Long-term follow-up after intensive care

Development of an ICU-specific questionnaire

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COVER Results from paper I.

ART The art in this doctoral thesis was created by the AI text-generator ChatGPT® and the AI image-generator Midjourney®. ChatGPT® was asked to enter the minds of the artists, imagine them surviving intensive care, and describe what they would create to depict their emotions.
These prompts, fed into Midjourney®, bring the artists' emotional landscapes to life. The resulting art capture the essence of resilience and the deeply personal nature of survival.
The prompts are displayed alongside the art. The pieces exist solely within the pages of this doctoral thesis and are not subject to copyright restrictions. They offer an exclusive, unencumbered glimpse into the intersection of technology, imagination, and human emotion.

LONG-TERM FOLLOW-UP AFTER INTENSIVE CARE
DEVELOPMENT OF AN ICU-SPECIFIC QUESTIONNAIRE

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SVANENMÄRKET
Trycksak
3041 0234

TO MY FAMILY.

GUSTAV KLIMT
would paint a golden tree of life to illustrate the preciousness of life, using rich, detailed patterns and shimmering metallic accents that evoke a sense of wonder and gratitude for the beauty of existence.

ABSTRACT

Background

With improved results in intensive care comes a shift in focus – from survival to survivorship. Studies show that ICU survivorship includes effects on, for example, mental and physical health, cognition, ADL, ability to return to work, and sensory organ functions. Measuring quality of life and burden of disease after intensive care is fundamental and needs to be facilitated by a relevant tool, explicitly developed for ICU survivorship.

Aim

This doctoral thesis reports on the first steps taken toward a specific questionnaire tailored for long-term follow-up on quality of life and burden of disease in ICU survivors.

Methodology

Interviews were conducted with long-term ICU survivors from the general ICU at Sahlgrenska University Hospital to extract as many post-intensive care issues as possible. All unique issues from the interviews were converted into questions and tested in a sample of ICU survivors and a non-ICU-treated control group. Alternative explanatory factors for differences between the two groups were evaluated, and the structure of quality of life was assessed.

Results

From interviews with 32 ICU survivors in PAPER I, questions in 13 areas were identified and included in a provisional questionnaire, subsequently distributed to 518 ICU survivors and 231 controls. The ICU survivor group had a significantly worse state in 77% of issues.

In PAPER II, we showed that neither significant differences in comorbidity between the two groups, nor educational level, had a major impact on explaining the differences in the responses to our questionnaire. Associations between ICU survivorship and issues were moderated by comorbidity, or educational level, in only six of 218 (2.8%) and 34 of 218 issues (15.6%), respectively.

In PAPER III, we found that only a minority of issues were related to quality of life in both groups, with different patterns in the ICU survivor and non-ICU-treated control groups.

Finally, PAPER IV found that quality of life was best described in separate, domain-specific, quality of life-subscales rather than as an overarching construct.

Conclusion

This doctoral thesis reports on the initial work on creating a questionnaire specifically for evaluating long-term effects in quality of life and burden of disease after intensive care. After further validation and reduction of the number of questions, the questionnaire may be used in clinical evaluations of ICU survivors, as well as an outcome measure in trials.

Keywords

INTENSIVE CARE • CRITICAL ILLNESS • INTENSIVE CARE UNIT • QUALITY OF LIFE • LONG-TERM FOLLOW-UP • SURVIVORSHIP • HEALTH-RELATED QUALITY OF LIFE • BURDEN OF DISEASE

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PABLO PICASSO
would paint a vibrant, energetic piece featuring distorted figures, as if they are breaking free from confinement, to illustrate a sense of liberation and rebirth after surviving a life-threatening condition.

SVENSK SAMMANFATTNING

Med allt fler patienter som överlever intensivvård ökar behovet av att korrekt kunna utvärdera hur de före detta patienterna mår på lång sikt. Under de senaste 20-30 åren har studier påvisat besvär inom bland annat fysisk och mental hälsa, sömn, fatigue, smärta, kognitiv förmåga, samt möjlighet att komma tillbaka i arbete.

Avhandlingen är i första hand metodologisk och syftar till att beskriva de första stegen mot ett frågeformulär som är skapat specifikt för utvärdering av IVA-överlevares livskvalitet och besvär. Den övergripande utgångspunkten har varit att ett sådant frågeformulär bäst grundar sig på IVA-överlevarnas egna beskrivningar, varför en kvalitativ metodik med semi-strukturerade intervjuer valdes som initial ansats. Fynden från dessa intervjuer har sedan jämförts med icke intensivvårdade kontrollpersoner ytterligare analyserats, allt för att med så hög precision som möjligt kunna extrahera just de besvär som är unika för IVA-överlevare.

I **ARTIKEL I** intervjuade jag via Sahlgrenska Universitetssjukhusets post IVA-mottagning 32 IVA-överlevare för att få fram de besvär som uppstått efter utskrivning.

Över 200 funna besvär sorterades in i 13 domäner: Kognition, fatigue, fysisk hälsa, smärta, ADL, mental hälsa, sömn, känselorganen, aptit och alkoholbruk, sexuell hälsa, gastrointestinala besvär, urinvägsbesvär och arbetslivsbesvär. I det här skedet ströks inga ämnen eftersom en

framtida frågereducering planerades. Ämnena omformulerades till frågeform och svarsskalor utformades för att matcha frågorna innehållsmässigt. I majoriteten av frågorna användes "den senaste månaden" som tidsperspektiv. Ett mindre antal frågor från existerande områdesspecifika frågeformulär adderades.
I en efterföljande tvärsnittsstudie testades det preliminära frågeformuläret på 518 vuxna IVA-överlevare och 231 kontrollpersoner, ej tidigare intensivvårdade. Inklusionskriterier för IVA-överlevarna var intensivvård i minst 72 timmar, samtliga inläggningsdiagnoser utom uttalat neurologiska/neurokirurgiska, samt svensk adress och en rimlig förståelse för det svenska språket. Kontrollpersonerna randomiserades från Västra Götalandsregionen via Svenskt Personadressregister, efter att ha matchats till ålder och kön.

Av de som tackat ja till deltagande inkom 395 (76.2%) av IVA-överlevare och 197 (85.3%) av kontrollpersoner med ett frågeformulär. IVA-överlevarna hade ett signifikant sämre resultat på 77% av frågorna jämfört med kontrollpersonerna.

I **ARTIKEL II** utvärderade vi till vilken grad de skillnader vi fann i tvärsnittsstudien kunde bero på skillnader i andra faktorer än grupptillhörighet. Eftersom våra två grupper skilde sig signifikant i komorbiditet (samsjuklighet) kunde detta vara en tänkbar förklaring till de observerade skillnaderna mellan grupperna. Ytterligare en tänkbar alternativ förklaring till skillnaderna är socioekonomiska faktorer, i vårt fall bäst mätt genom utbildningsnivå. Teorin i **ARTIKEL II** var att om någon av dessa faktorer, komorbiditet eller utbildningsnivå, istället skulle vara förklaringen till att IVA-överlevarna mådde sämre än kontrollpersonerna, så borde skillnaden mellan de två grupperna variera med nivån av dessa faktorer, så kallad effektmodifiering. Våra resultat i **ARTIKEL II** visar dock att så inte var fallet. Genom den statistiska modell som sattes upp kunde vi visa att det mycket sällan fanns en sådan effektmodifiering (2.8% respektive 15.6% av frågorna för komorbiditet respektive utbildningsnivå). I den mån det fanns en effekt av komorbiditetsskillnader eller av utbildningsnivå alls, så existerade denna effekt istället oftast parallellt med effekten av att tillhöra IVA-överlevargruppen jämfört med att tillhöra kontrollgruppen. Det är ett viktigt fynd då det visar att det fortfarande är relevant att jämföra intensivårdsöverlevare med friskare populationer trots skillnader i komorbiditet. Dessutom påvisar det behovet av ökad komplexitet i såväl statistiska modeller som förklaringsdito.

I **ARTIKEL III** utgick vi från hypotesen att inte alla de besvär vi funnit påverkar livskvaliteten. Varje kapitel i vårt frågeformulär avslutades med en sammanfattande livskvalitetsfråga: ***Hur mycket påverkar besvär med*** *[kapitel] din livskvalitet?* Genom en explorativ faktoranalys utvärderade vi, simultant i de bägge grupperna, domänernas dimensionalitet. På så sätt kunde vi utvärdera vilka frågor i varje domän som korrelerade starkt i samma dimension som livskvalitetsfrågan, och vilka frågor som trots att de var viktiga ändå inte korrelerade med just en effekt på livskvalitet. Resultaten från ARTIKEL III visade att en minoritet av de besvär som vårt stickprov av IVA-överlevare hade korrelerade med en effekt på livskvalitet. Mönstren för vilka frågor som korrelerade med livskvalitet och vilka som är av mer alldaglig karaktär skiljer sig också mellan IVA-överlevare och kontrollgruppen i flera domäner. Fynden underlättar en framtida reducering av antalet frågor i formuläret, och kan vara till hjälp om man specifikt vill mäta enbart livskvalitetsrelaterade besvär.

Artikel IV fortsätter analyserna från ARTIKEL III kring livskvalitet, men med metoder ämnade till att bättre förstå den övergripande strukturen av livskvalitet enbart hos vårt stickprov av IVA-överlevare. Efter att ha extraherat de frågor inom respektive domän som korrelerar tillräckligt starkt till livskvalitetsfrågan framkommer att livskvalitet bäst beskrivs som ett fenomen på domänbasis snarare än som ett övergripande fenomen.

KEITH HARING
would paint an exuberant crowd of dancing figures, pulsating with vibrant energy, to celebrate his newfound appreciation of life after surviving a life-threatening illness, using vibrant pops of color, capturing the excitement of the moment.

