claim for one or more ICU days in the year 2013 and were 18 years or older during the year of ICU admission. On the basis of this Vektis ICU subset, a population-based control group was created from all registered inhabitants of the Netherlands in the Vektis database. The control population, who had no claims for ICU care during the year 2013, was weighted on the combination of the variables age (in years), gender and quartiles of SES. Only ICU patients with no missing items for gender, age and SES were used in the weighting process.

Linking and matching processes

To link cost data of the Vektis database to clinical data of the NICE database, records were linked anonymously using a deterministic linkage algorithm [21] and linked in three steps [22]. First, records were linked if gender, date of birth, hospital of admission, and both the date of ICU admission date and ICU discharge date were identical in both datasets. Records which could not be linked during the first step proceeded to the second step. In the second step records were linked if gender, date of birth, hospital of admission and ICU admission date were identical. Records which could not be linked during the second step proceeded to the third step. In the third step records were linked if, besides gender, date of birth and hospital of admission, the ICU discharge date was identical in both databases. Records which were not linked after the third step were excluded.

After linking the NICE database and the Vektis database, we created our four study populations: the VOPs, the ICU 18-65, the ICU 65-80 patients, and a very elderly population control group. All ICU patients aged 80 years or older were included in the VOP population. This VOP population was matched 1:1 with very elderly control persons in the combined database on the basis of equal age, gender and quartile of SES. The VOP population was also matched 1:1 with ICU patients aged 18-65 years and ICU patients aged 65-80 years in the combined database. Matching for these two populations was done on the basis of equal gender and quartile of SES.

Primary outcome

Total healthcare costs were only available as a total sum in euros per person per calendar year. The total healthcare costs are based on all reimbursement data available from health insurance companies and also include costs for long-term facilities and nursing homes. The primary outcome of this study is the median healthcare costs. We analysed costs of 3 years: (1) the year before ICU admission, defined as 1 January 2012 until 31 December 2012; (2) the year of ICU admission, defined as 1 January 2013 until 31 December 2013; and (3) the year after ICU admission, defined as 1 January 2014 until 31 December 2014. For the readability, we will use the term median healthcare costs in the year before, during and after ICU admission. We will also report the mean healthcare costs, as from a societal perspective, the mean costs enable one to calculate a total burden for society.

Secondary outcome

The secondary outcome of this study is the median healthcare costs per day alive during the year before, the year of and the year after ICU admission. Costs per day alive are the total healthcare costs per patients per year divided by the number of days alive. The healthcare costs per day alive are calculated for the total population, and for subgroups based on mortality, comorbidities, APACHE IV predicted mortality, i.e. low risk (predicted mortality ≥ 0-30%), medium risk (predicted mortality ≥30 - 70%) and high risk (predicted mortality ≥ 70%) [19], gender, SES and admission category. Subgroup analyses were performed for survivors and non-survivors and we analysed the patients who survived the 3-year study period separately to identify drivers for increased costs.

Statistical analysis

Descriptive statistics were used to characterize the demographic data. Mean and standard deviation (SD) were used for normally distributed data, median and interquartile ranges (IQR) for non-normally distributed data; numbers and proportions were used to present categorical data.

Table 5.1 Characteristics of the 4 populations during the year of ICU admission

Socio-demographic characteristics	VOPs (n=9,068)	ICU 18-65 (n=9,068)	ICU 65-80 (n=9,068)	Control 80+ (n=9,068)
Male[a]	4,709 (52%)	4,709 (52%)	4,709 (52%)	4,709 (52%)
Age[b]	83 (81; 86)	54 (44; 60)	72 (68; 76)	83 (81; 86)
SES[b]	0.13 (-0.61; 0.75)	0.15 (-0.60; 0.76)	0.15 (-0.60; 0.75)	0.14 (-0.61; 0.76)
Died during 2013[a]	3,191 (35%)	1,029 (11%)	1,903 (21%)	748 (8%)
Died during 2014[a]	933 (10%)	443 (5%)	666 (7%)	701 (8%)
Characteristics of the first ICU admission				
Admission type[a]				
• Medical	4,338 (48%)	4,484 (49%)	3,658 (40%)	
• Planned surgery	3,219 (35%)	3,383 (37%)	4,348 (48%)	
• Emergency surgery	1,466 (16%)	1,157 (13%)	1,030 (11%)	
• Missing	45 (0.5%)	44 (0.5%)	32 (0.4%)	
Acute diagnoses[a]				
• CPR	493 (5%)	421 (5%)	461 (5%)	
• Burns	8 (0.1%)	16 (0.2%)	2 (0.02%)	
• Cardiac dysrhythmia	1,340 (15%)	543 (6%)	913 (10%)	
• GI bleeding	264 (3%)	154 (2%)	177 (2%)	
• CVA	396 (4%)	330 (4%)	334 (4%)	
• Intracranial mass effect	149 (2%)	427 (5%)	258 (3%)	
• Sepsis	1,055 (12%)	638 (7%)	827 (9%)	
• OHCA	321 (4%)	296 (3%)	275 (3%)	
• SAH	26 (0.3%)	185 (2%)	76 (0.8%)	
• Trauma	667 (7%)	537 (6%)	288 (3%)	
Mechanical ventilation during the first 24 hrs of ICU admission[a]	4142 (46%)	4256 (47%)	5046 (56%)*	
Length of ICU stay[bcd]	1.12 (0.79; 2.89)	0.99 (0.76; 2.55)	1.07 (0.81; 2.90)	
Length of hospital stay[bc]	10 (6; 16.57)	8 (4; 14)	9 (6; 16)	
APACHE III score[bef]	65 (52; 84)	41 (29; 61)	57 (44; 75)	
APS[bef]	45 (32; 63)	35 (24; 54)	41 (29; 58)	

COPD chronic obstructive pulmonary disease, *CPR* cardiopulmonary resuscitation, *GI* gastrointestinal, *CVA* cerebrovascular accident, *OHCA* out of hospital cardiac arrest, *SAH* subarachnoid haemorrhage

*Not significant

[a] Number and percentage (%)

[b] Median and IQR

[c] Length of ICU stay and length of hospital stay significantly different ($p<0.001$)

[d] Average costs of 1 day in the ICU in the Netherlands are about €2,500

[e] APACHE III and APS scores significantly different between groups ($p<0.001$)

[f] Only calculated for ICU admissions which met the APACHE IV inclusion criteria (VOPs n=8,481,ICU 18-65 n=8,510 and ICU 65-80 n=8,580)

The non-parametric Kruskal Wallis test was used to test the differences in median healthcare costs and in median healthcare costs per day alive between the study groups.

General linear modelling was used to estimate the cohort effect on the healthcare costs during the year before, the year of and the year after ICU admission. The healthcare costs per patient were skewed to the right and therefore the natural logarithm of the healthcare costs was used. Because of multiple comparisons a more stringent *p*-value of less than 0.001 was considered to indicate a statistically significant difference.

All statistical analyses were performed in SAS software (version 7.1; SAS Institute Inc, Cary, NC).

RESULTS

The NICE database contains 75,690 ICU admissions in 2013, of which 10,425 admissions were of VOPs (13.8%). When linked with the Vektis database, 71,018 ICU (94%) admissions of 65,731 individual ICU patients remained, including 9,749 admissions of 9,272 individual VOPs. After 1:1 matching, all four study groups consisted of 9068 unique individuals, as we excluded 204 (2%) patients that could not be matched. Figure 5.1 gives an overview of the data linkage and matching process, and the patient characteristics are shown in Table 5.1. The median APACHE III and APS (APACHE III score based on physiological disturbance, without reason for admission, age and comorbidities) scores of VOPs were higher than the scores of the younger ICU populations (all $p<0.001$).

Hospital mortality rates of the VOPs, the ICU 18-65 and the ICU 65-80 population were 24.2%, 8.5% and 14.9% respectively ($p<0.001$). Of the VOPs 35% died in 2013 and another 10% died in 2014 versus 11% and 5% of the ICU 18-65 population, 21% and 7% of the ICU 65-80 population, and 8% in 2013 as well as in 2014 for the very elderly control population ($p<0.001$).

Median and mean healthcare costs are shown in Figure 5.2. Median costs per patient for VOPs in the year before, during and after ICU admission (€5,944, €35,653 and €12,565) are higher than for the ICU 18-65 population (€3,022, €30,223 and €5,052, all $p<0.001$) and the very elderly control population costs (€3,590, €4,238 and €4,723, all $p<0.001$). Compared to the ICU 65-80 population, costs of VOPs are higher in the year before (€5,944 vs. €4,323 $p<0.001$) and the year after ICU admission (€12,565 vs. €6,750, $p<0.001$), but comparable in the year of ICU admission (€35,653 vs. €34,448, $p=0.95$).

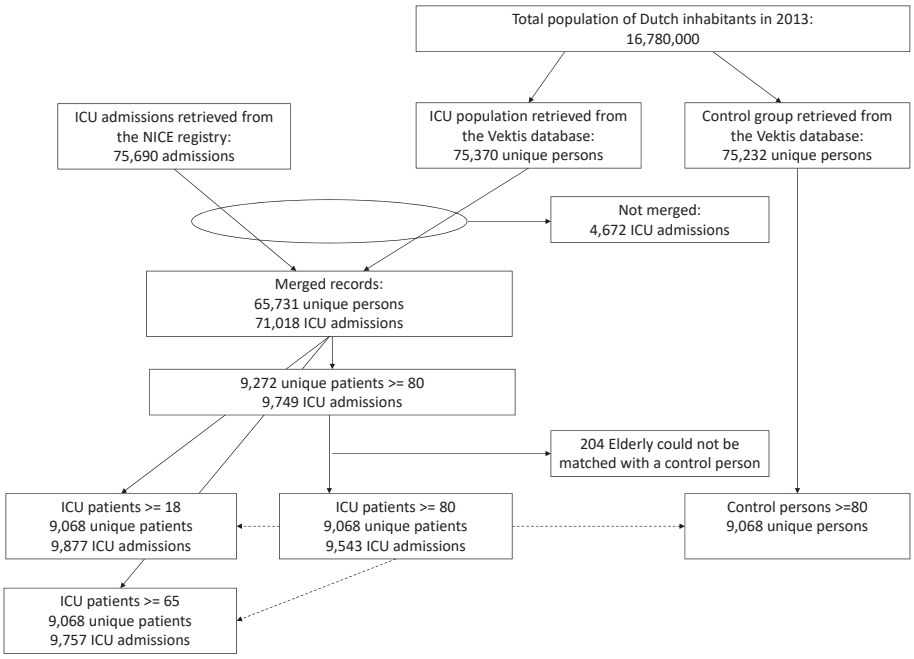


Figure 5.1 Overview of the data linkage process

The median healthcare costs per day alive during the year before, the year of and the year after ICU admission are higher for VOPs than for all the other study groups (p<0.001) (Figure 5.3).

Subgroup analyses are presented in detail in the Appendices (Appendix 5.2 to 5.11). VOPs have more chronic conditions in the year prior to admission and healthcare costs increase with increasing number of chronic conditions. During the year of ICU admission, healthcare costs are significantly higher for patients in the higher-risk group based on APACHE IV mortality prediction, for female patients, patients with a lower SES and patients admitted because of emergency surgery.

DISCUSSION

In this study, we evaluated healthcare costs of VOPs in comparison with two groups of younger ICU patients and a very elderly population control group in the year before, during and after ICU admission. VOPs required more healthcare resources during all three study years compared to the other study groups, with one exception: during the year of ICU admission costs of VOPs are similar to the costs of ICU 65-80 patients. However, healthcare costs per day alive are substantially higher for VOPs than for the other study groups in all studied

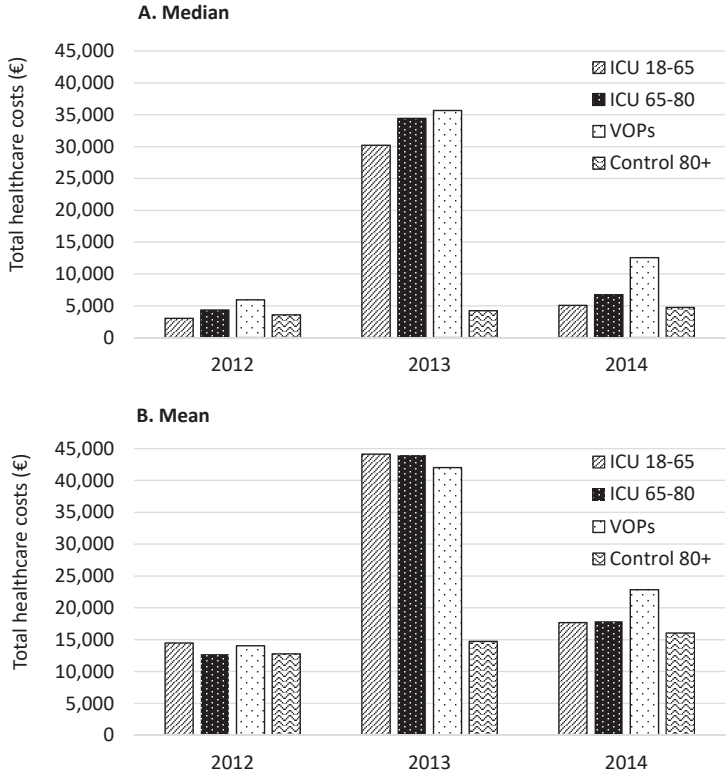


Figure 5.2 Median (A) and mean (B) total healthcare costs for the four study groups

years. Costs per day alive of VOPs are, compared to the ICU 18-65 patients, respectively 2, 1.5 and 3 times higher in the year before, the year of and the year after ICU admission, while remaining life expectancy is significantly lower.

Comparing our results to earlier studies is complicated for several reasons, including the different methods of cost calculation that are used and the various types of costs that are reported. Obviously, the absolute healthcare-related costs also depend on other factors, including country, region and healthcare system, and as a consequence, previous studies report a wide range of healthcare costs for older ICU patients. Our results are in contrast with a study in the USA, which showed that daily and total hospital costs were lower in older patients [23], but comparable with the results of a Canadian study on costs of ICU treatment in VOPs. The average costs in this study were $31,679 per ICU admission, $48,744 per ICU survivor and $61,783 per 1-year survivor [24]. These studies showed that the costs of ICU care of elderly patients are substantial, but only used direct ICU-associated costs and did not look beyond hospital discharge. Knowing that many of the healthcare-related or societal costs are made outside the hospital, we also included costs in the year before and

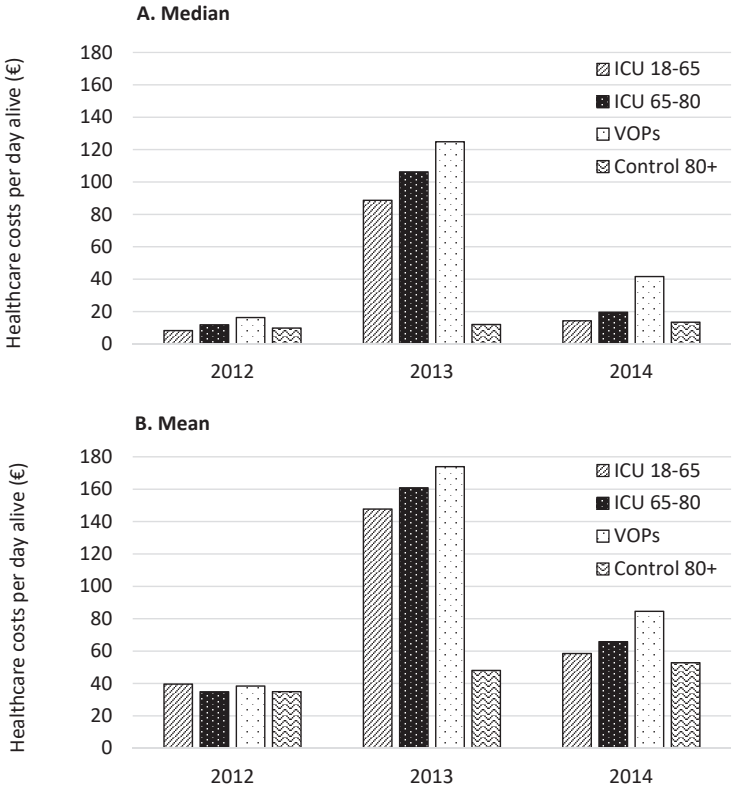


Figure 5.3 Median (A) and mean (B) healthcare costs per day alive for the four study groups

after ICU admission. In all age groups, costs were significantly higher in the year after ICU admission compared to the year before ICU admission, but this difference was most explicit in VOPs. It is known that ICU survivors, from all ages, suffer long-term physical, cognitive and/or psychiatric disabilities, defined as the post-intensive care syndrome (PICS) [25], with increased healthcare costs. However, after discharge the VOPs are more likely to be readmitted and are more dependent of long-term care facilities, nursing homes or rehabilitation centres compared to younger people [26-28].

In times of scarce healthcare resources, it is frequently questioned what society should accept to pay for a gained life year [value of the statistical life year (VOSL)]. These numbers will differ between persons and countries. In addition, in interpreting our results it is important to realize that for many very elderly subjects, preserving quality of life (QoL) is more important than prolonging their life and many of them prefer a lesser intensity of care, without undergoing invasive procedures [29, 30]. This reinforces the importance of early goals of care discussions. Unfortunately, we were not able to analyse functional outcome and QoL as this was not

included in our datasets. If QoL data had been available, we could have calculated costs per quality adjusted life year (QALY). It is important to keep in mind, however, that QALYs are often based on surveys that incorporate physical functioning which is often lower in the elderly. Also life expectancy in very elderly persons is generally low [31, 32]. Simply calculating QALYs may not do justice to these nuances and carries the risk of unjustly suggesting that only limited resources should be allocated to these patients. In the Netherlands, a maximum of 80,000 euro per QALY was once suggested in cost utility analyses, but never enforced because of several shortcomings and ethical objections [31, 33]. Provided that QoL is good, the costs of VOPs that we found in our study would have been within these limits, although it might be unrealistic to assume that all VOPs have a good QoL after ICU discharge. HRQoL studies suggest that some older ICU survivors may accommodate to a degree of physical disability and still report good emotional and social wellbeing [34, 35], but it is also important to realize that these HRQoL studies are subject to survivorship and proxy response bias [36].

To our knowledge no studies exist in which healthcare-related costs of older versus younger ICU patients in the years around ICU admission are compared. Another strength of our study is that we used total healthcare costs, inpatient as well as outpatient costs of care and preceding and following ICU admission, rather than ICU costs only. This is important since many of these patients have extended hospitalizations and a prolonged recovery period. We used both total healthcare costs as costs per day alive. The linkage between the national health insurance claims database and the national clinical ICU registry, covering almost the entire country, provides valuable insight into the healthcare utilization of VOPs in comparison with younger ICU patients and a general population control group.

The study has limitations as well. One is that the total costs per patient, based on all reimbursement data available from health insurance companies, were only available as a total sum in euros per person per calendar year. We translated these costs into median and mean healthcare costs per patient per year and per patient per day alive. A limitation of the first, costs per patient per year, is mainly that it depends on the number of days alive, since follow-up periods in these groups might differ. However, a limitation of the second, costs per patient per day alive, is that if mortality is high, costs per day will likely be higher, since costs (including the high ICU costs) are spread out over fewer days alive. We believe that by reporting both outcome measures we provide good insight. A second limitation is that our study illustrates that substantial healthcare costs are accrued by ICU patients of all ages, both in the year of their ICU admission and the year thereafter, but does not provide an answer to the important question whether these costs are justified. A third limitation is that we did not adjust costs for severity of illness. The VOPs were more severely ill as both the median APACHE III and APS scores in the VOPs were significantly higher at ICU admission. The APACHE III score is dependent on age and more points are appointed for the older patients. However, the acute

physiology score (points based only physiological parameters) was also higher in VOPs. This suggests more severe derangement at admission. This could, at least partially, be explained by a lower fraction of VOPs being admitted after elective surgery. Both severity of illness and type of admission will contribute to higher costs and mortality in VOPs. Another limitation is that we have no insights into the exact composition of the healthcare costs and that we only included the total amount of healthcare cost reimbursed by health insurance companies. The total healthcare costs do not include services paid for out of pocket or reimbursements via voluntary additional insurance, but we think this has not (or barely) affected our results, since our cost data included the most important parts of healthcare costs. Since the point of view of our analysis was the healthcare perspective and not the societal perspective, we did not include factors like loss of a job and other societal losses.

These limitations notwithstanding, we believe our results provide valuable insight into the healthcare utilization of VOPs in comparison to younger ICU patients and a very elderly control population.

In conclusion, we showed that VOPs required more healthcare resources in the year before, during and after ICU admission compared to the ICU 18-65 population and a very elderly control group. Compared to the ICU 65-80 population, VOPs required more healthcare resources in the year before and after ICU admission, but not in the year of ICU admission. However, costs corrected per day alive are substantially higher for VOPs in all three study years and compared to both other ICU populations and the very elderly control population. Our study illustrates that substantial healthcare costs are accrued by ICU patients of all ages, both in the year of their ICU admission and the year thereafter. Our study does not provide an answer to the difficult question whether these costs can always be justified. Because ICU resources are often limited, as are the number of life years that can be gained in good health in VOPs, there is a need for studies that evaluate cost per QALY in VOPs admitted to the ICU.

APPENDICES

Appendix 5.1 Overview of the number of chronic conditions* of the studied populations during the year before ICU admission.

	ICU 18-65 (n=9,068)	ICU 65-80 (n=9,068)	VOPs (n=9,068)	CO 80+ (n=9,068)
No chronic condition	4,949 (55%)	3,145 (35%)	2,775 (31%)	3,770 (42%)
One or more chronic conditions	4,119 (45%)	5,923 (65%)	6,393 (71%)	5,298 (58%)
Two or more chronic conditions	1,336 (15%)	2,279 (25%)	2,497 (28%)	1,691 (19%)

* Vektis also collects claims for pharmaceutical care, stored in the Pharmacy Information System. This information system contains information on provided drugs, including the Anatomical Therapeutic Chemical (ATC) code, the quantity that was supplied and the date the drug was supplied [37].
To determine chronic conditions, pharmaceutical cost groups (PCGs) were used as a proxy. PCGs are based on the idea that a patient with a certain chronic condition can be identified by claims known to be prescribed for that chronic condition [38,39]. An insured person is included into a specific PCG if more than a certain amount (accounting for approximately half a year of use e.g. over 180 defined daily doses) of prescribed drugs has been prescribed during a calendar year. The PCG are classified annually and different ATC codes of one PCG can be combined in order to reach the minimum defined daily doses. A person can be included in multiple PCGs. The definition of pharmaceutical cost groups is maintained by the 'Zorginstituut Nederland' (National Institute for Health Care) and classification is routinely performed by Vektis [40].

Appendix 5.2 Subgroups analyses

Median costs per patient and per patient per day alive for the different mortality groups are shown in Appendix 5.3 to Appendix 5.6, respectively. Additional subgroup analyses have been performed for patients who survived the whole 3-years study period. Among this group of survivors we first divided the elderly ICU group, the younger ICU group and the matched control group into groups based upon their number of chronic conditions (0, 1, 2 or more) (Appendix 5.7). Second we looked at severity of illness based upon the APACHE IV predicted mortality (Appendix 5.8). Furthermore, we analysed the differences in costs between subgroups, based on gender (Appendix 5.9) and quartiles of SES (Appendix 5.10). Finally, we grouped the three ICU populations by type of ICU admission (Appendix 5.11), based on the definitions of the NICE registry [16].

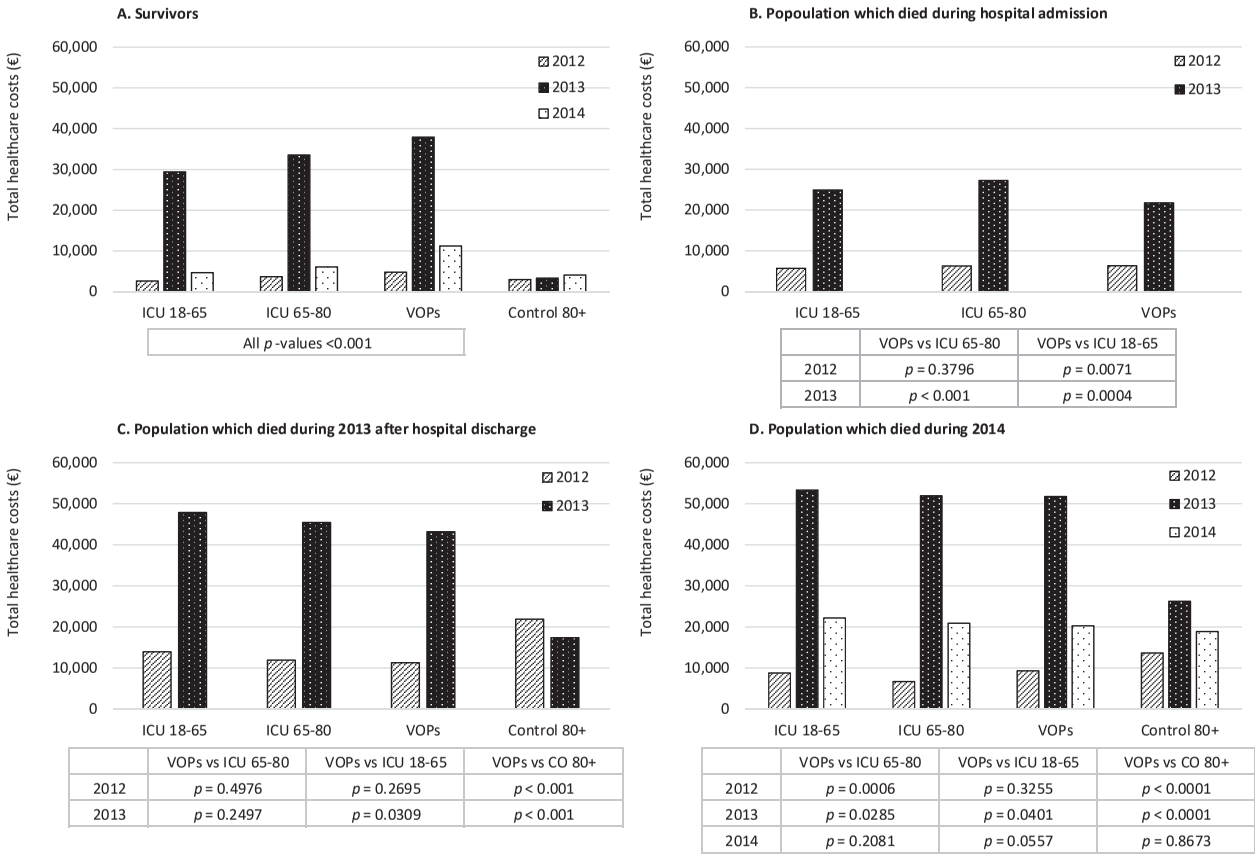
VOPs have more chronic conditions in the year prior to admission compared to the ICU 18-65 population, the ICU 65-80 population and the control population (p<0.0001) (Appendix 5.1). Healthcare costs increase with increasing number of chronic conditions and this is seen for all four study groups and in all three study years (p<0.0001) (Appendix 5.7). Stratifying the healthcare costs by chronic conditions showed great deviations and demonstrated that more chronic conditions means higher costs. These increased costs with more chronic conditions were seen in all three study years; before, during and after ICU admission and for all four studies populations, indicating that chronic conditions largely contribute to the healthcare costs.

During the year before ICU admission, survivors of the high mortality risk group have lower healthcare costs compared to survivors of the low mortality risk group (p<0.0001). During the year of ICU admission, healthcare costs are significantly higher for higher Apache IV risks groups (p<0.0001). During the year after ICU admission survivors of the median mortality risk group have the highest healthcare cost (p<0.0001) (Appendix 5.8).

Female patients are more expensive than male patients in all three years of the study period (p<0.0001) within the ICU 65-80 population and the VOPs. In the ICU 18-65 population, female patients are significantly more expensive in the year before (p<0.0001) and the year after ICU admission (p<0.0001), but during the year of ICU admission the difference between men and women of this study population is not significant (p<0.42) (Appendix 5.9).

Patients with a higher SES had significantly less healthcare costs compared to people with a lower SES, in all four study populations, during the year before and the year after admission (p<0.0001) (Appendix 5.10).

Survivors with a medical admission were most expensive in the year before and after ICU admission, compared to survivors of the elective and emergency surgery groups in these years (all p-values <0.0001). During the year of ICU admission, patients admitted because of emergency surgery were the most expensive, for all three ICU populations (p<0.0001, Appendix 5.11). For emergency patients, healthcare costs during the year of ICU admission were higher for the VOP population than for the ICU 18-65 population (p-value for interaction p=0.0004), but the differences between VOPs and the ICU 65-80 population was not significant (p-value for interaction p=0.9942).

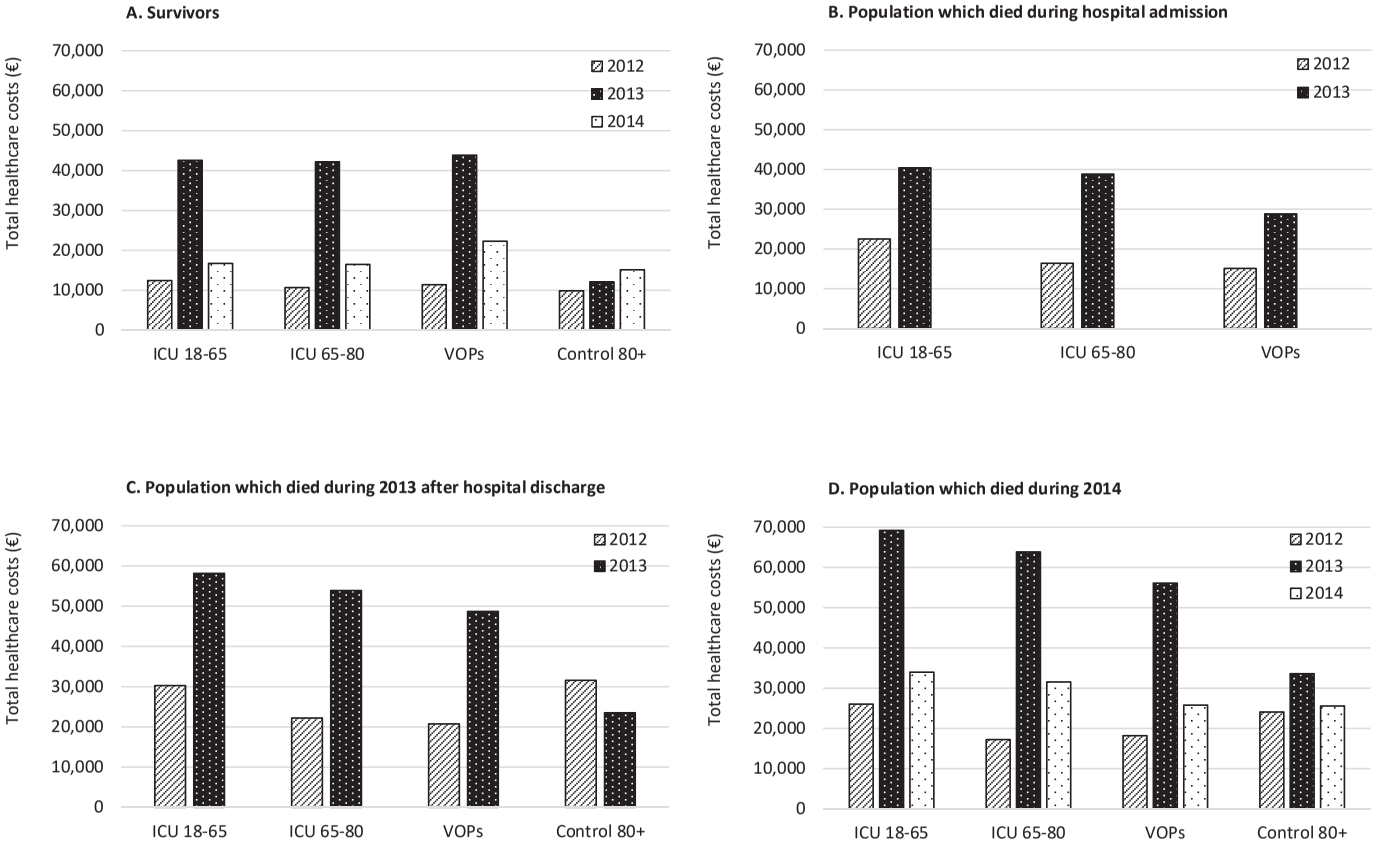


	VOPs vs ICU 65-80	VOPs vs ICU 18-65
2012	$p = 0.3796$	$p = 0.0071$
2013	$p < 0.001$	$p = 0.0004$

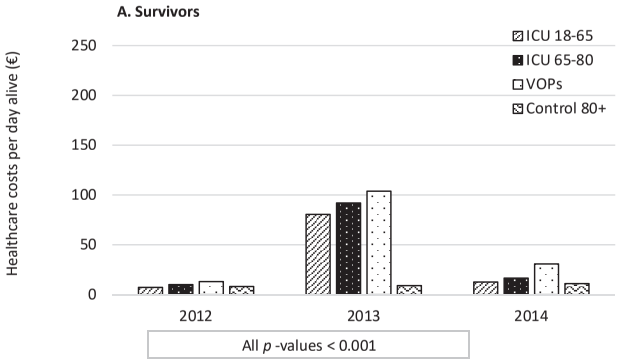
	VOPs vs ICU 65-80	VOPs vs ICU 18-65	VOPs vs CO 80+
2012	$p = 0.4976$	$p = 0.2695$	$p < 0.001$
2013	$p = 0.2497$	$p = 0.0309$	$p < 0.001$

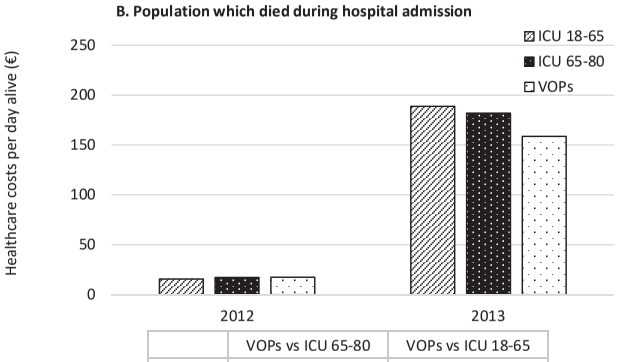
	VOPs vs ICU 65-80	VOPs vs ICU 18-65	VOPs vs CO 80+
2012	$p = 0.0006$	$p = 0.3255$	$p < 0.0001$
2013	$p = 0.0285$	$p = 0.0401$	$p < 0.0001$
2014	$p = 0.2081$	$p = 0.0557$	$p = 0.8673$

Appendix 5.3 Median total healthcare costs for the four study groups, divided in subgroups by mortality: A. Survivors, B. Population which died during hospital admission, C. Population which died during 2013 after hospital discharge and D. Population which died during 2014

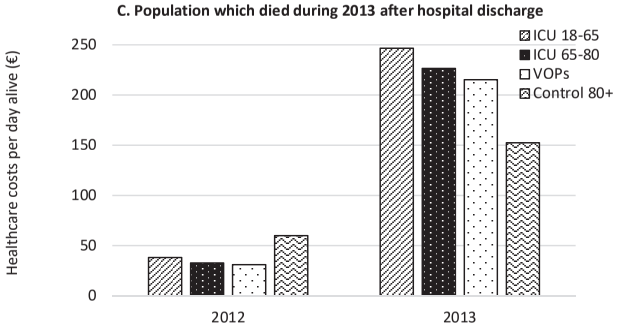


Appendix 5.4 Mean total healthcare costs for the four study groups, divided in subgroups by mortality: A. Survivors, B. Population which died during hospital admission, C. Population which died during 2013 after hospital discharge and D. Population which died during 2014

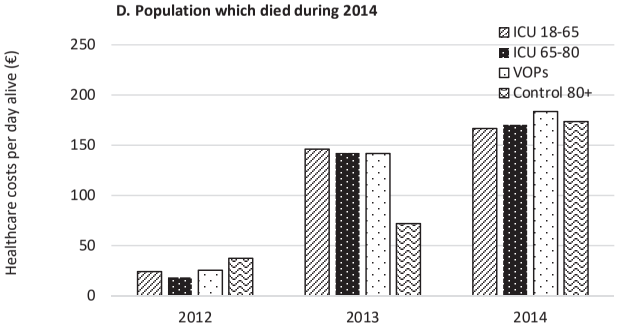




	VOPs vs ICU 65-80	VOPs vs ICU 18-65
2012	$p = 0.3796$	$p = 0.0071$
2013	$p < 0.0001$	$p = 0.0004$