LIST OF PAPERS

This doctoral thesis is based on the following papers:

I

Malmgren J, Waldenström AC, Rylander C, Johannesson E, Lundin S
Long-term health-related quality of life and burden of disease after intensive care:
Development of a patient-reported outcome measure.
Crit Care. 2021;25(1):82.

II

Malmgren J, Waldenström AC, Rylander C, Lundin S, Johannesson E
Effect modification of comorbidity and educational level on quality of life after intensive care:
Analysis of a cross-sectional study
Submitted

III

Malmgren J, Waldenström AC, Rylander C, Lundin S, Johannesson E
Quality of life-related and non-quality of life-related issues
in ICU survivors and non-ICU-treated controls:
A multi-group exploratory factor analysis of a cross-sectional study
Manuscript

IV

Malmgren J, Waldenström AC, Rylander C, Lundin S, Johannesson E
Evaluating the structure of quality of life after intensive care:
Confirmatory factor analysis and bifactor modelling of a cross-sectional study
Manuscript

WASSILY KANDINSKY
would paint an explosion of vivid shapes and colors, as if his soul had burst open and given birth to new life, in order to express his overwhelming gratitude for having cheated death and been given a second chance at life.

CONTENTS

FRANCISCO GOYA
would paint the horrors of his physical suffering and the fear of impending death, using dark colors and grotesque images, to express his existential anguish, using thick brushstrokes that give the impression of deep pain and suffering.

ABBREVIATIONS

ADL	Activities of Daily Living
AIC	Akaike Information Criterion
ARDS	Acute Respiratory Distress Syndrome
AVE	Average Variance Extracted
BIC	Bayesian Information Criterion
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
EFA	Exploratory Factor Analysis
EORTC	European Organisation of Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
GT	Grounded Theory
HRQoL	Health-Related Quality of Life
ICU	Intensive Care Unit

PICS	Post Intensive Care Syndrome
MG-EFA	Multi-group Exploratory Factor Analysis
PROM	Patient-Reported Outcome Measures
PTSD	Post-Traumatic Stress Syndrome
QoL	Quality of Life
RCT	Randomised Controlled Trial
RMSEA	Root Mean Square Error of Approximation
SAPS3	Simplified Acute Physiology Score III
SES	Socioeconomic Status
SF-36	Short Form 36
SPAR	Svenskt Personadressregister
SRMR	Standardised Root Mean Square Residual
SWD	State Worse than Death
TLI	Tucker-Lewis Index
WAI	Work Ability Index

JEAN-MICHEL BASQUIAT would paint an explosive composition that reflects his euphoric, triumphant feelings of having survived. Bright, bold colors and erratic lines would dominate, imbuing the work with frenetic energy and vitality. He would use mixed media, emphasizing the gritty, raw nature of his state.

NOMENCLATURE & EXPLANATIONS

> *"The single biggest problem in communication is the illusion that it has taken place.*
>
> *George Bernard Shaw, or someone else*

THIS doctoral thesis contains a nomenclature perhaps unfamiliar to the intended reader. As is the case in various fields, specific terminology has evolved, acquiring unique uses and connotations that may diverge from those commonly understood outside the discipline.

Some definitions may be necessary to aid both the reading and any eventual discussion.

Construct	A *construct* is an abstract, intangible concept being measured by, for example, a questionnaire. Examples of a construct are *self-esteem*, *intelligence*, and *motivation*. The central construct discussed in this doctoral thesis is *quality of life*.
Dimension & factor	A term fundamental to factor analysis, *dimension* is best thought of as a specific aspect of a construct. Unmeasurable concepts are explored in factor analysis through surrogate variables to evaluate whether they consist of different subsets. Dimensions help break down complex constructs into measurable parts. For example, socioeconomic status is a variable impossible to measure. However, we may measure indicators such as income and education. These indicators then represent different dimensions (i.e., of socioeconomic status). However, dimensions themselves are often complex and untangible, and if so, they too have to be measured through proxy variables. For example, the construct of intelligence may have multiple dimensions, such as mathematical and verbal ability both which could be measured with a number of different tests. *Dimension* and *factor* are often used interchangeably in the context of factor analysis. Generally, both terms refer to subsets of the underlying latent construct measured by a set of observable variables. However, there can be subtle differences in how these terms are used. For example, a *factor* often refers to an identified latent variable resulting from a factor analysis. In contrast, *dimension* is often used more broadly to refer to any subset of an underlying construct measured by a set of variables, regardless of whether or not a factor analysis has been performed. In practice, the choice of terminology can depend on the specific context and the preferences of the researcher.
Domain	The easiest way of thinking of *domain* is simply substituting the word for "chapter". In our context, a domain equals a chapter about a specific area of problems. For example, mental health is one domain/chapter, while physical health is another.

Issue	***Issue*** is the agreed-upon word defining a single problem/trouble/dysfunction etc. When reading the doctoral thesis, including the papers, an issue denotes the problem, while a ***question*** simply is the issue rewritten into question form.
Item	When an issue is rewritten into question form, convention states it is an ***item***. Thus, ***item, issue*** and ***question*** become almost interchangeable.
Long-term	For this context, ***long-term*** is used to characterise everything beyond six months after ICU discharge.
Validity	Older terminology, e.g., ***construct validity***, will be used throughout the doctoral thesis instead of the newer ***evidence of construct validity***. This is not a polemic statement against the *American Psychiatry Association* but a decision made considering that the reader may be more used to the former nomenclature and unaware of the debate on semantics.

MARC CHAGALL
would paint a dreamy, whimsical scene of himself flying through the sky, surrounded by vibrant, otherworldly colors to illustrate his joy and gratitude for being given a second chance at life.

INTRODUCTION

MANY years ago, I cared for two patients in their late twenties. One had been admitted in severe septic shock and ended up spending over two months in our intensive care unit (ICU), with amputated arms and legs, on dialysis, with a tracheostomy, and almost blind. The other had a very brief cardiac arrest with excellent bystander resuscitation, return of spontaneous circulation after not even one minute, and spent only a few days in the ICU. About a year later, at follow-up, the patient with septic shock told me he felt completely "back on track in life". The patient in cardiac arrest, however, had severe cognitive dysfunction, fatigue, mental health problems, and could no longer live by herself but had moved back in with her parents.

My inability to predict these outcomes was one piece of the puzzle that resulted in this doctoral thesis, another one being my luck to be surrounded by much wiser people who could merge ideas from their own clinical and scientific experience with mine.

At the core of this doctoral thesis is the blending of three areas: Intensive care survivorship, quality of life, and questionnaires.

1.1 ON INTENSIVE CARE

1.1.1 In the beginning

Perhaps depending on whether you are Scandinavian or American, the story of intensive care either starts in Copenhagen or Crimea. One of the many improvements Florence Nightingale implemented in the Crimean War was to keep the sickest patients in a separate area close to the nurses, which could be said to be the birth of intensive care *thinking*.[1] Her attempt to implement smaller, more sanitary wards in the UK failed. Still, a direct consequence of using larger wards was that the sickest patients slowly, over time, were put in separate units with special-duty nurses. In the 1920s, neurosurgeon Walter Dandy created a small post-operative unit for his neurosurgical patients at Johns Hopkins Hospital. The concept quickly rose in popularity and the intensive *care* provided in these post-operative units was mainly based on a higher degree of nurse presence. It was not until the 1940s that advances in lifesaving medical technologies such as securing airways with tracheostomies defined the new era of intensive care, although still mainly single-organ failures in post-operative patients.

The polio epidemic in 1952 is well known to all Scandinavian intensivists and is often highlighted as the birth of intensive care. As the story goes, Blegdam Hospital in Copenhagen served as the only hospital for infectious diseases and received almost 3000 patients in five months.[2] With hundreds of these patients needing respirators of which the hospital had only seven, the chief physician, Henry Lassen, called a meeting, desperate for a solution. Invited to the meeting was anaesthesiologist Björn Ibsen, who recently returned from his training at Massachusetts General Hospital in Boston. Having studied hypoventilation in Boston, Ibsen realised that the mortality from polio was primarily from respiratory complications. This contrasted with the idea of a lethal cerebral viral load, a common perception among epidemiologists, including Lassen, without access to blood gas sampling.[3] Ibsen's model of the pathophysiology included the notion that the hypoventilation depended on the paralysis of the chest muscles and that the lungs could function much longer, were they to be helped mechanically. At the meeting, he suggested using tracheostomies, at this time much more commonly used in the US than in Denmark, but with positive pressure instead of the widespread use of negative pressure.[4] Lassen permitted him to try this combination the next day on Vivi Ebert, a twelve-year-old girl. Long story short, Ebert survived, and we now celebrate *Ibsen Day* on the 27th of August. As so often in everything's history, though, it must be noted that Ibsen's idea was not his own. The use of positive pressure for ventilating polio patients with tracheostomies had already been used in Los Angeles since 1948, with published results brought to Lassen's attention by Ibsen.[2]

Although the polio ward was not a true intensive care *unit*, it still provided intensive *care*. However, Ibsen is recognised as the pioneer of the first ICU in the world too: Within a year of the polio epidemic, his application to become the head of the Department of Anaesthesia at Rigshospitalet in Copenhagen was rejected.[5] As a result, he accepted the position of Senior Resident anesthesiologist in the Department of Surgery at Kommunehospitalet. There was disagreement among senior surgeons regarding the best fluid therapy, and to resolve this issue, Ibsen was asked to direct the treatment of surgical patients. On December 21, 1953, he transformed a purely surgical post-operative ward into a unit that provided professional assistance to all types of patients – the world's first ICU.

1.2.2 The long-term outcomes

Vivi Ebart was eventually discharged from hospital after seven years of recuperation. She was quadriplegic and moved in with her mother, who became her assistant, helping her with basic activities of daily living (ADL), such as eating and visiting the toilet.[6] Every night, Vivi was moved to a unit in the house to be put on a ventilator. In 1971, she died from sepsis, once again admitted to Blegdam Hospital.

From Ibsen's and everyone else's early start, the development of intensive care naturally expanded immensely during the following decades. With more structured care came more structured data, and by the very nature of intensive care, mortality was the first relevant outcome measure. The perhaps earliest published report on long-term outcomes outside the polio epidemic is a short letter in 1973, published in *Critical Care Medicine* by Cullen and Briggs at Massachusetts General Hospital in Boston, notably the same hospital where Ibsen received his training.[7] It is a preliminary report of an attempt to follow up mortality and functional status of their patients. Perhaps a bit more fateful than we need to be today, much of their finalising words could have been stated at any intensive care meeting today, exactly 50 years later:

> “*These preliminary data demonstrate an astounding investment of dollars and limited human resources (such as nurse, physician and ancillary personnel, whole blood, blood fractions, and human albumin solutions [sic])! The high mortality rate and limited restoration of functional recovery raise very difficult questions. Can we learn to predict with better accuracy who should and who should not receive extraordinary and heroic means of life support? To what extent are less critically ill patients deprived of better medical care, lower morbidity and mortality, when so many resources are directed toward other patients with a very limited prognosis? Suppose we applied the same efforts to less ill patients. Would postoperative morbidity be reduced? Would recovery be more rapid? And what point does the teaching and research value of maintaining life become subordinate to allowing a patient to die without pain, inexpensively, and with some measure of dignity?*

Increasingly improved results in intensive care have gradually reduced mortality as a valuable outcome measure in trials, replacing it with survivorship. And as exemplified by the fate of Vivi Ebert, survivorship may come with a price.

1.2 ON QUALITY OF LIFE

1.2.1 On the (very) early history of quality of life

Most, if not all, texts on quality of life begin with Aristoteles' *Nicomachean Ethics*, a collection of ten papyrus scrolls believed to be notes from his lectures at the Lyceum temple. Although the tenth book and its chapter 6-8 is specifically about well-being – *eudaimonia* – "the good things in life" is a central theme throughout the text:

> *[…]both the multitude and the refined few call it, and "living well" and "doing well" they conceive to be the same with "being happy;" but about the Nature of this Happiness, men dispute, and the multitude do not in their account of it agree with the wise. For some say it is some one of those things which are palpable and apparent, as pleasure or wealth or honour; in fact, some one thing, some another; nay, oftentimes the same man gives a different account of it; for when ill, he calls it health; when poor, wealth […]*
>
> *Aristotle*[8]
> *Nicomachean Ethics*
> *Book I · Chapter 2*

Notably, the term "quality of life" did not exist when this was written. However, over the centuries since, Aristotle's reasoning about the subject has come to represent the very first known definition.

Just a few years later, Epicurus expanded the concept of eudaimonia with his introduction of *ataraxia*, a state of tranquillity and freedom from fear and pain. According to Epicurus, achieving ataraxia involves satisfying basic physical needs, cultivating virtuous friendships, and seeking knowledge to dispel fears and misconceptions, especially those related to death and the afterlife:

> *The limit of the greatness of the pleasures is the removal of everything which can give pain. And where pleasure is, as long as it lasts, that which gives pain, or that which feels pain, or both of them, are absent.*
>
> *Epicurus*[9]
> *Sovran Maxim · Doctrine 3*

During well over thousand years to follow, the scarce philosophical ideas regarding anything close to quality of life were mainly based on spirituality, clearly separating themselves from the secular themes of old Greek and Roman philosophers. With Augustin in his *Confessions*[10] and Boethius in his *The Consolation of Philosophy*[11], quality of life is instead achieved through the search for wisdom, moral character and virtue. Remarkably close to the politicisation of the health-related quality of life (HRQOL) concept in the 1960s and 1970s, philosophers like John Locke and Jean-Jacques Rousseau during the *Enlightenment* turned their attention to the role of government and society in promoting individual well-being. Locke, in his belief that humans had natural rights such as life, liberty, and property, thought that governments should protect these rights:

> “*But though this be a state of liberty, yet it is not a state of licence: though man in that state have an uncontroulable liberty to dispose of his person or possessions, yet he has not liberty to destroy himself, or so much as any creature in his possession, but where some nobler use than its bare preservation calls for it. The state of nature has a law of nature to govern it, which obliges every one: and reason, which is that law, teaches all mankind, who will but consult it, that being all equal and independent, no one ought to harm another in his life, health, liberty, or possessions.*
>
> *John Locke*[12]
> *Two Treatises of Government*
> *Chapter II · Sec 6.*

Rousseau, on the other hand, posited that society often corrupts individuals and leads to inequalities:

> “*Each of us puts his person and all his power in common under the supreme direction of the general will, and, in our corporate capacity, we receive each member as an indivisible part of the whole.*
>
> *Jean-Jacques Rosseau*[13]
> *The Social Contract*
> *Book I · Chapter VI*

He suggested that the quality of life could be improved through a social contract, wherein individuals give up certain freedoms in exchange for the protection and benefits provided by the collective.
Finally, what is a short exposé on quality of life without referencing *utilitarianism*? Jeremy Bentham and John Stuart Mill, both English

philosophers, developed the moral theory of utilitarianism, which focuses on maximising overall happiness or pleasure. Bentham's version of utilitarianism sought to maximise happiness for the greatest number of people, promoting a higher quality of life:

> “*By the principle of utility is meant that principle which approves or disapproves of every action whatsoever, according to the tendency it appears to have to augment or diminish the happiness of the party whose interest is in question: or, what is the same thing in other words, to promote or to oppose that happiness. I say of every action whatsoever, and therefore not only of every action of a private individual, but of every measure of government.*
>
> *Jeremy Bentham*[14]
> *An Introduction to the Principles of Morals and Legislation*
> *Chapter I · II*

Mill expanded on Bentham's ideas by differentiating between higher and lower pleasures:

> “*It is quite compatible with the principle of utility to recognise the fact, that some kinds of pleasure are more desirable and more valuable than others. It would be absurd that while, in estimating all other things, quality is considered as well as quantity, the estimation of pleasures should be supposed to depend on quantity alone.*
>
> *John-Stuart Mill*[15]
> *Utilitarianism*
> *Chapter 2 “What Utilitarianism Is”*

Through this, he argued that pursuing intellectual, moral, and aesthetic pleasures, rather than merely seeking physical satisfaction, would lead to a higher quality of life.

1.2.2 On the 20th century and the deluge of scales

Jumping to the 20th century, there was an initial focus on measuring functional status in the general public. A project initialised by the *New York's City Research Bureau of Welfare Council, City Department of Public Welfare* and *State Department of Social Welfare* published a general classification scale of functional status in 1937.[16] The focus was on analysing differences

> *[…] between those who are […] incapacitated in various ways for normal living and those whose capacity for normal living is not seriously impaired*

By then, at least one disease-specific scale already existed – the well-known *New York Heart Association Classification*. It was an attempt to facilitate communication among physicians and researchers regarding cardiac patients, a need emerging soon after the establishment of the world's first cardiac clinics in New York in the 1910s.[17] However, while the classification included a "Functional" class, it was simply a list of heart dysfunctions such as arrhythmias and angina pectoris, and it seems the modern concept of functional status was not included until the seventh edition, in 1973, with the term functional capacity added even later.[18]

Several scales on functional status were developed and published in the post-World War II era of the 1940s and 1950s, including the three well-known indices of *Karnofsky performance status scale* for patients with cancer in 1948[19], the *Katz Index of Independence of Activities of Daily Living* for patients with hip fractures in 1958[20] and 1959[21], and the *Barthel Index* for patients with musculoskeletal or neuromuscular disease in 1958[22]. All three scales have expanded their target groups since and are still used today in various populations far from the originally intended. For this discussion, though, it must be noted that these scales only evaluate one dimension and can not be considered for measuring quality of life.

In parallel to the development of functional status indices, there was a growing movement within social sciences creating different kinds of indices. The first published scale that included mental and emotional status was the PULSES[23] profiles, developed for evaluation of functional status in soldiers, and inspired by the well-known WHO definition from 1948, where health is

> *[...] a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*[24]

Social factors became increasingly important in the evaluation of well-being. Multiple instruments were developed in the late 1960s and the 1970s, and a new journal, *Social Indicators Research*, was even devoted to "quality of life research". Perhaps partly due to the political movements at the time, subjective well-being was now being explored. One of the most influential theories on quality of life was published in

1976 – Campbell et al.'s *The Quality of American Life*, demonstrating that subjective indicators could be measured.[25] The group had published the framework in 1972, but the 1976 text expanded on the theory and provided interviews with ordinary US citizens regarding their life and their view on life satisfaction. Several scales came from these interviews, including the *Overall Scale of Life Satisfaction* and *Index of Well-being*, both early attempts at creating a quality of life index. Building on these ideas, Andrews and Withey, in their *Developing measures of perceived life quality: Results from several national surveys*, the very first article published in the *Social Indicators Research* journal, published a questionnaire with 123 items thought to represent quality of life.[26]

In the early part of this 20th-century development, there is very little evidence of an interest in these issues from health sciences. Perhaps the earliest clinical trial using such outcome measures was a study in breast cancer patients published in 1966, measuring "quality of survival".[27] The first use of quality of life instead of quality of survival in a clinical article was published only later in the same year in an article on renal failure patients, describing the horrifics of dialysis therapy for the poorest:

> "*While an effective degree of life prolongation was obtained for some of these patients, for most the quality of life was unacceptable.*[28]

Seemingly uninterested in using existing instruments for quality of life, the clinical literature lacked instruments until the publication of the *Vitagram Index* and the *Life Units* in 1970. While none of these two gained notable popularity, Priestman and Baum's use of the *Linear Analogue Self Assessment Scale* technique was the first instrument to do so.[29] The method is nowadays mostly known as the VAS scale for pain assessment.