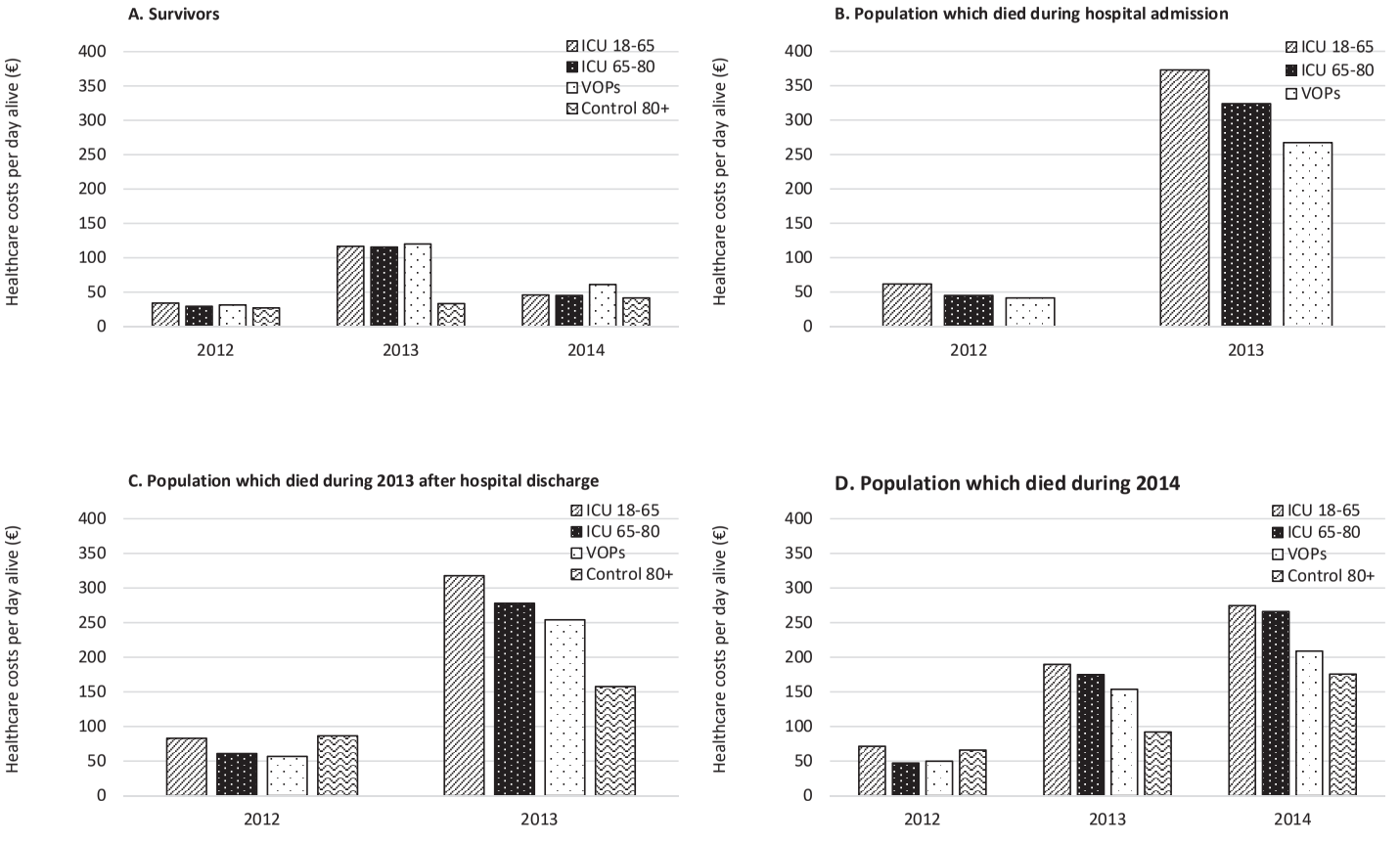


	VOPs vs ICU 65-80	VOPs vs ICU 18-65	VOPs vs CO 80+
2012	$p = 0.4976$	$p = 0.2695$	$p < 0.0001$
2013	$p = 0.2497$	$p = 0.0309$	$p < 0.0001$

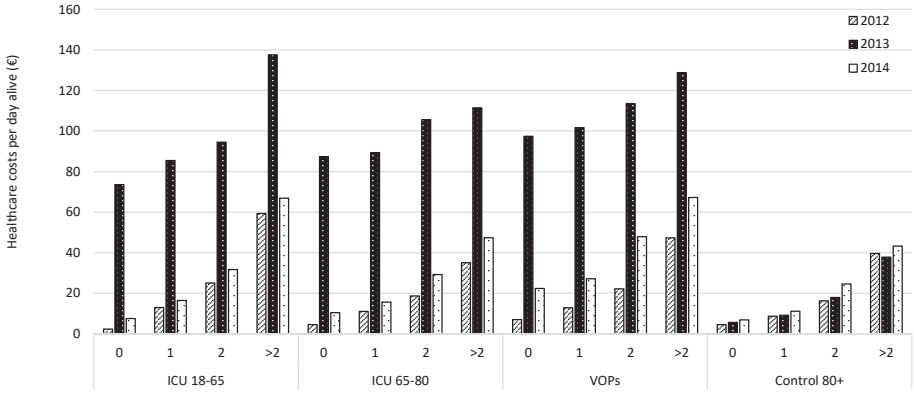


	VOPs vs ICU 65-80	VOPs vs ICU 18-65	VOPs vs CO 80+
2012	$p = 0.0006$	$p = 0.3255$	$p < 0.0001$
2013	$p = 0.0285$	$p = 0.0401$	$p < 0.0001$
2014	$p = 0.5036$	$p = 0.3692$	$p = 0.0149$

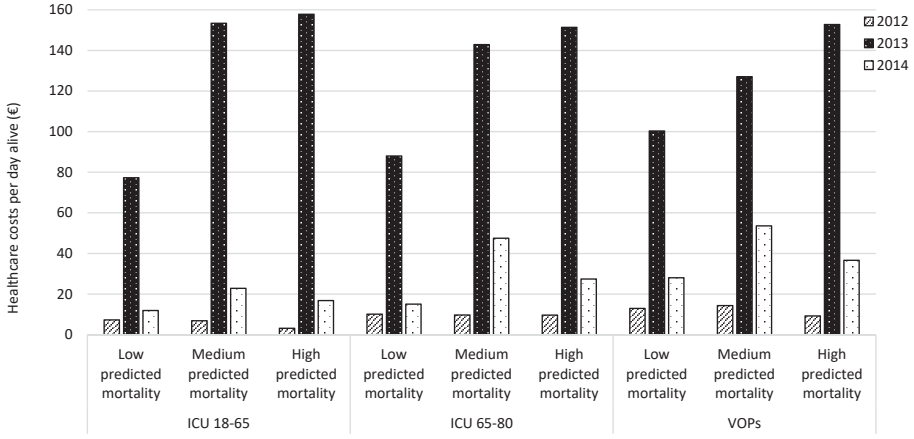
Appendix 5.5 Median total healthcare costs per day alive for the four study groups, divided in subgroups by mortality: A. Survivors, B. Population which died during hospital admission, C. Population which died during 2013 after hospital discharge and D. Population which died during 2014



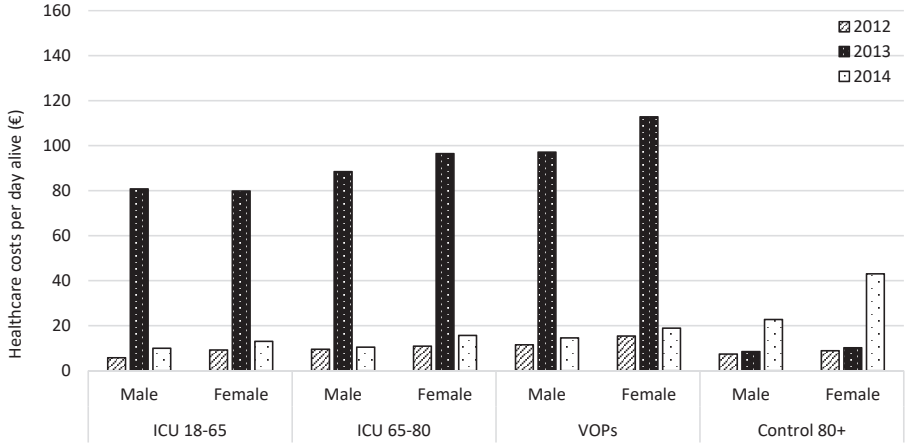
Appendix 5.6 Mean total healthcare costs per day alive for the four study groups divided, in subgroups by mortality: A. Survivors, B. Population which died during hospital admission, C. Population which died during 2013 after hospital discharge and D. Population which died during 2014



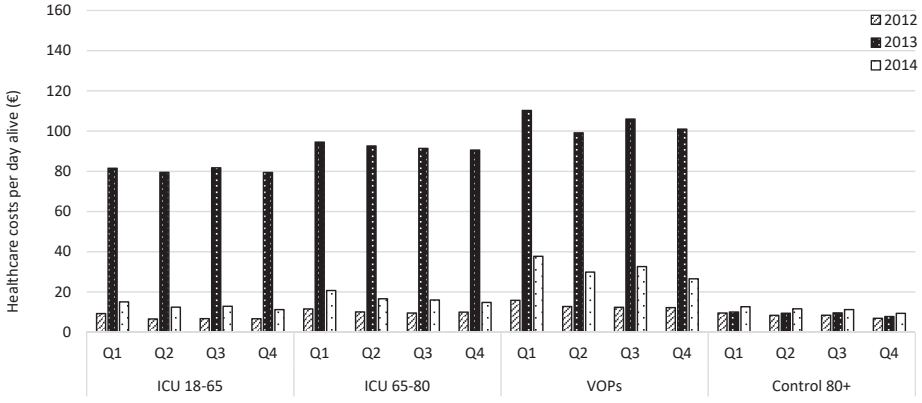
Appendix 5.7 Median healthcare costs per day alive of survivors, stratified by number of chronic conditions



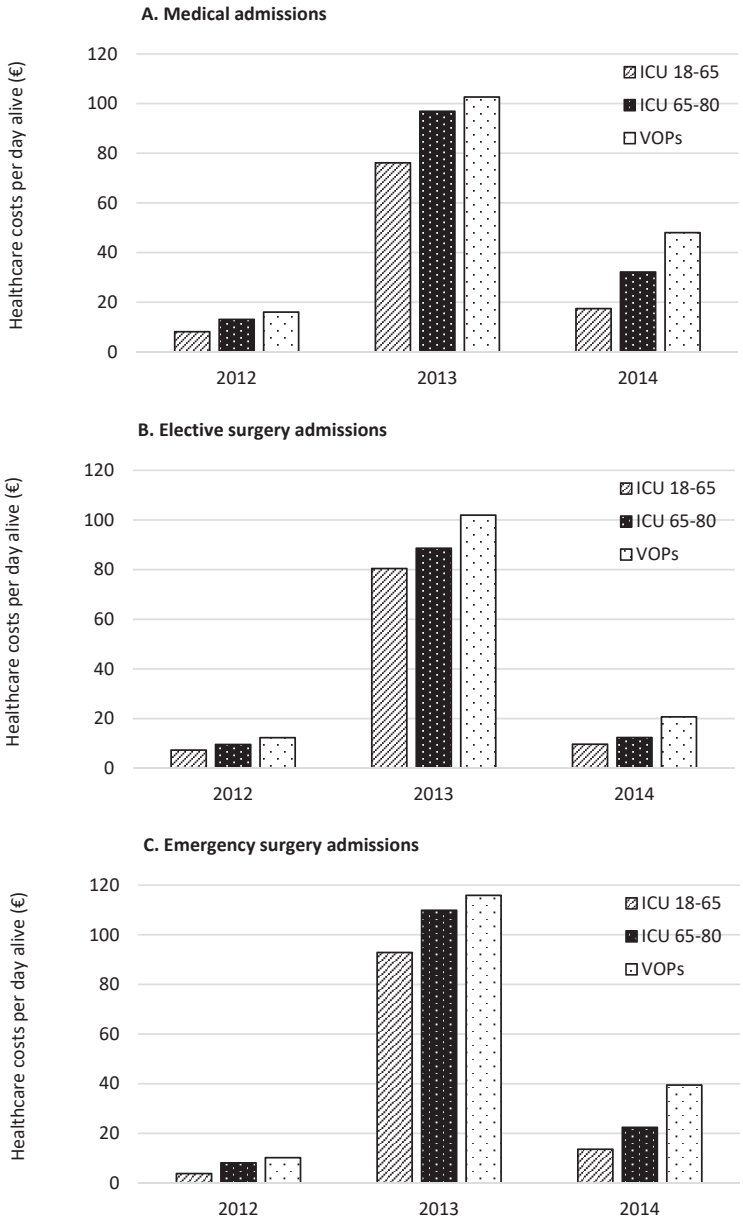
Appendix 5.8 Median healthcare costs per day alive of survivors, stratified by APACHE IV mortality risk-group



Appendix 5.9 Median healthcare costs per day alive of survivors, stratified by gender



Appendix 5.10 Median healthcare costs per day alive of survivors, stratified by socioeconomic status quartile



Appendix 5.11 Median healthcare costs per day alive of survivors, divided in subgroups by type of ICU admission: A. Medical admissions, B. Elective surgery admissions and C. Emergency surgery admissions

REFERENCES

1. Centraal Bureau voor de Statistiek (CBS). Statline. http://statl ine.cbs.nl/ Statw eb/dome/defau lt.aspx. Accessed 2 Jan 2018
2. Halpern NA, Goldman DA, Tan KS, Pastores SM (2016) Trends in critical care beds and use among population groups and Medicare and Medicaid beneficiaries in the United States: 2000-2010. Crit Care Med 44:1490-1499. https://doi.org/10.1097/CCM.00000 00000 001722
3. Rhodes A, Ferdinande P, Flaatten H et al (2012) The variability of critical care bed numbers in Europe. Intensive Care Med 38:1647–1653. https://doi.org/10.1007/s0013 4-012-2627-8
4. https ://www.zorgcijfersdata bank.nl. Accessed 2 Jan 2018
5. Lone NI, Seretny M, Wild SH et al (2013) Surviving intensive care: a systematic review of healthcare resource use after hospital discharge. Crit Care Med 41:1832–1843. https://doi.org/10.1097/CCM.0b013 e3182 8a409c
6. Bagshaw SM, Webb SA, Delaney A et al (2009) Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care 13:R45. https://doi.org/10.1186/cc776 8
7. Nielsson MS, Christiansen CF, Johansen MB et al (2014) Mortality in elderly ICU patients: a cohort study. Acta Anaesthesiol Scand 58:19–26. https://doi.org/10.1111/aas.12211
8. Haas LEM, Karakus A, Holman R et al (2015) Trends in hospital and intensive care admissions in the Netherlands attributable to the very elderly in an ageing population. Crit Care 19:353. https://doi.org/10.1186/s13054-015-1061-z
9. Flaatten H, de Lange DW, Artigas A et al (2017) The status of intensive care medicine research and a future agenda for very old patients in the ICU. Intensive Care Med. https://doi.org/10.1007/s00134-017-4718-z
10. Vosylius S, Sipylaite J, Ivaskevicius J (2005) Determinants of outcome in elderly patients admitted to the intensive care unit. Age Ageing 34:157–162 (34/2/157)
11. Garrouste-Orgeas M, Timsit JF, Montuclard L et al (2006) Decision-making process, outcome, and 1-year quality of life of octogenarians referred for intensive care unit admission. Intensive Care Med 32:1045–1051. https://doi.org/10.1007/s0013 4-006-0169-7
12. Fuchs L, Chronaki CE, Park S et al (2012) ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med 38:1654–1661. https://doi.org/10.1007/s00134-012-2629-6
13. Docherty AB, Anderson NH, Walsh TS, Lone NI (2016) Equity of access to critical care among elderly patients in Scotland: a national cohort study. Crit Care Med 44:3–13. https://doi.org/10.1097/CCM.00000 00000 00137 7
14. Flaatten H, De Lange DW, Morandi A et al (2017) The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). Intensive Care Med 43:1820–1828. https://doi.org/10.1007/s0013 4-017-4940-8
15. Karakus A, Haas LEM, Brinkman S et al (2017) Trends in short-term and 1-year mortality in very elderly intensive care patients in the Netherlands: a retrospective study from 2008 to 2014. Intensive Care Med 43:1476–1484. https ://doi.org/10.1007/s0013 4-017-4879-9
16. Dutch National Intensive Care Evaluation (NICE) registry. http://www.stichting-nice.nl. Accessed 2 Jan 2018
17. Vektis. http://www.vekti s.nl. Accessed 2 Jan 2018

18. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF (2015) Data resource profile: the Dutch National Intensive Care Evaluation (NICE) registry of admissions to adult intensive care units. Int J Epidemiol 44:1850-h. https ://doi.org/10.1093/ije/dyv29 1
19. Zimmerman JE, Kramer AA, McNair DS, Malila FM (2006) Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 34:1297–1310. https://doi.org/10.1097/01.CCM.00002 15112 .84523 .F0
20. Knol FA. Sociaal en cultureel planbureau. Van hoog naar laag: van laag naar hoog. De sociaal-ruimtelijke ontwikkeling van wijken tussen 1971-1995. [from high to low: from low to high. The socio-spatial developments of neighbourhoods between 1971 and 1995]. 13 juli 2009. Cahier,152. Elsevier, Den Haag. ISBN 9057491176
21. Roos LL, Wajda A (1991) Record linkage strategies. Part I: estimating information and evaluating approaches. Methods Inf Med 30(117–123):91020117
22. van Beusekom I, Bakhshi-Raiez F, de Keizer NF et al (2017) Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: a descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care 44:345–351
23. Chelluri L, Mendelsohn AB, Belle SH et al (2003) Hospital costs in patients receiving prolonged mechanical ventilation: does age have an impact? Crit Care Med 31:1746–1751. https://doi.org/10.1097/01.CCM.0000063478 .91096 .7D
24. Chin-Yee N, D'Egidio G, Thavorn K et al (2017) Cost analysis of the very elderly admitted to intensive care units. Crit Care 21:109–017–1689–y. https://doi.org/10.1186/s1305 4-017-1689-y
25. Needham DM, Davidson J, Cohen H et al (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 40:502–509. https://doi.org/10.1097/CCM.0b013 e3182 32da7 5
26. Rady MY, Johnson DJ (2004) Hospital discharge to care facility: a patient-centered outcome for the evaluation of intensive care for octogenarians. Chest 126:1583–1591
27. Feng Y, Amoateng-Adjepong Y, Kaufman D et al (2009) Age, duration of mechanical ventilation, and outcomes of patients who are critically ill. Chest 136:759–764
28. Conti M, Friolet R, Eckert P, Merlani P (2011) Home return 6 months after an intensive care unit admission for elderly patients. Acta Anaesthesiol Scand 55:387–393. https://doi.org/10.1111/j.1399-6576.2011.02397.x
29. Philippart F, Vesin A, Bruel C et al (2013) The ETHICA study (part I): elderly's thoughts about intensive care unit admission for life-sustaining treatments. Intensive Care Med 39:1565–1573. https://doi.org/10.1007/s00134-013-2976-y
30. Heyland DK, Barwich D, Pichora D et al (2013) Failure to engage hospitalized elderly patients and their families in advance care planning. JAMA Intern Med 173:778–787. https://doi.org/10.1001/jamainternmed.2013.180
31. Raad voor Volksgezondheid en Zorg [Council for Health and Care]. Zicht op zinnige en duurzame zorg [A view on sensible and sustainable care]. 2006, publicationnumber 06/07. ISBN-10: 90-5732-172-6
32. Heyland DK, Garland A, Bagshaw SM et al (2015) Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. Intensive Care Med 41:1911–1920. https://doi.org/10.1007/s0013 4-015-4028-2
33. Kaarlola A, Tallgren M, Pettila V (2006) Long-term survival, quality of life, and quality-adjusted life-years among critically ill elderly patients. Crit Care Med 34:2120–2126. https://doi.org/10.1097/01.CCM.00002 27656.31911 .2E

34. Andersen FH, Flaatten H, Klepstad P et al (2015) Long-term survival and quality of life after intensive care for patients 80 years of age or older. Ann Intensive Care 5:53. https://doi.org/10.1186/s1361 3-015-0053-0
35. Tabah A, Philippart F, Timsit JF et al (2010) Quality of life in patients aged 80 or over after ICU discharge. Crit Care 14:R2. https ://doi.org/10.1186/cc823 1
36. Baldwin MR (2015) Measuring and predicting long-term outcomes in older survivors of critical illness. Minerva Anestesiol 81:650–661
37. WHO Collaborating Centre for Drug Statistics Methodology. Available at: https://www.whocc.no/. Accessed 10.6.2018
38. Lamers LM: Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. Med Care 1999; 37:824-30
39. Lamers LM, van Vliet RC: The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy 2004; 68:113-21
40. National Health Care Institute. Available at: https://english.zorginstituutnederland.nl. Accessed 08.11.2016

Chapter 6

The healthcare costs of intoxicated patients who survive ICU admission are higher than non-intoxicated ICU patients: a retrospective study combining healthcare insurance data and data from a Dutch national quality registry

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ABSTRACT

Background: The aim of this study was to describe the healthcare costs of intoxicated ICU patients in the year before and the year after ICU admission, and to compare their healthcare costs with non-intoxicated ICU patients and a population based control group.

Methods: We conducted a retrospective cohort study, combining a national health insurance claims database and a national quality registry database for ICUs. Claims data in the timeframe 2012 until 2014 were combined with the clinical data of patients who had been admitted to an ICU during 2013. Three study populations were compared and matched according to socioeconomic status, type of admission, age and gender: an 'ICU population', an 'intoxication population' and a 'control population' (who had never been on the ICU).

Results: 2,591 individual 'intoxicated ICU patients' were compared to 2,577 general 'ICU patients' and 2,591 patients from the 'control population'. The median and interquartile ranges (IQR) healthcare costs per day alive for the 'intoxicated ICU patients' were higher during the year before ICU admission (€20.3 (IQR €3.6; €76.4)) and the year after ICU admission (€23.9 (IQR €5.1; €82.4)) compared to the ICU population (€6.1 (IQR €0.9; €29.3) and €13.6 (IQR €3.3; €54.9) respectively) and a general control population (€1.1 (IQR €0.3; €4.6) and €1.1 (IQR €0.4; €4.9) respectively). The healthcare associated costs in intoxicated ICU patients were correlated with the number of chronic conditions present prior ICU admission ($p<0.0001$).

Conclusions: Intoxicated patients admitted to the ICU had in the year before and after ICU admission much higher median healthcare costs per day alive compared to other ICU patients and a general population control group. Healthcare costs are greatly influenced by the number of psychiatric and other chronic conditions of these intoxicated patients.

BACKGROUND

It has been suggested that Intensive care Unit (ICU) survivors often suffer from long-term sequelae that may significantly increase healthcare costs to society [1]. Indeed, it has been shown that over a 2-year period, patients admitted to the ICU with sepsis have monthly healthcare expenditures three times higher than prior to their ICU admission [1, 2]. Depending on region and healthcare system it is estimated that between 2.7% and 40% of patients seen in the emergency room are subsequently admitted to the ICU and between 3.4% to 14% of ICU admissions are admitted for intoxications [3-5].

The majority of intoxication in developed countries are accidental [6]. For example, in the Netherlands half of the information requests to the Dutch Poison Information Center (DPIC) involve human medications, in 14% patients are exposed to house hold products, 12% to food additives or drugs of abuse [7]. In 33% of the intoxications small children are involved (age 0-4 years). These intoxications are almost all accidental. In 40% of the inquiries to the DPIC involve adults of ≥ 18 years old. In these adult patients only half of the intoxications is accidental, the other half is often with a suicidal intent. Some of the accidental intoxications do not need medical treatment and are not referred to a hospital. More severe intoxications (both accidental or intentional) in adults are treated in the emergency department and many of those patients are admitted to the hospital (or even to the Intensive Care Unit (ICU) [8, 9]. Many of the intoxicated ICU patients have a short length of stay on the ICU and the hospital and long-term mortality are relatively low [10]. This suggests that cost/effectiveness ratio, which is defined by the cost of treatment divided by the expected years alive, is supposedly very good for intoxicated patients. However, long-term sequelae are often ignored in these analyses.

Therefore, the aim of this study is to evaluate the healthcare-related costs of intoxicated patients in the year before their ICU admission in comparison to the costs in the year after their ICU admission and to compare these costs to that of non-intoxicated ICU patients and the general population.

MATERIALS AND METHODS

Study design

We performed a retrospective cohort study using the Dutch National Intensive Care Evaluation (NICE) registry [11]. The NICE registry is a national quality registry in which all Dutch ICUs participate and collect clinical, demographic, physiologic, and outcome data from all admitted patients. This includes all variables required to quantify the severity of illness and to calculate case-mix adjusted mortality risks according to the Acute Physiology and Chronic Health Evaluation (APACHE) IV model [12].

We combined data from the NICE registry and the insurance claims database (Vektis) [13]. Health insurance is obligatory for all Dutch citizens and 99% have private healthcare insurance. Vektis is an insurance claims database where all reimbursements of healthcare costs are registered [14]. Although insurance claims information of patients is aggregated in the Vektis database Dutch patients do not directly contact nor reimburse the Vektis database.

Subjects

All patients from the NICE registry aged ≥ 18 years during the year of ICU admission, admitted to an ICU during 2013, and discharged from the hospital before January 1st 2014 were included in the NICE registry subset.

Patients from the Vektis database were identified as ICU patients when they had a claim for an ICU day in the year 2013. All patients of 18 years or older during the year of ICU admission were included in the ICU-subset of the Vektis database.

Based on this ICU-subset a comparable population was extracted from the registered inhabitants of the Netherlands in the Vektis database. This population-based control group was weighted on the combination of the variables gender, age and socio-economic status (SES) and had no claims for ICU care during 2013. For every ICU patient in the Vektis ICU-subset, one control patient was selected. If one of the three variables used for weighting was missing, such a control patient was not selected.

Setting

The year before ICU admission is defined as January 1st 2012 until December 31st 2012, the year of ICU admission was defined as January 1st 2013 until December 31st 2013 and the year after ICU admission is defined as January 1st 2014 until December 31st 2014.

Linking process

Clinical data from the NICE database were anonymously linked to cost data from the Vektis database using a deterministic linkage algorithm [15]. The process of linking the NICE database and the Vektis database is published previously [2].

Matching

After linking the two databases (Vektis and NICE) patients who were admitted to the ICU with an intoxication were selected using the APACHE IV admission diagnosis of intoxication in the NICE registry (Appendix 6.1). These patients made up the 'intoxication population'. The latter was matched 1:1 with patients in the combined database who were admitted to the ICU for reasons other than intoxication (the so-called 'ICU population'). Matching was done based upon age, gender, admission type and SES. An ICU patient could only be

matched if there were no missing items used for matching. The intoxication population was matched 1:1 with people in the combined database not admitted to the ICU. Matching for this 'control population' was done based upon age, gender and SES.

Comorbidities and chronic diseases

Healthcare costs are related to chronic conditions requiring pharmacological and other medical treatments. We determined the underlying medical conditions present at admission to the ICU from the APACHE IV severity of illness model. Additionally we looked at proxies for underlying medical conditions and concomitant diseases from the Vektis database. For example, patients with reimbursed costs for diabetic medications were attributed a diabetes comorbidity (Appendix 6.2). Costs per day were analysed in relation to the number of underlying medical conditions, as described previously [2].

Statistical analysis

The primary outcomes of this study are the healthcare costs per day alive of intoxicated patients in comparison to the healthcare costs of the ICU population and the control population, during the year before ICU admission, the year of ICU admission and the year after ICU admission.

The healthcare costs are only available as a total sum per person per calendar-year. We converted the total costs per calendar-year into healthcare costs per day alive, presented in euros. ICU patients who did not survive their ICU admission were excluded from all analyses as these patients have by definition no (costs per) day alive after IC admission.

Descriptive statistics were used to characterize the demographic data of the study populations. Mean and standard deviation (SD) are given for normally distributed data, median and IQR are provided for non-normally distributed data, numbers and proportions are used to present categorical data.

General linear modelling was used to estimate the cohort effect on the healthcare costs per day alive during the year before ICU admission, on the healthcare cost per day alive during the year of ICU admission and on the healthcare cost per day alive during the year after ICU admission. As healthcare costs per day alive were skewed to the right the natural logarithm of the healthcare costs per day alive was used. Because of multiple comparisons a more stringent p-value of <0.01 was considered to indicate a statistically significant difference.

Subgroups analyses

Previous research has shown that healthcare costs are higher in the last 120 days prior to death [16]. Therefore, a survival curve was constructed to gain insight in the long-term

mortality of all three study populations. For the survival analyses, the period at risk starts at January1st, 2013.

Analyses were performed for the total study population, for a subgroup which died during 2013, for a subgroup which died during 2014, and for a subgroup which survived the entire study period. Additionally, for all three-study populations we created subgroups based on the number of chronic medical conditions.

The intoxication population and the ICU population were divided into subgroups based on the APACHE IV predicted mortality; i.e. low-risk (predicted mortality <30%), medium-risk (predicted mortality ≥ 30 and < 70%) and high-risk (predicted mortality ≥ 70%). Analyses regarding the APACHE IV predicted mortality were only preformed for ICU admissions which met the APACHE IV inclusion criteria. Furthermore, we grouped the intoxication population and the ICU population by length of stay (LOS) of their first ICU admission. Groups were made of patients with a LOS of < 2 days and patients with a LOS of ≥2 days.

Ethics

The Medical Ethics Committee of the Academic Medical Center approved this study (number W18_010 # 18.021).

RESULTS

The final dataset included 2,591 patients admitted to the ICU for intoxication. These 2,591 patients had 2,968 ICU admissions in 2013. Intoxication was the underlying reason for 95.8% (n=2,843) of admissions whereas 4.2% (n=125) were admitted for reasons other than an intoxication. Based on the intoxication population, 2,577 ICU patients were matched 1:1. Some patients (n=14 ICU patients) could not be matched 1:1 due to missing information. The ICU patients were (re)admitted 2,945 times to the ICU. Finally, 2,591 control persons were matched 1:1 with the intoxication population. Figure 6.1 gives an overview of the data linkage and data matching process.

Table 6.1 gives an overview of the characteristics of the three study populations. The mortality of the 'ICU population' was significantly higher than that of the 'intoxication population' (p<0.0001). Appendix 6.3 illustrates survival curves for the intoxication, ICU and control population.

The healthcare costs per day alive of the intoxication group survivors were compared to the ICU group survivors and to the control group survivors. The healthcare costs of the intoxication population were higher during the year before ICU admission (€20.3 (IQR €3.6; €76.4)),

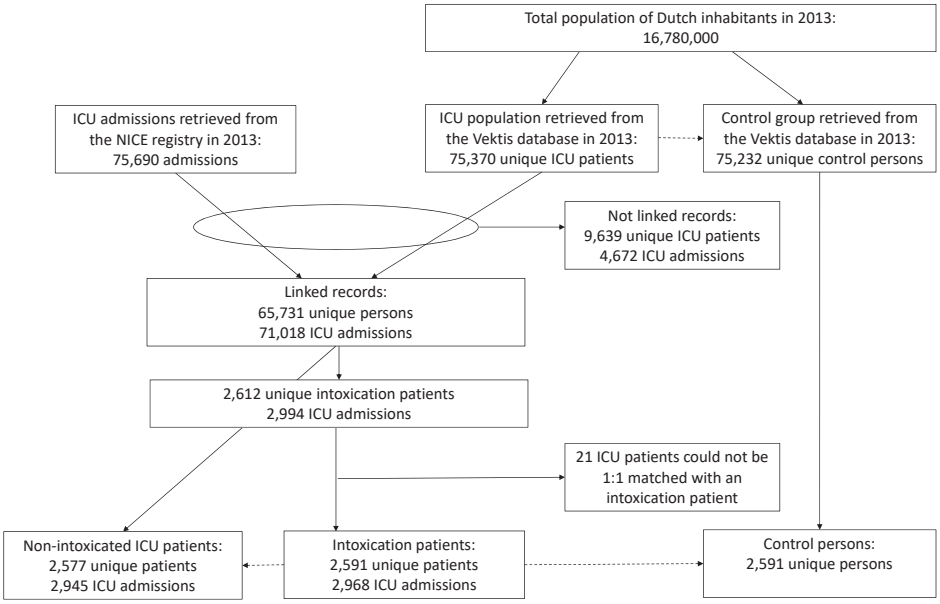


Figure 6.1 Flow of patients and the linking process

compared to those of the ICU population (€6.1 (IQR €0.9; €29.3)) (p<0.0001) and compared to those of the control population (€1.1 (IQR €0.3; €4.6)) (p<0.0001). During the year of ICU admission the costs per day alive for the intoxication population were €60.5 (IQR €27.4; €132.8) in comparison to the ICU population (€72.1 (IQR €37.0; €164.6), p<0.0001). In the year after ICU admission the costs per day alive for the intoxication population were €23.9 (IQR €5.1; €82.4) in comparison to the ICU population (€13.6 (IQR €3.3; €54.9), p<0.0001) and in comparison to the control population (€1.1 (IQR €0.4; €4.9), p<0.0001) (see Figure 6.2).

Those within the intoxication group surviving all three years who were intoxicated with 'sedatives' had the highest median healthcare costs per day alive during the total study period (p<0.0001). An overview of the cost per day alive for various intoxication groups is provided in Appendix 6.4.

Fifty-three percent (1,389/2,591) of patients in the intoxication group had one or more underlying medical conditions at the time of their ICU admission, compared to 40.3% (1038/2577) in the ICU group. Approximately 19% (489/2,591) of those in the control group had one or more medical condition (Appendix 6.2). The most prevalent accompanying conditions in the intoxication population were depression (n=599), psychoses, Alzheimer's disease and

Table 6.1 Characteristics of the intoxication patients, the other ICU patients and the control population

	Intoxication patients (n=2,591)	Other ICU patients (n=2,577)	Control population (n=2,591)
Male (n %)	1,185 (45.7%)	1,179 (45.8%)	1,185 (45.7%)
Age (median IQR)	45 (32; 55)	45 (32; 55)	45 (32; 55)
SES (median IQR)	0.1 (-0.8; 0.7)	0.1 (-0.8; 0.7)	0.1 (-0.8; 0.7)
Died during 2013 (n %)	141 (5.4%)	488 (18.9%)	17 (0.7%)
Died during 2014 (n %)	107 (4.4%)	96 (4.6%)	11 (0.4%)
Characteristics of the first (intoxication related) ICU admission			
Admission type (n %)			
• Medical	2,563 (98.9%)	2,563 (99.5%)	
• Planned surgery	6 (0.2%)	6 (0.2%)	
• Emergency surgery	8 (0.3%)	8 (0.3%)	
• Missing	14 (0.5%)	-	
APACHE IV score*	38 (24; 62)	49 (31; 76)	
Length of ICU stay (days, median, IQR)	0.8 (0.5; 1.3)	1.7 (0.8; 3.6)	
Length of hospital stay (days, median, IQR)	1 (1; 3)	8 (4; 15)	
Mechanical ventilation	537 (20.7%)	1016 (39.4%)	
Subgroups of intoxications (n %)			
• Alcohol	277 (10.7%)	-	
• Analgesics	110 (4.2%)	-	
• Antidepressant	282 (10.9%)	-	
• Street drug	357 (13.8%)	-	
• Sedatives	836 (32.3%)	-	
• Poisoning	11 (0.4%)	-	
• Other	364 (14.0%)	-	
• Combination	354 (13.7%)	-	
Acute diagnosis (n %)			
• CPR	26 (1.0%)	218 (8.5%)	-
• Burns	2 (0.1%)	13 (0.5%)	-
• Cardiac dysrhythmia	97 (3.7%)	238 (9.2%)	-
• GI bleeding	6 (0.2%)	79 (3.1%)	-
• CVA	14 (0.5%)	118 (4.6%)	-
• Intracranial mass effect	8 (0.3%)	113 (4.4%)	-
• Sepsis	8 (0.3%)	316 (12.3%)	-
• OHCA	22 (0.8%)	168 (6.5%)	-
• SAH	0 (0.0%)	60 (2.3%)	-
• Trauma	54 (2.1%)	287 (11.1%)	-

*only calculated for patients which met the APACHE IV inclusion criteria which was n=2,456 for intoxication patients group and n=2,392 for ICU patients group

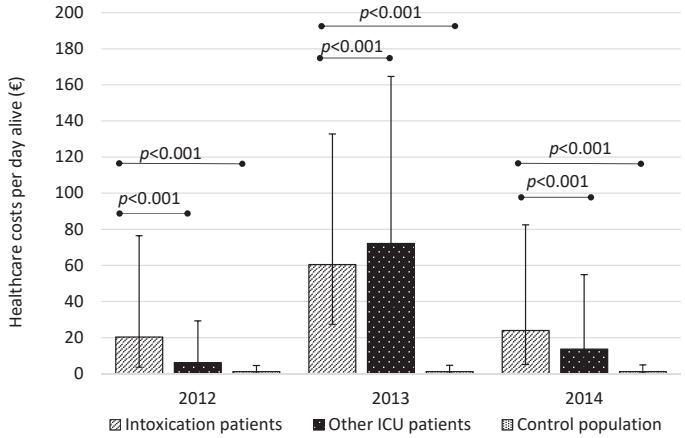


Figure 6.2 The median healthcare costs per day alive (IQR) of the intoxication patients, other ICU patients and the control population that survived all 3 years

addictions (n=357) and high cholesterol (n=151). More details are provided in the Appendix 6.5 and Appendix 6.6.

The costs per day alive in relation to the number of underlying medical conditions is depicted in Figure 6.3. The intoxication population showed an increase in healthcare costs per day alive in relation to the number of comorbidities. In the year after ICU, people with a greater number of chronic conditions had higher healthcare costs per day as well. During the year after ICU admission, the effect of number of chronic conditions on the healthcare costs was the same within the ICU population and the intoxication population (*p*-value for interaction: *p*=0.44).

The costs in relation to severity of disease has been depicted in Appendix 6.7.