At the end of the 1970s, a new generation of scales was oriented toward general health evaluation. The *Sickness Impact Profile* (SIP)[30] and the *Nottingham Health Profile* (NHP)[31] focused on physical health, the impact of illness, perceived distress, mental health and general content with life. Although the authors never described them as quality of life instruments, they indeed contain areas now considered fundamental in quality of life instruments. The SIP has several benefits that would make it suitable for use in an intensive care context. For example, it is based on behaviour, thus useful with proxies, and it has no floor effect, making it able to discriminate between very low health states. The NHP is one of very few older questionnaires developed from interaction with the target population; it is constructed from 2200 statements on quality of life made by over 700 people. Both SIP and NHP played a part in intensive care follow-up in the 1990s before suddenly evanesce by the start of the new millennium, perhaps inequitable.

Toward the end of the 1980s, intensive care received its first specific questionnaire. Patrick et al. measured quality of life in 69 ICU survivors using several existing scales, including SIP.[32] However, they had also developed a scale specifically for their study; the *Perceived Quality of Life* scale (PQOL). It consisted of 11 questions, each focusing on perceived satisfaction in areas such as health, income, happiness, and family. The PQOL was used in just over ten studies, including some by the creators, during the first half of the 1990s before rapidly fading in popularity.

With the beginning of the 1990s came the rise of SF-36 and later the EQ-5D.[33][34] To understand the development over the last 30 years, we need to understand ICU survivorship further.

1.3 ON INTENSIVE CARE AND QUALITY OF LIFE

Moving to the modern day, long-term sequelae after surviving intensive care have been described in several areas. As just single examples from various aspects, Myhren et al. found post-traumatic stress syndrome (PTSD) in 25% of ICU survivors one year after discharge, including a subgroup of 16% discharged without symptoms of PTSD but developing such symptoms during the following year.[35] Pandharipande et al. found that in an ICU cohort of 821 survivors, 40% had a cognitive function score corresponding to moderate traumatic brain injury, and 26% had a score corresponding to mild Alzheimer, measured at three months after ICU discharge.[36] There was minimal improvement at a repeated measurement one year after discharge. The study had no control group for comparison. However, only 6% had a pre-admission cognitive impairment. Herridge et al. measured a cohort of 109 survivors of acute respiratory distress syndrome (ARDS) at several points for five years regarding physical functioning.[37] While pulmonary functioning returned to normal, physical functioning did not. Hodgson et al. studied factors for returning to work after intensive care.[38] In their sample of 107 working adults, 29% had not returned to work for health reasons six months after ICU admission. The subset of ICU survivors that had not been able to return to work reported a lower HRQOL, measured with EQ-5D, than those that had been able to return to work. Ulvik et al. found that 41% of trauma patients rated their sex life worse after the trauma than before.[39] Of these, 38% reported physical factors and 7% psychological factors. Koster-Brouwer et al., evaluating three cohorts of almost 1000 ICU survivors, found new chronic pain in nearly one-fifth of participants measured one year after ICU discharge.[40] Finally, Alexopoulou et al. evaluated sleep quality on two occasions in ICU survivors and found poor sleep quality at the first examination ten days after hospital discharge with frequent interruptions and airway obstruction.[41] At six months, deep sleep had improved, although overall sleep quality was still poor. The range of the areas has induced a need to gather the discussion under an overall term — Post Intensive Care Syndrom (PICS).[42] However, just as with medical syndromes, creating such a nomenclature reflects state-of-the-art knowledge at the time of creation, and as such is prone to be outdated with the next trial, and, thus, either become diluted in a new definition or obsolete.[43]

With such findings, it is plausible to infer that ICU survivors may have an impaired quality of life. However, inferences need data, and data needs measurements.

1.3.3 On what to measure and how to do it

At least two main approaches can be identified in measuring quality of life in medical populations. The most common is to use a generic tool, most often SF-36 or EQ-5D. These tools were initially developed to evaluate health states in various populations not necessarily ill, and their use incorporates the possibility of comparing groups with different diagnoses. Furthermore, they, or their shortened derivatives, may be used to calculate the cost-effectiveness of various treatments as a remnant of being developed in the era of quality-adjusted life years (QALYS) and disability-adjusted life years (DALYS).[44]
The other approach is questionnaires specific to a particular disease or treatment. For example, the Division of Clinical Cancer Epidemiology at Sahlgrenska University Hospital has developed different questionnaires for women treated for ovarian cancer and men treated for prostate cancer, thus acknowledging any potential differences while allowing similarities to exist.[45] [46] The philosophy of this second approach is the antithesis of the generic instruments. While the questions in the SF-36 were taken from existing questionnaires from the 1940s, 1950s and 1960s[31], without any patient involvement, the second approach contrasts this and builds its items mainly from interviews with representatives from the intended target populations.

It is crucial to recognise that both approaches fall under the umbrella of patient-reported outcome measures (PROM). Consequently, the term PROM possesses a misleading sense of precision. As demonstrated in the historical exposé, numerous scales developed since the 1960s can be categorised as PROMS, long before the term was established.

During the past decades, as we have seen, only a few attempts have been made to develop an intensive care-specific tool for measurements, but no one did reach any particular usage level.[29] [47] [48] In the late 1990s, Chrispin et al. tested SF-36 on an ICU cohort of mainly post-operative patients.[49] The same group had previously attempted to create a questionnaire on quality of life after intensive care by combing questions from different questionnaires but gained no impact with their instrument.[50] Although the SF-36 had not previously been used in an intensive care setting, it was already widely spread as a generic instrument for measuring HRQOL, used in a variety of populations. The history of the SF-36 is muddled since most questions were taken from the older SF-18 and SF-20.[31] All three were created by the same group, an old defence industry think-tank partly involved in the insurance industry, and built to be used in a longitudinal study on the effect of different health insurance on health status and utilisation.

With the study by Chrispin et al., SF-36 took off as a tool for measuring HRQOL after intensive care. It should be noted that the original study did not validate the SF-36 for use in long-term follow-up. Instead, the patients were given the questionnaire before being discharged from the ICU. Of the participating 166 patients, 49% of all eligible patients, almost 60% were admitted electively, thus raising some concern about the generalisability to an average ICU patient today.

The SF-36 was joined in the batch of follow-up measurement tools of ICU survivors by EQ-5D in the 2000s, and the two have been considered golden standards ever since.[51] The EuroQoL group, researchers from the UK, the Netherlands, Norway, Finland, and Sweden, had met already in 1987.[34] The purpose was to create an HRQOL questionnaire unspecific to any disease, with the ability to create a single index value for each health state. The areas covered in the EQ-5D were selected after studying existing questionnaires such as the SIP and the NHP, and in all, the EQ-5D consists of 6 questions. The first use in intensive care was published by Badia et al., co-authored by Patrick, the first author of the PQOL study, in *Intensive Care Medicine* in 1996. Former ICU patients were approached in a step-down unit at least 48 hours after being discharged from the ICU. They were asked to fill in the EQ-5D twice: First recalling their state before ICU admission, and a second time later the same day, evaluating their current state.[52] Results were compared to those estimated by proxies and to those given by a healthy control group.

Recognising the need for measurement of quality of life after intensive care, a round-table meeting at the annual Brussels intensive care conference in 2002 recommended using SF-36 and EQ-5D until a questionnaire developed specifically for use in the ICU survivor population was created.[53]

Though easy to use and with data readily comparable to other groups of patients, SF-36 and EQ-5D are still tainted with problems. Concerns have been raised in a few studies in which ICU survivors considered both questionnaires inadequate. For example, Lim et al. created a framework by interviewing 40 ICU survivors and categorising post-ICU quality of life issues.[54] Subsequently, the same survivors were to fill out SF-36 and EQ-5D and asked to comment on the adequacy of the questions. While the questions on physical health were considered adequate, the questions on emotional/psychological status, cognition, ADL, and physical zone of comfort were deemed inadequate. Even more serious, compared to the framework found during the interviews, SF-36 and EQ-5D lacked questions in seven areas, such as relationships, finance, and personality.

So. What if the measurement tool does not measure as well as we would wish? What are the implications for this apparent mismatch in what we think we measure and what the target population hopes we would measure? What if, for example, interventions aimed at improving quality of life are measured with questions unrelated to quality of life according to the target population?

HILMA AF KLINT
would paint an ethereal and vibrant garden, where the blooming flowers, delicate vines, and glittering gems symbolize the miraculous experience of surviving a serious illness, through the lens of spiritualism and theosophy, using bold brushstrokes and a harmonious palette that evokes both heavenly and earthly realms.

AIMS

THE overarching aim of the doctoral thesis is to report the first steps in developing a questionnaire specifically for long-term follow-up of quality of life and burden of disease in intensive care survivors.

This aim is completed through four objectives:

1. First, we need to collect as much data as possible regarding issues experienced by ICU survivors.
2. Second, we need to compare the magnitude of these findings between ICU survivors and a non-ICU-treated control group and consider alternative explanations for potential differences.
3. Third, we need to explore the concept of quality of life and relate all found issues to this construct.
4. Finally, we need to reduce the number of questions to a minimal but still clinically relevant amount.

The following are the aims of the individual papers:

Paper I	To develop a provisional questionnaire based on interviews with ICU survivors, test its practicality in a scientific setting as well as its ability to identify differences in the magnitude of issues between ICU survivors and non-ICU-treated controls.
Paper II	To explore the mutual roles of ICU survivorship, comorbidity and educational level in relation to previously found issues.
Paper III	To explore which issues are related to quality of life and which are not.
Paper IV	To explore the factorial structure of quality of life in our sample and reduce the number of questions.

ROY LICHTENSTEIN
would paint a pop art depiction of a superhero, bursting out of a comic book panel, to illustrate the excitement and energy of having survived a near-death experience.

METHODOLOGY & SOME STATISTICS

THE four papers comprising this doctoral thesis contain two data collections, both conducted as part of **PAPER I**, combining qualitative and quantitative methodologies.

The papers contain multiple statistical methods, spanning different areas and sometimes schools. The variety of statistical methods illustrates a few ways our data may be analysed and used, and specific aspects of our statistical methodology may be new to the general reader. While the more common methods in **PAPER I**, such as the Mann-Whitney U or Fisher's exact test, will not be discussed, others will be given a more in-depth explanation, including brief rationales to aid the reader.

2.1 METHODOLOGY
PAPER I

Paper I consists of a qualitative first part with interviews of ICU survivors and a second, quantitative, part in which we performed a cross-sectional study using the findings from the first part.

2.1.1 PART 1 | THE QUALITATIVE PART

2.1.1.1 Methodological framework and considerations

There are multiple ways of conducting qualitative interviews, with different frameworks as the foundation. We decided to build upon previous experience in the group in creating similar questionnaires within oncology. This experience comes from work both within the Division of Clinical Cancer Epidemiology at Sahlgrenska University Hospital and with the *European Organisation for Research and Treatment of Cancer* (EORTC). These similar approaches are pragmatic since they do not overtly refer to a specific framework. Numerous published studies have successfully used both approaches,[55] and guidelines are available for the EORTC process.[56]

Parts of the approach, such as data saturation for deciding sample size and parallel collection and data analysis, align with the *Grounded Theory* (GT) framework.[57] However, notable differences from the GT framework exist, including using an interviewer, me, with domain knowledge. In line with previous experience in the group and with the EORTC guidelines, we decided to use an interviewer with clinical expertise, i.e., domain knowledge, hypothesising it would be more effective.[56]

Also unlike GT, we allowed actively utilising prior knowledge by discussing scientific findings and other questionnaire results with the interviewee when they could not offer any further information.

To summarise the reasoning behind the method used, we had no intention of creating a phenomenological framework, nor dynamic hypotheses as in GT. Thus, we were not limited to a specific methodology. We simply aimed to create a list of issues, where the most important factor was for the list to be as comprehensive as possible.

2.1.1.2 Study setting

At the beginning of the project, I was clinically involved with the post-ICU clinic at Sahlgrenska University Hospital. The clinic routinely attempts to follow up on all former patients having an ICU length of stay of at least 72 hours. In addition, patients with a shorter stay may contact the clinic to schedule a visit, and other patients having had a shorter stay may have been identified by the ICU staff as suitable for a visit. For the study, eligible ICU survivors were identified at the clinic between February 2015 and May 2015. Due to practical circumstances at the time, few survivors visited the clinic earlier than about six months after ICU discharge. This coincided with our decision to use six months as a cut-off for defining long-term issues.

2.1.1.3 Sampling strategies and considerations

Several techniques are available when selecting a sampling method. Based on previous experience and recommendations from the EORTC, we decided to use data saturation, which also determines the sample size.[56] Data saturation denotes the point in time when an interview adds no new information to what previous interviews have already given. However, to minimise the risk of a scenario where one obtains so much information from an early interviewee that the following interviewee adds no new information, i.e., reaching data saturation prematurely, we decided a priori to conduct three additional interviews after saturation was reached to confirm the found saturation.

While we are accustomed to randomised sampling being the golden standard in quantitative research, qualitative interviewing introduces several options. First, it should be noted that a randomisation process in our qualitative sampling would be possible, albeit cumbersome. For example, we could define our target population as all individuals visiting the post-ICU clinic and randomise a sample from this population. However, it would be ineffective, not only in its duration but also concerning the endpoint – data saturation. In a study simulating three different sampling strategies; randomisation, minimal information, and maximal information, van Rijnsoever found maximal information to perform best, with randomisation clearly worst, specifically with issues with a low prevalence.[58] For example, for an issue with a mean probability of being observed of 0.1, randomisation requires between 500 and over 1000 sampling steps (interviews), while the maximum information strategy requires about 20 for the issue to be captured.
Instead, we used a purposive, maximum variation sampling approach. The purposive sampling technique belongs to the subgroup of non-probability sampling methods and may be helpful when attempting to gain

detailed knowledge about a phenomenon rather than making statistical inferences. As such, it differs from, for example, convenience sampling, which simply includes the most accessible individuals. A purposive sampling strategy uses the researcher's knowledge to select the individuals most likely to be "information-rich" regarding the purpose of the research. In our case, it meant finding individuals that had not only post-ICU issues but that also could talk about these issues, including with help from family members. Helpful in this approach was the choice to ask about participation after the visit to the post-ICU clinic instead of in advance, thus making the regular visit conversation a selection step. Adding the term "maximum variation" to the method means that individuals are selected based on an attempt to capture a wide range of perspectives. In our case, it meant trying to interview former patients of both sexes, of all ages, with different admission diagnoses, length of stay and different socioeconomic statuses. All non-probability sampling methods are naturally subject to selection bias, although purposive maximum variation sampling is less so than convenience sampling, voluntary response sampling and others.

2.1.1.4 Interviews

Interviews were conducted using a semi-structured technique, starting with the question ***We are asking for your help in creating a questionnaire which will be used to identify and follow the experiences of patients who have survived intensive care. I would like to ask you a few things about your health. Can you tell me about the experiences you may have had as a result of your intensive care stay and the time between discharge and today?*** Initial questions were open-ended, but we did not restrain from asking about specific details such as effects on social life, quality of life or others.

Interviews were recorded and transcribed verbatim. However, careful notes were taken during the interviews, and ultimately these contained all valuable information. These notes were further used to summarise the interview and read for the interviewee at the end to allow for comments and corrections.

2.1.1.5 Analysis and conversion of issues to questions

In parallel with conducting interviews, completed interviews were analysed. Duplicates were removed, and extended quotes were shortened while the fundamental meaning of the issues was maintained. To minimise subjectiveness during this process, we attempted to use as exact wording from the interviewees as possible. Subsequently, all issues were converted into questions. Care was taken not to ask about more than one issue per question (for example, ***Have you felt any anxiety or hopelessness before going to bed?*** being two questions). Finally, questions were categorised into domains.

A policy to require an issue to be mentioned at minimum, for example, five times to be added, as recommended by the EORTC guidelines, drastically decreases the probability of rare topics being included.[56] This, combined with the knowledge that this was a provisional questionnaire to be reduced in the future, made us decide to include all issues mentioned, no matter how rarely.

Software for qualitative, thematic content analysis was not used. While these might have aided with thematic analysis, the project did not aim at such content analyses but simply to extract as many issues as possible.

2.1.1.6 Additional questions

We added two composite questions at the end of each domain: One regarding the domain-specific quality of life ***To what extent have difficulties with [domain] affected your quality of life for the past month?*** and one regarding domain-specific future concerns ***For the past month, have you been worried about your future regarding [domain]?*** In addition, we added a request for missed issues or comments after each domain.

Before conducting the interviews, numerous questionnaires were reviewed for information and inspiration. In the cases where an issue brought up by the ICU survivor was identical to an item in such a questionnaire, the item from the existing questionnaire was incorporated after adaptation to match our semantics.

Finally, questions regarding demographics, comorbidities, visits to the post-ICU clinic, and the questionnaire itself were added at the end.

2.1.1.7 Response scales and timeframe

All response scales were designed to align as closely as possible with each conceptual entity. Care was taken to include the option *Not applicable* where relevant to prevent forcing either inaccurate or omitted answers. For example, the leg-amputated patient, however rare, has difficulties answering the question regarding the ability to kneel in SF-36. Finally, great care was taken not to overlap between alternatives and to make alternatives both mutually exclusive and exhaustive:

Consider this hypothetical question:

When were you discharged from the hospital?

1. *Less than a month ago*
2. *1-3 months ago*
3. *4-6 months ago*
4. *More than 6 months ago*

The choices are mutually exclusive, with no overlap, but they are not exhaustive since not all possible answers are covered. How do you answer if you were discharged between 3 and 4 months ago?

Now consider the following question:

How many times have you felt the need for painkillers in the past month?

1. *1*
2. *2-5*
3. *5-10*
4. *> 10*

These choices are exhaustive – there are no gaps – but they are not mutually exclusive. Which option would you choose if you took painkillers five times?

Instead of using the exact same wording for all response scales as in a proper Likert scale, we used mainly incidence, prevalence, intensity and agreement.[59] This is based on the established experience from previous work of the Division of Clinical Cancer Epidemiology at Sahlgrenska University Hospital, the pragmatic rationale being that difficulties in understanding may affect response rates.

We decided to use as few timeframes as possible in the response scales and decided one month to be the most pragmatic solution. A longer timeframe would raise the risk of recall bias, and a shorter one would risk not covering the incidence of certain activities, for example, some social activities.

2.1.1.8 Content validity and cognitive interviews

Content validity refers to the extent to which a questionnaire, or any other tool, contains the relevant aspects of the construct it intends to measure, in our case, issues faced after intensive care. However, content validity not only includes which issues are addressed in the questions, but also factors such as comprehensiveness, the wording of the questions, the clarity of instructions, and the use of appropriate response scales and recall period. In compliance with the *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR) guidelines for testing content validity, all questions were subjected to cognitive interviews with additional ICU survivors chosen using the same criteria as the initial participants.[60] These interviews were recorded as well.