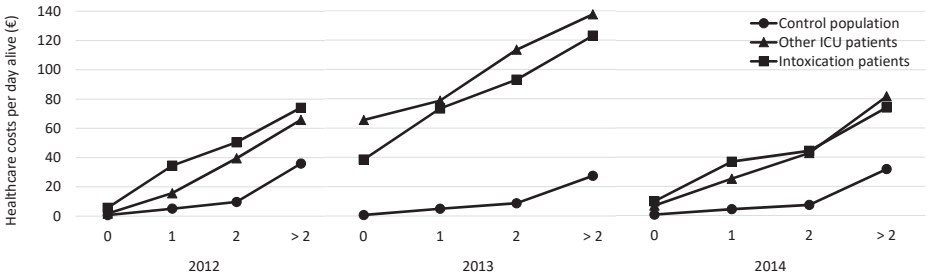


Figure 6.3 The median healthcare costs per day alive of the intoxication patients, other ICU patients and the control population that survived all 3 years in relation to the number of comorbidities

DISCUSSION

The primary finding of this study is that patients admitted to the ICU for an acute intoxication have higher healthcare costs per day alive in the year prior to their admission, compared to non-intoxicated ICU patients or matched controls. Furthermore, healthcare costs per day alive remain elevated in the year following their admission.

Previous studies on the costs of intoxicated patients admitted to the ICU only focused on direct ICU-associated or hospital-associated expenditures [17-25]. Obviously, the costs per ICU treatment depends on country, region, healthcare system and type of intoxication. Only very few studies have looked at the healthcare associated costs beyond hospital admission. Indeed, many of these studies identified this as a limitation of their studies as many of the costs are associated with newly instigated or intensified treatment for underlining psychiatric illnesses or newly acquired organ dysfunction [26]. For example, in a nationwide, Japanese study 17 per 100,000 inhabitants were admitted to acute care hospitals for accidental or intentional intoxications. More than 60% had been assessed by a psychiatrist in the 90 days preceding their intoxication [27]. After hospital discharge approximately 12% were transferred to a psychiatric department. This suggests that a proportion of healthcare costs are being made outside the acute care setting. One of the few studies that assessed patients 6-months beyond discharge found that intoxications had the lowest cost/effectiveness ratio, defined as the cost of treatment divided by the expected years alive [28]. If this life expectancy is corrected by the health-related quality of life (HRQoL), then the costs of ICU treatment would be 620 United States dollars per quality adjusted life year (QALY). However, the sample of intoxicated patients in that study was very small (n=23) and the healthcare costs after hospital discharge were, again, not incorporated [28]. We, unfortunately, could not calculate QALYs as HRQoL was not in our database. However, from a small study of Dutch survivors of intoxications we know that the HRQoL was statistically significantly lower than that of the general Dutch population [29]. Moreover, 25% of these patients had very low HRQoL. This suggests that the cost/effectiveness ratio of the Dutch intoxicated patients surviving ICU admission may be poorer despite reasonable survival rates in this population.

We have shown that the healthcare related costs for intoxicated patients were high(er) in the year prior to ICU admission. This is a well-known phenomenon in many other subgroups. In a general ICU population factors present before ICU admission, such as comorbidities and pre-ICU hospitalizations, were stronger predictors of hospital resource use than acute severity of illness [30]. In this latter study the Simplified Acute Physiology Score II (SAPS II) was used whereas the APACHE IV model was used in the present study. The APACHE IV model includes more chronic factors compared to the SAPS II model, and for this reason we would expect that ICU patients within the highest mortality risk group would consume the most healthcare resources during the year before and the year after ICU admission. Indeed, the patients in

the 'intoxication subgroup' had the highest prevalence of comorbidities or accompanying conditions in comparison to the 'other ICU patients' and the 'control subgroup'.

We have also shown that intoxicated patients have more chronic conditions prior to ICU admission than other patients admitted to the ICU. This surplus of accompanying conditions and comorbidities is driven by neuropsychiatric disorders in this particular population. Stratifying the healthcare costs per day alive by the amount of chronic conditions showed great deviation from the median healthcare cost per day alive, indicating that those factors largely contribute to the healthcare costs.

Our study has several limitations. First, the total costs per patient were only known per calendar-year. It is unclear which aspects of healthcare were most utilized or which aspects were most expensive. For example, patients admitted in December will have a spill over of costs in the next calendar year and, vice versa, such patients will be cheaper during the first months of the year of ICU admission. This might exaggerate the difference between the costs in the year prior to ICU admission in comparison to the year after ICU admission. Second, because costs were provided as total costs per year we could not dissect which components of care (e.g. mechanical ventilation, haemodialysis, salaries of healthcare workers, laboratory assessments, etc.) were important drivers of the costs. However, previous research has shown that costs of human resources made up an important part of the total costs [6]. Last, we did not have a control group of intoxicated patients that was not admitted to the ICU. These patients could not be identified in both databases. We are, therefore, unaware of the increase in costs per day alive of those patients. We can only speculate that these patients (admitted to other wards of the hospital) also have intensified (psychiatric) care after their intentional intoxication.

Despite these limitations, the linkage between the national health insurance claims database and the national clinical ICU registry, covering almost the entire country, provides valuable insight in the healthcare utilization of intoxicated patients who are admitted to the ICU.

CONCLUSIONS

We showed that intoxicated people who were admitted to an ICU had higher healthcare costs per day alive compared to another ICU population and a control population. The difference in healthcare costs is already present in the year before ICU admission and continues during the year after discharge. The healthcare costs before and after ICU admission are greatly influenced by the chronic and psychiatric conditions of patients.

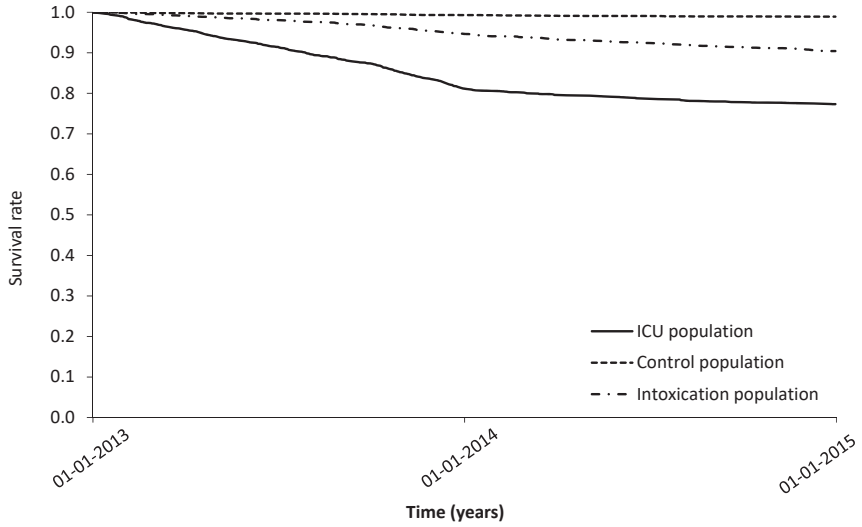
APPENDICES

Appendix 6.1 Definition of intoxication subtypes

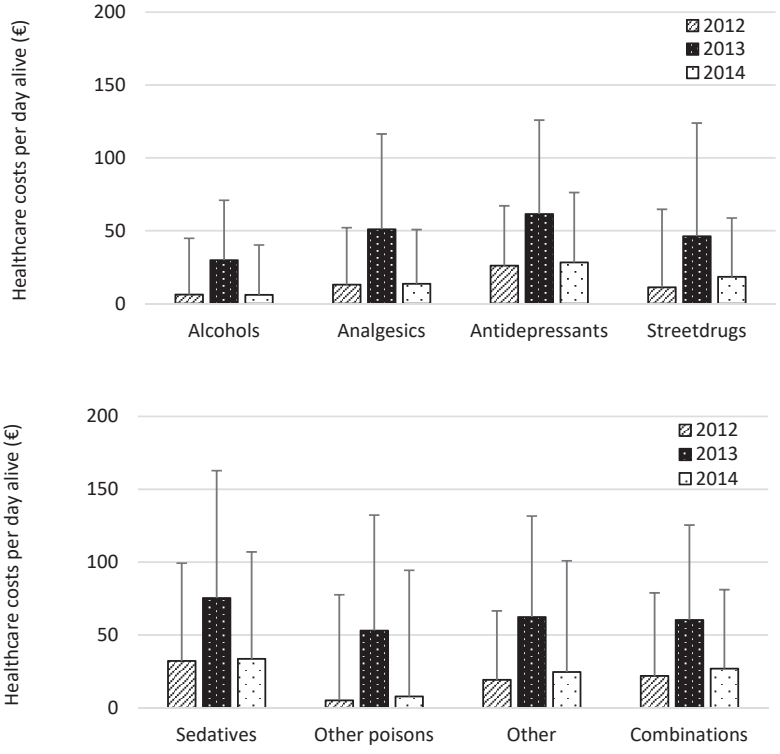
Subtype of intoxication	APACHE IV description
Alcohol	Overdose, alcohols (e.g. ethanol, methanol, ethylene glycol, etc.)
Analgesic	Overdose, analgesic (e.g. aspirin, cetaminophen, paracetamol, etc.)
Antidepressant	Overdose, antidepressants (e.g. cyclic, lithium)
Street drug	Overdose, street drugs (e.g. opiates, cocaine, amphetamine)
Sedatives	Overdose, sedatives, hypnotics, antipsychotics, benzodiazepines
Poisoning	Poisoning, carbon monoxide, arsenic, cyanide
Other	Overdose with other toxin, poison or drug
Combination	Any combination of the above APACHE IV codes

Appendix 6.2 Chronic conditions derived from the Pharmaceutical Cost Groups in the Vektis database

Chronic conditions during 2012	Intoxication patients (n=2,591)	Other ICU patients (n=2,577)	Control population (n=2,591)
Population with one or more chronic conditions	1,389 (53.6%)	1,038 (40.2%)	489 (18.9%)
Asthma	126 (4.9%)	140 (5.4%)	54 (2.1%)
COPD	100 (3.9%)	151 (5.9%)	23 (0.9%)
Crohn's disease	7 (0.3%)	7 (0.3%)	6 (0.2%)
Cystic fibrosis / pancreas enzymes	5 (0.2%)	14 (0.5%)	3 (0.1%)
Depression	599 (23.1%)	188 (7.3%)	102 (3.9%)
Diabetes Mellitus type 1	86 (3.3%)	176 (6.8%)	26 (1.0%)
Diabetes Mellitus type 2	60 (2.3%)	96 (3.7%)	60 (2.3%)
Diseases of the central neurological system	17 (0.7%)	20 (0.8%)	2 (0.1%)
Epilepsy	105 (4.1%)	68 (2.6%)	18 (0.7%)
Glaucoma	21 (0.8%)	26 (1.0%)	12 (0.5%)
Heart diseases	104 (4.0%)	201 (7.8%'	46 (1.8%)
High cholesterol	151 (5.8%)	149 (5.8%)	121 (4.7%)
HIV/AIDS	13 (0.5%)	11 (0.4%)	3 (0.1%)
Hormone sensitive tumors	10 (0.4%)	13 (0.5%)	9 (0.3%)
Kidney diseases	6 (0.2%)	32 (1.2%)	2 (0.1%)
Neuropathic pains	132 (5.1%)	56 (2.2%)	11 (0.4%)
Parkinson's disease	7 (0.3%)	3 (0.1%)	5 (0.2%)
Psychoses, Alzheimer's disease and addictions	357 (13.8%)	68 (2.6%)	19 (0.7%)
Rheumatism	9 (0.3%)	19 (0.7%)	13 (0.5%)
Thyroid diseases	57 (2.2%)	80 (3.1%)	51 (2.0%)
Transplantations	7 (0.3%)	31 (1.2%)	8 (0.3%)



Appendix 6.3 Kaplan Meier survival curve of the intoxication patients, other ICU patients and the control population



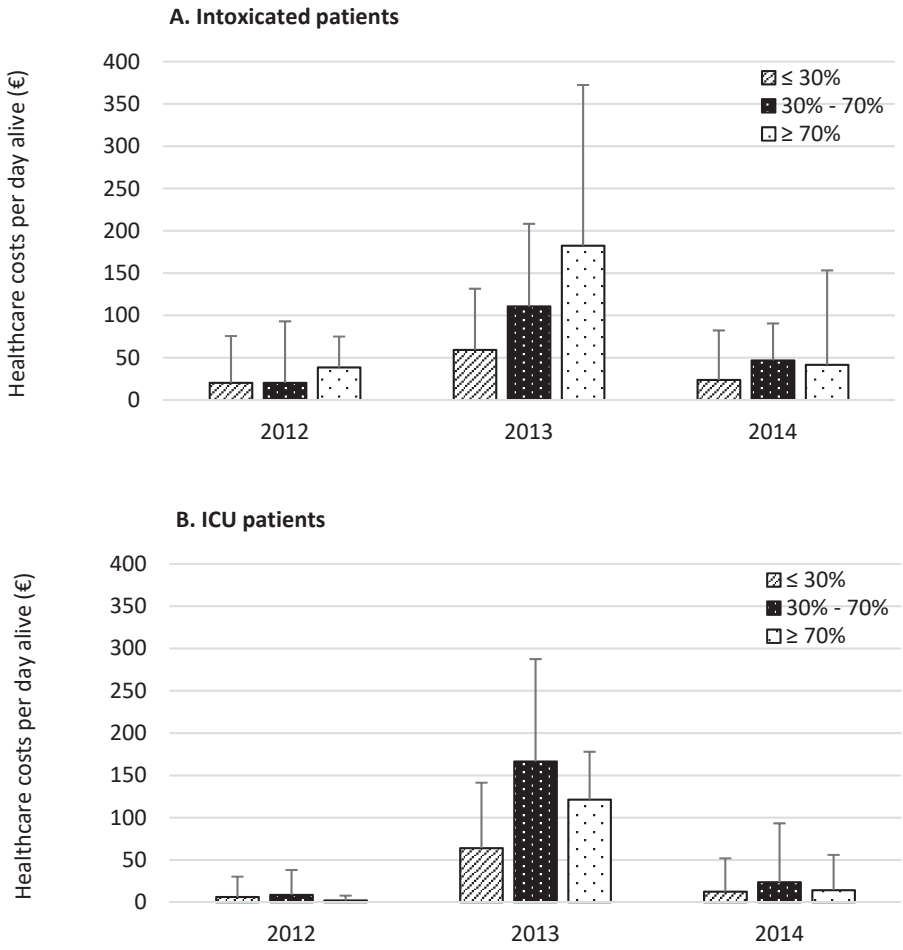
Appendix 6.4 The median healthcare costs per day alive (75th percentile) for various types of intoxications (based upon the APACHE IV admission diagnoses for intoxications)

Appendix 6.5 Population with one or two chronic conditions

Population with one chronic condition					
Intoxication (n=943)		IC (n=666)		Control (n=404)	
Depression	408	DM type I	97	High cholesterol	90
Psychoses, Alzheimer's disease and addictions	224	Depression	94	Depression	71
Asthma	48	High cholesterol	83	Asthma	45
High cholesterol	44	Heart diseases	75	DM type II	44
Neuropathic pains	40	Asthma	63	Heart diseases	31
Population with 2 chronic conditions					
Intoxication (n=334)		IC (n=264)		Control (n=68)	
High cholesterol and depression	30	DM type II and heart diseases	17	High cholesterol and depression	8
Epilepsy and psychoses, Alzheimer's disease and addictions	26	High cholesterol and COPD	15	Depression and thyroid diseases	6
Asthma and depression	18	COPD and depression	15	High cholesterol and thyroid diseases	5
High cholesterol and Psychoses, Alzheimer's disease and addictions	16	COPD and heart diseases	12	COPD and heart diseases	4
COPD and depression	15	Asthma and depression/ DM type I and heart diseases	11	High cholesterol and COPD/ High cholesterol and rheumatism/ COPD and DM type II/ DM type II and Psychoses, Alzheimer's disease and addictions	3

Appendix 6.6 Commonest comorbid conditions and type of intoxication

• Alcohol	27	21	4	9
• Analgesics	14	10	9	2
• Antidepressant	124	39	15	11
• Street drug	30	49	17	8
• Sedatives	231	143	49	44
• Poisoning	3	0	0	0
• Other	70	35	13	14
• Combination	100	60	25	17



Appendix 6.7 The median healthcare costs per day alive in relation to the APACHE IV predicted mortality

REFERENCES

1. Koster-Brouwer ME, van de Groep K, Pasma W, et al. Chronic healthcare expenditure in survivors of sepsis in the intensive care unit. Intensive Care Med. 2016;42(10):1641–2.
2. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, et al. Healthcare cost of ICU survivors are higher before and after ICU admission compared to a population based control group: a descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care. 2017;44:345–51.
3. Lam SM, Lau AC, Yan WW. Over 8 years experience on severe acute poisoning requiring intensive care in Hong Kong, China. Hum Exp Toxicol. 2010;29(9):757–65.
4. Henderson A, Wright M, Pond SM. Experience with 732 acute overdose patients admitted to an intensive care unit over six years. Med J Aust. 1993; 158(1):28–30.
5. Brandenburg R, Brinkman S, de Keizer NF, et al. In-hospital mortality and long-term survival of patients with acute intoxication admitted to the ICU. Crit Care Med. 2014;42(6):1471–9.
6. Green SL, Dargan DI, Jones AL. Acute poisoning: understanding 90% of cases in a nutshell. Postgrad Med J. 2005;81:204–16.
7. NVIC Jaaroverzicht 2017. Acute vergiftigingen bij mens en dier. NVIC Rapport 07/2018, Nationaal Vergiftigingen Informatie Centrum, Universitair Medisch Centrum Utrecht, 2018. [Acute poisonings in humans and animals Rapport 07/2018]. Available through http://www.umcutrecht.nl/nvic. Last Accessed 29 Nov 2018.
8. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med. 2010;38:65–71.
9. Lefrant JY, Garrigues B, Pribil C, et al. The daily cost of ICU patients: a microcosting study in 23 French intensive care units. Anaesth Crit Care Pain Med. 2015;34(3):151–7.
10. Böll R, Romanek K, Schmoll S, et al. Independent validation of the ICU requirement score in a cohort of acutely poisoned adults. Clin Toxicol. 2017; 16:1–3.
11. Dutch National Intensive Care Evaluation (NICE) foundation. Dutch National Intensive Care Evaluation (NICE) foundation. Available from: http://www.stichting-nice.nl. Last Assessed 29 Nov 2018.
12. Zimmerman JE, Kramer AA, McNair DS, et al. Acute physiology and chronic health evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34(5):1297–310.
13. Statistics Netherlands Database. Available through https://opendata.cbs.nl/statline/#/CBS/en/. Accessed 10 Jan 2019.
14. The Vektis Database is available through http://www.vektis.nl. Accessed 10 Jan 2019.
15. Roos LL, Wajda A. Record linkage strategies. Part I: estimating information and evaluating approaches. Methods Inf Med. 1991 Apr;30(2):117–23.
16. Tanuseputro P, Wodchis WP, Fowler R, et al. The healthcare cost of dying: a population-based retrospective cohort study of the last year of life in Ontario, Canada. PLoS One. 2015;10(3):e0121759.
17. Sut N, Memis D. Intensive care costs of acute poisoning cases. Clin Toxicol (Phila). 2008;46(5):457–60.
18. Ramchandani P, Murray B, Hawton K, et al. Deliberate self poisoning with antidepressant drugs: a comparison of the relative hospital costs of cases of overdose of tricyclics with those of selective-serotonin re-uptake inhibitors. J Affect Disord. 2000;60(2):97–100.
19. Serinken M, Karcioglu O, Sengul C, et al. Hospital costs of managing deliberate self-poisoning in Turkey. Med Sci Monit. 2008;14(3):CR152–8.

20. Kapur N, House A, Creed F, et al. General hospital services for deliberate self-poisoning: an expensive road to nowhere? Postgrad Med J. 1999; 75(888):599–602.
21. Shahid M, Khan MM, Naqvi H, et al. Cost of treatment of deliberate selfharm. A study from Pakistan. Crisis. 2008;29(4):213–5.
22. D'Mello DA, Finkbeiner DS, Kocher KN. The cost of antidepressant overdose. Gen Hosp Psychiatry. 1995;17(6):454–5.
23. Yeo HM. The cost of treatment of deliberate self-harm. Arch Emerg Med. 1993;10(1):8-14.
24. Kavalci G, Ethemoglu FB, Batuman A, et al. Epidemiological and cost analysis of self-poisoning cases in Ankara, Turkey. Iran Red Crescent Med J. 2014; 16(11):e10856.
25. McMahon A, Brohan J, Donnelly M, et al. Characteristics of patients admitted to the intensive care unit following self-poisoning and their impact on resource utilisation. Ir J Med Sci. 2014;183(3):391–5.
26. Kittelsen SS, Barber JA, Harrington R. Factors that influence the cost of deliberate self-poisoning in children and adolescents. J Ment Health Policy Econ. 2001;4(3):113–21.
27. Okumura Y, Sakata N, Takahashi K, et al. Epidemiology of overdose episodes from the period prior to hospitalization for drug poisoning until discharge in Japan: an exploratory descriptive study using a nationwide claims database. J Epidemiol. 2017;27(8):373–80.
28. Sznajder M, Aegerter P, Launois R, et al. A cost-effectiveness analysis of stays in intensive care units. Intensive Care Med. 2001;27(1):146–53.
29. Brandenburg R, Soliman IW, Meulenbelt J, et al. Raising awareness for a low health-related quality of life in intoxicated ICU patients. Clin Toxicol (Phila). 2015;53(6):585.
30. Lone NI, Gillies MA, Haddow C, et al. Five-year mortality and hospital costs associated with surviving intensive care. Am J Respir Crit Care Med. 2016; 194(2):198–208

Chapter 7

ICU survivors have a substantial higher risk of developing new chronic conditions compared to a population-based control group

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ABSTRACT

Objectives: To describe the types and prevalence of chronic conditions in an ICU population and a population-based control group during the year before ICU admission and to quantify the risk of developing new chronic conditions in ICU patients compared with the control group.

Design: We conducted a retrospective cohort study, combining a national health insurance claims database and a national quality registry for ICUs. Claims data in the timeframe 2012-2014 were combined with clinical data of patients who had been admitted to an ICU during 2013. To assess the differences in risk of developing new chronic conditions, ICU patients were compared with a population-based control group using logistic regression modelling.

Setting: Eighty-one Dutch ICUs.

Patients: All patients admitted to an ICU during 2013. A population-based control group was created, and weighted on the age, gender, and socio-economic status of the ICU population.

Interventions: None.

Measurements and Main Results: ICU patients (n=56,760) have more chronic conditions compared with the control group (n=75,232) during the year before ICU admission (p<0.0001). After case-mix adjustment ICU patients had a higher risk of developing chronic conditions, with odds ratios ranging from 1.67 (CI 1.29; 2.17) for asthma to 24.35 (CI 14.00; 42.34) for epilepsy, compared with the control group.

Conclusions: Due to the high prevalence of chronic conditions and the increased risk of developing new chronic conditions, ICU follow-up care is advised and may focus on the identification and treatment of the new developed chronic conditions.

INTRODUCTION

ICU patients are life threatening ill. Five decades ago, at the onset of ICU care, up to 33% of the patients did not survive their ICU admission [1, 2]. As a result of improved medical technology, knowledge and treatment, the mortality rates dropped to 10-15% during the last decade [3-6]. Due to this decrease in mortality, the focus on ICU outcome measures shifted from solely ICU mortality to long-term survival, morbidity, and quality of life after discharge.

After hospital discharge, many ICU survivors suffer long-term complaints as part of the post-intensive care syndrome (PICS) leading to financial difficulties, restrictions in societal participation and decreased quality of life [7, 8]. The term 'PICS' was introduced to describe the presence of one or more impairments in mental, cognitive, and physical functioning after critical illness [9].

Recent studies have shown that ICU patients have increased healthcare costs and increased hospital admissions before their ICU admission [10-12]. Comorbidities present before ICU admission have been recognized as predictors for hospital resource use before and after ICU discharge [11-13]. This might indicate that patients have an impaired health status even before ICU admission, since comorbidities, in general, are associated with mortality, morbidity, and quality of life [13, 14]. Yet, little is known about the prevalence of chronic conditions within the total ICU population before ICU admission, the types of chronic conditions ICU patients suffer, and the risk of developing new chronic conditions after ICU discharge. Furthermore, it is unknown whether there is a difference between ICU patients and the general population with respect to the types, prevalence and the development of chronic conditions.

The aim of this study was: 1) to describe the types and prevalence of chronic conditions in an ICU population and a population-based control group during the year before ICU admission and 2) to quantify the risk of developing new chronic conditions in ICU patients and the population-based control group during the year after ICU admission.

MATERIALS AND METHODS

We conducted a retrospective cohort study, combining data of the Dutch National Intensive Care Evaluation (NICE) registry [15] with data of the health insurance claims database of Vektis [16].

Dutch NICE Database

The NICE registry is a national quality registry in which, during the study period, 90% of all Dutch ICUs are participating [15]. The ICUs are collecting data for all patients admitted to their ICU, which includes: age, gender, ICU admission and discharge data, primary diagnosis at ICU

admission, severity of illness, ICU mortality, and in-hospital mortality. Extensive information about the collected items, data quality, and data reliability has been published before [17].

All patients from the NICE registry, 18 years old of age or older during the year of ICU admission, admitted to an ICU during the year 2013 and discharged from the ICU before January 1, 2014, were included in the NICE registry subset.

Vektis Insurance Claims Database

Health insurance is compulsory for Dutch citizens, and 99% of the Dutch inhabitants have private healthcare insurance [18]. The Vektis databases [16] contain reimbursement data on all medical treatments paid for by Dutch insurance companies, as well as demographic information, such as gender, date of birth, socio-economic status (SES), and a proxy for date of death, for all registered residents of the Netherlands.

Vektis also contains claims for pharmaceutical care, including information on provided drugs, the Anatomical Therapeutic Chemical (ATC) code, the date the drug was supplied, and the quantity supplied. To determine the chronic conditions, Pharmaceutical Cost Groups (PCGs) were used as a proxy. PCGs are based on the idea that a patient with a certain chronic condition can be identified by claims for specific prescribed drugs [19, 20].

We used the PCGs to identify chronic conditions during the whole study period since clinical diagnosis are not available from NICE or Vektis. The validity of pharmacy-based claims data for the assessment of chronic conditions and prevalence estimates have been demonstrated before in different country's [20-24]. A complete description of the definitions of chronic conditions and ATC codes, as used in the year 2014, is given in Appendix 7.1.

All patients in the Vektis database who had a claim for an ICU day in the year 2013 and were 18 years of age or older during the year of ICU admission were included in the ICU-subset of the Vektis database. Based on this ICU-subset, a population-based control group was created from all registered inhabitants of the Netherlands in the Vektis database. The population-based control group was frequency matched based on the combination of the age, gender, and SES of patients from the ICU-subset, and had no claims for ICU care during 2013. Only ICU patients with no missing data for gender, age, and SES were used in the frequency matching process which was undertaken before the linking process.

Linking Process

The subset extracted from the NICE database and the ICU-subset of the Vektis database were linked using a deterministic linkage algorithm [25]. The linking process is extensively described in a previous published study [12].

Statistical Analysis

The year before ICU admission is defined as January 1, 2012, until December 31, 2012, and the year after ICU admission as January 1, 2014, until December 31, 2014.

Median and interquartile ranges are given for non-normally distributed data and numbers, and proportions are used to present categorical data. The chi-square test was used to test for differences in proportions between the ICU population and control group. A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

To assess the difference in risk of developing one or more new chronic conditions after ICU discharge, logistic regression modelling was used, with age, gender, and SES as possible explanatory variables. When a person did not have any chronic conditions during 2012 and 2013 and did have a chronic condition during 2014, we considered the chronic condition new and thus developed after ICU discharge. We plotted the estimated risk of developing one or more new chronic conditions, for both study populations, as a function of age and corrected for median SES and gender. Only people with no chronic conditions during 2012 and 2013 were taken into account.

For the most prevalent new chronic conditions within the ICU population, the differences in risk of developing the specified chronic condition, between ICU patients and the control group were evaluated. The specified chronic condition was the independent variable and age, gender, SES, and having pre-existing chronic conditions before admission were taken into account as possible explanatory variables. Only people which did not have the specified chronic condition during 2012 and 2013 were taken into account.

For analyses regarding the differences between 2012 and 2014, only people who survived at least until the December 31, 2014 were taken into account. For all analyses, only the first ICU admission of ICU patients was included. Statistical analyses were performed in SAS software (Version 7.1; SAS Institute, Cary, NC).

The control group was divided into two subgroups, and post hoc analyses were performed. Control persons who had been admitted to a hospital or had an outpatient appointment with a specialist were identified as 'hospital population' and control persons who had not been admitted to a hospital nor had an outpatient appointment with a specialist were identified as 'nonhospital population.' A detailed description of the two subpopulations is given in Appendix 7.1.

Ethics

The need for ethical approval for this study was waived by the Medical Ethics Committee of the Academic Medical Center and stored under number W17_296.

RESULTS

The study population consisted of 56,760 ICU patients and 75,232 control persons. Figure 7.1 gives an overview of the data linking process. ICU patients who could not be linked between the two registries (12.8%) or who did not survive hospital admission (13.6%) were excluded from all analyses. Of the 56,760 unique ICU patients, 3,732 patients (6.6%) were admitted to the ICU more than once, with the number of readmissions ranging from 1 to 11 times. Table 7.1 gives insight in the characteristics of the ICU population and the control group. Of the ICU population, 55.4% had one or more chronic conditions during the year before admission, within the control group this was 38.4%. Table 7.2 describes the prevalence of specific chronic conditions within both study populations during 2012.

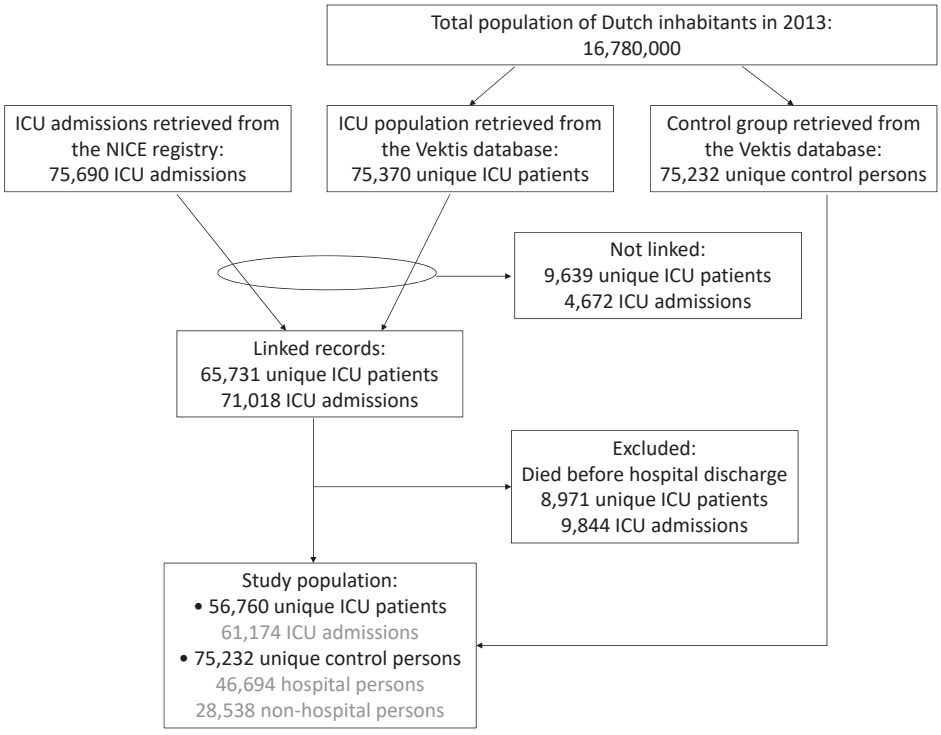

Figure 7.1 Flowchart of the linking process

Table 7.1 Characteristics of the ICU population and the control group during 2012

Characteristics	ICU population (n=56,760)	Control group (n=75,232)
Male [a]	34,111 (60.1%)	44,742 (59.5%)
Age [b]	65 (53; 73)	65 (55; 74)
SES [b]	0.2 (-0.6; 0.8)	0.2 (-0.6; 0.8)
Died during 2013 [a]	3,465 (6.1%)	1,659 (2.2%)
Died during 2014 [a]	4,291 (8.1%)	1,685 (2.3%)

[a] Number and percentage
[b] Median and IQR

Table 7.2 Prevalence of chronic conditions within the ICU population and the control group during 2012

	ICU population (n=56,760)	Control group (n=75,232)	*p*-value
Population with one or more chronic conditions	31,472 (55.4%)	28,902 (38.4%)	<0.0001
Population with two or more chronic conditions	10,856 (19.1%)	7,029 (9.3%)	<0.0001
Chronic condition			
High cholesterol	9,348 (16.5%)	10,576 (14.1%)	<0.0001
Heart diseases	7,954 (14.0%)	4,997 (6.6%)	<0.0001
COPD	4,454 (7.8%)	2,445 (3.2%)	<0.0001
DM 2	4,274 (7.5%)	4,087 (5.4%)	<0.0001
DM 1	3,705 (6.5%)	2,254 (3.0%)	<0.0001
Depression	3,427 (6.0%)	2,656 (3.5%)	<0.0001
Asthma	2,808 (4.9%)	2,418 (3.2%)	<0.0001
Thyroid diseases	1,954 (3.4%)	2,058 (2.7%)	<0.0001
Glaucoma	1,432 (2.5%)	1,924 (2.6%)	0.69
Neuropathic pains	1,106 (1.9%)	543 (0.7%)	<0.0001
Psychoses, Alzheimer's disease and addictions	1,018 (1.8%)	601 (0.8%)	<0.0001
Epilepsy	983 (1.7%)	551 (0.7%)	<0.0001
Rheumatism	609 (1.1%)	551 (0.7%)	<0.0001
Hormone sensitive tumours	553 (1.0%)	692 (0.9%)	0.31
Kidney diseases	489 (0.9%)	151 (0.2%)	<0.0001
Transplantations	419 (0.7%)	163 (0.2%)	<0.0001
Crohn's disease	263 (0.5%)	246 (0.3%)	<0.0001
Parkinson's disease	243 (0.4%)	346 (0.5%)	0.39
Diseases of the central neurological system	201 (0.4%)	56 (0.1%)	<0.0001
Cystic fibrosis / pancreas enzymes	153 (0.3%)	49 (0.1%)	<0.0001
HIV	87 (0.2%)	59 (0.1%)	<0.0001

Appendix 7.2 provides an overview of the logistic regression analyses. Since the variables age, gender, SES, and pre-existing chronic conditions were frequently found effect modifiers, crude odds are reported, the odds for males and females with a median age, a median SES and no pre-existing chronic conditions, and the effects of the interaction terms within the study populations.

The odds of developing one or more new chronic conditions are estimated to be 5.29 (CI 4.90; 5.72) times higher for male ICU patients compared with similar persons from the control group and 4.39 (CI 3.99; 4.83) times higher for female ICU patients compared with similar persons from the control group. Within the ICU population, women are less likely to develop one or more new chronic conditions, compared with men (odds ratio [OR] 0.76, CI 0.70; 0.83). The difference between men and women in the control group was not significant (p=0.06). Figure 7.2 gives an overview of the risk of developing one or more new chronic conditions for both populations in relation to age and gender.

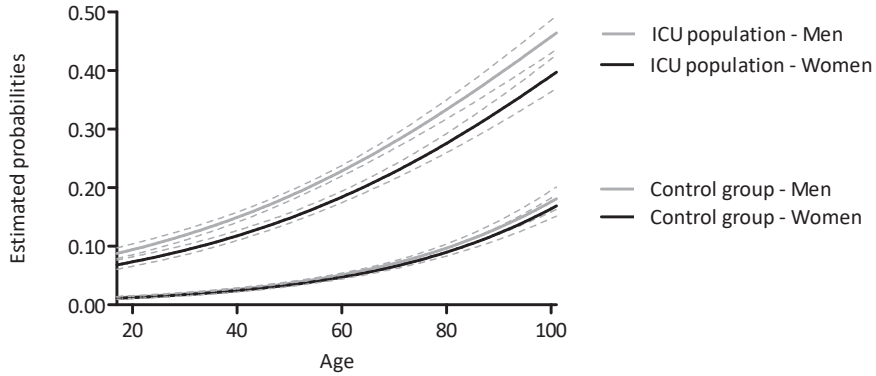

Figure 7.2 Risk of developing one or more new chronic conditions

High cholesterol, heart diseases, chronic obstructive pulmonary disease (COPD), depression, diabetes mellitus (DM) 2, asthma, epilepsy, and DM 1 are the most prevalent newly developed chronic conditions in the ICU population during the year after ICU admission (Appendix 7.3). ICU patients had a higher risk of developing those chronic conditions (Appendix 7.2).

Within both study populations, older people had a higher risk of developing most specified chronic conditions. However, within both study populations older patients are less likely to develop depression, and within the ICU population, older people are less likely to develop epilepsy (OR 0.99, CI 0.98; 0.99).

Women in the ICU population are less likely to develop high cholesterol and DM 2 compared with men in the ICU population and women in the control group are less likely to develop

high cholesterol, heart diseases, COPD, DM 2, and DM 1 compared with men in the control group.

ICU patients with pre-existing chronic conditions are more likely to develop heart diseases, COPD, DM 2, and DM 1 compared with ICU patients with no pre-existing chronic conditions. Within the control group, persons with pre-existing chronic conditions have a higher risk of developing all studied chronic conditions compared with control persons with no pre-existing chronic conditions.

The results of the post hoc analyses are described in Appendix 7.3, Appendix 7.4, Appendix 7.5, Appendix 7.6, Appendix 7.7, and Appendix 7.8, respectively. Male ICU patients have an odds of 8.46 (CI 7.54; 9.49) for developing one or more new chronic conditions compared with similar persons from the nonhospital population and an odds of 3.86 (CI 3.53; 4.21) compared with similar persons from the hospital population.

DISCUSSION

Our analysis demonstrated that ICU patients have more chronic conditions during the year before ICU admission compared with a population-based control group. Furthermore, ICU survivors without pre-existing chronic conditions were five-fold more likely to develop a chronic condition compared with surviving control patients without pre-existing chronic conditions. Additional chronic conditions increase complexity of care for patients surviving critical illness or injury. These data support the need for routine ICU follow-up to assist with assessment of chronic condition persistence, severity, impact on cognitive and motor function, and coordination of healthcare.

To our knowledge, this is the first study that describes in depth the differences in the prevalence of chronic conditions between an ICU population and a population-based control group during the year before ICU admission and the development of new chronic conditions over time. Studies have used the count of pre-existing Charlson Comorbidities Index to compare the number of chronic conditions during admission. They reported that ICU patients had significantly more chronic conditions compared with a hospitalized control group [11, 26]. The results of these studies are in line with the results of our study.

The fact that ICU patients have more chronic conditions and have a higher chance of developing new chronic conditions after discharge is important insight. Previous studies have shown that people with more chronic conditions generally have a higher risk of dying, a decreased quality of life, a decreased functional status, and an increased healthcare resource use [12-14]. ICU follow-up care has been recommended to address the long-term, and

severe complains ICU patients suffer after discharge. In sight of the results of our study, we suggest that ICU follow-up care should be offered to ICU survivors and special attention should be given to identifying new chronic conditions in an early stage so they can be treated accurately.

Female gender is a common risk factor for (multi)morbidity [27, 28] and studies have shown that women experience a lower self-reported health status, more (multi)morbidity and higher healthcare resource use compared with men [12, 29-31]. Our study is partly in line with those studies and shows that within the ICU population women have a higher prevalence of chronic conditions at baseline compared with men (data not shown). However, our study also shows that within both study populations, men had higher estimated risk of developing new chronic conditions compared with women. A possible explanation for these outcomes is that on average men have less consultations with general practitioners (GPs) [32]. Since chronic conditions are primarily diagnosed and managed by GPs, men could be less likely to be diagnosed before ICU admission. Furthermore, since PCGs measure treatment rather than the condition per se, we cannot exclude that the lower baseline prevalence in men represents (in part) under-treatment. If so, the higher estimated risk of developing a new chronic condition would, at least in part, represent a higher degree of treated patients rather than more patients with a chronic condition.

Although ICU patients have more chronic conditions during the year before ICU admission, the most prevalent types of chronic conditions are comparable among the ICU population and the general population. We adjusted for some demographic differences between the two populations. However, it might be that other demographic factors not included in our dataset, might further explain the differences in risk of developing new chronic conditions. Nevertheless, we believe that factors related to the ICU admission, such as the acute illness, side-effects of treatment or complications, may play an important role in the development of new chronic conditions in ICU patients. Further research on this topic is essential.

A limitation of this study is the use of administrative claims data to identify chronic conditions and not the clinical diagnoses described in the healthcare records of the patient. However, all drugs that were used for the classification of the chronic conditions can only be prescribed by a medical doctor. Furthermore, a latent chronic condition can be diagnosed during ICU admission and treated from that moment onwards, whereas a latent chronic condition in the control group may not be diagnosed during our study. This can lead to a overestimation of the differences in the development of new chronic conditions between the ICU population and the control group. Therefore, with post hoc analyses, we identified subpopulations of the control group: hospital population and nonhospital population. The supplementary analyses showed that ICU patients had still a higher risk of developing new chronic condi-

tions compared with the hospital population. Furthermore, we excluded people who did not survive the entire study period for the analyses regarding the development of new chronic conditions. Within the ICU population, the mortality rate and the prevalence of chronic conditions are higher compared with the control group. People with more chronic conditions are more likely to have worse health outcomes and are more likely to pass away. By excluding deceased ICU patients, we expect that the differences in development of new chronic conditions between the ICU population and the control group are slightly larger than we estimated. There is limited evidence on the relation between mechanisms common to critical illness and the development of chronic conditions. A recently performed systematic review and meta-analysis concluded that stress hyperglycaemia during ICU admission is associated with increased risk of incident diabetes. However, the strength of that association remains uncertain because of statistical and clinical heterogeneity among the included studies [33]. We were not able to find an association between ICU related mechanisms and all other new chronic conditions described in our study. Further research is necessary to gain more insight in the association between mechanisms common to critical illness and/or the treatments provided in the ICU and the development of chronic conditions in order to coordinate ICU (follow-up) care.

Despite these limitations, we still believe the differences we found are clinically significant. Through the unique collaboration of a national health insurance claims database and a national clinical ICU registry, we were able to include almost all patients admitted to a Dutch ICU. Since we included almost all ICU patients of an entire country, we also believe that the results we found are representative for other western countries with similar healthcare systems.

CONCLUSION

We showed that ICU patients have more chronic conditions during the year before ICU admission compared with a population-based control group and a five times higher odds on developing one or more new chronic conditions compared with the control group. Due to the high prevalence of chronic conditions and the increased risk of developing new chronic conditions ICU follow-up care is advised and may focus on the identification and treatment of the new developed chronic conditions. To this end, further research on the relation of ICU related factors and development of chronic conditions after ICU discharge is essential.

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APPENDICES

Appendix 7.1 Variables based on data of the Vektis database

Socio-economic status
The SES was derived from the postcode of the person and the SES score for that postcode as determined by the Netherlands Institute for Social Research [34]. The SES score is based on the mean income of a postcode where a person lives, the fraction of people with a low income, the fraction of people with low education and the fraction of unemployed people. The SES score is ranked and the national mean is 0 (range -6.65; 3.02). A lower score indicates a lower SES and a higher scores indicates a higher SES.

Chronic conditions based on Pharmaceutical Cost Groups
Primary health insurance is compulsory for all Dutch citizens and within the Dutch healthcare system, all insurance companies are obliged to accept citizens applying for primary healthcare insurance. The healthcare insurance companies receive an equalization contribution from the Healthcare Insurance Fund each year. The amount of the equalization contribution depends on the composition of the insured population. The Zorginstituut Nederland (National Institute for Health Care) calculates the equalization contribution per healthcare insurance company [35]. Health insurance companies are by law obligated to periodically supply data to the National Institute for Health Care. The equalization contribution is calculated based on, among others, the age and gender of the insured population, the nature of income of the insured population (e.g. incapacity benefit, social assistance benefit or paid employment), the socio-economic status of the insured population and the PCGs of the insured population [35]. PCGs are based on the idea that a patient with a certain chronic condition can be identified by claims known to be prescribed for that chronic condition [19, 20]. An insured person is included into a specific PCG if more than a certain amount (accounting for approximately half a year of use e.g. over 180 defined daily doses) of prescribed drugs has been prescribed during a calendar year. The PCG are classified annually and different ATC codes of one PCG can be combined in order to reach the minimum defined daily doses. A person can have more chronic conditions and thus can be included in multiple PCGs [35]. The Vektis database includes claims for pharmaceutical care, stored in the Pharmacy Information System. This information system contains information on the ATC code of the provided drugs, the date the drug was supplied, and the quantity supplied [36]. Appendix tables 1a to 1u describe the ATC codes and the defined daily doses used for the classification of the PCGs. The definition of PCG is maintained by National Institute for Health Care and classification is routinely performed by Vektis [37]. The validity of pharmacy based claims data for the assessment of chronic conditions and prevalence estimates has been demonstrated before in different countries such as The Netherlands, Italy, Switzerland and Canada [20-24]. Databases on prescribed drugs are a valuable source for measuring population's burden of disease, when clinical data are missing [21].

Variable '>=1 new chronic conditions'	We created the dichotomous outcome variable >=1 new chronic conditions. If a person had no chronic condition during 2012, no chronic condition during 2013 and no chronic condition during 2014 then >=1 new chronic conditions was 0. If a person had no chronic condition during 2012, no chronic condition during 2013 and >=1 chronic condition during 2014, then >=1 new chronic conditions was 1.

Appendix 7.1 Variables based on data of the Vektis database (continued)

Variable 'pre-existing chronic conditions'	Within the logistic regression analyses, having >= 1 chronic conditions before ICU admission was taken into account as possible explanatory variable. We created a dichotomous variable: if a person had no chronic condition during 2012 and no chronic condition during 2013 then pre-existing chronic condition was 0, if a person had >=1 chronic condition during 2012 or >=1 chronic condition during 2013 then pre-existing chronic condition was 1.

Hospital and non-hospital population
The hospital population and the non-hospital population are subgroups of the control group and are created based on the Diagnosis Treatment Combinations (DTCs), in Dutch Diagnose Behandel Combinatie (DBC). DTCs are used in the Netherlands for hospital funding. A DTC is defined as all activities and services of hospital and medical specialists originating from the demand for care for which the patient consults the specialist. It covers the complete process of care: from the first consultation of the medical specialist until the completion of the treatment and therefore DTCs cover both outpatient costs and inpatient costs. Apart from these direct costs, indirect costs such as education, research and emergency care are also included [38, 39]. The medical specialist decides on the choice of the DTC to be assigned to a patient upon first contact. The choice for a DTC is made by using a set of guidelines on how to open, close and determine the type of DTC. Every specialty has its own set of instructions, which are updated if necessary. A new DTC is opened when (a) a patient visits a medical specialist for the first time with a new demand for care, (b) when the patient consults a specialist from a different specialty, (c) when a patient is transferred to another provider organization or (d) when a new demand for care arises that will lead to substantially higher costs and effort. A DTC is closed when either the whole treatment has come to an end or after 365 days [38]. DTC maintenance is an independent foundation responsible for adjusting and updating the DBC system. The hospital care providers are obliged to provide their DBC data to the DBC information system [39].

Hospital population	For the hospital population we included all persons which had a DTC declaration starting between 01-01-2013 and 31-12-2013 or a DTC declaration ending between 01-01-2013 and 31-12-2013 and thus had a hospital admission or a consultation with a specialist.
Non-hospital population	For the non-hospital population we included all persons with no DTC declaration starting or ending between 01-01-2013 and 31-12-2013 and thus had no hospital admission during 2013 nor seen a specialist during 2013.

Appendix 7.1a Defined daily doses for asthma

ATC code	Inhalation (aerosol)		Inhalation (powder)		Inhalation (solution)		Oral		Parenteral		Rectal	
R03AC02	0.8	mg	0.8	mg	10	mg						
R03AC03	2	mg	2	mg	20	mg						
R03AC12	0.1	mg	0.1	mg								
R03AC13	24	mcg	24	mcg								
R03AK06	4	do	2	do								
R03AK07	4	do	24	mcg								
R03BA01	0.8	mg	0.8	mg	1.5	mg						
R03BA02	0.8	mg	0.8	mg	1.5	mg						
R03BA05	0.6	mg	0.6	mg	1.5	mg						
R03BA08	0.16	mg										
R03BC01	40	mg	80	mg	80	mg						
R03BC03	8	mg										
R03CC02							12	mg	12	mg		
R03DA04							0.4	g	0.4	g	0.4	g
R03DC03							10	mg				

g: gram, mcg: microgram, mg: milligram, do: dose
Restriction: only if there is no ATC code for COPD/heavy asthma

Appendix 7.1b Defined daily doses for COPD/heavy asthma

ATC code	Inhalation (aerosol)		Inhalation (powder)		Inhalation (solution)	
R03AC18			150	mcg		
R03AK03	6	do	3	do		
R03AK04	6	do			7.5	ml
R03BB01	0.12	mg	0.12	mg	0.3	mg
R03BB04			18	mcg	5	mcg

mg: milligram, ml: milliliter, mcg: microgram, do: dose

Appendix 7.1c Defined daily doses for Crohn's disease/colitis ulcerosa

ATC code	Oral		Rectal	
A07EA04			100	ml
A07EA06	9	mg	1	tabl
A07EC02	1.5	g	1.5	g
A07EC03	1	g		

g: gram, ml: milliliter, mg: milligram, tabl: tablet

Appendix 7.1d Defined daily doses for Cystic Fibrosis/pancreas enzymes

ATC code	Inhalation (powder)		Inhalation (solution)		Oral	
A09AA02					4-6	tabl/caps
J01GB01			0.3	g		
J01XB01	3	miljU				
R05CB13			2.5	mg		

g: gram, miljU: million international unit, mg: milligram, tabl/caps: tablet/capsule

Appendix 7.1e Defined daily doses for depression

ATC code	Oral		Parenteral	
N06AA02	0.1	g	0.1	g
N06AA04	0.1	g	0.1	g
N06AA10	75	mg	30	mg
N06AA12	0.1	g	0.1	g
N06AA16	0.15	g		
N06AA21	0.1	g	0.1	g
N06AB03	20	mg		
N06AB04	20	mg	20	mg
N06AB05	20	mg		
N06AB06	50	mg		
N06AB08	0.1	g		
N06AB10	10	mg		
N06AF03	60	mg		
N06AF04	10	mg		
N06AG02	0.3	g		
N06AX01	50	mg		
N06AX03	60	mg		
N06AX05	0.3	g		
N06AX11	30	mg		
N06AX12	0.3	g*		
N06AX16	0.1	g		
N06AX22	25	mg		

g: gram, mg: milligram
Restriction: only if there is no ATC code for Psychoses, Alzheimer's disease and addictions, *drugs used to quit smoking excluded

Appendix 7.1f Defined daily doses for Diabetes Mellitus type I

ATC code	Parenteral	
A10AB01	40	IU
A10AB04	40	IU
A10AB05	40	IU
A10AB06	40	IU
A10AC01	40	IU
A10AD01	40	IU
A10AD04	40	IU
A10AD05	40	IU
A10AE04	40	IU
A10AE05	40	IU

IU: international unit

Appendix 7.1g Defined daily doses for Diabetes Mellitus type II

ATC code	Oral		Parenteral		Parenteral depot	
A10BA02	2	g				
A10BB01	10	mg				
A10BB03	1.5	g				
A10BB09	60	mg				
A10BB12	2	mg				
A10BD02	2	tabl				
A10BD03	2	tabl				
A10BD04	1	tabl				
A10BD05	2	tabl				
A10BD07	2	tabl				
A10BD08	2	tabl				
A10BD11	2	tabl				
A10BF01	0.3	g				
A10BG02	6	mg				
A10BG03	30	mg				
A10BH01	0.1	g				
A10BH02	0.1	g				
A10BH03	5	mg				
A10BH05	5	mg*				
A10BX02	4	mg				
A10BX04			15	mcg	286	mcg*
A10BX07			1.2	mg		

g: gram, mcg: microgram, mg: milligram, tabl: tablet
Restriction: Only if there is no ATC code for DM type I, * Added by the WHO since 01-01-2013

Appendix 7.1h Defined daily doses for diseases of the central neurological system

ATC-code	Oral		Parenteral	
L03AB07			4.3	mcg
L03AB08			4	miljU
L03AX13			20	mg
L04AA27	0.5	mg		
M03BX01	50	mg	0.55	mg
M03BX02	12	mg		
N07XX02	0.1	g		
N07XX08			20	mg

g: gram, mcg: microgram, mg: milligram, miljU: million international unit

Appendix 7.1i Defined daily doses for epilepsy

ATC-code	Oral		Parenteral		Rectal	
N03AA02	0.1	g	0.1	g		
N03AA03	1.25	g				
N03AB02	0.3	g	0.3	g		
N03AD01	1.25	g				
N03AE01	8	mg	8	mg		
N03AF01	1	g			1	g
N03AF02	1	g				
N03AF03	1.4	g				
N03AG01	1.5	g	1.5	g	1.5	g
N03AG04	2	g				
N03AX03	0.4	g				
N03AX09	0.3	g				
N03AX10	2.4	g				
N03AX11	0.3	g				
N03AX14	1.5	g	1.5	g		
N03AX15	0.2	g				
N03AX17	1	g				
N03AX18	0.3	g	0.3	g		
N03AX21	0.9	g*				
N05BA09	20	mg				

g: gram, mg: milligram
* Added by the WHO since 01-01-2013

Appendix 7.1j Defined daily doses for glaucoma

ATC-code	Oral		Parenteral		Ocular	
S01EA02					0.2	ml
S01EA03					0.3	ml
S01EA05					0.2	ml
S01EB01					0.4/40	ml/mg
S01EC01	0.75	g	0.75	g		
S01EC03					0.3	ml
S01EC04					0.2	ml
S01ED01					0.2	ml
S01ED02					0.2	ml
S01ED03					0.2	ml
S01ED04					0.2	ml
S01ED05					0.2	ml
S01ED51					0.1/0.2	ml
S01ED54					0.3	ml
S01EE01					0.1	ml
S01EE03					0.1	ml
S01EE04					0.1	ml
S01EE05					0.3	ml

mg: milligram, ml: milliliter

Appendix 7.1k Defined daily doses for heart diseases

ATC-code	Oral		Oral (aerosol)		Parenteral		Sublingual		Transdermal	
C01AA05	0.25	mg			0.25	mg				
C01BA01	1.2	g								
C01BA03	0.4	mg			0.4	mg				
C01BB01					3	g				
C01BC03	0.3	g			0.3	g				
C01BC04	0.2	g			0.2	g				
C01BD01	0.2	g			0.2	g				
C01CA16	0.3	g								
C01CE02					50	mg				
C01CE03					1	g				
C01DA02	5	mg	2.5	mg	10	mg	2.5	mg	5	mg
C01DA08	60	mg	20	mg	10	mg	20	mg	0.1	g
C01DA14	40	mg								
C01DX16	40	mg								
C01EB17	10	mg								
C03CA01	40	mg			40	mg				
C03CA02	1	mg			1	mg				

g: gram, mg: milligram

Appendix 7.1l Defined daily doses for high cholesterol

ATC code	Oral		Parenteral	
C04AD02	0.9	g	0.9	g
C10AA01	30	mg		
C10AA03	30	mg		
C10AA04	60	mg		
C10AA05	20	mg		
C10AA07	10	mg		
C10AB02	0.6	g		
C10AB04	1.2	g		
C10AB08	0.1	g		
C10AC01	14	g		
C10AC04	3.75	g		
C10AD02	2	g		
C10AD06	0.5	g		
C10AX09	10	mg		
C10BA02	1	tabl		

g: gram, tabl: tablet, mg: milligram
Restriction: only if there is no ATC code for heart diseases, DM type I or DM type II

Appendix 7.1m Defined daily doses for HIV/AIDS

ATC-code	Oral		Parenteral	
J05AB06	3	g	0.5	g
J05AB14	0.9	g		
J05AD01			6.5	g
J05AE01	1.8	g		
J05AE02	2.4	g		
J05AE03	1.2	g		
J05AE04	2.25	g		
J05AE06	0.8	g		
J05AE07	1.4	g		
J05AE08	0.3	g		
J05AE09	1	g		
J05AE10	1.2	g		
J05AF01	0.6	g	0.6	g
J05AF02	0.4	g		
J05AF04	80	mg		
J05AF05	0.3	g		
J05AF06	0.6	g		
J05AF07	0.245	g		
J05AF09	0.2	g		
J05AG01	0.4	g		
J05AG03	0.6	g		
J05AG04	0.4	g		
J05AG05	25	mg		
J05AR01	2	tabl		
J05AR02	1	tabl		
J05AR03	1	tabl		
J05AR04	2	tabl		
J05AR06	1	tabl		
J05AR08	1	tabl		
J05AX07			0.18	g
J05AX08	0.8	g		
J05AX09	0.6	g		

g: gram, tabl: tablet, mg: milligram
* Added by the WHO since 01-01-2013

Appendix 7.1n Defined daily doses for hormone sensitive tumours

ATC-code	Oral		Parenteral		Parenteral depot		Nasal		Implantation	
H01CA03									0.137	mg
H01CB05			1.2	mg						
L02AB01	0.16	g								
L02AB02	1	g	1	g						
L02AE01			1.5	mg			1.2	mg	0.11	mg
L02AE02			1	mg	0.134	mg				
L02AE03									0.129	mg
L02BA01	20	mg								
L02BA03			8.3	mg						
L02BB01	0.75	g								
L02BB02	0.3	g								
L02BB03	50	mg								
L02BG03	1	mg								
L02BG04	2.5	mg								
L02BG06	25	mg								
L02BX01			3.571	mg						
L02BX02			2.7	mg						

g: gram, mg: milligram
Restriction: Only if there is no ATC code for cancer

Appendix 7.1o Defined daily doses for kidney diseases

ATC-code	Oral		Parenteral	
B03XA01			1000	IU
B03XA02			4.5	mcg
B03XA03			4	mcg
V03AE01	45	mg		
V03AE02	6.4	g		
V03AE03	2.25	g		
V03AE04	6	tabl		

g: gram, tabl: tablet, mg: milligram, IU: international Unit, mcg: microgram

Appendix 7.1p Defined daily doses for neuropathic pains

ATC-code	Oral		Parenteral		Transdermal	
N01BX04					4	g
N03AX12	1.8	g				
N03AX16	0.3	g				
N06AA09	75	mg	75	mg		
N06AX21	60	mg				

g: gram, mg: milligram

Appendix 7.1q Defined daily doses for Parkinson's disease

ATC-code	Oral		Parenteral		Transdermal	
N04BA02	0.6	g				
N04BA03	0.45	g				
N04BB01	0.2	g				
N04BC01	40	mg				
N04BC02	3	mg				
N04BC04	6	mg				
N04BC05	2.5	mg				
N04BC07			20	mg		
N04BC09					6	mg
N04BD01	5	mg				
N04BD02	1	mg				
N04BX01	0.45	g				
N04BX02	1	g				

g: gram, mg: milligram

Appendix 7.1r Defined daily doses for psychoses, Alzheimer's disease and addictions

ATC-code	Oral		Parenteral		Parenteral depot		Rectal		Transdermal		Sublingual	
N05AA01	0.3	g	0.1	g			0.3	g				
N05AB02	10	mg	1	mg								
N05AB03	30	mg	10	mg	7	mg	16	mg				
N05AC01	50	mg	20	mg								
N05AD01	8	mg	8	mg	3.3	mg						
N05AD05	0.2	g										
N05AD06	10	mg	10	mg	3.3	mg						
N05AE03	16	mg										
N05AF01	6	mg	4	mg								
N05AF03	0.3	g	50	mg								
N05AF05	30	mg	30	mg	15	mg						
N05AG01			0.7	mg								
N05AG02	4	mg										
N05AG03	6	mg										
N05AH02	0.3	g	0.3	g								
N05AH03	10	mg	10	mg	10	mg						
N05AH04	0.4	g										
N05AL01	0.8	g	0.8	g								
N05AX08	5	mg			2.7	mg						
N05AX12	15	mg	15	mg								
N05AX13	6	mg			2.5	mg						
N06DA03	9	mg							9.5	mg		
N06DA04	16	mg										
N06DX01	20	mg										
N07BB01	0.2	g										
N07BB03	2	g										
N07BB04	50	mg										
N07BC01											8	mg
N07BC02	25	mg	25	mg								
N07BC51											8	mg

g: gram, mg: milligram

Appendix 7.1s Defined daily doses for rheumatism

ATC-code	Oral		Parenteral		Rectal	
A07EC01	2	g			2	g
L01BA01			3.571	mg		
L04AA13	20	mg				
L04AX03	2.5	mg				
M01CB01			2.4	mg		
M01CC01	0.5	g				
P01BA02	0.516	g				

g: gram, mg: milligram

Appendix 7.1t Defined daily doses for thyroid diseases

ATC-code	Oral		Parenteral	
H03AA01	0.15	mg	0.15	mg
H03AA02	60	mcg	60	mcg
H03BA02	0.1	g		
H03BB01	15	mg		
H03BB02	10	mg		

g: gram, mg: milligram, mcg: microgram

Appendix 7.1u Defined daily doses for transplantations

ATC-code	Oral		Parenteral	
L04AA06	2	g	2	g
L04AA10	3	mg		
L04AA18	1.5	mg		
L04AD01	0.25	g	0.25	g
L04AD02	5	mg	5	mg
L04AX01	0.15	g	0.15	g

g: gram, mg: milligram

Appendix 7.2 Details of logistic regression analyses for the ICU population compared to the control group

Outcome variable		ICU population	Control group
One or more chronic conditions	Crude OR	4.44 (4.19; 4.71)	
	OR for males *	5.29 (4.90; 5.72)	
	OR for females *	4.39 (3.99; 4.83)	
	Age	1.03 (1.02; 1.03)	1.04 (1.03; 1.04)
	Gender	0.76 (0.70; 0.83)	0.92 (0.84; 1.00)
	SES	0.98 (0.94; 1.01)	0.96 (0.92; 0.99)
High cholesterol	Crude OR	3.41 (3.17; 3.68)	
	OR for males ‡	5.30 (4.79; 5.87)	
	OR for females ‡	3.26 (2.83; 3.75)	
	Age	1.03 (1.03; 1.04)	1.04 (1.03; 1.04)
	Gender	0.46 (0.41; 0.51)	0.75 (0.66; 0.84)
	SES	0.98 (0.94; 1.02)	0.96 (0.91; 1.01)
	Pre-existing chronic conditions	0.78 (0.69; 0.87)	1.32 (1.15; 1.51)
Heart diseases	Crude OR	5.02 (4.62; 5.47)	
	OR for males ‡	7.46 (6.22; 8.95)	
	OR for females ‡	9.9 (8.11; 12.08)	
	Age	1.05 (1.05; 1.06)	1.09 (1.08; 1.10)
	Gender	1.14 (1.04; 1.25)	0.86 (0.74; 1.00)
	SES	0.96 (0.92; 1.00)	0.88 (0.82; 0.93)
	Pre-existing chronic conditions	1.69 (1.52; 1.87)	2.39 (2.04; 2.80)
COPD	Crude OR	3.60 (3.18; 4.07)	
	OR for males ‡	4.32 (3.33; 5.59)	
	OR for females ‡	6.01 (4.49; 8.05)	
	Age	1.02 (1.02; 1.03)	1.04 (1.03; 1.05)
	Gender	0.99 (0.86; 1.14)	0.71 (0.57; 0.89)
	SES	0.93 (0.88; 0.99)	0.95 (0.87; 1.04)
	Pre-existing chronic conditions	1.64 (1.38; 1.94)	2.71 (2.14; 3.42)
Depression	Crude OR	2.84 (2.51; 3.22)	
	OR for males ‡	3.13 (2.45; 4.01)	
	OR for females ‡	3.09 (2.44; 3.91)	
	Age	0.99 (0.98; 0.99)	0.99 (0.98; 1.00)
	Gender	1.65 (1.42; 1.91)	1.67 (1.36; 2.04)
	SES	1.06 (0.99; 1.13)	1.02 (0.93; 1.12)
	Pre-existing chronic conditions	1.08 (0.92; 1.28)	1.42 (1.14; 1.77)

Appendix 7.2 Details of logistic regression analyses for the ICU population compared to the control group (continued)

Outcome variable		ICU population	Control group
DM 2	Crude OR	2.09 (1.83; 2.38)	
	OR for males ‡	2.99 (2.23; 4.02)	
	OR for females ‡	3.49 (2.50; 4.88)	
	Age	1.02 (1.01; 1.02)	1.01 (1.00; 1.01)
	Gender	0.80 (0.67; 0.97)	0.69 (0.56; 0.85)
	SES	0.86 (0.80; 0.93)	0.92 (0.85; 1.00)
	Pre-existing chronic conditions	1.93 (1.56; 2.40)	4.80 (3.78; 6.10)
Asthma	Crude OR	1.73 (1.51; 1.98)	
	OR for males ‡	1.67 (1.29; 2.17)	
	OR for females ‡	2.41 (1.85; 3.13)	
	Age	1.01 (1.00; 1.02)	1.01 (1.00; 1.02)
	Gender	1.67 (1.38; 2.02)	1.16 (0.95; 1.41)
	SES	0.95 (0.87; 1.03)	1.02 (0.94; 1.12)
	Pre-existing chronic conditions	1.10 (0.89; 1.35)	1.56 (1.27; 1.93)
Epilepsy	Crude OR	11.86 (8.96; 15.7)	
	OR for males ‡	24.35 (14.00; 42.34)	
	OR for females ‡	20.91 (11.77; 37.15)	
	Age	0.99 (0.98; 0.99)	1.01 (0.99; 1.03)
	Gender	1.06 (0.88; 1.29)	1.24 (0.73; 2.10)
	SES	1.01 (0.93; 1.10)	1.05 (0.83; 1.33)
	Pre-existing chronic conditions	0.63 (0.51; 0.77)	2.46 (1.36; 4.44)
DM 1	Crude OR	4.06 (3.39; 4.86)	
	OR for males ‡	9.17 (4.69; 17.93)	
	OR for females ‡	13.80 (6.80; 28.00)	
	Age	1.00 (1.00; 1.01)	0.99 (0.98; 1.00)
	Gender	0.96 (0.79; 1.17)	0.64 (0.46; 0.89)
	SES	0.94 (0.86; 1.01)	1.00 (0.87; 1.14)
	Pre-existing chronic conditions	4.73 (3.42; 6.55)	21.82 (11.89; 40.06)

*OR given for population with median age (65 year) and median SES (0.2)

‡ OR given for population with median age (65 year) and median SES (0.2) and pre-existing chronic conditions = no

Interaction term references: gender = male, pre-existing chronic condition = no

Appendix 7.3 New developed chronic conditions within the ICU population and the control subgroups during 2014

	ICU population (n=49,004)	Hospital population (n=44,017)	*p*-value*	Non-hospital population (n=27,871)	*p*-value‡
Population with one or more new chronic conditions	6,222 (12.7%)	2,786 (6.3%)	<0.0001	869 (3.1%)	<0.0001
Chronic conditions					
High cholesterol	2,638 (5.4%)	1,031 (2.3%)	<0.0001	391 (1.4%)	<0.0001
Heart diseases	2,102 (4.3%)	659 (1.5%)	<0.0001	92 (0.3%)	<0.0001
COPD	841 (1.7%)	306 (0.7%)	<0.0001	63 (0.2%)	<0.0001
DM 2	610 (1.2%)	316 (0.7%)	<0.0001	110 (0.4%)	<0.0001
DM 1	433 (0.9%)	143 (0.3%)	<0.0001	22 (0.1%)	<0.0001
Depression	747 (1.5%)	274 (0.6%)	<0.0001	123 (0.4%)	<0.0001
Asthma	585 (1.2%)	371 (0.8%)	<0.0001	115 (0.4%)	<0.0001
Thyroid diseases	312 (0.6%)	141 (0.3%)	<0.0001	45 (0.2%)	<0.0001
Glaucoma	153 (0.3%)	189 (0.4%)	0.0018	23 (0.1%)	<0.0001
Neuropathic pains	324 (0.7%)	71 (0.2%)	<0.0001	6 (0.0%)	<0.0001
Psychoses, Alzheimer's disease and addictions	284 (0.6%)	116 (0.3%)	<0.0001	28 (0.1%)	<0.0001
Epilepsy	434 (0.9%)	45 (0.1%)	<0.0001	10 (0.0%)	<0.0001
Rheumatism	102 (0.2%)	94 (0.2%)	0.8466	10 (0.0%)	<0.0001
Hormone sensitive tumours	122 (0.2%)	116 (0.3%)	0.6351	13 (0.0%)	<0.0001
Kidney diseases	239 (0.5%)	48 (0.1%)	<0.0001	2 (0.0%)	<0.0001
Transplantations	211 (0.4%)	16 (0.0%)	<0.0001	0 (0.0%)	<0.0001
Crohn's disease	46 (0.1%)	26 (0.1%)	0.0566	6 (0.0%)	0.0002
Parkinson's disease	46 (0.1%)	52 (0.1%)	0.2483	3 (0.0%)	<0.0001
Diseases of the central neurological system	71 (0.1%)	8 (0.0%)	<0.0001	1 (0.0%)	<0.0001
Cystic fibrosis / pancreas enzymes	136 (0.3%)	12 (0.0%)	<0.0001	1 (0.0%)	<0.0001
HIV	39 (0.1%)	5 (0.0%)	<0.0001	0 (0.0%)	<0.0001

* *p*-value given for differences in prevalence between ICU population and hospital population
‡ *p*-value given for differences in prevalence between ICU population and non-hospital population

Appendix 7.4 Characteristics of the ICU population and the control subgroups during 2012

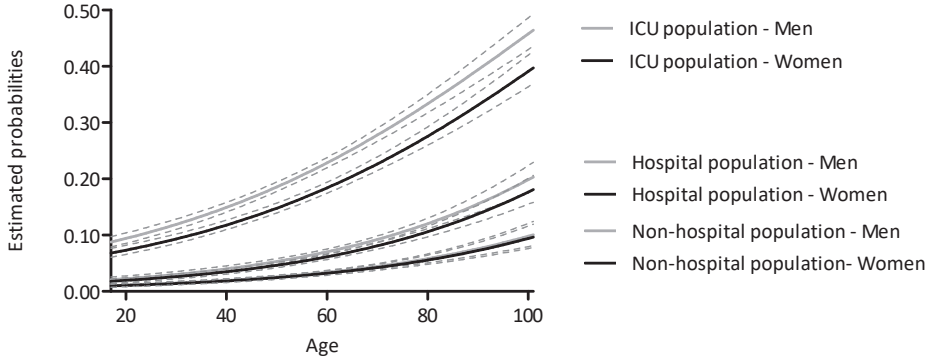
Characteristics	ICU population (n=56,760)	Hospital population (n=46,694)	Non-hospital population (n=28,538)
Male [a]	34,111 (60.1%)	27,377 (58.6%)	17,365 (60.9%)
Age [b]	65 (53; 73)	68 (60; 76)	59 (47; 68)
SES [b]	0.2 (-0.6; 0.8)	0.1 (-0.6; 0.8)	0.2 (-0.6; 0.8)
Died during 2013 [a]	3,465 (6.1%)	1,325 (2.8%)	334 (1.2%)
Died during 2014 [a]	4,291 (8.1%)	1,352 (3.0%)	333 (1.2%)

[a] Number and percentage
[b] Median and IQR

Appendix 7.5 Prevalence of chronic conditions within the ICU population and the control subgroups during 2012

	ICU population (n=56,760)	Hospital population (n=46,694)	*p*-value*	Non-hospital population (n=28,538)	*p*-value‡
Population with one or more chronic conditions	31,472 (55.4%)	23,293 (49.9%)	<0.0001	5,609 (19.7%)	<0.0001
Chronic condition					
High cholesterol	9,348 (16.5%)	8,061 (17.3%)	0.0010	2,515 (8.8%)	<0.0001
Heart diseases	7,954 (14.0%)	4,543 (9.7%)	<0.0001	454 (1.6%)	<0.0001
COPD	4,454 (7.8%)	2,126 (4.6%)	<0.0001	319 (1.1%)	<0.0001
DM 2	4,274 (7.5%)	3,332 (7.1%)	0.0131	755 (2.6%)	<0.0001
DM 1	3,705 (6.5%)	2,059 (4.4%)	<0.0001	195 (0.7%)	<0.0001
Depression	3,427 (6.0%)	1,906 (4.1%)	<0.0001	750 (2.6%)	<0.0001
Asthma	2,808 (4.9%)	1,924 (4.1%)	<0.0001	494 (1.7%)	<0.0001
Thyroid diseases	1,954 (3.4%)	1,611 (3.5%)	0.9815	447 (1.6%)	<0.0001
Glaucoma	1,432 (2.5%)	1,848 (4.0%)	<0.0001	76 (0.3%)	<0.0001
Neuropathic pains	1,106 (1.9%)	453 (1.0%)	<0.0001	90 (0.3%)	<0.0001
Psychoses, Alzheimer's disease and addictions	1,018 (1.8%)	401 (0.9%)	<0.0001	200 (0.7%)	<0.0001
Epilepsy	983 (1.7%)	457 (1.0%)	<0.0001	94 (0.3%)	<0.0001
Rheumatism	609 (1.1%)	542 (1.2%)	0.1883	9 (0.0%)	<0.0001
Hormone sensitive tumours	553 (1.0%)	677 (1.4%)	<0.0001	15 (0.1%)	<0.0001
Kidney diseases	489 (0.9%)	150 (0.3%)	<0.0001	1 (0.0%)	<0.0001
Transplantations	419 (0.7%)	159 (0.3%)	<0.0001	4 (0.0%)	<0.0001
Crohn's disease	263 (0.5%)	233 (0.5%)	0.4180	13 (0.0%)	<0.0001
Parkinson's disease	243 (0.4%)	334 (0.7%)	<0.0001	12 (0.0%)	<0.0001
Diseases of the central neurological system	201 (0.4%)	48 (0.1%)	<0.0001	8 (0.0%)	<0.0001
Cystic fibrosis / pancreas enzymes	153 (0.3%)	46 (0.1%)	<0.0001	3 (0.0%)	<0.0001
HIV	87 (0.2%)	58 (0.1%)	0.2106	1 (0.0%)	<0.0001

* *p*-value given for differences in prevalence between ICU population and hospital population
‡ *p*-value given for differences in prevalence between ICU population and non-hospital population



Appendix 7.6 Risk of developing >= 1 new chronic conditions for the ICU population and the control subgroups

Appendix 7.7 Details of logistic regression analyses for the ICU population compared to the hospital population