Interviewees in this phase were initially instructed to complete the questionnaire while thinking aloud, but as the two first interviewees failed to comply with this request, we adapted to a retrospective probing method. Under this approach, questions were not posed until each domain was completed, following the EORTC guidelines for questionnaires with a vast number of questions.[56]

2.1.1.9 Final design

When finalising the design of the questionnaire, detailed instructions were added to the beginning of each chapter:

> “ *If you require assistance, you may reach out to a family member for support. This could range from help with recalling to something as straightforward as reading and completing the form.*
>
> “ *If you encounter any confusing or unclear instructions, do not hesitate to contact us. We are here to help and answer any questions you may have.*
>
> “ *Completing the questionnaire may seem like a daunting task with its many questions. We encourage you to take breaks as needed and return later if required.*
>
> “ *If you want to comment on a question or add something, feel free to write in the margin next to the question.*

In addition, space was provided after all domains to allow further comments.

2.1.2 PART 2 | THE QUANTITATIVE PART

In the second, quantitative, part of **PAPER I**, the provisional questionnaire was sent to ICU survivors and a non-ICU-treated control group. Participating ICU survivors were eligible if they had been admitted to any of the three general ICUs at Sahlgrenska University Hospital (Sahlgrenska, Östra, Mölndal) between February 2013 and December 2015 (discharged 6-36 months before the study started) with an ICU length of stay of at least 72 hours. Survivors admitted primarily for neurological or neurosurgical reasons were excluded, partially because we had plans to create a similar questionnaire for use in a neurointensive care context. In addition, survivors with a limited understanding of Swedish or without Swedish personal numbers or a Swedish address were excluded. To create a control group, we sent information on responders' age and gender to *Statens Personadressregister* (SPAR) for randomisation from the population of Västra Götaland. For the version of the questionnaire addressing the control group, we removed all questions requiring a previous ICU stay (e.g., ***Have you had difficulties describing your ICU experiences?***) and added one question checking for previous intensive care. Exclusion criteria for the control group were a previous ICU stay or a limited understanding of Swedish.

The questionnaire was sent to the ICU survivors between April 2016 and October 2017 and the control group between March 2017 and December 2017. A database was created to supervise logistics. A small call centre was set up where three ICU nurses and I constituted the small group handling the logistics. Several steps were taken to maximise participation and response rates:

» First, eligible participants in both groups received an invitational letter with information about the study, followed by a phone call within a few days.

» Participation was interpreted as consent.

» A pre-paid return envelope was sent together with the questionnaire.

» After two weeks, participants were reminded by phone. Multiple attempts were made to reach participants, at different times of the day.

Participants were classified as lost to follow-up after several failed attempts to be reached, although no specific threshold for the number of attempts was set. A list of different reasons for withdrawal was put together in an attempt were made to categorise responses.

2.2 METHODOLOGY & STATISTICS PAPER II

Is it possible to compare two groups with different characteristics? Could factors other than intensive care explain differences between the two groups in our paper I? What if our ICU survivors have a significantly higher burden from comorbidity than the control group?

As a secondary finding in **PAPER I**, our sample of ICU survivors did, on average, suffer from a higher level of morbidity than our non-ICU-treated control group. The possibility of this affecting our findings of differences between the groups in most tested issues was kindly pointed out in a *Letter to the Editor*, inspiring us to investigate the matter further.[61]

Historically, comorbidity was not considered in trials. Instead, patients were grouped based on a single diagnosis and matched by age, sex, and sometimes race. Feinstein, in 1970, first recognised this problem of not correcting for other diseases and coined the comorbidity term as we know it today.[62] Regarding intensive care, Charlson is, with her *Medical patients at high risk for catastrophic deterioration* in May 1987, the first to report deterioration based on comorbidity in a study attempting to predict the need for intensive care.[63] The observant reader notices that this is Mary Charlson, who, the very same year, published the well-known *Charlson Comorbidity Index*.[64]

Suffering from the difficulties of obtaining pre-ICU data, all studies on quality of life after intensive care will inherently be subject to interpretative difficulties. Therefore, the exact role of the higher comorbidity burden in an ICU survivor population compared to a non-ICU-treated population is uncertain. In an attempt to gain further insight into the roles of various potential alternative explanations, the rationale for the analyses in **PAPER II** is the following: If the higher level of comorbidity is the explanation for the lower quality of life in our sample of ICU survivors, would this effect not vary with the degree of comorbidity? Methodologically, this can easily be tested since comorbidity would be a so-called third-variable acting as a moderator. A concept more known in epidemiology than in biomedicine, "third-variable" is a term for a few different effects stemming from a variable other than the independent (exposure) and the dependent (outcome) variable. A third-variable may act as a confounder, mediator, or moderator (moderation can also be called effect modification or interaction, with only minor differences in denotation, not crucial for this discussion). Although often misinterpreted, confounding is likely the most known of these three, with mediation and moderation lesser so. Moderation is the phenomenon in which the effect of one variable on another variable varies with the levels of the third-variable. A moderating effect in our findings would mean, on a question-per-question basis, that the difference in responses to a question between the ICU survivor group and the non-ICU-treated control group would be larger, the larger difference in comorbidity or educational level. If so, one might conclude that the difference in responses between the two groups could be explained by comorbidity or educational level differences.

Two statistical models were created for **PAPER II**:

One in which comorbidity was added as a third-variable, acting both as an additional independent variable as well as a moderating variable, and one model in which the comorbidity variable was exchanged for educational level. The comorbidity variable was defined as the number of comorbidities (0 to 19), as answered when filling in the questionnaire. Educational level was used as a proxy variable for socioeconomic status (SES) and constructed as a scale from 0 ('No post-compulsory school') to 5 ('University'), as answered when filling in the questionnaire. The decision to use educational level as a substitute for SES was primarily influenced by data availability. Numerous variables have been used as proxies for the latent variable SES, single-handedly or in various combinations.[65] [66] [67] However, few of these variables were available in our dataset as we initially did not attempt to analyse SES further. Educational level has been shown to be a good proxy for SES and is, for example, the single largest risk factor for cardiovascular mortality and disease.[68] Thus, this was the most viable proxy in our dataset.

Finally, one of the independent variables is defined by the groups; belonging to the ICU survivor group versus belonging to the non-ICU-treated control group. This means that what we compare is whether belonging to the ICU survivor group has a significant effect on each item or not. That is, we do not compare intensive care treatment per se, only the effect of being someone having been treated in an ICU. To denominate belonging to this group in a comprehensive way, this "affiliation" to the ICU survivor group will henceforth be denoted *ICU survivorship*. The rationale is that you must have survived to be a survivor and must have been treated in an ICU to be an ICU survivor. What you bring into the ICU, you carry with you at discharge. Therefore, ICU survivorship will be used as a proxy term for belonging to the ICU survivor group versus belonging to the non-ICU-treated control group.

The statistical model allowed for several different relationships to be measured simultaneously (Figure 2.2):

1. First, the association between ICU survivorship and item$_n$ (arrow A).

2. Second, the association between the third-variables (comorbidity or educational level, respectively) and item$_n$ (arrow B). Note that the model allows for these two first associations to be significant simultaneously, thus allowing for the associations to exist in parallel.

3. Third, a moderating effect by either of the third-variables on the association between ICU survivorship and item$_n$ (arrow C). Again, any finding of a moderation effect should be interpreted, such as the effect of ICU survivorship on that particular item varies with the degree of the third-variable. The third-variable will be treated as continuous, and moderation effect analysis will be conducted along this continuity, with conclusions drawn from the estimates at +1SD, average, and -1SD.

4. Finally, the model will identify collider bias between group belonging and item$_n$ (arrows D). These associations should be considered distorted and not true since they are merely a subgroup of selection bias.[69]

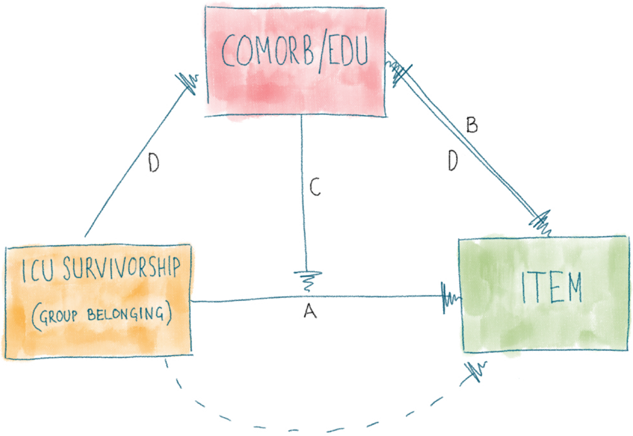


Figure 2.2 Schematic figure of the two models (equal models for comorbidity and educational level, respectively). Arrows A & B represent associations tested for. Arrow C represent a moderation effect of the third-variable on the relationship between ICU survivorship and the item tested. Arrows D and dotted arrow represent a distorted association (collider bias).

To identify change after introducing the third-variables, we conducted an initial set of independent bivariable correlation analyses to compare the responses from the two groups. Subsequently, multiple linear regression was used to analyse each pair independently in a multi-variable analysis. This allowed us to separate the effects from the independent and moderating variables. Note that no questions were excluded between the bivariable and the multi-variable analyses. We considered p values < 0.05 to be statistically significant.