Outcome variable		ICU population	Hospital population
One or more chronic conditions	Crude OR	3.03 (2.84; 3.24)	
	OR for males *	3.86 (3.53; 4.21)	
	OR for females *	3.39 (3.05; 3.77)	
	Age	1.03 (1.02; 1.03)	1.03 (1.03; 1.03)
	Gender	0.76 (0.70; 0.83)	0.87 (0.78; 0.97)
	SES	0.98 (0.94; 1.01)	0.97 (0.93; 1.02)
High cholesterol	Crude OR	2.58 (2.37; 2.81)	
	OR for males ‡	4.12 (3.66; 4.63)	
	OR for females ‡	2.62 (2.24; 3.06)	
	Age	1.03 (1.03; 1.04)	1.03 (1.02; 1.03)
	Gender	0.46 (0.41; 0.51)	0.72 (0.63; 0.83)
	SES	0.98 (0.94; 1.02)	0.96 (0.90; 1.02)
	Pre-existing chronic conditions	0.78 (0.69; 0.87)	1.09 (0.94; 1.28)
Heart diseases	Crude OR	3.36 (3.07; 3.67)	
	OR for males ‡	5.20 (4.26; 6.35)	
	OR for females ‡	6.66 (5.37; 8.25)	
	Age	1.05 (1.05; 1.06)	1.08 (1.07; 1.09)
	Gender	1.14 (1.04; 1.25)	0.89 (0.76; 1.04)
	SES	0.96 (0.92; 1.00)	0.89 (0.84; 0.95)
	Pre-existing chronic conditions	1.69 (1.52; 1.87)	1.95 (1.64; 2.31)

Appendix 7.7 Details of logistic regression analyses for the ICU population compared to the hospital population (continued)

Outcome variable		ICU population	Hospital population
COPD	Crude OR	2.61 (2.29; 2.98)	
	OR for males ‡	3.17 (2.38; 4.22)	
	OR for females ‡	3.99 (2.91; 5.48)	
	Age	1.02 (1.02; 1.03)	1.03 (1.02; 1.04)
	Gender	0.99 (0.86; 1.14)	0.79 (0.62; 0.99)
	SES	0.93 (0.88; 0.99)	0.95 (0.86; 1.04)
	Pre-existing chronic conditions	1.64 (1.38; 1.94)	2.15 (1.66; 2.80)
Depression	Crude OR	2.48 (2.15; 2.86)	
	OR for males ‡	2.75 (2.06; 3.65)	
	OR for females ‡	2.83 (2.16; 3.72)	
	Age	0.99 (0.98; 0.99)	0.99 (0.98; 0.99)
	Gender	1.65 (1.42; 1.91)	1.59 (1.25; 2.03)
	SES	1.06 (0.99; 1.13)	1.05 (0.95; 1.17)
	Pre-existing chronic conditions	1.08 (0.92; 1.28)	1.45 (1.12; 1.89)
DM 2	Crude OR	1.70 (1.47; 1.97)	
	OR for males ‡	2.48 (1.77; 3.47)	
	OR for females ‡	2.71 (1.87; 3.94)	
	Age	1.02 (1.01; 1.02)	1.00 (0.99; 1.01)
	Gender	0.80 (0.67; 0.97)	0.73 (0.57; 0.94)
	SES	0.86 (0.80; 0.93)	0.90 (0.81; 0.99)
	Pre-existing chronic conditions	1.93 (1.56; 2.40)	3.76 (2.81; 5.04)
Asthma	Crude OR	1.38 (1.19; 1.59)	
	OR for males ‡	1.26 (0.95; 1.67)	
	OR for females ‡	1.91 (1.43; 2.54)	
	Age	1.01 (1.00; 1.02)	1.01 (1.00; 1.02)
	Gender	1.67 (1.38; 2.02)	1.10 (0.87; 1.38)
	SES	0.95 (0.87; 1.03)	1.01 (0.92; 1.12)
	Pre-existing chronic conditions	1.10 (0.89; 1.35)	1.27 (1.00; 1.61)
DM 1	Crude OR	2.82 (2.33; 3.41)	
	OR for males ‡	8.44 (3.52; 20.23)	
	OR for females ‡	11.95 (4.86; 29.40)	
	Age	1.00 (1.00; 1.01)	0.99 (0.98; 1.01)
	Gender	0.96 (0.79; 1.17)	0.68 (0.47; 0.97)
	SES	0.94 (0.86; 1.01)	0.99 (0.86; 1.14)
	Pre-existing chronic conditions	4.73 (3.42; 6.55)	22.29 (9.74; 51.03)

*OR given for population with median age (65 year) and median SES (0.2)
‡ OR given for population with median age (65 year). median SES (0.2) and pre-existing chronic conditions = no
Interaction term references: gender = male, pre-existing chronic conditions = no
Epilepsy not analysed due to lack of power

Appendix 7.8 Details of logistic regression analyses for the ICU population compared to the non-hospital population

Outcome variable		ICU population	Non-hospital population
One or more chronic conditions	Crude OR	7.55 (6.93; 8.22)	
	OR for males *	8.46 (7.54; 9.49)	
	OR for females *	6.76 (5.86; 7.79)	
	Age	1.03 (1.02; 1.03)	1.03 (1.02; 1.03)
	Gender	0.76 (0.70; 0.83)	0.95 (0.81; 1.12)
	SES	0.98 (0.94; 1.01)	0.93 (0.87; 0.99)
High cholesterol	Crude OR	5.31 (4.74; 5.95)	
	OR for males ‡	7.30 (6.28; 8.49)	
	OR for females ‡	4.47 (3.64; 5.51)	
	Age	1.03 (1.03; 1.04)	1.04 (1.03; 1.05)
	Gender	0.46 (0.41; 0.51)	0.75 (0.60; 0.93)
	SES	0.98 (0.94; 1.02)	0.94 (0.86; 1.03)
	Pre-existing chronic conditions	0.78 (0.69; 0.87)	1.72 (1.28; 2.32)
Heart diseases	Crude OR	16.95 (13.75; 20.89)	
	OR for males ‡	16.04 (11.15; 23.08)	
	OR for females ‡	24.73 (15.87; 38.53)	
	Age	1.05 (1.05; 1.06)	1.09 (1.07; 1.11)
	Gender	1.14 (1.04; 1.25)	0.74 (0.48; 1.14)
	SES	0.96 (0.92; 1.00)	0.77 (0.65; 0.91)
	Pre-existing chronic conditions	1.69 (1.52; 1.87)	2.54 (1.68; 3.85)
COPD	Crude OR	8.39 (6.49; 10.84)	
	OR for males ‡	6.55 (4.28; 10.03)	
	OR for females ‡	15.88 (8.6; 29.33)	
	Age	1.02 (1.02; 1.03)	1.05 (1.03; 1.07)
	Gender	0.99 (0.86; 1.14)	0.41 (0.23; 0.73)
	SES	0.93 (0.88; 0.99)	0.97 (0.78; 1.21)
	Pre-existing chronic conditions	1.64 (1.38; 1.94)	3.41 (2.04; 5.69)
Depression	Crude OR	3.67 (3.01; 4.46)	
	OR for males ‡	3.62 (2.56; 5.13)	
	OR for females ‡	3.38 (2.41; 4.74)	
	Age	0.99 (0.98; 0.99)	0.99 (0.98; 1.00)
	Gender	1.65 (1.42; 1.91)	1.76 (1.22; 2.53)
	SES	1.06 (0.99; 1.13)	0.95 (0.81; 1.12)
	Pre-existing chronic conditions	1.08 (0.92; 1.28)	0.82 (0.48; 1.41)

Appendix 7.8 Details of logistic regression analyses for the ICU population compared to the non-hospital population (continued)

Outcome variable		ICU population	Non-hospital population
DM 2	Crude OR	3.09 (2.51; 3.81)	
	OR for males ‡	3.49 (2.32; 5.23)	
	OR for females ‡	5.14 (3.10; 8.53)	
	Age	1.02 (1.01; 1.02)	1.01 (1.00; 1.03)
	Gender	0.80 (0.67; 0.97)	0.55 (0.36; 0.83)
	SES	0.86 (0.80; 0.93)	1.00 (0.85; 1.19)
	Pre-existing chronic conditions	1.93 (1.56; 2.40)	7.03 (4.65; 10.61)
Asthma	Crude OR	2.76 (2.22; 3.42)	
	OR for males ‡	2.65 (1.82; 3.86)	
	OR for females ‡	3.47 (2.35; 5.14)	
	Age	1.01 (1.00; 1.02)	1.00 (0.99; 1.02)
	Gender	1.67 (1.38; 2.02)	1.27 (0.86; 1.88)
	SES	0.95 (0.87; 1.03)	1.05 (0.88; 1.26)
	Pre-existing chronic conditions	1.10 (0.89; 1.35)	1.91 (1.23; 2.97)

*OR given for population with median age (65 year) and median SES (0.2)

‡ OR given for population with median age (65 year). median SES (0.2) and pre-existing chronic conditions = no

Interaction term references: gender = male, pre-existing chronic conditions = no

Epilepsy and DM 1 not analysed due to lack of power

REFERENCES

1. Baskett PJ: Is an intensive care unit really necessary? Bristol Med Chir J 1965; 80:82-6
2. Pearce DJ: Experiences in a small respiratory unit of a general hospital with special reference to the treatment of tetanus. Anaesthesia 1961; 16:308-16
3. Brinkman S, de Jonge E, Abu-Hanna A, et al: Mortality after hospital discharge in ICU patients. Crit Care Med 2013; 41:1229-36
4. Wunsch H, Angus DC, Harrison DA, et al: Variation in critical care services across North America and Western Europe. Crit Care Med 2008; 36:2787-93
5. Australian and New Zealand Intensive Care Society: ANZICS Centre for Outcome and Resource Evaluation Annual Report 2014-2015. Melbourne: 2016.
6. Canadian Institute for Health Information: Care in Canadian ICUs. Ottawa, ON: 2016.
7. van der Schaaf M, Beelen A, Dongelmans DA, et al: Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med 2009; 41:1041-8
8. van der Schaaf M, Beelen A, Dongelmans DA, et al: Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med 2009; 41:360-6
9. Needham DM, Davidson J, Cohen H, et al: Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med 2012; 40:502-9
10. Koster-Brouwer ME, van de Groep K, Pasma W, et al: Chronic healthcare expenditure in survivors of sepsis in the intensive care unit. Intensive Care Med 2016; 42:1641-2
11. Lone NI, Gillies MA, Haddow C, et al: Five Year Mortality and Hospital Costs Associated With Surviving Intensive Care. Am J Respir Crit Care Med 2016; 194:198-208
12. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, et al: Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: A descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care 2017; 44:345-51
13. Gijsen R, Hoeymans N, Schellevis FG, et al: Causes and consequences of comorbidity: a review. J Clin Epidemiol 2001; 54:661-74
14. Fortin M, Lapointe L, Hudon C, et al: Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2004; 2:51
15. Dutch National Intensive Care Evaluation (NICE) registry Available at: http://www.stichting-nice.nl Accessed 08.11.2016
16. Vektis. Available at: http://www.vektis.nl. Accessed 08.11.2016
17. van de Klundert N, Holman R, Dongelmans DA, et al: Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol 2015; 44:1850-
18. Centraal Bureau voor de Statistiek (CBS). Statline. Available at: http://statline.cbs.nl/Statweb/dome/default.aspx. Accessed 17.01.2019
19. Lamers LM: Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. Med Care 1999; 37:824-30
20. Lamers LM, van Vliet RC: The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy 2004; 68:113-21
21. Huber CA, Szucs TD, Rapold R, et al: Identifying patients with chronic conditions using pharmacy data in Switzerland: an updated mapping approach to the classification of medications. BMC Public Health 2013; 13:1030

22. Maio V, Yuen E, Rabinowitz C, et al: Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. J Health Serv Res Policy 2005; 10:232-8
23. Chini F, Pezzotti P, Orzella L, et al: Can we use the pharmacy data to estimate the prevalence of chronic conditions? a comparison of multiple data sources. BMC Public Health 2011; 11:688
24. Tamblyn R, Lavoie G, Petrella L, et al: The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995; 48:999-1009
25. Roos LL, Wajda A: Record linkage strategies. Part I: Estimating information and evaluating approaches. Methods Inf Med 1991; 30:117-23
26. Hill AD, Fowler RA, Pinto R, et al: Long-term outcomes and healthcare utilization following critical illness - a population-based study. Crit Care 2016; 20:76
27. Marengoni A, Angleman S, Melis R, et al: Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011; 10:430-9
28. van den Akker M, Buntinx F, Metsemakers JF, et al: Multimorbidity in general practice: prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol 1998; 51:367-75
29. Bertakis KD, Azari R, Helms LJ, et al: Gender differences in the utilization of health care services. J Fam Pract 2000; 49:147-52
30. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, et al: Gender differences in the utilization of health-care services among the older adult population of Spain. BMC Public Health 2006; 6:155
31. Roberts KC, Rao DP, Bennett TL, et al: Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. Health Promot Chronic Dis Prev Can 2015; 35:87-94
32. Centraal Bureau voor de Statistiek (CBS): Door de huisarts geregistreerde contacten; leeftijd en geslacht. Available at: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=80191ned&D1=0,4&D2=0&D3=5-20,24-26&D4=0&D5=6&HDR=G3,G1,G4&STB=T,G2&VW=T. Accessed 01.04.2018
33. Ali Abdelhamid Y, Kar P, Finnis ME, et al: Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care 2016; 20:301
34. Knol F. Van hoog naar laag; van laag naar hoog. Den Haag: Sociaal en Cultureel Planbureau / Elsevier Bedrijfsinformatie; 1998.
35. Zorginstituut Nederland. Available at: https://www.zorginstituutnederland.nl/financiering/risicoverevening-zvw/wat-is-risicoverevening. Accessed 10.06.2018
36. WHO Collaborating Centre for Drug Statistics Methodology. Available at: https://www.whocc.no/. Accessed 10.6.2018
37. National Health Care Institute. Available at: https://english.zorginstituutnederland.nl. Accessed 08.11.2016
38. Hasaart F. Incentives in the Diagnosis Treatment Combination payment system for specialist medical care. A study about behavioral responses of medical specialists and hospitals in the Netherlands.: University of Maastricht; 2011.
39. Schafer W, Kroneman M, Boerma W, et al: The Netherlands: health system review. Health Syst Transit 2010; 12:v-xxvii, 1-228

Chapter 8

The influence of ICU related clinical variables on the risk of developing chronic conditions within a population of ICU survivors

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Submitted

ABSTRACT

Purpose: To gain insight in the association of clinical variables, measured during the first 24-hours of ICU admission, and the development of specified chronic conditions within a population of ICU survivors.

Materials and methods: A retrospective cohort study, combining a national health insurance claims database and a national quality registry for ICUs. Claims data from 2012-2014 were combined with clinical data of patients admitted to an ICU during 2013. To assess the association of clinical variables and the development of chronic conditions, logistic regression was used.

Results: The study population consisted of 49,004 patients. ICU length of stay was associated with the development of heart diseases, asthma or COPD and depression. The reason of ICU admission was an important risk factor for the development of all chronic conditions with ORs ranging from 2.05 (CI 1.56; 2.69) for kidney diseases to 5.14 (CI 3.99; 6.62) for depression.

Conclusions: ICU related clinical variables are associated with the development of chronic conditions, especially the reason of ICU admission. Follow-up care should be offered to ICU survivors in order to address the complaints ICU survivors suffer after discharge and the found risk factors should be taken into consideration as inclusion criteria for follow-up care.

INTRODUCTION

Intensive care unit (ICU) patients are life threatening ill and after hospital discharge they have a decreased quality of life because they suffer long-term and severe complaints such as physical and cognitive problems, social problems, financial difficulties, and restrictions in return to home because of their health status [1, 2]. The term post-intensive care syndrome (PICS) was introduced to identify the presence of one or more impairments after critical illness [3]. In addition to these complaints, ICU survivors have a fivefold higher risk of developing chronic conditions compared to a general population based control group [4].

It is important to gain more insight in the development of chronic conditions, since people having multiple chronic conditions are more prone to have a decreased quality of life [5, 6] and comorbidities have been recognised as predictors for increased healthcare costs [7, 8]. The prevalence of chronic conditions is increasing worldwide and this causes great stress on the healthcare system [9].

Factors such as gender, age, socio-economic status (SES) and Body Mass Index (BMI) are frequently mentioned risk factors for developing chronic conditions [10, 11]. However, these factors might partly explain the differences in risk of developing chronic conditions between a general population based control group and ICU patients, but not all [4].

There is evidence that mechanisms common to critical illness and treatments provided in the ICU may contribute to PICS. For example, ICU acquired weakness (ICU-AW) due to pathophysiological mechanisms and inactivity leading to delayed recovery of physical function [12] and the occurrence of delirium during critical illness leading to decreased neuropsychological functioning and post-traumatic stress disorder after hospital discharge [13].

However, there is limited evidence on which ICU related clinical variables lead to an increased risk of developing chronic conditions. Identifying ICU related risk factors for developing chronic conditions is important for the prevention of PICS, targeted care such as ICU follow-up care and, eventually, reducing healthcare expenditure. Therefore, the aim of this study was to gain insight in the association of ICU related clinical variables and the development of specified chronic conditions after hospitalization.

METHODS

We conducted a retrospective cohort study, combining data of the Dutch National Intensive Care Evaluation (NICE) registry [14] with data of the insurance claims database of Vektis [15].

Vektis insurance claims database

Health insurance is compulsory for all Dutch citizens and essentially all (99%) of the Dutch inhabitants have private healthcare insurance [16]. The Vektis databases [15] contain reimbursement data on all medical treatments paid for by Dutch insurance companies, as well as demographic information, such as gender, date of birth and a proxy for date of death, for all registered residents of the Netherlands. The SES was derived from the post code, and the SES score for that post code was determined by the Netherlands Institute for Social Research [17]. The SES score is based on the mean income of an post code where a person lives, the fraction of people with a low income, the fraction of people with low education and the fraction of unemployed people. The SES score is ranked and the national mean is 0 (range -6.65; 3.02). A lower score indicates a lower SES and a higher scores indicates a higher SES.

Vektis also includes claims for pharmaceutical care in the Pharmacy Information System. This information system contains information on provided drugs, including the Anatomical Therapeutic Chemical (ATC) code, the date the drug was supplied, and the quantity that was supplied. To determine chronic conditions, pharmaceutical cost groups (PCG) were used as a proxy. PCGs are based on the idea that a patient with a certain chronic condition can be identified by claims for specific prescribed drugs [18, 19].

The definition of PCGs is maintained by the Zorginstituut Nederland (National Health Care Institute) and classification is routinely performed by Vektis [20]. A complete description of the ATC codes and chronic conditions, as used in the year 2014, are extensively described in a previous published study [4].

All patients in the Vektis database who had a claim for an ICU day in the year 2013 and were >= 18 years during the year of ICU admission were included in the ICU-subset of the Vektis database.

Dutch National Intensive Care Evaluation database

The NICE registry is a national quality registry in which during the study period 90% of all Dutch ICUs participated [21]. All participating ICUs are collecting at least demographic data, clinical data and physiologic data of the first 24 hours of ICU admission of all consecutively admitted patients. This includes: age, gender, ICU admission and discharge data, primary diagnosis at ICU admission, ICU mortality and in-hospital mortality, ventilation dependency and all variables required to quantify the severity of illness and to calculate case-mix adjusted mortality risks according to, among others, the Acute Physiology and Chronic Health Evaluation (APACHE) IV model [14]. Extensive information about the collected items, data quality and data reliability has been published before [22].

Data of all patients from the NICE registry, admitted to a Dutch ICU during the year 2013 and discharged from the ICU before January 1st 2014, and aged 18 years or older during the year of ICU admission, were included in the NICE registry subset.

Linking process

The dataset extracted from the NICE database and the dataset extracted from the Vektis database were linked anonymously using a deterministic linkage algorithm, as described earlier [12]. Records were linked in three steps. Firstly, records were linked if gender, date of birth, hospital of admission, ICU admission date, and ICU discharge date were identical in both datasets. If records could not be linked, they proceeded to the second step. In the second step records were linked if gender, date of birth, hospital of admission and ICU admission date were identical in both datasets. If records could not be linked, they proceeded to the third step and were linked if gender, date of birth, hospital of admission and ICU discharge date were identical in both datasets.

Statistical analysis

Descriptive statistics were used to characterise the demographic information. Mean and standard deviation (SD) are given for normally distributed data. The median and inter-quartile ranges (IQR) are given for non-normally distributed data, numbers and proportions are used to present categorical data.

When a person had no PCG for a specified chronic condition during 2012 and 2013, and did had a PCG for that chronic condition during 2014, we considered the chronic condition a new case. For the readability of this paper we will refer to it as a newly developed chronic condition even though it can also be the diagnosis of a latent chronic condition or the exacerbation of a non-medically treated chronic condition. For all analyses regarding the development of chronic conditions, only people who survived at least until the 31st of December 2014 were taken into account, because the PCGs are calculated annually.

All nineteen chronic conditions that could be identified based on PCGs were examined. Based on the highest number of new cases and expert opinion on a theoretically possible association between ICU treatment or mechanisms common to critical illness and the chronic conditions, five chronic conditions (heart diseases, Chronic Obstructive Pulmonary Disease (COPD) or asthma, Diabetes mellitus (DM) type II, depression and kidney diseases) were used as outcome variables in further analyses.

We constructed multiple logistic regression models to assess associations between the clinical variables and outcome variables. Only people with a new case for the outcome variable were taken into account for the regression analyses. The clinical variables added to the model were

present in the NICE database and identified as possible risk factors in previous published literature or by expert opinion. Every model included only variables that satisfied the criteria for confounding [23]. Existing chronic conditions were taken into account as a confounder when they were present during the year 2012 and 2013.

One risk factor might be the reason of ICU admission. For each of the five chronic conditions, a dichotomous variable was created, indicating a group of reasons for ICU admission that might influence the chronic condition. For this variable, the APACHE IV reasons for ICU admission which were possible risk factors of developing the chronic condition were grouped, based on expert opinion. For example, APACHE IV reasons for admission such as 'pneumonia', 'respiratory arrest', 'smoke inhalation' and 'pulmonary sepsis' were grouped and used as a possible confounder in the regression model for developing asthma or COPD. These dichotomous variables were only included in the regression model that tested the association with the particular chronic condition. The five dichotomous variables based on APACHE IV reasons for admission are described in appendix 8.1.

Results of the logistic regression analyses are reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed in SAS software (version 7.1; SAS Institute Inc, Cary, NC).

RESULTS

The study population consisted of 49,004 ICU patients. Figure 8.1 gives an overview of the data linkage process. ICU patients who could not be linked between the two registries (12.8%) or who did not survive the study period (22.2%) were excluded from all analyses. Table 8.1 gives an overview of the characteristics, including the chronic conditions, of the total ICU population during the year before ICU admission.

Tables 8.2 to table 8.6 give an overview of the crude and adjusted estimated odds ratios for developing heart diseases, COPD or asthma, DM type II, depression and kidney diseases.

Length of stay (LOS) ICU was associated with the development of the five studied chronic conditions, however after adjustment the association did not always remain significant. Only for heart diseases, COPD or asthma and depression, patients with a longer ICU stay had a higher adjusted odds on developing one of those chronic conditions compared to patients with a shorter ICU stay.

After adjustment, ICU patients who received mechanical ventilation during the first 24 hours of ICU admission had a higher estimated odds on the development of heart diseases (OR

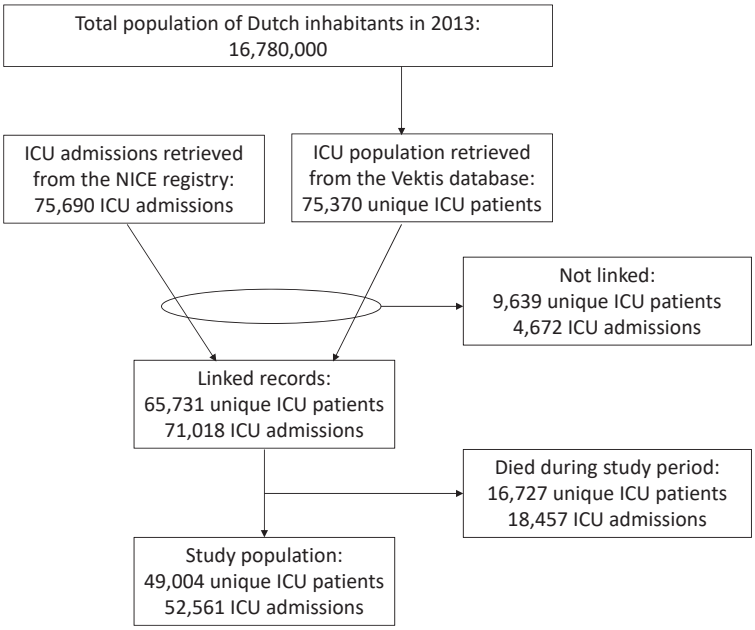

Figure 8.1 Flowchart of the linking process

1.34 (CI 1.19; 1.50)) compared to ICU patients who did not receive mechanical ventilation during the first 24 hours of ICU admission. Mechanical ventilation was not significantly associated with the development of COPD or asthma, DM type II, kidney diseases or depression.

After adjustment, the acute physiology score (APS) was associated with the development of heart diseases, DM type II, kidney diseases and depression. People with a higher APS had a higher odds on developing one of those chronic conditions compared to people with a lower APS, ranging from 1.00 (CI 1.00; 1.01) to 1.02 (CI 1.02; 1.03).

The reason of ICU admission was an important risk factor for most chronic diseases. For heart diseases, people with a cardiovascular reason of ICU admission had a 2.56 (CI 2.33; 2.81) higher odds on developing chronic heart diseases after ICU discharge compared to ICU patients with another reason of ICU admission. For DM type II, the adjusted odds are estimated to be 3.87 (CI 1.69; 8.83) times higher for ICU patients with a diabetic related reason of ICU admission compared to patients with other reasons of admission. For kidney diseases, the adjusted odds are estimated to be 2.05 (CI 1.56; 2.69) times higher for ICU patients with a renal related reason of ICU admission compared to patients with other reasons of admission. An Intoxication-related reason of ICU admission is associated with developing depression after ICU discharge (OR 5.14 (CI 3.99; 6.62)) and a respiratory reason of ICU admission is associated with developing COPD or asthma after ICU discharge.

For developing DM type II there was a significant association with the glucose score during the first 24 hours of ICU admission. Patients with a larger deviation from the normal glucose range (60-199 mg/dl) had a 1.36 (CI 1.30; 1.42) times higher OR on developing DM type II compared to patients with a glucose level within the normal range.

After adjustment, the Mean Arterial Pressure (MAP) score was not significantly associated with the development of heart diseases of DM type II after ICU discharge.

Table 8.1 Characteristics of the ICU population during the year before ICU admission (i.e. 2012) and new cases during the year after admission (2014)

Characteristics	ICU population (n=49,004)	
Male (n %)	29,525 (60.3%)	
Age (median IQR)	64 (52; 72)	
SES (median IQR)	0.18 (-0.58; 0.79)	
Population with one or more chronic conditions	26,438 (54.0%)	
Population with two or more chronic conditions	8,634 (17.6%)	
Chronic conditions	(2012)	New cases (2014)
Heart diseases*	6,071 (12.4%)	2,102 (4.3%)
Asthma or COPD*	5,774 (11.8%)	1,011 (2.1%)
Diabetes Mellitus type II*	3,575 (7.3%)	610 (1.2%)
Diabetes Mellitus type I	3,045 (6.2%)	433 (0.9%)
Depression*	2,946 (6.0%)	747 (1.5%)
Thyroid diseases	1,678 (3.4%)	312 (0.6%)
Glaucoma	1,145 (2.3%)	153 (0.3%)
Neuropathic pains	931 (1.9%)	324 (0.7%)
Psychoses, Alzheimer's disease and addictions	851 (1.7%)	284 (0.6%)
Epilepsy	826 (1.7%)	434 (0.9%)
Rheumatism	515 (1.1%)	102 (0.2%)
Hormone sensitive tumours	402 (0.8%)	122 (0.2%)
Kidney diseases*	324 (0.7%)	239 (0.5%)
Transplantations	338 (0.7%)	211 (0.4%)
Crohn's disease	219 (0.4%)	46 (0.1%)
Parkinson's disease	184 (0.4%)	46 (0.1%)
Diseases of the central neurological system	155 (0.3%)	71 (0.1%)
Cystic fibrosis / pancreas enzymes	118 (0.2%)	136 (0.3%)
HIV/AIDS	75 (0.2%)	39 (0.1%)

* Selected chronic conditions for further analysis based on highest number of new cases and expert opinion on a theoretically possible association between ICU treatment or mechanisms common to critical illness and the chronic condition

Table 8.2 Crude OR and adjusted OR for likelihood of developing heart diseases

Variable	Crude OR (CI)	Adjusted OR (CI)
LOS ICU[a]	1.02 (1.02; 1.03)	1.02 (1.01; 1.03)
Mechanical ventilation[b]	2.05 (1.87; 2.24)	1.34 (1.19; 1.50)
APS[c]	1.02 (1.02; 1.02)	1.01 (1.01; 1.01)
Cardiovascular reason of ICU admission[d]	2.95 (2.70; 3.22)	2.56 (2.33; 2.81)
MAP score[e]	1.05 (1.04; 1.06)	1.01 (1.00; 1.02)

a: Adjusted for age, gender, SES, mechanical ventilation, APS, APACHE IV admission diagnosis, kidney diseases, DM type I, DM type II, BMI
b: Adjusted for age, gender, SES, APACHE IV admission diagnosis, kidney diseases, DM type I, DM type II, BMI
c: Adjusted for age, gender, SES, mechanical ventilation, APACHE IV admission diagnosis, kidney diseases, DM type I, DM type II, BMI
d: Adjusted for age, gender, SES, kidney diseases, DM type I, DM type II, BMI
e: Adjusted for age, gender, SES, mechanical ventilation, APS (without the MAP score), kidney diseases, DM type I, DM type II, BMI

Table 8.3 Crude OR and adjusted OR for likelihood of developing COPD or asthma

Variable	Crude OR (CI)	Adjusted OR (CI)
LOS ICU[a]	1.02 (1.02; 1.03)	1.01 (1.01; 1.02)
Mechanical ventilation[b]	1.01 (0.89; 1.14)	0.89 (0.79; 1.02)
APS[c]	1.01 (1.01; 1.01)	1.00 (1.00; 1.01)
Respiratory reason of ICU admission[d]	3.56 (2.99; 4.25)	3.64 (3.05; 4.35)

a: Adjusted for age, gender, SES, mechanical ventilation, APS and APACHE IV admission diagnosis
b: Adjusted for age, gender, SES and APACHE IV admission diagnosis
c: Adjusted for age, gender, SES, mechanical ventilation and APACHE IV admission diagnosis
d: Adjusted for age, gender and SES

Table 8.4 Crude OR and adjusted OR for likelihood of developing DM type II

Variable	Crude OR (CI)	Adjusted OR (CI)
LOS ICU[a]	1.01 (1.00; 1.02)	1.00 (0.99; 1.02)
Mechanical ventilation[b]	1.21 (1.02; 1.44)	1.11 (0.93; 1.33)
APS[c]	1.01 (1.00; 1.01)	1.00 (1.00; 1.01)
Diabetic related reason of ICU admission[d]	3.16 (1.39; 7.17)	3.87 (1.69; 8.83)
Glucose score[e]	1.34 (1.29; 1.39)	1.36 (1.30; 1.42)
MAP score[f]	1.02 (1.00; 1.04)	1.01 (0.99; 1.03)

a: Adjusted for age, gender, SES, mechanical ventilation, APS, APACHE IV admission diagnosis and BMI
b: Adjusted for age, gender, SES, APACHE IV admission diagnosis and BMI
c: Adjusted for age, gender, SES, mechanical ventilation, APACHE IV admission diagnosis and BMI
d: Adjusted for age, gender, SES and BMI
e: Adjusted for age, gender, SES, APS (without the glucose score) and BMI
f: Adjusted for age, gender, SES, APS (without the MAP score) and BMI

Table 8.5 Crude OR and adjusted OR for likelihood of developing depression

Depression	Crude OR (CI)	Adjusted OR (CI)
LOS ICU[a]	1.02 (1.01; 1.03)	1.02 (1.01; 1.03)
Mechanical ventilation[b]	0.80 (0.69; 0.93)	0.92 (0.79; 1.08)
APS[c]	1.00 (1.00; 1.01)	1.01 (1.00; 1.01)
Intoxication-related reason of ICU admission[d]	5.19 (4.11; 6.54)	5.14 (3.99; 6.62)

a: Adjusted for age, gender, SES, mechanical ventilation, APS, APACHE IV admission diagnosis and total number of chronic conditions
b: Adjusted for age, gender, SES, APACHE IV admission diagnosis and total number of chronic conditions
c: Adjusted for age, gender, SES, mechanical ventilation, APACHE IV admission diagnosis and total number of chronic conditions
d: Adjusted for age, gender, SES and total number of chronic conditions

Table 8.6 Crude OR and adjusted OR for likelihood of developing kidney diseases

Variable	Crude OR (CI)	Adjusted OR (CI)
LOS ICU[a]	1.02 (1.01; 1.03)	1.01 (0.99; 1.02)
Mechanical ventilation[b]	0.91 (0.71; 1.18)	0.91 (0.70; 1.18)
APS[c]	1.02 (1.02; 1.03)	1.02 (1.02; 1.03)
Renal related reason of ICU admission[d]	2.13 (1.62; 2.79)	2.05 (1.56; 2.69)
Glucose score[e]	1.14 (1.07; 1.23)	1.05 (0.98; 1.13)
MAP score[f]	1.03 (1.00; 1.05)	0.97 (0.94; 1.00)

a: Adjusted for age, gender, SES, mechanical ventilation, APS and APACHE IV admission diagnosis
b: Adjusted for age, gender, SES and APACHE IV admission diagnosis
c: Adjusted for age, gender, SES, mechanical ventilation and APACHE IV admission diagnosis
d: Adjusted for age, gender and SES
e: Adjusted for age, gender, SES and APS (without the glucose score)
f: Adjusted for age, gender, SES and APS (without the MAP score)

DISCUSSION

The aim of this study was to gain insight in the association of ICU related clinical variables and the development of specified chronic conditions after discharge from the hospital. We found that LOS ICU and APS were associated with the development of chronic conditions, however not all. The reason of ICU admission was an important risk factor for the development of all chronic conditions with ORs ranging from 2.05 (CI 1.56; 2.69) for kidney diseases to 5.14 (CI 3.99; 6.62) for depression after adjustment.

Our finding, that the reason of ICU admission is associated with the development of chronic conditions, is in itself not surprising. However, in our view the implication of this finding is extremely important. ICU follow-up care has been suggested as a potential mean to address the complaints ICU survivors suffer after discharge [3, 24]. Studies performed to assess the (cost)efficiency of ICU follow-up care selected their study population mainly based on the length of ICU stay or on the length of mechanical ventilation [25] and all ICU patients within

those studies received the same training program. The results of our study imply that not only the length of ICU stay or mechanical ventilation should be used as inclusion criteria for follow-up care, but the reason of ICU admission has to be taken into consideration too. Follow-up care should focus on possible risk factors for PICS and on the developing chronic conditions and should be customized based on the needs of the ICU survivor.

A systematic review about depressive symptoms after critical illness showed no association between ICU length of stay and depressive symptoms [26]. This is conflicting with our results, as we found that LOS ICU was significantly associated with an increased risk of developing depression. We found an OR of 1.02 (CI 1.01; 1.03) per day on the ICU after adjustment. Moreover, in our analyses the association of LOS ICU and the development of heart diseases and asthma or COPD was significant too.

We found that a glucose range deviating from the normal range was associated with the development of DM type II. This finding is supported by previous research, where it was stated that hyperglycaemia in critically ill patients is a risk factor for the development of type II diabetes mellitus [27]. This finding empowers our idea of customized follow-up care and we advise healthcare providers to screen patients with extreme levels of glucose during their ICU stay for DM type II after hospital discharge.

Comparing our results with other studies is challenging as there are large variations across studies with respect to the way the data was obtained, the population studied, the way the chronic conditions were defined and diagnosed, the number of different diagnoses included and the way the data was obtained and the population studied [6, 28].

A limitation of this study is the use of administrative insurance claims data to identify new developed chronic conditions and not the clinical diagnoses described in the healthcare records of the patient. The validity of pharmacy based claims data for the assessment of chronic conditions and prevalence estimates has been demonstrated before in different countries [19, 29-32] and databases on prescribed drugs are a valuable source for measuring population's burden of disease, when clinical data are missing [29]. Moreover, all the drugs used for the identification of the chronic conditions can only be prescribed by a medical doctor. Though, if a person did not use drugs for the chronic condition (for example psychotherapy as treatment for depression), this person could not be identified in our study. Furthermore, it can be argued that in some instances a disease-specific ICU admission may have 'unmasked' pre-existing untreated disease rather than subsequently be part of the causal pathway for new disease. For this study, if the chronic condition was identified during the ICU admission and treated from that moment onwards, we considered the chronic condition as a new case. Another limitation is that we excluded patients who did not survive the entire study period

for the analyses regarding the development of new chronic conditions. People with more chronic conditions are more likely to have worse health outcomes and are more likely to pass away. Therefore, the OR's of developing chronic conditions might be slightly different in reality, we still believe the OR's we found are clinically significant. Finally, there are important clinical risk factors for the development of the chronic conditions we studied, which we could not include in the models. For example the presence of delirium during ICU admission as a possible risk factor for developing depression [26] or a longer duration of mechanical ventilation as a risk factor for pulmonary impairments [33] are lacking in our dataset.

These limitations notwithstanding, we believe that merging data of a national health insurance claims database, covering 99% of the total Dutch population and a national clinical ICU registry database, covering 90% of all Dutch ICUs, is quite unique. Since we included almost all ICU patients of an entire nation, we believe that the results we found are representative for other countries with similar healthcare systems.

CONCLUSION

We showed that ICU related clinical variables were associated with the development of chronic conditions, especially the reason of ICU admission. In sight of these results, we believe that follow-up care should be offered to ICU survivors in order to address the complaints ICU survivors suffer after discharge and that the reason of ICU admission as well as other found risk factors have to be taken into consideration as inclusion criteria for follow-up care.

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APPENDICES

Appendix 8.1 Definition of variables and confounders

SES	Vektis retrieves the socio-economic status (SES) from the Netherlands Institute for Social Research [4]. The SES score is calculated based on the mean income of an area code where a person lives, the fraction of people with a low income, fraction of people with low education and fraction of unemployed people. The SES score is ranked and the national mean is 0. A lower score indicates a lower SES and a higher scores indicates a higher SES.
Mechanical ventilation	Mechanical ventilation during the first 24h of ICU admission is a dichotomous variable and derived from the NICE database.
APS score	The APS Score is based on calculations of the APACHE IV model and a continuous variable. The variables necessary for the calculation of the APS score are derived from the NICE database. When the APS score was a taken into account as a confounder, sub-scores, such as the MAP score and the glucose score, were subtracted from the APS score when appropriated.
BMI	The BMI is a continuous variable and calculated according the formula: BMI = Weight / Lenth^2 In this formula, weight measured in kilograms and length in meters
Confounders based on the APACHE IV admission diagnosis. Dichotomous variables are created for all chronic conditions	
Cardiovascular reason of ICU admission	• Complications of previous open-heart surgery, surgery for (i.e. bleeding, infection, mediastinal rewiring, leaking aortic graft etc.) • Graft, aorto-femoral bypass • Graft, aorto-iliac • Graft, femoral-femoral bypass • Graft, femoral-popliteal bypass • Grafts, all other bypass (except renal) • Grafts, all renal bypass • Mitral valve repair • Mitral valve replacement • Tricuspid valve surgery • Aortic and Mitral valve replacement • Aortic valve replacement (isolated) • CABG alone, coronary artery bypass grafting • CABG alone, redo • CABG redo with other operation • CABG redo with valve repair/replacement • CABG with aortic valve replacement • CABG with double valve repair/replacement • CABG with mitral valve repair • CABG with mitral valve replacement • CABG with other operation

Appendix 8.1 Definition of variables and confounders (continued)

Cardiovascular reason of ICU admission	• CABG with pulmonic or tricuspid valve repair or replacement only. • CABG, Minimally invasive; Mid-CABG • Cardiac arrest (with or without respiratory arrest) • Rhythm disturbance (atrial, supraventricular) • Rhythm disturbance (conduction defect) • Rhythm disturbance (ventricular) • Shock, cardiogenic • Angina, stable (asymp or stable pattern of symptoms w/meds) • Angina, unstable (angina interferes w/quality of life or meds are tolerated poorly) • CHF, congestive heart failure • Complications of previous open heart surgery (i.e. bleeding, infection etc.) • Hypertension, uncontrolled (for cerebrovascular accident-see Neurological System) • Infarction, acute myocardial (MI), ANTERIOR • Infarction, acute myocardial (MI), INFEROLATERAL • Infarction, acute myocardial (MI), NON Q Wave • Infarction, acute myocardial (MI), none of the above • MI admitted > 24hrs after onset of ischemia
Respiratory reason of ICU admission	• Arrest, respiratory (without cardiac arrest) • ARDS-adult respiratory distress syndrome, non-cardiogenic pulmonary edema • Asthma • Pneumonia, aspiration • Pneumonia, bacterial • Pneumonia, fungal • Pneumonia, other • Pneumonia, parasitic (i.e. Pneumocystis pneumonia) • Pneumonia, viral • Restrictive lung disease (i.e. sarcoidosis, pulmonary fibrosis) • Smoke inhalation • Weaning from mechanical ventilation (transfer from other unit or hospital only) • Sepsis, pulmonary
Diabetic related reason of ICU admission	• Kidney transplant • Kidney-pancreas transplant • Pancreas transplant • Peritoneal lavage • Peritonitis, surgery for • Graft for dialysis, insertion of • Hypoglycemia • Diabetic hyperglycemic hyperosmolar nonketotic coma (HHNC) • Diabetic ketoacidosis

Appendix 8.1 Definition of variables and confounders (continued)

Intoxication-related reason of ICU admission	• Overdose, alcohols (bethanol, methanol, ethylene glycol) • Overdose, analgesic (aspirin, cetaminophen) • Overdose, antidepressants (cyclic, lithium) • Overdose, other toxin, poison or drug • Overdose, sedatives, hypnotics, antipsychotics, benzodiazepines • Overdose, street drugs (opiates, cocaine, amphetamine)
Renal related reason of ICU admission	• Aneurysm, dissecting aortic • Cardiac arrest (with or without respiratory arrest) • Cardiomyopathy • Hemorrhage • Hypertension, uncontrolled • Infarction, acute myocardial (MI), Anterior • Infarction, acute myocardial (MI), Inferolateral • Infarction, acute myocardial (MI), Non Q wave • Infarction, acute myocardial (MI), None of the above • Papillary muscle rupture • Rhythm disturbance (atrial, supraventricular) • Rhythm disturbance (ventricular) • Sepsis, cutaneous/soft tissue • Sepsis, GI • Sepsis, gynecologic • Sepsis, other • Sepsis, pulmonary • Sepsis, renal/UTI (including bladder) • Sepsis, unknown • Shock, cardiogenic • Tamponade, pericardial • Bleeding, GI from esophageal varices/portal hypertension • Bleeding, GI-location unknown • Bleeding, lower GI • Bleeding, upper GI • Hemorrhage, intra/retroperitoneal • Hemorrhage, postpartum (female) • Renal obstruction • Hyperthermia • Rhabdomyolysis • Aneurysm, abdominal aortic • Aneurysm, abdominal aortic; with dissection • Aneurysm, abdominal aortic; with rupture • Aneurysm, thoracic aortic • Aneurysm, thoracic aortic; with dissection • Aneurysm, thoracic aortic; with rupture • Nephrectomy (other reasons) • Nephrectomy for neoplasm

REFERENCES

1. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med. 2009;41:13.
2. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009;41:5.
3. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:2.
4. van Beusekom I, Bakhshi-Raiez F, van der Schaaf M, Busschers W, de Keizer NF, Dongelmans DA. ICU survivors have a substantial higher risk of developing new chronic conditions compared to a population-based control group. Crit Care Med. 2019;47:3.
5. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. J Clin Epidemiol. 2001;54:7.
6. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes. 2004;2.
7. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH et al. Five Year Mortality and Hospital Costs Associated With Surviving Intensive Care. Am J Respir Crit Care Med. 2016;194:2.
8. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, van der Schaaf M, Busschers WB, Dongelmans DA. Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: A descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care. 2017;44.
9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:11.
10. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380:9836.
11. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev. 2011;10:4.
12. Wiencek C, Winkelman C. Chronic critical illness: prevalence, profile, and pathophysiology. AACN Adv Crit Care. 2010;21:1.
13. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ. 2015;350.
14. Montuclard L, Garrouste-Orgeas M, Timsit JF, Misset B, De Jonghe B, Carlet J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. Crit Care Med. 2000;28:10.
15. Vektis. http://www.vektis.nl. Accessed 08.11.2016.
16. Centraal Bureau voor de Statistiek (CBS). Statline. http://statline.cbs.nl/Statweb/dome/default.aspx. Accessed 17.01.2019.
17. Knol F. Van hoog naar laag; van laag naar hoog. Den Haag: Sociaal en Cultureel Planbureau / Elsevier Bedrijfsinformatie; 1998.
18. Lamers LM. Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. Med Care. 1999;37:8.

19. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy. 2004;68:1.
20. National Health Care Institute. https://english.zorginstituutnederland.nl. Accessed 08.11.2016.
21. Dutch National Intensive Care Evaluation (NICE) registry http://www.stichting-nice.nl Accessed 08.11.2016.
22. van de Klundert N, Holman R, Dongelmans DA, de Keizer NF. Data Resource Profile: the Dutch National Intensive Care Evaluation (NICE) Registry of Admissions to Adult Intensive Care Units. Int J Epidemiol. 2015;44:6.
23. Jager KJ, Zoccali C, Macleod A, Dekker FW. Confounding: what it is and how to deal with it. Kidney Int. 2008;73:3.
24. Meyer J, Brett SJ, Waldmann C. Should ICU clinicians follow patients after ICU discharge? Yes. Intensive Care Med. 2018;44:9.
25. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42:5.
26. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. Crit Care Med. 2016;44:9.
27. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care. 2016;20:1.
28. Fortin M, Hudon C, Haggerty J, Akker M, Almirall J. Prevalence estimates of multimorbidity: a comparative study of two sources. BMC Health Serv Res. 2010;10.
29. Huber CA, Szucs TD, Rapold R, Reich O. Identifying patients with chronic conditions using pharmacy data in Switzerland: an updated mapping approach to the classification of medications. BMC Public Health. 2013;13.
30. Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. J Health Serv Res Policy. 2005;10:4.
31. Chini F, Pezzotti P, Orzella L, Borgia P, Guasticchi G. Can we use the pharmacy data to estimate the prevalence of chronic conditions? a comparison of multiple data sources. BMC Public Health. 2011;11.
32. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995;48:8.
33. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. Crit Care Med. 2011;39:2.

Chapter 9

Dutch ICU survivors have more consultations with general practitioners before and after ICU admission compared to a matched control group from the general population

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ABSTRACT

Background: General Practitioners (GPs) play a key role in the healthcare trajectory of patients. If the patient experiences problems that are typically non-life-threatening, such as the symptoms of post-intensive-care syndrome, the GP will be the first healthcare professional they consult. The primary aim of this study is to gain insight in the frequency of GP consultations during the year before hospital admission and the year after discharge for ICU survivors and a matched control group from the general population. The secondary aim of this study is to gain insight into differences between subgroups of the ICU population with respect to the frequency of GP consultations.

Methods: We conducted a retrospective cohort study, combining a national health insurance claims database and a national quality registry for ICUs. Clinical data of patients admitted to an ICU in 2013 were enriched with claims data from the years 2012, 2013 and 2014. Poisson regression was used to assess the differences in frequency of GP consultations between the ICU population and the control group.

Results: ICU patients have more consultations with GPs during the year before and after admission than individuals in the control group. In the last four weeks before admission, ICU patients have 3.58 (CI 3.37; 3.80) times more GP consultations than the control group, and during the first four weeks after discharge they have 4.98 (CI 4.74; 5.23) times more GP consultations. In the year after hospital discharge ICU survivors have an increased GP consultation rate compared to the year before their hospital admission.

Conclusions: Close to hospital admission and shortly after hospital discharge, the frequency of GP consultations substantially increases in the population of ICU survivors. Even a year after hospital discharge, ICU survivors have increased GP consultation rates. Therefore, GPs should be well informed about the problems ICU patients suffer after discharge, in order to provide suitable follow-up care.

INTRODUCTION

ICU survivors suffer long-term and severe complaints such as physical, mental, and cognitive impairments, limitations in daily and social activities, and problems affecting their work and employment, [1, 2] all leading to a reduced quality of life. The term post-intensive care syndrome (PICS) was introduced to describe the presence of one or more physical, cognitive or mental impairments after critical illness [3]. Although the exact prevalence of PICS among ICU survivors is unknown, it is estimated that 25-50% of ICU survivors will suffer from some component of PICS after hospital discharge [4-6].

ICU follow-up care has been suggested as a means to address the problems faced after discharge, but it is unknown which (combination of) interventions are most (cost)effective [7, 8]. There is currently insufficient awareness with regards to PICS among clinicians, survivors, families, healthcare administrators, and policymakers, resulting in insufficient treatment of the complete scope of PICS [3, 9, 10]. Moreover, there is evidence that half of the ICU survivors with complaints had no contact with the appropriate health professional at three months after hospital discharge [10].

As in many North-western European countries, in the Dutch healthcare system the general practitioner (GP) plays a key role in the healthcare trajectory of all patients and acts as a gatekeeper between the patient and other healthcare providers. If the patient experiences problems that are typically non-life-threatening, the GP will be the first healthcare professional they consult. If needed, the GP refers the patients to the right healthcare provider. This raises the question of whether this is also the case when ICU survivors consult their GP about complaints experienced as part of PICS.

A first step is to gain insight in the current situation. To date, it is unknown whether ICU survivors contact their GP more often compared to the general population, and if this changes over time. In addition, little is known about differences between ICU subgroups with respect to number of GP consultations. This knowledge could be of great importance for GPs, policy makers, intensivists, healthcare insurers and care planners in order to get insight into the potential role of GPs in organising care tailored to the needs of ICU survivors. Therefore, the primary aim of this study is to gain insight in the frequency of GP consultations during the year before hospital admission and the year after hospital discharge, and investigate trends in time for ICU survivors, compared to people who have not been admitted to an ICU. The secondary aim of this study is to gain insight in the frequency of GP consultations within subgroups of ICU patients.

METHODS

For this project, we combined data from the Dutch National Intensive Care Evaluation (NICE) registry [11] with data from the health insurance claims database of Vektis [12] and conducted a retrospective cohort study.

Databases

Dutch National Intensive Care Evaluation database

The NICE registry is a national quality registry and during the study period 90% of all Dutch ICUs were participating [11]. All participating ICUs collect demographic, clinical, and physiological data for all patients admitted to their ICU. The registry includes among others: age, gender, ICU admission and discharge data, primary diagnosis at ICU admission, ICU mortality, in-hospital mortality and all variables required to quantify the severity of illness and to calculate case-mix adjusted mortality risks according to the Acute Physiology and Chronic Health Evaluation (APACHE) IV model [13]. All patients from the NICE registry, aged 18 years or older during the year of ICU admission, admitted to an ICU during the year 2013 and discharged from the ICU before January 1st 2014, were included in the NICE registry subset for this study.

Vektis insurance claims database

Healthcare insurance is compulsory for all Dutch residents and essentially all (99%) of the Dutch inhabitants have private healthcare insurance [14]. The Vektis databases [12] contain reimbursement data on all medical treatments paid for by Dutch insurance companies, as well as demographic information, such as gender, date of birth and a proxy for date of death.

Vektis includes all claims of GPs in the GP Information System. This information system contains information about all claims for GP consultations (face-to-face, telephone, mail) and all medical examinations and tests performed by the GP. Claims for consultations with nurse practitioners, working under the responsibility of the GP, are present in the dataset as well, along with claims for the capitation fees. For this study all claims for consultations, medical examinations and tests are included as well as all consultations with nurse practitioners.

For the treatment and supervision of specified chronic conditions (DM type II, cardiovascular risk management, COPD) the GP can, if desired, make arrangements with healthcare insurance companies. For people with 'multidisciplinary care arrangements', there is a fixed price for all care from the GP for the treatment of the specific chronic condition. This is why separate consultations for the specified conditions are not registered. All other consultations of these patients that have no relation to the specified chronic condition are registered. Therefore we can only include the GP consultations with no relation to the specified chronic condition in the analyses for people with multidisciplinary care arrangements.

Vektis also contains claims for pharmaceutical care, including information on provided drugs, the Anatomical Therapeutic Chemical (ATC) code, the date the drug was supplied, and the quantity supplied. To determine the chronic conditions, Pharmaceutical Cost Groups (PCGs) were used as a proxy. PCGs are based on the idea that a patient with a certain chronic condition can be identified by claims for specific prescribed drugs [15, 16]. We used the PCGs to identify chronic conditions during the whole study period since clinical diagnosis are not available within the NICE registry or the Vektis databases. A complete description of the definitions of chronic conditions and ATC codes is published before [17].

The socio-economic status (SES) was derived from the postal code of a person and the SES score for that postal code as determined by the Netherlands Institute for Social Research [18]. The SES score is based on the mean income of a code where a person lives, the fraction of people with a low income, the fraction of people with low education and the fraction of unemployed people. The SES score is ranked and the national mean is 0 (range -6.65; 3.02). A lower score indicates a lower SES and a higher scores indicates a higher SES.

All patients in the Vektis database who were 18 years or older and had a claim for an ICU day in the year 2013 were included in the ICU-subset of the Vektis database. Based on this ICU-subset, a population based control group was created from all registered inhabitants of the Netherlands in the Vektis database. The population based control group was frequency matched based on the combination of the age, gender, and SES of patients from the ICU-subset from the Vektis database, and had no claims for ICU care during 2013. Only ICU patients with no missing data for gender, age and SES were used in the frequency matching process. The frequency matching process was undertaken before the linking process.

Linking and 1:1 matching process

The ICU-subset extracted from the Vektis database and the NICE database were linked using a deterministic linkage algorithm [19]. A detailed description of the linking process is published previously [20]. Before the 1:1 matching process, ICU patients who did not survive their hospital admission were excluded, as these patients have no GP consultations during the year after discharge. The remaining ICU patients were matched 1:1 with control persons. The 1:1 matching was performed on age, gender and quartile of SES.

Outcome measures

The primary outcome of this study is the difference in GP consultation rate between the ICU population and the control group during the year before hospital admission and the year after hospital discharge. Based on the hospital admission date of the ICU patient, all contacts with the GP during the year before hospital admission were identified. The hospital discharge date associated with the last ICU admission during 2013 was used to identify all contacts

with the GP during the year after hospital discharge. For the control patients, the hospital admission date and the hospital discharge date of their 1:1 matched ICU patient were used to calculate the year before admission and the year after discharge.

Statistical analysis

Descriptive statistics were used to characterize demographic data of both study populations. Medians and IQR are provided for continuous data and numbers and proportions are used to present categorical data. The Chi-square test was used to test for differences in proportions between the ICU population and control group.

The mean number of GP consultations per week is calculated to gain insight in the trend over time. The difference in number of GP consultations between the ICU population and the control group, expressed as a Risk Ratio, was estimated using Poisson regression. Overdispersion was taken into account by adding a scale parameter to the estimated variance parameter and time at risk was taken into account by adding this as an offset to the regression model. Age, gender, quartiles of SES and number of chronic conditions were considered as confounders and as possible effect modifiers. Age was stratified into the following subgroups: <=29, 30-39, 40-49, …, 70-79, 80-89, >=90 and number of chronic conditions was categorized as zero chronic conditions, one chronic condition, two chronic conditions and more than two chronic conditions.

Analyses were performed for the total study period, the year before hospital admission and the year after hospital discharge. Furthermore, the year before admission and the year after discharge were each divided into three timeframes based on the discontinuity of patterns in mean number of GP consultations.

For the secondary aim, the ICU population was divided into subgroups based on the type of ICU admission (medical admission, emergency surgery or elective surgery), the length of ICU stay categorized as <2 days, 2 days to 5 days and >=5 days, and for the APACHE IV predicted mortality [13] categorized as low-risk (predicted mortality <30%), medium-risk (predicted mortality 30%-70%) and high-risk (predicted mortality ≥70%). We performed sub-analyses for these subgroups and age, gender and quartiles of SES were taken into account as confounders.

All statistical analyses were performed in SAS software (version 7.1; SAS Institute Inc, Cary, NC) and a *p*-value of <0.05 was considered to indicate a statistically significant difference.

RESULTS

The final study population consisted of 56,267 ICU patients and an equal number of matched persons in the population-based control group. An overview of the data linkage and data matching process is given in Fig 1. Demographic information of the ICU patients and the control group is given in table 1.

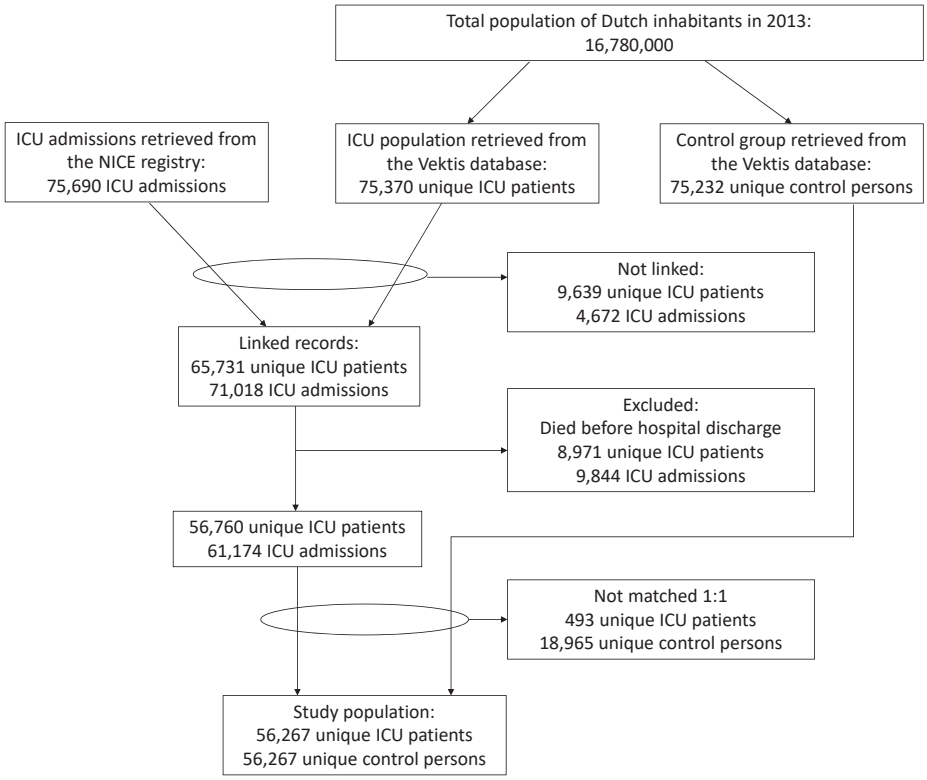

Figure 9.1 Flowchart of the linking process

During the year before hospital admission, 3.9% of ICU patients had no contact with a GP. Within the control group this was 16.8% (p<0.0001). During the year after hospital admission, 5.2% of the ICU population and 17.9% of the control group had no contact with the GP (p<0.0001).

The number of ICU patients with multidisciplinary care arrangements during the year before hospital admission was 12,820 (22.8%) and within the control group this was 9,927 (17.6%) (p<0.0001). During the year after hospital discharge 13,083 (23.3%) ICU patients had multidisciplinary care arrangements and 10,860 (19.5%) individuals of the control group (p<0.0001).

Table 9.1 Demographic information of the ICU population and the control group

	ICU population (n= 56,267)	Control group (n= 56,267)
Gender (male)	33,825 (60.1%)	33,825 (60.1%)
Age	65 (54; 73)	65 (54; 73)
SES	0.17 (-0.60; 0.79)	0.17 (-0.60; 0.79)
Mortality during study period (2012-2014)	5,923 (10.5%)	1,644 (2.9%)
Population with >= 1 chronic conditions	31,278 (55.6%)	21,187 (37.7%)
Population with >= 2 chronic conditions	10,799 (19.2%)	5,012 (8.9%)
Characteristics of the first ICU admission		
Admission type		
• Medical	22,527 (40.0%)	
• Planned surgery	26,714 (47.5%)	
• Emergency surgery	6,844 (12.2%)	
Length of ICU stay in days	1.0 (0.8; 2.5)	
Length of hospital stay in days	9.0 (5.6; 16.0)	
APACHE IV score*[13]	49 (36; 65)	

* Only calculated for ICU admissions which met the APACHE IV inclusion criteria: n=53,737 (95.5%) [13]
APACHE IV: Acute Physiology and Chronic Health Evaluation IV; ICU: Intensive Care Unit; SES: Socioeconomic status

Based on the discontinuity of patterns in mean number of GP consultations, the year before admission (Fig 2a) and the year after discharge (Fig 2b) were each divided into three timeframes: 4 weeks before hospital admission/after hospital discharge (period 1 and 4, respectively), 4 weeks to 17 weeks before hospital admission/after hospital discharge (period 2 and 5, respectively) and >= 17 weeks before hospital admission/after hospital discharge (period 3 and 6, respectively).

During the year before hospital admission, ICU patients had 1.82 (CI 1.80; 1.85) times more GP consultations compared to the control group. During the year after hospital discharge, the RR was 2.28 (CI 2.24; 2.31) (Fig 2 and S1 Fig).

After adjustment for age, SES and number of chronic conditions, males in the ICU population had 1.36 (CI 1.34; 1.37) times more GP consultations during period 1 compared to males in the control group (table 2). The RR was 3.46 (CI 3.40; 3.53) during period 3. During period 6, the RR was still increased compared to the same period before hospital admission (RR 1.78 (CI 1.76; 1.79) table 2). For women within the ICU population as opposed to women of the control group a similar trend was observed.

Women had 1.36 (CI 1.35; 1.37) times more GP consultations compared to men during period 1 (table 3). During period 3 the difference between men and women in the ICU

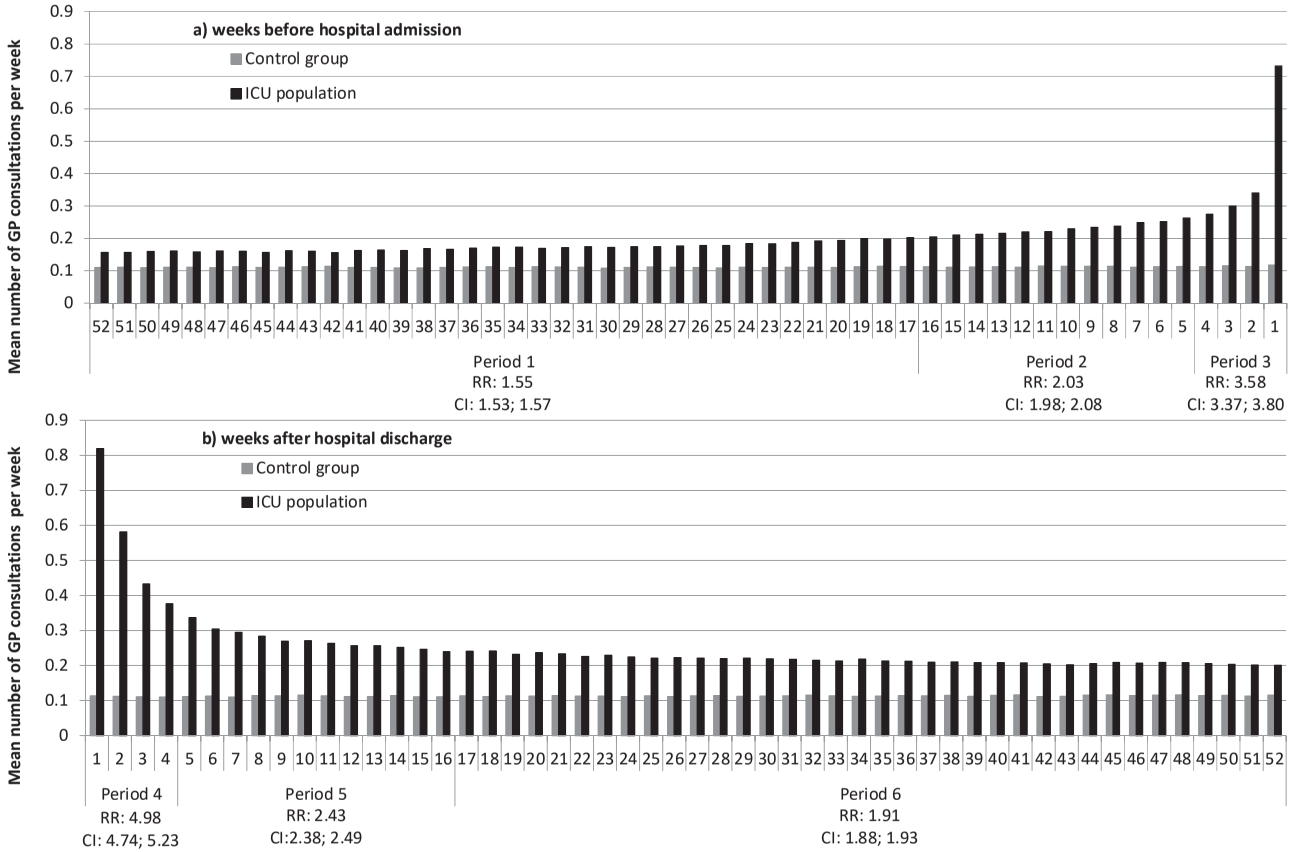

Figure 9.2 Mean number of GP contacts per week and the crude risk ratio (95% CI) of GP consultations among ICU patients compared to the control group for the different time periods

Table 9.2 Risk ratios (95% CI) of GP consultations among ICU patients comparted to the control group for different subgroups

	Year before hospital admission			Year after hospital discharge		
	ICU population Period 1 (week 52-17)	ICU population Period 2 (week 16-5)	ICU population Period 3 (weeks 4-1)	ICU population Period 4 (week 1-4)	ICU population Period 5 (week 5-16)	ICU population Period 6 (week 17-52)
Interaction population*gender ‡	*p*=0.0022	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*=0.0596
Male	1.36 (1.34; 1.37)	1.90 (1.87; 1.92)	3.46 (3.40; 3.53)	4.89 (4.81; 4.97)	2.29 (2.27; 2.32)	1.78 (1.76; 1.79)
Female	1.38 (1.37; 1.40)	1.79 (1.77; 1.81)	3.17 (3.11; 3.24)	3.98 (3.91; 4.06)	2.11 (2.09; 2.14)	1.76 (1.74; 1.77)
Interaction population*SES ¥	*p*=0.0471	*p*<0.0001	*p*=0.0009	*p*<0.0001	*p*<0.0001	*p*<0.0001
SES Q1	1.35 (1.33; 1.37)	1.77 (1.74; 1.80)	3.17 (3.09; 3.26)	4.04 (3.94; 4.14)	2.10 (2.07; 2.14)	1.70 (1.68; 1.72)
SES Q2	1.38 (1.37; 1.40)	1.86 (1.83; 1.89)	3.34 (3.24; 3.43)	4.48 (4.37; 4.59)	2.21 (2.17; 2.25)	1.77 (1.75; 1.80)
SES Q3	1.37 (1.35; 1.39)	1.85 (1.82; 1.88)	3.38 (3.28; 3.47)	4.63 (4.52; 4.75)	2.25 (2.21; 2.28)	1.80 (1.77; 1.82)
SES Q4	1.38 (1.36; 1.39)	1.91 (1.88; 1.95)	3.42 (3.33; 3.52)	4.75 (4.64; 4.87)	2.28 (2.24; 2.32)	1.80 (1.78; 1.83)
Interaction population*age †	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001
Age 18-29	1.86 (1.79; 1.94)	2.14 (2.03; 2.26)	3.93 (3.61; 4.28)	4.97 (4.62; 5.36)	2.30 (2.18; 2.42)	2.01 (1.93; 2.09)
Age 30-39	1.84 (1.77; 1.91)	2.28 (2.17; 2.40)	4.22 (3.90; 4.57)	5.52 (5.16; 5.91)	2.52 (2.40; 2.65)	2.08 (2.01; 2.16)
Age 40-49	1.77 (1.73; 1.82)	2.28 (2.21; 2.36)	4.48 (4.26; 4.71)	5.69 (5.44; 5.95)	2.66 (2.57; 2.74)	2.16 (2.10; 2.21
Age 50-59	1.63 (1.60; 1.66)	2.14 (2.09; 2.19)	3.90 (3.76; 4.05)	5.37 (5.20; 5.54)	2.55 (2.49; 2.61)	2.12 (2.08; 2.16)
Age 60-69	1.41 (1.39; 1.43)	1.99 (1.96; 2.03)	3.57 (3.47; 3.67)	5.03 (4.91; 5.14)	2.35 (2.31; 2.39)	1.86 (1.84; 1.89)
Age 70-79	1.25 (1.23; 1.26)	1.73 (1.71; 1.76)	2.98 (2.90; 3.06)	4.18 (4.09; 4.27)	2.10 (2.07; 2.14)	1.63 (1.61; 1.65)
Age 80-89	1.15 (1.13; 1.17)	1.49 (1.46; 1.53)	2.75 (2.66; 2.85)	3.23 (3.13; 3.33)	1.83 (1.79; 1.86)	1.48 (1.46; 1.51)
Age >=90	1.03 (0.98; 1.08)	1.30 (1.21; 1.39)	2.50 (2.24; 2.79)	2.75 (2.47; 3.05)	1.60 (1.49; 1.72)	1.28 (1.21; 1.35)
Interaction population*chronic conditions ǂ	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001	*p*<0.0001
0 chronic condition	1.50 (1.49; 1.52)	2.23 (2.20; 2.26)	4.35 (4.26; 4.44)	5.84 (5.74; 5.94)	2.63 (2.60; 2.67)	2.03 (2.01; 2.05)
1 chronic condition	1.32 (1.30; 1.33)	1.74 (1.72; 1.77)	3.04 (2.98; 3.11)	4.14 (4.06; 4.21)	2.07 (2.05; 2.10)	1.64 (1.62; 1.66)
2 chronic conditions	1.24 (1.22; 1.26)	1.51 (1.48; 1.54)	2.59 (2.50; 2.67)	3.19 (3.10; 3.28)	1.80 (1.77; 1.84)	1.50 (1.47; 1.52)
>2 chronic conditions	1.22 (1.19; 1.26)	1.45 (1.40; 1.50)	2.29 (2.16; 2.41)	2.86 (2.72; 3.01)	1.72 (1.66; 1.79)	1.50 (1.45; 1.54)

The control group is used as the reference population. With respect to the control population: The complete year before hospital admission is used for the analyses with respect to the year before hospital admission, since Figure 9.2 showed no differences in mean number of general practitioner consultations during the year before hospital admission for the control group. The complete year after hospital discharge is used for the analyses with respect to the year after hospital discharge, since Figure 9.2 showed no differences in mean number of general practitioner consultations during the year after hospital discharge for the control group.

[‡] Corrected for SES age and chronic conditions

[¥] Corrected for gender, age and chronic conditions

[†] Corrected for gender SES and chronic conditions

[ł] Corrected for gender, SES and age

CI: Confidence Interval; ICU: Intensive Care Unit; SES: Socioeconomic status

Table 9.3 Risk ratios (95% CI) of GP consultations for different risk factors for the ICU population and the control group separately

	Year before hospital admission				Year after hospital discharge			
	Control group week 52-1	ICU population Period 1 (week 52-17)	ICU population Period 2 (week 16-5)	ICU population Period 3 (weeks 4-1)	Control group week 1-52	ICU population Period 4 (week 1-4)	ICU population Period 5 (week 5-16)	ICU population Period 6 (week 17-52)
Male (reference)	1	1	1	1	1	1	1	1
Female[‡]	1.33 (1.32; 1.34)	1.36 (1.35; 1.37)	1.26 (1.24; 1.28)	1.22 (1.19; 1.25)	1.31 (1.29; 1.33)	1.07 (1.04; 1.09)	1.21 (1.19; 1.22)	1.29 (1.28; 1.30)
SES Q1 (reference)	1	1	1	1	1	1	1	1
SES Q2[¥]	0.96 (0.95; 0.98)	0.99 (0.98; 1.00)	1.01 (0.99; 1.03)	1.01 (0.97; 1.04)	0.96 (0.95; 0.98)	1.07 (1.04; 1.10)	1.01 (0.99; 1.03)	1.01 (1.00; 1.02)
SES Q3[¥]	0.96 (0.95; 0.98)	0.98 (0.97; 0.99)	1.00 (0.98; 1.02)	1.02 (0.99; 1.06)	0.94 (0.92; 0.96)	1.08 (1.05; 1.11)	1.01 (0.99; 1.03)	1.00 (0.98; 1.01)
SES Q4[¥]	0.92 (0.91; 0.94)	0.94 (0.93; 0.96)	1.00 (0.98; 1.02)	0.99 (0.96; 1.03)	0.91 (0.90; 0.93)	1.08 (1.04; 1.11)	0.99 (0.97; 1.01)	0.97 (0.96; 0.98)
Age 18-29 (reference)	1	1	1	1	1	1	1	1
Age 30-39[†]	1.05 (1.01; 1.10)	1.04 (1.00; 1.08)	1.12 (1.06; 1.19)	1.13 (1.02; 1.25)	1.06 (1.00; 1.12)	1.17 (1.08; 1.28)	1.16 (1.09; 1.22)	1.09 (1.05; 1.13)
Age 40-49[†]	1.12 (1.08; 1.16)	1.07 (1.03; 1.10)	1.20 (1.14; 1.26)	1.28 (1.18; 1.40)	1.13 (1.08; 1.18)	1.29 (1.20; 1.39)	1.30 (1.24; 1.37)	1.21 (1.18; 1.25)
Age 50-59[†]	1.21 (1.17; 1.25)	1.06 (1.03; 1.09)	1.22 (1.17; 1.28)	1.22 (1.12; 1.32)	1.22 (1.17; 1.27)	1.32 (1.23; 1.41)	1.35 (1.29; 1.42)	1.29 (1.26; 1.33)
Age 60-69[†]	1.37 (1.32; 1.41)	1.04 (1.01; 1.07)	1.29 (1.23; 1.35)	1.26 (1.17; 1.37)	1.43 (1.37; 1.49)	1.45 (1.35; 1.54)	1.46 (1.40; 1.53)	1.33 (1.30; 1.37)
Age 70-79[†]	1.76 (1.70; 1.81)	1.18 (1.15; 1.21)	1.46 (1.39; 1.52)	1.37 (1.27; 1.48)	1.87 (1.79; 1.95)	1.57 (1.47; 1.68)	1.70 (1.62; 1.77)	1.52 (1.48; 1.56)
Age 80-89[†]	2.28 (2.21; 2.36)	1.41 (1.37; 1.45)	1.64 (1.57; 1.72)	1.65 (1.53; 1.79)	2.49 (2.39; 2.60)	1.62 (1.51; 1.73)	1.95 (1.87; 2.05)	1.83 (1.77; 1.88)
Age >=90[†]	3.06 (2.92; 3.20)	1.69 (1.61; 1.77)	1.92 (1.78; 2.06)	2.02 (1.78; 2.28)	3.29 (3.09; 3.50)	1.82 (1.62; 2.03)	2.25 (2.09; 2.43)	2.07 (1.97; 2.17)
0 chronic condition (reference)	1	1	1	1	1	1	1	1
1 chronic condition[ŧ]	1.59 (1.58; 1.61)	1.40 (1.38; 1.41)	1.21 (1.19; 1.23)	1.08 (1.05; 1.11)	1.48 (1.46; 1.50)	1.05 (1.03; 1.07)	1.16 (1.14; 1.18)	1.21 (1.20; 1.23)
2 chronic conditions[ŧ]	2.16 (2.13; 2.19)	1.79 (1.76; 1.81)	1.41 (1.39; 1.44)	1.23 (1.19; 1.27)	1.99 (1.95; 2.03)	1.09 (1.06; 1.12)	1.36 (1.33; 1.38)	1.49 (1.48; 1.51)
>2 chronic conditions[ŧ]	2.84 (2.76; 2.91)	2.31 (2.27; 2.35)	1.78 (1.74; 1.83)	1.42 (1.36; 1.49)	2.51 (2.43; 2.60)	1.23 (1.18; 1.28)	1.63 (1.59; 1.68)	1.88 (1.85; 1.92)

With respect to the control population: The complete year before hospital admission is used for the analyses with respect to the year before hospital admission, since Figure 9.2 showed no differences in mean number of general practitioner consultations during the year before hospital admission for the control group. The complete year after hospital discharge is used for the analyses with respect to the year after hospital discharge, since Figure 9.2 showed no differences in mean number of general practitioner consultations during the year after hospital discharge for the control group.