2.3 METHODOLOGY & STATISTICS PAPER III

> *What if not all problems we asked about in the provisional questionnaire affect quality of life? What if one could let the data reveal patterns regarding which questions affect quality of life and which constitute mere day-to-day troubles? What if there are differences in these patterns between our ICU survivors and our non-ICU-treated controls?*

Considering the amount and range of issues in our provisional questionnaire, it would be plausible to think that not all issues necessarily affect quality of life. Hypothetically, some issues could very well be prevalent but of a relatively minor character that they would simply be nuisances in daily life rather than quality of life-affecting. This reasoning constitutes the basis for **PAPER III**. Additionally, it could be equally plausible to hypothesise that the patterns of which issues affect quality of life and which are mere issues without an effect on quality of life could differ between the two groups. Both pre-existing characteristics not measured in our studies and response shift are potential explanations for these eventual differences. A known phenomenon from oncology, response shift is part of a transformation after significant life events such as cancer and is a combination of recalibration, reconceptualisation and reprioritisation.[70]
It has rarely been evaluated in intensive care, speculatively, because pre-ICU data on quality of life is hard to gather. It is nevertheless an attractive and reasonable explanation for eventual shifts in quality of life of ICU survivors.[71]

Multiple statistical alternatives exist for grouping data, with exploratory factor analysis (EFA) seemingly suitable for our initial questions. However, regular EFA does not fit our purpose since we have two groups to compare. Analysing two different groups separately and only subsequently comparing the results manually does not allow the variance of the two groups to affect each other. In other words, comparing two groups analysed separately risks being too much of a simplification. Multi-group exploratory factor analysis (MG-EFA) is a modelling technique that allows the inclusion of two groups simultaneously into the same model. This, however, adds a level of complexity when interpreting results – the results of any of the groups have to be considered in relation to the other group instead of separately. Suppose ordinary EFA is well-suitable for studying variables of a multidimensional nature, such as quality of life, in a single sample. Then the structure of MG-EFA makes it suitable for studying the same variables but simultaneously across groups, since it may aid in evaluating differences and similarities.

The basis of the analysis in **PAPER III** is the summarising quality of life question finalising all domains (henceforth denominated $Question_{QoL}$): ***To what extent do problems within [domain] affect your quality of life?*** By ending each domain with this question for both groups, we allowed for analysing the structure of quality of life using MG-EFA. An EFA table shows each item's correlation coefficient on each dimension and with inter-item correlation. In short, items loading strongly on a dimension can be shown to correlate with each other. Thus, we can conclude that items that load strongly in the same dimension(s) as the $Question_{QoL}$ correlate strongly to our sample's domain-specific quality of life (henceforth referred to as $[Domain]_{QoL}$).

To specify definitions for the results of **PAPER III**, questions loading in the same dimension as the $Question_{QoL}$ are defined as having a reasonable probability of being part of quality of life for that particular domain in our sample. Questions not loading in the same dimension as the $Question_{QoL}$ question are defined as having a low probability of being part of the $[Domain]_{QoL}$ for the studied sample. These definitions somehow constitute a study-specific framework in which quality of life can be described on an objective, group-based level rather than on a subjective and individual level.

2.3.1 Model fit

We need a basic understanding of model fit to move deeper into the statistics.

The number of dimensions within a domain can be determined by optimal *model fit*, decided by so-called information criteria. Multiple information criteria are available, with two of the most common being Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Information criteria have their historical base in information theory and its interpretation of entropy as a quantification of uncertainty.[72] They estimate prediction error outside the sample; in other words, they quantify how "off" the model may be in its prediction if one were to apply the model to the entire population that the model tries to represent. When finding the optimal model fit for a statistical model, one has to balance the goodness of fit and the model's simplicity: If everything is put in the model, it might be very good, even unnecessary so, but at the same time, too complex – *overfitting*. Think, for example, of a model with everything in it; there are as many clusters as data points. It would have no outliers, but it would not be a useful model. Conversely, by excluding too many variables, the model risk explaining one's data less accurately – *underfitting*.

A set of statistical models is compared to find the right balance, creating a criterion score for each model. Liberally interpreted, the score could be seen as a measure of loss of information where the lowest score equals the least loss of information. The model with the lowest score is the best possible, given the data.

Different information criteria have different properties and trade-offs, thus making it common to use multiple criteria in the same selection process. AIC and BIC can mathematically be described as the following:

$$\mathrm{AIC} = 2p - 2\ln(\hat{L})$$

$$\mathrm{BIC} = p\ln(n) - 2\ln(\hat{L})$$

where p = numbers of parameters; $\hat{L}$ = Maximum likelihood function (the parameter with the highest probability of correctly representing the relationship between the input and output); n = sample size

As can be understood by the equations, adding complexity by adding parameters (p) raises the score as a penalty. Conversely, an increase in $\hat{L}$ will decrease the score, thereby rewarding simplicity. Finally, a larger sample size is penalised.

In **PAPER III**, AIC and BIC indicate whether adding one more dimension to the model is better than the current model, the one with one less dimension. Explained simpler, imagine we analyse the results from our questions on cognition and, for didactic reasons, label "dimensions" as "aspects of cognition". First, a model where cognition is represented by a single aspect, including all measured items, will be analysed. After that, a model will be analysed where the items on cognition are divided into two different aspects. Note that the data do not tell us what these two aspects represent; that is up to us as researchers to interpret. For example, inspecting the data, we might find that they reflect memory problems and executive functions. In a third step, a model with three aspects will be tested, and so forth. A score representing the fit will be calculated for each models, and as long as this score gets lower, we try a new model with an additional aspect of cognition. Further analyses are stopped as soon as a new model increases the score. Since a decrease in the score is associated with improved fit and, thus, a better model, the lowest AIC/BIC is the best trade-off between model fit and complexity.

Both AIC and BIC are frequently used together when comparing models, and we report both these indicators for model selection. If there is a disagreement between the two, BIC will be used as the primary criteria for determining the number of dimensions for each domain across both groups.

2.3.2 Interpretation

Reading an MG-EFA table is similar to reading an ordinary EFA table in that all items load on all dimensions within their domain. The following may help in the interpretation our results:

- » The number of dimensions within a domain is not decided by the researcher but by the model fit, i.e., the data itself (see above).
- » The so-called "loadings" are correlation coefficients and estimate the strength between the item and the dimension.
- » Items that load strongly within the same dimension are linearly correlated.
- » All items may load on all dimensions. Important for **PAPER II**, it means that the $Question_{QoL}$ could load strongly on all dimensions, signalling that all issues in that particular domain correlate with quality of life for the sample.

2.3.3 Reliability

Additionally, reliability measures will be reported, i.e., how consistently the questionnaire measures something. Responses to a questionnaire could be considered to consist of the sum of the true score plus any error. This error includes both systematic error and random error. While random error is normally distributed, systematic error is, by definition, either too high or too low, thereby still driving the reliability consistently even with being an error term (although adding bias). Therefore, since reliability is between zero and one, the true score and the systematic errors push reliability toward one, while random error presses it toward zero.

There are at least four different subtypes of reliability:

- » *Internal consistency* (the extent to which the single items in a questionnaire measure the same construct).

» *Interrater* reliability (the results of the same questionnaire, but interpreted by different people).

» *Test-retest* reliability (the same questionnaire, but tested over multiple occasions, often two to three weeks apart to allow the participant to forget previous answers, but not too long for circumstances to change too much).

» *Parallel* or *equivalent forms* reliability (different versions of a questionnaire designed to be equivalent).

Interrater, test-retest, and parallel forms reliability do not apply to our data. However, internal consistency is a good measure of reliability when only one dataset is available.

We used two statistical measures, *McDonald's omega* and *Cronbach's alpha*, to evaluate reliability on a per-dimension basis. McDonald's omega is more robust than alpha for estimating questionnaire reliability but requires at least three factor loadings.[73] Thus, McDonald's omega was used for domains with three or more factor loadings, while Cronbach's alpha was used for domains with less than three factor loadings. Estimates with a poor statistic suggested item reduction in the questionnaire.

2.3.4 Handling of missing data

For missing data, full information maximum likelihood (FIML) was applied to missing data by default. FIML contrasts with many other methods for missing data by accounting for the uncertainty associated with the missing values. By doing this, all available information is used to estimate the model. The method estimates those population parameters that would most likely produce the estimates analysed from the sample. FIML has been demonstrated to generate accurate and unbiased estimates even when the normality assumption is violated as long as the missing mechanism is missing completely at random or missing at random.[74] Less than five participants had left out all questions on Sexual health, thus arguably being missing not at random. However, with this being such a small percentage of data missing, FIML can be assumed to work.

2.4 METHODOLOGY & STATISTICS PAPER IV

> *Considering the findings in paper III, could there be an overarching quality of life construct in our sample? That is, after finding the structure of the quality of life constructs in our sample of ICU survivors compared to non-ICU-treated controls, is it plausible to imagine a construct encompassing all aspects of quality of life for ICU survivors into a single one, rather than simply on a domain-basis?*

The goal of **PAPER IV** is to further evaluate the structure of the quality of life construct within our ICU survivor sample and, by doing that, aid in reducing the number of questions. To do this, we must have a certain understanding of factorial modelling.

Confirmatory factor analysis (CFA) with bifactor modelling is a way of gaining knowledge in similar questions. The approach includes several steps, explained below. However, we must first know which variables to use in the modelling. Therefore, an initial series of bivariable correlation analyses were performed, on a per-domain basis, between the question ***To what extent have difficulties with [domain] affected your quality of life for the past month?*** ($Question_{QoL}$) and all other items in the domain. As a threshold, correlations with a lower confidence level of ≥ 0.50 qualified the item for further analyses.

After deciding which variables to keep, CFA was employed in a second and third phase to examine the unidimensional and multidimensional factor structure, as well as the second-order and bifactor structure of quality of life domains (henceforth denominated $[Domain]^{QoL}$). The significant items in the first step formed the base for an a priori specified model. Since this is a confirmatory and not an exploratory analysis, the number of domains constitutes the number of factors. Standardised factor loadings > 0.50 were considered good.