[‡] Corrected for SES age and chronic conditions

[¥] Corrected for gender, age and chronic conditions

[†] Corrected for gender SES and chronic conditions

[ɬ] Corrected for gender, SES and age

CI: Confidence Interval; ICU: Intensive Care Unit; SES: Socioeconomic status

Table 9.4 Risk ratios (95% CI) for GP consultations for different risk factors among the ICU population

	Year before hospital admission			Year after hospital discharge		
	Period 1 (week 52-17)	Period 2 (week 16-5)	Period 3 (weeks 4-1)	Period 4 (weeks 1-4)	Period 5 (weeks 5-16)	Period 6 (weeks 17-52)
Admission type						
Medical (reference)	1	1	1	1	1	1
Emergency surgery	0.83 (0.82; 0.84)	0.87 (0.85; 0.89)	0.94 (0.84; 1.06)	1.08 (1.00; 1.17)	0.98 (0.96; 1.01)	0.90 (0.89; 0.91)
Elective surgery	0.86 (0.85; 0.87)	1.01 (0.99; 1.02)	0.65 (0.59; 0.70)	1.05 (1.00; 1.11)	0.88 (0.86; 0.89)	0.86 (0.85; 0.87)
Length of ICU stay						
< 2 days (reference)	1	1	1	1	1	1
>= 2 days < 5 days	1.03 (1.02; 1.05)	0.98 (0.96; 1.00)	1.21 (1.11; 1.32)	1.06 (1.00; 1.13)	1.09 (1.07; 1.11)	1.09 (1.08; 1.10)
>= 5 days	0.99 (0.97; 1.00)	0.92 (0.90; 0.94)	1.21 (1.09; 1.35)	0.97 (0.90; 1.05)	1.12 (1.10; 1.15)	1.14 (1.13; 1.16)
APACHE IV risk group						
Low (reference)	1	1	1	1	1	1
Medium	1.05 (1.03; 1.06)	1.03 (1.01; 1.06)	1.33 (1.19; 1.48)	1.02 (0.93; 1.11)	1.16 (1.13; 1.19)	1.14 (1.13; 1.16)
High	0.90 (0.87; 0.92)	0.88 (0.84; 0.93)	1.07 (0.86; 1.32)	0.91 (0.78; 1.07)	1.05 (1.00; 1.11)	1.01 (0.98; 1.04)

APACHE IV: Acute Physiology and Chronic Health Evaluation IV; CI: Confidence Interval; ICU: Intensive Care Unit

population was smaller (RR 1.22 (CI 1.19; 1.25) but still present. Women in the ICU population had 1.07 (CI 1.04; 1.09) more consultations compared to men during period 3 and 1.29 (CI 1.28; 1.30) more consultations during period 6.

ICU patients of all SES quartiles had more GP consultations compared to individuals from the control group during the year before hospital admission, these differences increased over time. For ICU patients with the highest SES quartile the difference increased most. During the year after hospital discharge a reversed trend was observed; ICU patients of all SES quartiles had more GP consultations compared to the control group but these differences decreased over time.

Within the ICU population, ICU patients from the lowest SES quartile had 1.12 (CI 1.09; 1.16) times more GP consultations compared to ICU patients from the highest SES quartile. During period 3 this difference was 1.06 (CI 1.00; 1.13) (table 3).

The difference in GP consultations between the ICU population and the control group with respect to age was most distinct within the younger age groups and this difference increased closer to the time of hospital admission. Within the ICU population, older patients had more GP consultations compared to younger patients. The differences between age groups within the ICU population became smaller closer to the time of admission.

ICU patients with an elective surgical admission or an emergency surgery admission had less consultations with the GP compared to ICU patients with a medical admission during period 1 with a RR of respectively 0.86 (CI 0.85; 0.87) and 0.83 (CI 0.82; 0.84). During period 4, ICU patients with an elective surgical admission or an emergency surgery had more consultations with the GP compared to ICU patients with a medical admission (RR 1.05 (CI 1.00; 1.11) and RR 1.08 (CI 1.00; 1.17) respectively) (table 4).

ICU patients with an ICU length of stay of 2 to 5 days had more consultations with a GP compared to ICU patients with a length of stay < 2 days during the year before admission and the year after discharge and ICU patients with a medium risk of mortality had more GP consultations compared to ICU patients with a low risk of mortality during the year before admission and the year after discharge (table 4).

DISCUSSION

This study showed that ICU patients have more consultations with GPs during the year before and the year after hospital admission compared to a matched control group. Shortly before hospital admission and shortly after hospital discharge, the number of GP consultstions is

substantially increased. During the last four weeks before admission, ICU patients have 3.58 (CI 3.37; 3.80) times more GP consultations compared to the control group. During the first four weeks after discharge, ICU patients have 4.98 (CI 4.74; 5.23) times more GP consultations. One year after hospital discharge, ICU patients have 1.91 (CI 1.88; 1.93) times more GP consultations compared to the control group; this is still higher than the same period before hospital admission (RR 1.55 (CI 1.53; 1.57).

During period 1 (52 to 17 weeks before hospital admission), ICU survivors already had more GP consultations compared to the control group. Gender, age, SES and multi morbidity are important risk factors for an increased number of GP consultations [21, 22]. Since we matched our two study populations 1:1 on age, gender and SES, and the number of chronic conditions was taken into account as a confounder within the Poisson regression, the difference can only be explained by another factor. We have reason to believe that ICU survivors have an impaired health status and therefore a decreased quality of life long before ICU admission. A systematic review reported that pre-ICU quality of life is low compared to that of the general population, indicating that ICU patients differ from the average population even before the onset of critical illness [23]. Other studies have reported that ICU survivors have a higher healthcare consumption preceding their ICU admission [20, 24] which can be an indication that they have a reduced quality of life long before ICU admission.

During the last four weeks before hospital admission (period 3), the number of GP consultations in the ICU population increased substantially. Other studies reported that prior to their ICU admission, ICU patients have an increased healthcare consumption [20, 24]. Possible explanations for the higher GP consultation rate during this period can be that people experience more health problems and consult a GP. Subsequently the GP can refer the patient to the hospital immediately, or the GP refers the patients to the hospital after a regular check-up, or the GP performs check-ups before elective surgery.

Possible explanations for the high GP consultation rate during the first four weeks after hospital discharge (period 4) are that the GPs contacts the patients since the GP received a discharge letter from the hospital, or the patient consults the GP because they experience health problems or they need a referral for another healthcare provider. Post-hoc analyses showed that the RR between the ICU population and the control group without all telephone consultstions is a only little lower (RR 4.11 (CI 3.92; 4.30)) during the first four weeks after discharge. Thus, the standard healthcare process (a phone call after hospital discharge) does not fully explain the difference in GP consult rate after discharge between ICU patients and the control group. Therefore, we hypothesize that ICU patients consults the GPs more often since they experience more health problems shortly after discharge.

In the period 17 weeks to 52 weeks after discharge (period 6), ICU patients had on average more GP consultations compared to the same weeks before hospital admission (period 1). Previously published studies reported similar findings [25, 26]. ICU patients have a five times higher risk of developing new chronic condition after ICU admission compared to a population-based control group, and they suffer long-term complaints after ICU discharge [17]. People with more chronic conditions have higher healthcare consumption and more GP consultations [20, 27]. This could partly be an explanation for the increased number of GP consultations compared to their situation before ICU admission.

ICU follow-up care has been suggested as a potential means to address the physical, cognitive and mental problems faced after discharge, but it is unknown which (combination of) interventions are most (cost)effective [7, 8]. Studies proposed that frequent visits to GPs allowed early recognition and proactive treatment of health problems that prevented further hospitalizations [28] and that the post-hospital collaboration among hospital, GP and community services regarding physical and neuropsychological rehabilitation should be strengthened [26]. However, a multi-centre study conducted in the Netherlands reported that, at three months after discharge, almost 70% of the ICU survivors had had contact with the GP. However, half of the ICU survivors with complaints had no contact with the appropriate health professional [10]. In light of these findings, we suggest that GPs should informed about the problems ICU patients can suffer after discharge in order to provide the care they need. Future research is necessary to gain insight into the potential role of GPs in organizing care tailored to the needs of ICU survivors.

A limitation of using claims data is that we have no insight into the purpose of the contact between ICU patients and the GP, and that we do not know who initiated the contact. Further research about the purpose of GP consultations and who initiated them could give more insight into the healthcare trajectory of ICU survivors after discharge. Another limitation of using claims data is that we do not have information about the GP consultations of people living in a nursing home. ICU patients have higher healthcare consumption and more chronic conditions before ICU admission and therefore it is possible that patients of the ICU population are more likely to live in a nursing home. This can lead to an underestimation of the true GP consultation rate, especially within the elderly ICU population.

Another limitation is the exclusion of all GP consultations that took place as part of a 'multidisciplinary care arrangement' with the insurer. Since more ICU patients had 'multidisciplinary care arrangements' than the control group we expect that the differences in GP consultations between the ICU population and the control group are slightly larger than we reported in this study. Despite these limitations, we still believe the differences we found are clinically relevant. A strength of this study is that all the data we used for this study was

routinely-collected data instead of self-reported data. Moreover, we were able to include almost all patients admitted to a Dutch ICU through the unique collaboration of a national health insurance claims database and a national clinical ICU quality database. This diminishes the risk of selection bias. Since we included almost all ICU patients of an entire country, we believe that the results we found are representative for other Western European countries with similar healthcare systems as well.

CONCLUSION

This study showed that ICU patients have more consultations with GPs during the year before and the year after hospital admission compared to a matched control group. Near the time of hospital admission and shortly after hospital discharge, the number of GP consultstions substantially increases within the ICU population. We suggest that GPs should informed about the problems ICU patients suffer after discharge, in order to provide the care they need. More research about how the care delivered by GPs can be integrated in ICU follow-up care is necessary, and is likely to might be beneficial for this large group of patients.

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Appendix 9.1 Number of participants, number of GP consultations, follow-up time and crude Risk Ratio of GP consultations among ICU patients compared to the control group for the different time periods

Period	Control group (n)	GP consultations (n)	Follow-up time (weeks)	ICU population (n)	GP consultations (n)	Follow-up time (weeks)	Risk Ratio (95% CI)
During the year before hospital admission	56,267	326,893	2,916,176	56,267	597,307	2,925,884	1.82 (1.80; 1.85)
1 (week 52-17)	56,267	225,086	2,022,398	56,267	349,410	2,025,612	1.55 (1.53; 1.57)
2 (week 16-5)	55,989	76,017	670,772	56,267	155,020	675,204	2.03 (1.98; 2.08)
3 (week 4-1)	55,774	25,790	223,006	56,267	92,877	225,068	3.58 (3.37; 3.80)
During the year after hospital discharge	55,719	326,380	2,868,684	56,267	707,305	2,733,090	2.28 (2.24; 2.31)
4 (week 1-4)	55,719	24,890	222,726	56,267	123,441	222,414	4.98 (4.74; 5.23)
5 (week 5-16)	55,617	75,081	665,947	54,872	178,058	648,892	2.43 (2.38; 2.49)
6 (week 17-52)	55,340	226,409	1,980,011	53,282	405,806	1,861,784	1.91 (1.88; 1.93)
Total study period	56,267	653273	5,784,860	56,267	1,304,612	5,658,974	2.04 (2.02; 2.06)

CI: Confidence Interval; GP: General practitioner; ICU: Intensive Care Unit

REFERENCES

1. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Poor functional recovery after a critical illness: a longitudinal study. J Rehabil Med. 2009;41:13.
2. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009;41:5.
3. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:2.
4. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med. 2007;33:11.
5. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:14.
6. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med. 2015;43:5.
7. Connolly B, Denehy L, Brett S, Elliott D, Hart N. Exercise rehabilitation following hospital discharge in survivors of critical illness: an integrative review. Crit Care. 2012;16:3.
8. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42:5.
9. van der Schaaf M, Beelen A, Nollet F, Dongelmans DA. Postintensive care syndrome, need for recognition, treatment, research, and expansion of included symptoms. Crit Care Med. 2012;40:9.
10. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, Dongelmans DA, van der Schaaf M. Lessons learnt during the implementation of a web-based triage tool for Dutch intensive care follow-up clinics. BMJ Open. 2018;8:9.
11. Dutch National Intensive Care Evaluation (NICE) registry http://www.stichting-nice.nl Accessed 08.11.2016.
12. Vektis. http://www.vektis.nl. Accessed 08.11.2016.
13. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006;34:5.
14. Centraal Bureau voor de Statistiek (CBS). Statline. http://statline.cbs.nl/Statweb/dome/default.aspx. Accessed 17.01.2019.
15. Lamers LM. Pharmacy costs groups: a risk-adjuster for capitation payments based on the use of prescribed drugs. Med Care. 1999;37:8.
16. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy. 2004;68:1.
17. van Beusekom I, Bakhshi-Raiez F, van der Schaaf M, Busschers W, de Keizer NF, Dongelmans DA. ICU survivors have a substantial higher risk of developing new chronic conditions compared to a population-based control group. Crit Care Med. 2019;47:3.
18. Knol F. Van hoog naar laag; van laag naar hoog. Den Haag: Sociaal en Cultureel Planbureau / Elsevier Bedrijfsinformatie; 1998.
19. Roos LL, Wajda A. Record linkage strategies. Part I: Estimating information and evaluating approaches. Methods Inf Med. 1991;30:2.

20. van Beusekom I, Bakhshi-Raiez F, de Keizer NF, van der Schaaf M, Busschers WB, Dongelmans DA. Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: A descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care. 2017;44.
21. Wang Y, Hunt K, Nazareth I, Freemantle N, Petersen I. Do men consult less than women? An analysis of routinely collected UK general practice data. BMJ Open. 2013;3:8.
22. Schellevis FG, Van de Lisdonk EH, Van der Velden J, Hoogbergen SH, Van Eijk JT, Van Weel C. Consultation rates and incidence of intercurrent morbidity among patients with chronic disease in general practice. Br J Gen Pract. 1994;44:383.
23. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38:12.
24. Lone NI, Gillies MA, Haddow C, Dobbie R, Rowan KM, Wild SH et al. Five Year Mortality and Hospital Costs Associated With Surviving Intensive Care. Am J Respir Crit Care Med. 2016;194:2.
25. Williams TA, Leslie GD, Brearley L, Dobb GJ. Healthcare utilisation among patients discharged from hospital after intensive care. Anaesth Intensive Care. 2010;38:4.
26. Agard AS, Lomborg K, Tonnesen E, Egerod I. Rehabilitation activities, out-patient visits and employment in patients and partners the first year after ICU: a descriptive study. Intensive Crit Care Nurs. 2014;30:2.
27. Glynn LG, Valderas JM, Healy P, Burke E, Newell J, Gillespie P et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. Fam Pract. 2011;28:5.
28. Jeitziner MM, Zwakhalen SM, Hantikainen V, Hamers JP. Healthcare resource utilisation by critically ill older patients following an intensive care unit stay. J Clin Nurs. 2015;24:9-10.

Chapter 10

General discussion

Annually, approximately 70,000 Dutch intensive care unit (ICU) patients survive their ICU admission and are discharged from the hospital alive [1]. Many of these ICU survivors suffer physical, cognitive, and/or mental health complaints, persisting long beyond the hospitalization. In this thesis, we aimed to gain insight in the burden ICU patients and their informal caregivers suffer after hospital discharge, and their need for healthcare after discharge. Furthermore, we aimed to gain insight into the healthcare consumption of ICU survivors during the year before and the year after ICU admission as a proxy for the health-related quality of life (HRQoL). To put things in perspective, we compared the healthcare consumption of ICU survivors with the healthcare consumption of people from the general population. In this chapter the main findings are presented as well as the implications for clinical practice and recommendations regarding the organization of ICU follow-up care. The strengths and limitations of the different studies are addressed and recommendations for further research are presented.

MAIN FINDINGS

In the first part of this thesis we focused on the burden ICU survivors and their informal caregivers face and the healthcare they need. In Chapter 2 we implemented a web-based triage tool to evaluate its feasibility. Furthermore we compared the outcomes of web-based questionnaires with the outcomes of paper-based questionnaires. Our study showed that the implementation of a web-based triage tool in daily practice might be difficult and there are important barriers to consider. About half of the health professionals found the software too complex to use and in order to successfully implement a new web-based triage tool, health professionals need time and support to use it.

Over 40% of the responding ICU survivors filled out the web-based questionnaires. Respondents who filled out the web-based questionnaires were significantly younger and had a significantly longer ICU stay than those who preferred the paper-based questionnaires. In both web-based and paper-based population, there was a large prevalence of ICU survivors with possible mental, physical and nutritional problems. Within the web-based questionnaires' group, 55.6% of the ICU survivors had possible mental problems and over half of them did not receive care for these complaints during the first three months after hospital discharge. Within the paper-based questionnaires' group similar results were found. Of the ICU survivors which filled out the web-based questionnaire, 68.5% had possible physical problems and of this group, 8.1% did not receive care for these complaints. Within the paper-based questionnaire group, 55.4% ICU survivors had possible physical problems and 17.1% of this population did not receive care for these complaints. Finally, 50.0% of the ICU survivors within the web-based questionnaire group had possible nutritional problems and almost half of this group did not receive care for these complaints. Within the paper-based

group 32.4% of the ICU survivors had possible nutritional problems and 75.0% did not receive care for these problems.

Critical illness and problems faced after ICU discharge have long-term effects on informal caregivers of ICU survivors as well (Chapter 3). Psychosocial symptoms of post-intensive care syndrome - family (PICS-F) are the most commonly reported burden in informal caregivers and at three months after discharge 24% to 63% of the informal caregivers is suffering anxiety, 12% to 26% depression, and 30% to 42% post-traumatic stress disorder.

In the second part of this thesis we gained insight into the healthcare consumption of ICU survivors during the year before ICU admission and during the year after ICU discharge. In Chapter 4 we showed that people who were admitted to an ICU had approximately three to five times higher healthcare costs per day alive compared to a control population, reflecting a reduced HRQoL. The differences in healthcare costs are present during the year before ICU admission and even increase during the year after discharge. Healthcare costs per day alive are substantially higher for very old ICU patients (≥80 years) than for the other study groups in the year before and the year after admission, while the remaining life expectancy after ICU discharge is significantly lower (Chapter 5). Patients admitted to an ICU for an acute intoxication have higher healthcare costs per day alive in the year prior to their admission, compared to non-intoxicated ICU patients and to matched controls (Chapter 6). Furthermore, the healthcare costs per day alive for intoxicated ICU patients remain elevated in the year following their admission and are higher compared to costs for non-intoxicated ICU patients. Our analysis described in Chapter 7 demonstrated that ICU patients have more chronic conditions during the year before ICU admission compared to a population based control group. Moreover, ICU survivors without pre-existing chronic conditions were 5-fold more likely to develop a chronic condition compared to surviving control patients without pre-existing chronic conditions. The ICU length of stay was associated with the development of heart diseases, COPD or asthma, and depression. The Acute Physiological Score (APS), a part of the Acute Physiology and Chronic Health Evaluation (APACHE) IV score, was associated with the development of heart diseases and kidney diseases. The reason for ICU admission was an important risk factor for the development of all studied chronic conditions (Chapter 8). Our study on general practitioner (GP) consultations (Chapter 9) showed that ICU patients have more consultations with GPs during the year before admission and the year after hospital discharge compared to a matched control group. Close to hospital admission and shortly after hospital discharge, the number of GP consultations strongly increases. During the last four weeks before admission, ICU patients have 3.58 (CI 3.37; 3.80) times more GP consultations compared to the control population. During the first four weeks after discharge ICU patients have 4.98 (CI 4.74; 5.23) times more GP consultations. Even one year after ICU admission the number remained elevated compared to before ICU admission.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

The clinical implications and the recommendations of this thesis will be addressed according to the healthcare trajectory of ICU survivors. First we will elaborate on the HRQoL of ICU survivors and their informal caregivers after hospital discharge. Secondly we will go into detail on how the gap between the need for healthcare of ICU survivors and the received healthcare might be closed.

Health-related quality of life of ICU survivors and their informal caregivers

In most of our studies (Chapter 4 to Chapter 10), we used healthcare consumption as a proxy for HRQoL. Our findings showed that ICU patients have an increased healthcare consumption during the year before and the year after ICU admission compared to a control group from the general population. Therefore we assume that ICU patients have a decreased HRQoL during the year before and the year after ICU admission compared to people from the general population. Studies which used validated questionnaires to gain insight in the HRQoL, such as the SF-36 and the EQ-5D, found similar results [2-7].

Multiple systematic reviews about the HRQoL after ICU discharge show that critically ill patients had a lower HRQoL compared to people from matched populations [5-7]. Only few studies reported on the HRQoL before ICU admission and a small number of them stated that ICU patients have a decreased HRQoL before ICU admission compared to controls from the general population [2-5]. Due to the methodological properties of questionnaires such as the SF-36, the HRQoL can only be queried up to four weeks before ICU admission. By studying the healthcare consumption we were able to show that ICU survivors have a decreased quality of life long before ICU admission compared to people from the general population.

Beside the decreased HRQoL, we reported in Chapter 2 that ICU survivors did not receive the appropriated care for the burden they faced during the first three months after hospital discharge. These findings are supported by another study performed in the Netherlands, where it was found that only 20% of the ICU survivors with a poor functional status received medical attention from a rehabilitation physician, half of the patients with poor functional status had physical therapy, and only 24% of the ICU survivors with psychological distress received treatment from a psychiatrist, psychologist or social worker one year after ICU discharge [8].

Closing the gap between the need for healthcare and the received healthcare

Because of the complexity and magnitude of the complaints ICU survivors suffer, multidisciplinary care after discharge is required [9]. ICU follow-up care aims to detect post-intensive care syndrome (PICS) in an early stage and the ICU survivors will be referred to the appropriate

health professional(s) during consultation. In some ICU guidelines, it is even recommended to have an ICU follow-up clinic [10]. Although ICU follow-up care has been suggested as a potential means to address PICS, there is no consensus on the way it should be organised and on its (cost-) effectiveness. Even though there is no evidence for the (cost-) effectiveness of ICU follow-up care at this moment, and examining the (cost-) effectiveness of ICU follow-up care is outside the scope of this thesis, we believe that by means of follow-up care the gap between the need for healthcare of ICU survivors and the received healthcare (as we showed in Chapter 2) can be closed.

Which ICU survivors need to be screened?

Identifying ICU survivors who are likely to have a decreased HRQoL after discharge and are therefore in need of ICU follow-up care will be an important first step. It was previously recommended to invite only those ICU survivors for ICU follow-up care who had more than 2 days of mechanical ventilation [11]. However, we found that ICU length of stay and duration of mechanical ventilation were not strongly associated with the development of certain chronic conditions, if significantly associated at all (Chapter 8). A previous published study reported that, only 9.8% of the variance of poor functional status was explained by ICU length of stay and APACHE II score [8]. Therefore we recommend that invitations for ICU follow-up care will be more personalised and not merely based on ICU length of stay or on length of mechanical ventilation. Based on this thesis, we recommend that ICU survivors with multiple ICU admissions, one or more chronic conditions prior to ICU admission, and high age are screened for PICS too. Moreover, the reason for ICU admission was an important risk factor for the development of chronic conditions during the year after discharge and having (multiple) chronic conditions is associated with a decreased HRQoL [12]. Therefore, we recommend that ICU survivors admitted to an ICU because of cardiovascular problems, diabetic related problems, renal related problems, intoxications or respiratory problems will be screened for PICS as well.

How can ICU survivors be screened?

It is recommended to screen ICU survivors for possible physical, mental and cognitive problems [9]. In Chapter 2 we implemented a web-based triage tool to evaluate its feasibility and found that not all patients were able to fill out the questionnaires online. This was partly due to the fact that that there were no e-mail addresses available in the hospital information systems. Our society is focussing and relying more and more on digital systems. In 2018, 97% of all Dutch inhabitants had an internet connection and among inhabitants aged 75 year or older this rate was 74% [13]. Web-based screening has major benefits compared to paper-based screening, for example, automated checking on completeness and correctness of data and easy storage of data, all leading to enhanced integrity and accuracy of outcome data [14, 15]. Moreover, web-based screening can reach many patients in an efficient way

and screen ICU survivors on the need for ICU follow-up care [16]. The outcomes of web-based questionnaires are directly available and patients can decide to give other healthcare professionals access to the outcomes of the questionnaires. Web-based screening has proved to be a convenient method to gain insight in patient-reported outcome measures as opposed to paper-based screening and is used within populations with rheumatism, cancer, asthma and pain [17]. After finishing the pilot study, the use of Electronic Health Records (EHRs) and patient portals increased significantly. The Dutch government financially supports the development of national patient portals and sharing information between patients and care providers through initiatives such as 'VIPP' and 'Medmij' [18, 19]. Through these patient portals, the infrastructures for digitally issuing questionnaires is already available.

When do ICU survivors need to be screened?

Literature shows that the prevalence of physical, cognitive, or mental impairments among ICU survivors is high at three months after hospital discharge [20-22] and the same accounts for their informal caregivers (Chapter 3). We found that the number of consultations with the GP declines rapidly during the first four weeks after hospital discharge (Chapter 9). Around two to three months after hospital discharge the mean number of GP visits per week stabilizes. However, at this point in time there is a large proportion of ICU survivors that did not receive healthcare for the problems they face (Chapter 2). Based on these findings, we can conclude that, even though a large proportion of the ICU survivors had contact with their GP, their complaints with respect to PICS are not recognized. Therefore we recommend that ICU survivors will be screened for PICS three months after hospital discharge, to make sure that all problems, experienced during the first three months after discharge, will not remain untreated. This is in line with the recommendations published before [11].

METHODOLOGICAL CONSIDERATIONS

Study population

Annually 10,000 ICU patients die during their hospitalization and it is estimated that these non-survivors had 12.4% more costs compared to survivors [23]. Even though this is a large proportion of ICU patients and they consume significant healthcare resources, we did not report on this sub-population in most of our studies because the aim of this thesis was to gain insight in the burden ICU patients and their informal caregivers suffer after hospital discharge.

We compared the ICU patients with a sample from the general Dutch population. This control population was frequency matched to the ICU population on a limited set of variables. Preferably we had created different population-based control groups for different studies

which was unfortunately not feasible due to resource and data-accessibility constraints at Vektis.

Chronic conditions are strong predictors for healthcare resource use and therefore, for examining the healthcare costs, it would be better to match the two study populations on chronic conditions before the ICU admission too. However, to gain insight in the differences in chronic conditions before and after ICU admission, chronic conditions should not be part of the matching process. Since matching the ICU population and the control population was performed only once for all studies on healthcare consumption, we decided to only include age, gender and SES in the matching process.

Another point to mention about the study population is that we have only information about the ICU admissions during 2013. It might be possible that individuals from the ICU population as well as individuals from the control population has been admitted to an ICU during 2012 or 2014. This could influence the healthcare costs of both populations and we therefore expect that this will not influence our conclusions.

Use of administrative databases

All chapters in this thesis which addressed the healthcare consumption are based on a national health insurance claims database. Insurance claims data can have major benefits: they tend to be case complete, contain large populations up to entire nations, and are ongoing resources available for research. Our studies based on claims data included almost all ICU survivors of an entire country (approximately 80.000 per year). Studies based on administered HRQoL questionnaires have a sample size generally ranging from 30 to 1,500 ICU patients and the response rate of questionnaire-driven data is ranging from 40% to 100% [5]. Due to the methodological properties of questionnaires such as the SF-36, only the HRQoL up to four weeks before ICU admission could be queried, whereas we were able to make assumptions about the HRQoL for a year preceding the ICU admission by using administrative databases.

However, there are some limitations which should be addressed as well. The healthcare costs were only available as a total sum in euros per person per calendar year. Patients admitted in December 2013 will have a spill over of costs in the next calendar year (2014) and will probably have higher healthcare costs during 2014 compared to ICU patients which are admitted in January 2013. Because costs were provided as total costs per year we could not dissect which components of care (e.g. mechanical ventilation, haemodialysis, salaries of healthcare workers, laboratory assessments, etc.) were important drivers of the costs. Only costs reimbursed by health insurance companies under the compulsory insurance were taken into account. The total amount of healthcare costs does not include services paid for out of

pocket or reimbursements via voluntary additional insurance. It is estimated that these costs are around €2 per person, per day [24]. People take a voluntary additional insurance policy if they expect to need additional care. ICU survivors have a lower HRQoL long before the ICU admission and are therefore more likely to have a voluntary additional insurance policy. The differences we found in healthcare costs between the ICU population and the control group can therefore be an underestimation of the true differences in healthcare costs between the ICU population and the control group.

To identify the chronic conditions we used pharmaceutical claims data and not the clinical diagnoses described in the NICE registry, since data in the pharmaceutical claims database is available for all inhabitants (independent of having an ICU admission) of the Netherlands and for the year before and after ICU admission. The validity of pharmacy based claims data for the assessment of chronic conditions and prevalence estimates has been demonstrated before in different countries such as the Netherlands, Italy, Switzerland and Canada [25-29]. Databases on prescribed drugs are a valuable source for measuring population's burden of disease, when clinical data are missing [26].

Since chronic conditions based on pharmaceutical claims data are calculated annually, we excluded individuals who did not survive the entire study period for the analyses regarding the development of new chronic conditions. Within the ICU population, the mortality rate and the prevalence of chronic conditions are higher compared with the control group. People with more chronic conditions are more likely to have worse health outcomes and are more likely to pass away. By excluding deceased ICU patients, we expect that the differences in development of new chronic conditions between the ICU population and the control group are slightly larger than we estimated. Additionally, a latent chronic condition can be diagnosed during ICU admission and treated from that moment onwards, whereas a latent chronic condition in the control group may not be diagnosed during our study. This can lead to an overestimation of the differences in the development of new chronic conditions between the ICU population and the control group. Therefore, we performed post hoc analyses where we identified a subpopulation of the control group which had been admitted to a hospital or had an outpatient appointment at a hospital and a subpopulation of the control group which had not been admitted to a hospital and had no outpatient visits at a hospital. These post hoc analyses showed that ICU patients still had a higher risk of developing new chronic conditions compared to the hospitalized population.

Generalizability of findings

The findings described in this thesis are all based on data from Dutch ICU survivors and dependent on the Dutch healthcare system. Although the patient characteristics of our stud-

ies were comparable to other studies about ICU survivors, the generalizability of data based on the Dutch healthcare system might be limited.

The total healthcare costs are calculated based on the costs of Diagnosis Treatment Combinations (DTC). A DTC is defined as all activities and services of hospital and medical specialists originating from the demand for care for which the patient consults the specialist. It covers the complete process of care: from the first consultation of the medical specialist until the completion of the treatment and therefore DTCs cover both outpatient costs and inpatient costs. Apart from these direct costs, indirect costs such as education, research and emergency care are also included [30, 31]. This is very specific for the Dutch healthcare system and therefore the real costs in euros might not be generalizable to other countries where they might use Diagnosis-related groups or completely other reimbursement systems.

The chronic conditions are calculated based on the pharmacy claims data. There are other western European countries where they use pharmacy based claims data [26-29]. The same methods used in our studies can be applied while investigating ICU patients from those countries, and it would be very interesting to compare the results of those studies to the results of the studies we presented in this thesis.

GPs are an important factor in the Dutch healthcare system and acts like a gatekeeper between the patient and other healthcare providers. The pattern of mean GP consults during the weeks before and after ICU admission might be generalizable to other Western-European countries where the GP fulfils the same role.

SUGGESTIONS FOR FUTURE RESEARCH

A growing number clinical trials has been published on the (cost)efficiency of follow-up care interventions for ICU survivors in order to improve their HRQoL after ICU discharge. However, recently published systematic reviews and meta-analyses reported no, or only limited, effect of ICU follow-up care interventions on the HRQoL [32-35]. A majority of the clinical trials on the (cost)efficiency of follow-up care interventions included ICU survivors based on the ICU length of stay or on the length of mechanical ventilation and all ICU patients within those studies received the same intervention. The results of studies described in this thesis imply that not only the ICU length of stay or mechanical ventilation should be used as inclusion criteria for follow-up care, but the chronic conditions present before ICU admission and the reason of ICU admission should to be taken into consideration too. We believe that if follow-up care interventions are more personalised on the needs of the ICU survivor, the outcomes of the interventions will become more (cost)effective.

Most chapters of this thesis are based on information collected by the NICE registry. The NICE registry was established to facilitate quality-monitoring and quality-improvement initiatives and to benchmark the performance of single ICUs to other comparable ICUs and to national values. In sight of this aim, the NICE registry might add variables to the database to help ICUs to gain insight in the HRQoL of ICU survivors and follow-up care. For example, the EQ-5D-5L [36] can be administered at ICU discharge since this questionnaire can be used for the calculation of quality-adjusted survival, a key measure of health effects for cost-effectiveness assessments. An example of a regional initiative is the MONITOR-IC study [37] of which the outcomes (5-year follow-up on HRQoL, physical, cognitive and mental symptoms, ICU survivors' care and support needs, healthcare use and related costs) will be merged with data of the NICE registry.

Our studies do not provide an answer to the question whether the healthcare consumption can always be justified. Because ICU resources are often limited, as are the number of life years that can be gained in good health. There is a need for studies that evaluate cost per quality-adjusted life year in ICU survivors as well as studies that evaluate value based healthcare. This would be interesting information for future benchmarking purposes.

CONCLUSION

ICU survivors have an increased healthcare consumption during the year before and the year after ICU admission compared to people from the general population. Therefore, we assume that ICU survivors have a decreased HRQoL during the year before ICU admission and the year after discharge. ICU survivors and their informal caregivers suffer severe and long-term complaints after hospital discharge and a large part of ICU survivors do not receive care for these complaints. Screening ICU survivors and their informal caregivers is highly recommended in order to give them the care they need and patient portals might be deployed for this aim. ICU survivors with multiple ICU admissions, one or more chronic conditions prior to ICU admission, and high age are at risk of having a decreased HRQoL after ICU discharge and therefore in need of ICU follow-up care.

REFERENCES

1. Dutch National Intensive Care Evaluation (NICE) registry http://www.stichting-nice.nl Accessed 08.11.2016.
2. Graf J, Koch M, Dujardin R, Kersten A, Janssens U. Health-related quality of life before, 1 month after, and 9 months after intensive care in medical cardiovascular and pulmonary patients. Crit Care Med. 2003;31:8.
3. Cuthbertson BH, Scott J, Strachan M, Kilonzo M, Vale L. Quality of life before and after intensive care. Anaesthesia. 2005;60:4.
4. Wehler M, Geise A, Hadzionerovic D, Aljukic E, Reulbach U, Hahn EG et al. Health-related quality of life of patients with multiple organ dysfunction: individual changes and comparison with normative population. Crit Care Med. 2003;31:4.
5. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38:12.
6. Dowdy DW, Eid MP, Sedrakyan A, Mendez-Tellez PA, Pronovost PJ, Herridge MS et al. Quality of life in adult survivors of critical illness: a systematic review of the literature. Intensive Care Med. 2005;31:5.
7. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med. 2010;38:5.
8. van der Schaaf M, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. J Rehabil Med. 2009;41:5.
9. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40:2.
10. Tan T, Brett SJ, Stokes T, Guideline Development G. Rehabilitation after critical illness: summary of NICE guidance. BMJ. 2009;338.
11. van der Schaaf M, Bakhshi-Raiez F, Van der Steen M, Dongelmans DA, De Keizer NF. Recommendations for the organization of intensive care follow-up clinics; report from a survey and conference of Dutch intensive cares. Minerva Anestesiol. 2015;81:2.
12. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes. 2004;2.
13. Centraal Bureau voor de Statistiek (CBS). Statline. http://statline.cbs.nl/Statweb/dome/default.aspx. Accessed 17.01.2019.
14. van Gelder MM, Bretveld RW, Roeleveld N. Web-based questionnaires: the future in epidemiology? Am J Epidemiol. 2010;172:11.
15. Coons SJ, Eremenco S, Lundy JJ, O'Donohoe P, O'Gorman H, Malizia W. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. Patient. 2015;8:4.
16. Cox CE, Wysham NG, Kamal AH, Jones DM, Cass B, Tobin M et al. Usability Testing of an Electronic Patient-Reported Outcome System for Survivors of Critical Illness. Am J Crit Care. 2016;25:4.
17. Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper-and-pencil administration of patient-reported outcome measures: a meta-analytic review. Value Health. 2008;11:2.
18. Versnellingsprogramma Informatie-uitwisseling Patiënt en Professional: de patiënt meer inzicht in zijn eigen zorg. 2019. https://www.vipp-programma.nl/. Accessed 17.01.2019.

19. MedMij. https://www.medmij.nl/. Accessed 17.01.2019.
20. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. Crit Care Med. 2016;44:9.
21. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2016;43.
22. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369:14.
23. Kramer AA, Dasta JF, Kane-Gill SL. The Impact of Mortality on Total Costs Within the ICU. Crit Care Med. 2017;45:9.
24. Centraal Bureau voor de Statistiek (CBS). Ruim 700 euro eigen betalingen aan zorg in 2015. https://www.cbs.nl/nl-nl/nieuws/2017/07/ruim-700-euro-eigen-betalingen-aan-zorg-in-2015. Accessed 10.10.2017.
25. Lamers LM, van Vliet RC. The Pharmacy-based Cost Group model: validating and adjusting the classification of medications for chronic conditions to the Dutch situation. Health Policy. 2004;68:1.
26. Huber CA, Szucs TD, Rapold R, Reich O. Identifying patients with chronic conditions using pharmacy data in Switzerland: an updated mapping approach to the classification of medications. BMC Public Health. 2013;13.
27. Maio V, Yuen E, Rabinowitz C, Louis D, Jimbo M, Donatini A et al. Using pharmacy data to identify those with chronic conditions in Emilia Romagna, Italy. J Health Serv Res Policy. 2005;10:4.
28. Chini F, Pezzotti P, Orzella L, Borgia P, Guasticchi G. Can we use the pharmacy data to estimate the prevalence of chronic conditions? a comparison of multiple data sources. BMC Public Health. 2011;11.
29. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995;48:8.
30. Hasaart F. Incentives in the Diagnosis Treatment Combination payment system for specialist medical care. A study about behavioral responses of medical specialists and hospitals in the Netherlands.: University of Maastricht; 2011.
31. Schafer W, Kroneman M, Boerma W, van den Berg M, Westert G, Deville W et al. The Netherlands: health system review. Health Syst Transit. 2010;12:1.
32. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I. Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med. 2015;41:5.
33. Teixeira C, Rosa RG. Post-intensive care outpatient clinic: is it feasible and effective? A literature review. Rev Bras Ter Intensiva. 2018;30:1.
34. Schofield-Robinson OJ, Lewis SR, Smith AF, McPeake J, Alderson P. Follow-up services for improving long-term outcomes in intensive care unit (ICU) survivors. Cochrane Database Syst Rev. 2018;11.
35. Mehlhorn J, Freytag A, Schmidt K, Brunkhorst FM, Graf J, Troitzsch U et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42:5.
36. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:10.
37. Geense W, Zegers M, Vermeulen H, van den Boogaard M, van der Hoeven J. MONITOR-IC study, a mixed methods prospective multicentre controlled cohort study assessing 5-year outcomes of ICU survivors and related healthcare costs: a study protocol. BMJ Open. 2017;7:11.

Contribution of authors

Chapter 2: IvB gave the training to use the triage tool, conducted all semi-structured interviews with the health professionals, transcribed the interviews verbatim, coded the interviews and drafted the manuscript. FBR gave the training to use the triage tool, coded the interviews and helped to draft the manuscript. NFdK participated in the design and coordination of this study. DAD helped in analysing and interpreting the results. MvdS participated in the design and coordination of this study. All authors discussed the themes and statements of the coding, read and approved the final manuscript.

Chapter 3: IvB carried out the literature search, screened the titles and abstracts of all articles to assess eligibility, filled out the data extraction for all the eligible articles and drafted the manuscript. FBR screened the titles and abstracts of 50 randomly selected articles to assess eligibility, filled out the data extraction for a selection of the eligible articles and helped to draft the manuscript. NFdK filled out the data extraction for a selection of the eligible articles and participated in the design and coordination of the review. DAD filled out the data extraction for a selection of the eligible articles and helped in analysing the results. MvdS filled out the data extraction for a selection of the eligible articles and participated in the design and coordination of the review. All authors read and approved the final manuscript.

Chapter 4: IvB performed the statistical analysis and drafted the manuscript. FBR helped with interpreting the results and writing the manuscript. WBB contributed to the methodological design of the manuscript and the interpretation of the results. NFdK and MvdS participated in the design and coordination of the manuscript. DAD supervised the design and coordination of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

Chapter 5: LH performed the analysis and drafted the manuscript. IvB, and FBR performed the statistical analysis and helped with interpreting the results and writing of the manuscript. MH contributed to drafting the manuscript. DvD, DdL and NFdK contributed to the interpretation of the results and drafting the manuscript, they participated in the design and coordination of the manuscript. Each author has contributed to the writing of the manuscript and finally has read and approved the submitted version.

Chapter 6: IvB performed all the analyses and wrote the manuscript, FBR supervised the analyses and edited the manuscript, NFdK supervised the analyses and edited the manuscript, DdL invented the study and wrote the manuscript. All authors read and approved the manuscript and agree with publication in BMC Emergency Medicine.

Chapter 7: IvB performed the statistical analysis and drafted the manuscript. WBB contributed to the methodological design of the manuscript and the interpretation of the results. FBR

helped with interpreting the results and writing the manuscript. NFdK and MvdS participated in the design and coordination of the manuscript. DAD supervised the design and coordination of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

Chapter 8: IvB performed the statistical analysis and drafted the manuscript. FBR helped with interpreting the results and writing the manuscript. WBB contributed to the methodological design of the manuscript and the interpretation of the results. MvdS and DAD participated in the design and coordination of the manuscript. NFdK supervised the design and coordination of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

Chapter 9: IvB performed the analysis and drafted the manuscript. FBR helped with interpreting the results and writing the manuscript. FT contributed to the methodological design of the manuscript and the interpretation of the results. NFdK, MvdS and DAD contributed to the interpretation of the results, drafting the manuscript and they participated in the design and coordination of the manuscript.

Summary

Annually, there are over 80,000 intensive care unit (ICU) admissions in the Netherlands. Over 70,000 ICU patients survive their ICU admission and many of these ICU survivors suffer severe and long-term complaints, all leading to restrictions in societal participation and a decreased quality of life. The term post-intensive care syndrome (PICS) was introduced in 2012 by the Society of Critical Care Medicine and is defined as '*new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization*'.

PICS and other problems faced after ICU discharge do not only affect the patient, but also reduce the physical, mental, social, and financial position of patients' informal caregivers, often family members, as well. The combination of problems affecting informal caregivers is known as PICS-Family (PICS-F).

There is an increasing number of studies published about PICS and PICS-F. Due to the methodological differences of these studies, the pooled outcomes can be conflicting and are lacking the ability to draw general and generalizable conclusions. Therefore, there is still need for more insight into the complete scope of burdens ICU survivors and their informal caregivers suffer after ICU discharge.

ICU follow-up care has been recommended to address the long-term and severe complains ICU patients suffer after discharge. ICU follow-up care aims to detect PICS in an early stage so that the ICU survivors will be referred to the appropriate health professional(s) during consultation and can be treated for symptoms of PICS. In some ICU guidelines, it is recommended to have an ICU follow-up clinic for ICU survivors and their informal caregivers. However, there is no evidence for the (cost-) effectiveness of ICU follow-up care. More research is necessary to identify which ICU survivors need which care at which moment in order to improve the (cost-) effectiveness of ICU follow-up care.

There is also a gap in knowledge with respect to the Health-related Quality of Life (HRQoL) of ICU patients before their ICU admission and its change over time. By comparing the HRQoL of ICU patients before ICU admission with their HRQoL after ICU discharge, we can gain insight in the impact of the critical illness and the effect of the ICU admission on the HRQoL. High use of healthcare resources is associated with an impaired health status and a reduced HRQoL. By studying the healthcare consumption of ICU patients, we can make assumptions about and make comparisons between the HRQoL of ICU patients before and after ICU admission. At the same time, it gives insight in the different types and quantities of healthcare consumed by ICU patients and can be used to identify the gap between the need for healthcare and the consumed healthcare.

The general aims of this thesis are 1) to gain insight in the burden ICU patients and their informal caregivers suffer after hospital discharge and their need for healthcare after discharge and 2) to gain insight into the healthcare consumption of ICU survivors during the year before and the year after ICU admission as opposed to a population based control group. Furthermore, we will identify subgroups of ICU survivors with high healthcare consumption, which are likely to benefit from ICU follow-up care. In Chapter 1, the background and rationale underlying the aims of this thesis are introduced.

In the first part of this thesis, we focus on the burden ICU survivors and their informal caregivers face and the healthcare they need. In Chapter 2 we describe the implementation and evaluation of the feasibility of a web-based triage tool in the ICU follow-up clinic, developed to collect patient-reported HRQoL data. Nine ICUs participated in this study and we included data of 128 ICU survivors. Our study showed that the implementation of a web-based triage tool in daily practice might be difficult and we identified important barriers to consider. About half of the health professionals found the software too complex to use and in order to successfully implement a new web-based triage tool, health professionals need time and support to use it. Additionally, outcomes gained by the web-based triage tool (n=54) were compared with those from conventional paper-based questionnaires (n=74) to assess the differences between these two groups. Respondents who filled out the web-based questionnaires were significantly younger and had a significantly longer ICU stay than those who preferred the paper-based questionnaires. The prevalence of mental, physical and nutritional problems was 55.6%, 68.5% and 50.0%, respectively, within the web-based questionnaires group and 50.0%, 55.4% and 32.4%, respectively, within the paper-based questionnaire group. Strikingly, for both groups, a large part of ICU survivors did not receive care for these complaints.

Critical illness and problems faced after ICU discharge have long-term effects on informal caregivers of ICU survivors as well (Chapter 3). We performed a literature review to provide a complete overview of the types of burdens reported in informal caregivers of adult ICU survivors, to make recommendations on which burdens should be assessed in this population, and which tools should be used. The search yielded 2,704 articles, of which we included 28 in our review. Psychosocial symptoms of PICS-F are the most commonly reported burden, and at three months after discharge 24% to 63% of the informal caregivers is suffering anxiety, 12% to 26% depression, and 30% to 42% post-traumatic stress disorder. We recommend that informal caregivers will be screened on symptoms of PICS-F, especially on anxiety, depression, PTSD, and HRQoL. Standardised questionnaires can be used such as the Hospital Anxiety and Depression Scale, the Impact of Event Scale and the Short Form-36. Screening informal caregivers could be integrated in the post-ICU care for ICU patients.

In the second part of this thesis, we gained insight into the healthcare consumption of ICU survivors during the year before ICU admission and during the year after ICU discharge. To study the healthcare consumption of ICU patients in the Netherlands, two databases were merged: the national health insurance claims database of Vektis and the database of the National Intensive Care Evaluation (NICE) registry, a national quality registry database for ICUs. To put things in perspective with respect to the healthcare consumption, we compared the healthcare consumption of ICU survivors with the healthcare consumption of people from the general population. With respect to the healthcare consumption we focused on 1) the total healthcare costs, 2) the types and prevalence of chronic conditions for which patients receive treatment, and the association of clinical variables with chronic conditions and 3) the frequency of general practitioner (GP) consultations during the year before and the year after hospital discharge.

In Chapter 4 we showed that ICU survivors had approximately three to five times higher healthcare costs per day alive compared to the control population, reflecting a reduced HRQoL. The difference in healthcare costs was present during the year before ICU admission (€3.04 (95% CI €2.99; €3.10) per day alive) and even increased to €5.11 (95% CI €5.02; €5.21) per day alive during the year after discharge. Healthcare costs per day alive are substantially higher for very old ICU patients (>= 80 year) in the year before and the year after admission (€13.05 (IQR €5.09; €38.66) and €30.76 (IQR €10.63; €89.67) than for the other study groups, while the remaining life expectancy after ICU discharge is significantly lower (Chapter 5). Patients admitted to an ICU for an acute intoxication have higher healthcare costs per day alive in the year prior to their admission, compared to non-intoxicated ICU patients and to matched controls (€20.3 (IQR €3.6; 76.4), €6.1 (IQR €0.9; €29.3) and €1.1 (IQR €0.3; €4.6), respectively) (Chapter 6). Furthermore, the healthcare costs per day alive for intoxicated ICU patients remain elevated in the year following ICU admission and are higher compared to costs for non-intoxicated ICU patients and to matched controls (€23.9 (IQR €5.1; €82.4), €13.6 (IQR €3.3; €54.9) and €1.1 (IQR €0.4; €4.9), respectively). Our analyses described in Chapter 7 demonstrated that 55.4% of the ICU population had one or more chronic conditions during the year before admission, while within the control group this was 38.4%. Moreover, ICU survivors without pre-existing chronic conditions were 5-fold more likely to develop a chronic condition compared to survivors of the control population without pre-existing chronic conditions. The ICU length of stay was associated with the development of heart diseases, COPD or asthma, and depression. The Acute Physiological Score, a part of the Acute Physiology and Chronic Health Evaluation IV severity of illness score, was associated with the development of heart diseases and kidney diseases. The reason of ICU admission was an important risk factor for the development of all studied chronic conditions (Chapter 8). Our study about GP consultations (Chapter 9) showed that ICU patients had 1.82 (95% CI 1.80; 1.85) times more GP consultations compared to a matched control

group during the year before hospital admission. During the year after hospital discharge, ICU patients had 2.28 (95% CI 2.24; 2.31) times more GP consultations. Close to hospital admission and shortly after hospital discharge, the number of GP contacts strongly increased. During the last four weeks before admission, ICU patients had 3.58 (95% CI 3.37; 3.80) times more GP consultations compared to the control population. During the first four weeks after discharge ICU patients had 4.98 (95% CI 4.74; 5.23) times more GP consultations. Even one year after discharge, the number of GP consultations remained elevated compared to the year before ICU admission.

In Chapter 10 we provided an overall discussion of the work in this thesis. In this chapter we compared our results with the existing literature and we discussed the implications for clinical practice. The strengths and limitations of the different studies are addressed and recommendations for further research are presented.

This thesis shows that ICU survivors have an increased healthcare consumption during the year before and during the year after ICU admission compared to people from the general population. Therefore, we assume that ICU patients have a decreased HRQoL during the year before ICU admission and the year discharge. ICU survivors and their informal caregivers suffer severe and long-term complaints after hospital discharge and a large part of ICU survivors do not receive care for these complaints. Screening ICU survivors and their informal caregivers is highly recommended in order to give them the care they need. Patient portals might be deployed for this aim. ICU survivors with multiple ICU admissions, one or more chronic conditions prior to ICU admission, and high age are at risk of having a decreased HRQoL after ICU discharge and therefore in need of ICU follow-up care.

Samenvatting

In Nederland worden jaarlijks meer dan 80.000 patiënten opgenomen op een intensive care (IC) afdeling. Meer dan 70.000 IC-patiënten overleven deze IC-opname, maar veel IC-overlevenden ervaren ernstige en langdurige klachten na ontslag. Deze klachten leiden tot beperkingen in het dagelijks functioneren en een verminderde kwaliteit van leven. De term post-intensive care syndroom (PICS) werd in 2012 geïntroduceerd door de Society of Critical Care Medicine en is gedefinieerd als 'nieuwe beperkingen of een verergering van beperkingen op fysiek, cognitief of mentaal gebied, die ontstaan na een levensbedreigende ziekte en aanhouden tot na de acute ziekenhuisopname'.

PICS en andere klachten die na IC-ontslag optreden hebben niet alleen betrekking op de IC-patiënt maar kunnen ook de fysieke, mentale, sociale en financiële positie van de mantelzorgers, vaak familieleden van IC-patiënten, negatief beïnvloeden. De combinatie van problemen bij mantelzorgers staat bekend als PICS-Family (PICS-F).

Er worden steeds meer onderzoeken gepubliceerd over PICS en PICS-F. Vanwege methodologische verschillen tussen deze onderzoeken kunnen er uit de samengevoegde uitkomsten geen algemene conclusies worden getrokken. Daarom is er nog steeds behoefte aan meer inzicht in de volledige reikwijdte van de klachten die IC-overlevenden en hun mantelzorgers hebben na IC-ontslag.

Om de langdurige en ernstige klachten van IC-patiënten na ontslag te verminderen wordt IC-nazorg geadviseerd. IC-nazorg is erop gericht om PICS in een vroeg stadium te herkennen, zodat de IC-overlevenden kunnen worden doorverwezen naar de juiste behandelaar(s) en kunnen worden behandeld voor symptomen van PICS. In sommige IC-richtlijnen wordt aanbevolen om een IC-nazorg poli te hebben voor IC-overlevenden en hun mantelzorgers. Er is echter nog geen bewijs voor de (kosten-) effectiviteit van IC-nazorg. Er is meer onderzoek nodig om te achterhalen welke IC-overlevenden, op welk moment, welke zorg nodig hebben om de (kosten-) effectiviteit van IC-nazorg te verbeteren.

Daarnaast is er een gebrek aan kennis met betrekking tot de kwaliteit van leven van IC-overlevenden voor IC-opname en de verandering in kwaliteit van leven in de loop van de tijd. Door de kwaliteit van leven voor de IC-opname te vergelijken met de kwaliteit van leven na IC-ontslag kunnen we inzicht krijgen in de impact van de levensbedreigende ziekte en het effect van de IC-opname op de kwaliteit van leven. Een hoge zorgconsumptie gaat gepaard met een verminderde gezondheid en een verminderde kwaliteit van leven. Door de zorgconsumptie van IC-overlevenden te bestuderen kunnen we aannames over de kwaliteit van leven maken en de kwaliteit van leven voor IC-opname vergelijken met de kwaliteit van leven na IC-ontslag. Tegelijkertijd geeft de zorgconsumptie inzicht in welke zorg door IC-overlevenden wordt gebruikt en in welke mate deze zorg wordt gebruikt. Hierdoor is

het mogelijk om het verschil tussen de behoefte aan zorg en de verbruikte zorg van IC-overlevenden te bestuderen.

Het doel van dit proefschrift is 1) om inzicht te krijgen welke klachten IC-overlevenden en hun mantelzorgers na ontslag uit het ziekenhuis ervaren en hun behoefte aan zorg na ontslag te inventariseren en 2) om inzicht te krijgen in de zorgconsumptie van IC-overlevenden in het jaar voor IC-opname en het jaar na IC-ontslag en deze vergelijken met de zorgconsumptie van een controlegroep uit de algemene Nederlandse bevolking. Bovendien zullen we subgroepen van IC-overlevenden in kaart brengen met een hoge zorgconsumptie, die waarschijnlijk baat hebben bij IC-nazorg. In Hoofdstuk 1 worden de achtergrond en doestellingen die aan dit proefschrift ten grondslag liggen geïntroduceerd.

In het eerste deel van dit proefschrift richten we ons op de klachten die IC-overlevenden en hun mantelzorgers ervaren en inventariseren we de zorg die ze nodig hebben. In Hoofdstuk 2 beschrijven we de implementatie van een online triage-tool en evalueren we de toepasbaarheid daarvan op de IC-nazorg poli. Deze online triage-tool is ontwikkeld om gegevens te verzamelen door middel van kwaliteit van leven vragenlijsten, ingevuld door Nederlandse IC-overlevenden. Negen IC-nazorg poli's hebben deelgenomen aan het onderzoek en we hebben gegevens van 128 IC-overlevenden meegenomen. Onze studie toont aan dat de implementatie van de tool in de dagelijkse praktijk moeilijk is en we hebben belangrijke obstakels in kaart gebracht voor de implementatie van een online tool. Ongeveer de helft van de behandelaars vond de software complex in gebruik. Om een nieuwe online triage-tool succesvol te implementeren hebben behandelaars tijd en ondersteuning nodig om de tool in gebruik te nemen. Daarnaast werden de resultaten van de online ingevulde vragenlijsten (n=54) vergeleken met die van conventionele papieren vragenlijsten (n=74) om de verschillen tussen deze twee groepen te beoordelen. Respondenten die de online vragenlijsten invulden waren significant jonger en hadden een aanzienlijk langere IC-ligduur dan degenen die de voorkeur gaven aan de papieren vragenlijsten. De prevalentie van mentale, fysieke en voedingsproblemen was respectievelijk 55.6%, 68.5% en 50.0% binnen de online vragenlijsten groep en respectievelijk 50.0%, 55.4% en 32.4% in papieren vragenlijsten groep. Opvallend was dat in beide groepen een groot deel van de IC-overlevenden geen zorg kreeg voor klachten die ze ervaarden.

Een levensbedreigende ziekte en problemen na IC-ontslag hebben ook langdurige effecten op mantelzorgers van IC-overlevenden (Hoofdstuk 3). We hebben een literatuuronderzoek uitgevoerd om een compleet overzicht te krijgen van klachten die werden beschreven door mantelzorgers van volwassen IC-overlevenden. Op basis van deze gegevens kunnen we aanbevelingen doen voor welke klachten deze populatie van mantelzorgers moet worden gescreend en welke vragenlijsten daarvoor gebruikt kunnen worden. De zoekopdracht

leverde 2.704 artikelen op, waarvan er 28 in onze literatuurstudie zijn meegenomen. De psychosociale klachten binnen PICS-F zijn de meest voorkomende klachten. Drie maanden na ontslag heeft 24% tot 63% van de mantelzorgers last van angst, 12% tot 26% last van depressie en 30% tot 42% last van posttraumatische stress. Wij adviseren dat mantelzorgers worden gescreend op symptomen van PICS-F, en vooral op angst, depressie, posttraumatische stress stressstoornissen en de kwaliteit van leven. Gestandaardiseerde vragenlijsten kunnen hiervoor gebruikt worden, zoals de Hospital Anxiety and Depression Scale, de Schokverwerkingslijst en de Short Form-36. Het screenen van mantelzorgers kan worden geïntegreerd in de IC-nazorg voor IC-patiënten.

In het tweede deel van dit proefschrift hebben we ons gericht op de zorgconsumptie van IC-overlevenden in het jaar voorafgaand aan IC-opname en gedurende het jaar na IC-ontslag. Om de zorgconsumptie van IC-overlevenden in Nederland te bestuderen, zijn twee databases samengevoegd: de nationale zorgdeclaratie-database van Vektis en de database van de Nationale Intensive Care Evaluatie (NICE), een nationale kwaliteitsregistratie voor IC's. Om de uitkomsten met betrekking tot de zorgconsumptie in perspectief te plaatsen, hebben we de zorgconsumptie van de IC-overlevenden vergeleken met de zorgconsumptie van een controlegroep uit de algemene Nederlandse populatie. Ten aanzien van de zorgconsumptie hebben we ons gericht op 1) de totale zorgkosten, 2) de soorten en prevalentie van chronische aandoeningen en de associatie van klinische variabelen met chronische aandoeningen en 3) de frequentie van huisartsconsulten in het jaar voor ziekenhuisopname en het jaar na ziekenhuisontslag.

In Hoofdstuk 4 tonen we aan dat de zorgkosten per dag in leven van IC-overlevenden drie tot vijf keer hoger zijn vergeleken met de zorgkosten per dag in leven van de controlegroep. We gaan ervan uit dat dit een verminderde kwaliteit van leven weerspiegelt. Het verschil in zorgkosten per dag in leven was al aanwezig tijdens het jaar voor IC-opname (€3,04 (95% BI €2,99; €3,10)) en steeg tot €5,11 (95% BI €5,02; €5,21) tijdens het jaar na ontslag. De zorgkosten per dag in leven zijn aanzienlijk hoger voor zeer oude IC-patiënten (>= 80 jaar) in het jaar voor en het jaar na opname (respectievelijk €13,05 (IQR €5,09; €38,66) en €30,76 (IQR €10,63; €89,67)) dan voor de andere studiegroepen, terwijl hun levensverwachting na IC-ontslag aanzienlijk lager is (Hoofdstuk 5). Patiënten die zijn opgenomen op de IC voor een acute intoxicatie hebben hogere zorgkosten per dag in leven gedurende het jaar voorafgaand aan hun opname, in vergelijking met niet-geïntoxiceerde IC-patiënten en met een controlegroep uit de algemene populatie (respectievelijk €20,30 (IQR €3,60; 76,40), €6,10 (IQR €0,90; €29,30) en €1,10 (IQR €0,30; €4,60),) (Hoofdstuk 6). De zorgkosten per dag in leven van geïntoxiceerde IC-patiënten blijven verhoogd in het jaar na IC-ontslag en zijn hoger in vergelijking tot de zorgkosten van niet-geïntoxiceerde IC-patiënten en de controlegroep (respectievelijk €23,90 (IQR €5,10; €82,40), €13,60 (IQR €3,30; €54,90) en €1,10 (IQR

€0,40; €4,90). Onze analyses beschreven in Hoofdstuk 7 tonen aan dat 55,4% van de IC-overlevenden in het jaar voor opname een of meer chronische aandoeningen had, terwijl dit bij de controlegroep 38,4% was. Bovendien hadden IC-overlevenden, die geen chronische aandoeningen hadden voor IC-opname, een 5-keer grotere kans op het ontwikkelen van een chronische aandoening in vergelijking met personen uit de controle populatie. De IC-ligduur was geassocieerd met het ontwikkelen van hartaandoeningen, COPD of astma en depressie. De acute fysiologische score, een onderdeel van de APACHE IV (een score voor de ernst van ziekte), was geassocieerd met het ontwikkelen van hartziekten en nierziekten. De reden van IC-opname was een belangrijke risicofactor voor de ontwikkeling van alle bestudeerde chronische aandoeningen (Hoofdstuk 8). Onze studie over huisartsconsultaties (Hoofdstuk 9) toont aan dat IC-overlevenden 1,82 (95% BI 1,80; 1,85) keer meer huisartsenconsulten hebben in het jaar voorafgaand aan ziekenhuisopname vergeleken met een controlegroep. Gedurende het jaar na ziekenhuisontslag hebben IC-overlevenden 2,28 (95% BI 2,24; 2,31) keer meer huisartsconsulten ten opzichte van de controlegroep. Kort voor ziekenhuisopname en kort na ziekenhuisontslag nam het aantal consulten sterk toe. Tijdens de laatste vier weken voor ziekenhuisopname hebben IC-overlevenden 3,58 (95% BI 3,37; 3,80) keer meer huisartsenconsulten vergeleken met de controlegroep. Gedurende de eerste vier weken na ziekenhuisontslag hebben IC-overlevenden 4,98 (95% BI 4,74; 5,23) keer meer huisartsenconsulten. Zelfs een jaar na ziekenhuisontslag bleef het aantal huisartsconsulten binnen de groep IC-overlevenden verhoogd vergeleken met het jaar voor ziekenhuisopname.

Hoofdstuk 10 bevat de algemene discussie van dit proefschrift. In dit hoofdstuk hebben we onze resultaten vergeleken met de bestaande literatuur en hebben we de implicaties voor de klinische praktijk besproken. De sterke punten en beperkingen van de verschillende onderzoeken worden behandeld en aanbevelingen voor verder onderzoek worden gepresenteerd.

Dit proefschrift toont aan dat IC-overlevenden een verhoogde zorgconsumptie hebben gedurende het jaar voor IC-opname en het jaar na IC-ontslag ten opzichte van mensen uit de algemene Nederlandse bevolking. Daarom gaan we ervan uit dat IC-overlevenden een verminderde kwaliteit van leven hebben in het jaar voor IC-opname en het jaar na IC-ontslag. IC-overlevenden en hun mantelzorgers hebben ernstige en langdurige klachten na ontslag uit het ziekenhuis en een groot deel van de IC-overlevenden krijgt geen zorg voor deze klachten. Het screenen van IC-overlevenden en hun mantelzorgers wordt aanbevolen om hen de zorg te geven die ze nodig hebben. Patiëntportalen kunnen hiervoor worden ingezet. IC-overlevenden met meerdere IC-opnamen, een of meer chronische aandoeningen voorafgaand aan de IC-opname en een hoge leeftijd hebben een grotere kans op een verminderde kwaliteit van leven na IC-ontslag en hebben daarom IC-nazorg nodig.

Curriculum vitae & Portfolio

CURRICULUM VITAE

Ilse van Beusekom werd op 26 juli 1985 geboren te Hoorn. In 2002 behaalde zij haar havo diploma aan het Werenfridus in Hoorn en in 2007 behaalde zij haar BSc Fysiotherapie aan de Hogeschool van Amsterdam. Ter afronding van haar BSc liep zij stage in Iten, Kenia met als doel het behandelen van cliënten in een particuliere (sport)praktijk, het geven van trainingen in het sportcentrum en het opleiden van Keniaanse jongeren tot (sport)masseur. Voor haar beroepsopdracht heeft Ilse een adviesrapport geschreven over de voorwaarden waar de opleiding fysiotherapie in Kenia aan moet voldoen, om gekwalificeerd te kunnen worden als bacheloropleiding. Ilse heeft vervolgens deeltijd de pre-master Gezondheidswetenschappen doorlopen en deeltijd gewerkt als fysiotherapeut bij het Centrum voor Arbeid en Gezondheid Amsterdam, onderdeel van het Jan van Breemen Instituut. Voordat zij begon aan de master Gezondheidswetenschappen heeft ze een jaar gereisd. Ter afronding van haar master heeft ze stage gelopen in Quezaltenango, Guatemala waar ze onderzoek deed naar borstvoeding en infectieziekten bij kinderen van 0 tot 2 jaar. Na haar afstuderen in 2011 heeft Ilse nog bijna een half jaar gereisd, gewerkt als International Medical Assistant bij Allianz Global Assistance en gewerkt als Datamanager bij het Traumacentrum Zuidwest-Nederland. In maart 2014 startte zij met haar promotieonderzoek binnen de NICE registratie onder leiding van Prof. Nicolette de Keizer en Dr. Ferishta Bakhshi-Raiez.

PORTFOLIO

Name PhD student: Ilse van Beusekom

PhD period: March 2014 - May 2019

Promotor: Nicolette F. de Keizer

1. PhD training		
	Year	Workload (ECTS)
General courses of the Graduate School		
AMC World of Science	2014	0.7
Practical Biostatistics	2014	1.1
Computing in R	2014	0.4
Clinical epidemiology: Systematic Reviews	2015	0.7
Project Management	2015	0.6
Qualitative Health Research	2015	1.9
Oral Presentation	2016	0.8
Career Development	2018	0.8
Specific courses		
Longitudinal and Incomplete Data, MIE conference, Munich, Germany	2016	0.3
eBROK, Amsterdam, The Netherlands	2019	1.0
Seminars, workshops and masterclasses		
Seminar 'Big data in the Critically ill', Amsterdam, The Netherlands	2018	0.1
Masterclass 'Professional Performance in de Praktijk', Amsterdam, The Netherlands	2018	0.1
Masterclass 'Saving Lives, Saving Costs', Amsterdam, The Netherlands	2018	0.1
Presentations (oral)		
Medical Informatics PhD days, AMC, Amsterdam, The Netherlands	2014-2017	1.0
ICU follow-up care pilot study, NICE Registry conference, Nieuwegein, The Netherlands	2015	0.5
ICU follow-up care pilot study, NVIC Intensivistendagen, Den Bosch, The Netherlands	2016	0.5
ICU survivors have a substantial higher risk of developing chronic conditions compared to a population based control group, ESICM conference, Vienna, Austria	2017	0.5
Healthcare consumption and chronic conditions before and after ICU admission, 6th European Conference on Weaning & Rehabilitation, Leuven, Belgium	2018	0.5
Zorgconsumptie van IC patiënten, NICE Registry conference, Nieuwegein, The Netherlands	2018	0.5

Chronic conditions in ICU survivors compared to a population based control group, SCCM 48th Critical Care Congress, San Diego, USA	2019	0.5

Presentations (poster)		
ICU follow-up care pilot study, MIE conference, Munich, Germany	2016	0.5
ICU follow-up care pilot study, Amsterdam Public Health Meeting, Amsterdam, The Netherlands	2016	0.5

(Inter)national conferences		
Annual NICE Registry Conference, Nieuwegein, The Netherlands	2014-2018	1.0
Annual Medical Informatics PhD days, Amsterdam, The Netherlands	2014-2018	1.0
Annual Amsterdam Public Health Meeting, Amsterdam, The Netherlands	2016-2017	0.4
Family and patient Centered Intensive Care, Putten, The Netherlands	2016	0.2
ESICM conference, Vienna, Austria	2017	1.0
Van Kritieke Ziekte naar Goede Gezondheid, Amsterdam, The Netherlands	2018	0.2
6th European Conference on Weaning & Rehabilitation, Leuven, Belgium	2018	1.0
PICS; (her)ken jij het?, Ede, The Netherlands	2018	0.2
SCCM 48th Critical Care Congress, San Diego, USA	2019	1.0

Other PhD training		
Medical Informatics research meetings, AMC, Amsterdam, The Netherlands	2014-2019	3.0
Organizer of Medical Informatics PhD day: PhD - An obstacle run (40 participants), AMC, Amsterdam, The Netherlands	2017	1.0

2. Teaching		
Supervising		
One month internship: Debby Schleeper, Literature study: The effect of an ICU admission on chronic diseases	2015	0.3
One month internship: Femke van Sinderen, Literature study: Intensive Care Unit Follow-Up Care	2016	0.3

3. Parameters of Esteem	
Awards and Prizes	
ESICM Abstract Award	2017

List of publications

PUBLISHED

van Beusekom I, Bakhshi-Raiez F, de Keizer NF, van der Schaaf M, Termorshuizen F, Dongelmans DA. Dutch ICU survivors have more consultations with general practitioners before and after ICU admission compared to a matched control group from the general population. PLoS ONE 14(5): e0217225.

van Beusekom I, Bakhshi-Raiez F, van der Schaaf M, Busschers WB, de Keizer NF, Dongelmans DA. ICU Survivors Have a Substantial Higher Risk of Developing New Chronic Conditions Compared to a Population-Based Control Group. Crit Care Med. 2019;47:3.

van Beusekom I, Bakhshi-Raiez F, de Keizer NF, de Lange DW. The healthcare costs of intoxicated patients who survive ICU admission are higher than non-intoxicated ICU patients: a retrospective study combining healthcare insurance data and data from a Dutch national quality registry. BMC Emerg Med. 2019;19:1.

Vossenaar M, van Beusekom I, Alvey J, Doak CM, Solomons NW. Several problem nutrients are identified in the complementary diet of 6 to 11 month old breastfed children in Western Guatemala. Asia Pac J Clin Nutr. 2018;27:5.

Haas LEM, van Beusekom I, van Dijk D, Hamaker ME, Bakhshi-Raiez F, de Lange DW et al. Healthcare-related costs in very elderly intensive care patients. Intensive Care Med. 2018;44:11.

van Beusekom I, Bakhshi-Raiez F, de Keizer NF, Dongelmans DA, van der Schaaf M. Lessons learnt during the implementation of a web-based triage tool for Dutch intensive care follow-up clinics. BMJ Open. 2018;8(9):e021249.

van Beusekom I, Bakhshi-Raiez F, de Keizer NF, van der Schaaf M, Busschers WB, Dongelmans DA. Healthcare costs of ICU survivors are higher before and after ICU admission compared to a population based control group: A descriptive study combining healthcare insurance data and data from a Dutch national quality registry. J Crit Care. 2018;44.

van Beusekom I, Bakhshi-Raiez F, de Keizer NF, Dongelmans DA, van der Schaaf M. Reported burden on informal caregivers of ICU survivors: a literature review. Crit Care. 2016;20.

Vossenaar M, Alvey J, van Beusekom I, Doak CM, Solomons NW. Energy contribution from non-breastmilk items in low-income Guatemalan infants in their sixth month of life. Salud Publica Mex. 2015;57:2.

Vossenaar M, van Beusekom I, Doak C, Solomons NW. Feeding patterns before 6 months of age: the relative validity of recall from interviews of mothers of Guatemalan infants and toddlers. Asia Pac J Clin Nutr. 2014;23:4.

van Beusekom I, Vossenaar M, Montenegro-Bethancourt G, Doak CM, Solomons NW. Estimates of exclusive breastfeeding rates among mother-infant dyads in Quetzaltenango, Guatemala, vary according to interview method and time frame. Food Nutr Bull. 2013;34:2.

Doak CM, van der Starre RE, van Beusekom I, Campos Ponce M, Vossenaar M, Solomons NW. Earlier introduction of aguitas is associated with higher risk of stunting in infants and toddlers in the Western Highlands of Guatemala. Am J Clin Nutr. 2013;97:3.

SUBMITTED

van Beusekom I, Bakhshi-Raiez F, van der Schaaf M, Dongelmans DA, Busschers WB, de Keizer NF. The influence of ICU related clinical variables on the risk of developing chronic conditions within a population of ICU survivors

Dankwoord

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