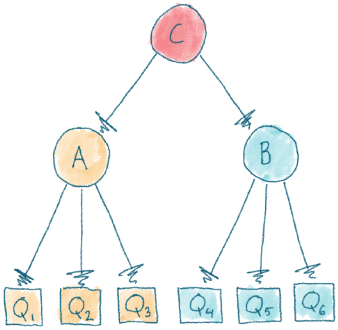
Model fit was assessed with the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardised Root Mean Square Residual (SRMR). As noted in **PAPER III**, all model fit indices have strengths and limitations. Threshold values for model fit should not be considered fixed but based on established recommendations and consensus, much as other statistical thresholds. Essential to know regarding the indices used in **PAPER IV**, while RMSEA and SRMR tend to remain stable, CFI and TLI risk worsening in model fit when more than five indicators of a latent variable are included. As a result, RMSEA and SRMR values will be primarily used to assess the overall model fit.

- For CFI and TLI, values above 0.950 represented excellent model fit, and values between 0.900 and 0.950 were regarded as acceptable model fit.
- For RMSEA, values below 0.050 represent an excellent fit, and values between 0.051 and 0.079 represent a good fit.
- For SRMR, values less than 0.080 are considered a good fit.

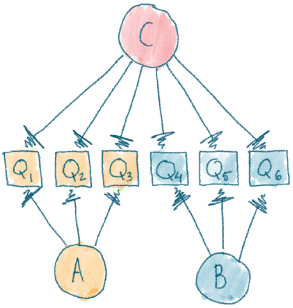
To determine *construct validity* – that the questionnaire is actually measuring what it is supposed to measure – both *convergent validity* and *discriminant validity* were assessed. Convergent validity, i.e., how closely a test is related to other tests measuring the same construct, is achieved when factor loadings surpass 0.50 combined with reflective indicators of latent variables loading with significant values on their corresponding theoretical constructs. Discriminant validity, i.e., that constructs that should not be related to each other are, in fact, unrelated, is established when the square root of the Average Variance Extracted (AVE) is greater than the correlation between pairs of the latent variables. Additionally, discriminant validity can be established when the loadings of measurement items on their primary variable are higher than those on other variables. We used composite reliability (CR) to assess the reliability of the domains. CR is a way to measure the shared variance between the observed variables used to represent our latent construct (in this case, [*Domain*]^{QoL}).

In the original unidimensional analysis, some domains – *Sleep*^{QoL}, *Alcohol use*^{QoL}, *Sexual health*^{QoL}, *Sensory functions*^{QoL}, and *Urinary tract functions*^{QoL} – only had two questions measuring their relationship to the overall construct of [*Domain*]^{QoL}. Due to negative degrees of freedom, the [*Domain*]^{QoL} can not be identified statistically in the unidimensional analysis with only two indicators. However, all of these dimensions were included in the multidimensional CFA except *Alcohol use*^{QoL} and *Work life*^{QoL} due to low covariance coverage. Thus, 12 domains and 58 questions were included in the multidimensional CFA to evaluate the correlations between first-order factors.

In two subsequent steps, the findings from the multidimensional CFA were used in a second-order CFA and bifactor analysis to assess the presence of a general quality of life factor. In a second-order CFA, we can estimate a higher-order factor using four or more correlating first-order factors. The idea behind this is to explain these correlations by positing the existence of a higher-order factor:



Bifactor modelling assesses whether the items in our questionnaire are sufficiently unidimensional (i.e., whether they all measure the same underlying construct). In our bifactor model, all included factors (general and domain-specific) are specified to be completely uncorrelated and independent of each other ("orthogonal" to one another, with no shared variance). This assumption simplifies the model since it is easier to see how each factor relates to the observed data. The model emphasises the factor loadings of the items in order to determine whether they are all measuring the same general construct or whether multiple constructs are being measured. The bifactor model assumes that covariation among the observable indicators can be explained by a general factor (defined by loadings from all items) and domain-specific factors (defined by loadings from questions in each domain), coexisting at the same conceptual level. The general factor in our study thus equals *overall post-ICU quality of life*. In other words, the bifactor model posits that there is a general factor common to all questions and domain-specific factors unique to each domain:



Analyses were performed with 95% confidence intervals. *P* values < 0.05 were considered statistically significant. All tests were two-sided.

HENRI MATISSE
would paint a colorful and joyous scene of a woman dancing – expressing his sense of liberation and renewal after surviving a life-threatening illness.

RESULTS & REASONING

BEFORE discussing the findings, one thing must be emphasised again, perhaps to some readers' disappointment. This doctoral thesis is not about how ICU survivors *feel* but how to best *measure it*. Thus, this chapter will not discuss the result of this or that question in-depth, even if there are plenty of interesting findings.

3.1 PAPER I

3.1.1 PART 1 | THE QUALITATIVE PART

3.1.1.1 Interviews

All invited patients accepted to be interviewed. Saturation, including additionally six cognitive interviews, was reached after interviewing 32 survivors.

Our result is somewhat in line with the literature regarding saturation. For example, a systematic review by Hennink and Kaiser from 2022 identified 17 articles using data saturation and found a maximum of interviewees of 17, thus a bit fewer than in our study.[75] Our slightly higher number could reflect the heterogeneity of an ICU population, although the review by Hennink and Kaiser included studies that, in particular, were considered interviewing heterogeneous samples. An alternative explanation could be the richness of the data generated from each interviewee. However, Ogden and Cornwell operationalised "richness" to a composite measure based on ten qualitative health studies and found that, for example, open questions were associated with richer data, something we were using liberally.[76]

It should come as no surprise that the amount of information gathered from each interviewee has a role in determining sample size, and hypothetically, ICU survivors may have more trouble communicating their troubles than samples from other populations, thus adding a need for more interviews than commonly used.

A partner was present in ten interviews, and all interviews but two were conducted in the post-ICU clinic at a median time of 49 minutes (range 15-113 minutes).

Using the post-ICU clinic as the platform for recruiting participants introduces an element of selection bias. Although the staff at the clinic is notoriously good at convincing former patients by phone to pay a visit, we have no data available on the subset that declined or retracted their participation. Several hypothetical explanations may be speculated upon, affecting our outcome differently. First, one could guess that the most ill patients simply were too ill to visit. This would mean that any issue experienced only by this group would be missed in the final questionnaire, limiting the ability to capture issues in this group correctly and, thus, the useability of the questionnaire. One strategy for minimising this bias was to include issues even if they were mentioned only once. Second, and reversely, one may hypothesise that the former patients with no or almost no issues simply did not see the need for a visit. If they had no post-ICU issues at all, then this would naturally not miss any issues, but if they had lesser issues, simple nuisances, then these may have been missed, thus lacking from the questionnaire. Lastly, certain groups of former patients, perhaps most likely those with a severe psychiatric diagnosis, may have been harder to reach, thus potentially risking misrepresentation in the final questionnaire.

3.1.1.2 Interviewees

The median age of the interviewees, including those for the cognitive interviews, was 55.5 years (20-82 years), and 33% were females. Their median ICU length of stay had been 4.9 days (1.7-76.1 days). The most common admission diagnosis was infection/sepsis (18.8%), followed by trauma and cardiac arrest (both 12.5%). The median time between ICU discharge and the interview was 14.7 months (7.6-68.0 months). These demographics differ slightly from the national average, where an approximate search in the national intensive care registry for the same period shows a median age of 65.5 years and 37.7% of females.[77] Among other possible explanations, the lower median age in our sample could be a random effect, reflect who chooses to visit the post-ICU clinic, or possibly indicate a bias with me when selecting interviewees.

3.1.1.3 Issues

The interviews gathered in total 437 issues. After removing duplicates and merging similar-appearing issues, 195 unique issues remained. Only minor language corrections resulted from the cognitive interviews and no new issues were identified. This aligns with a study by König et al., gathering similar issues specifically from sepsis survivors.[78] In their study, saturation was almost (95%) reached already after seven interviews (Figure 3.1.1.3). The difference between their study and ours may be a result of their focus on a single diagnosis.

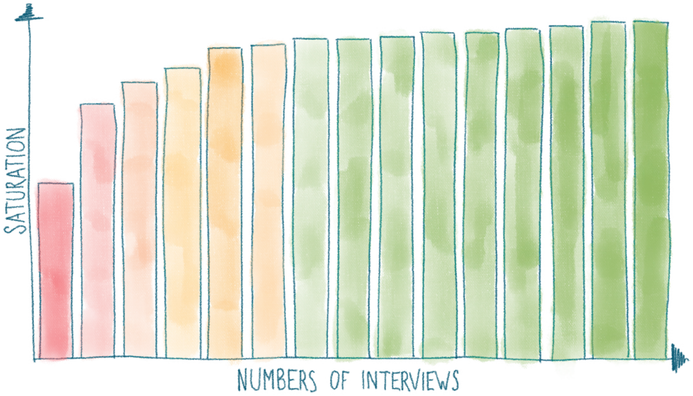


Figure 3.1.1.3 Relative cumulative frequency of all codes and subcodes per interview. As the analysis progresses, saturation is reached as few new codes or subcodes are added. Data saturation was already 95% after the first seven interviews. Later interviews only contributed 5% to the total number of codes and subcodes.
Adapted from König et al. Reproduced with permission from Springer Nature.

All remaining issues were grouped into 13 domains: Cognition, Fatigue, Physical health, Pain, Mental health, ADL, Sleep, Appetite and Alcohol use, Sexual health, Sensory functions, Gastrointestinal functions, Urinary tract functions, and Work life. At the end of each domain, two composite questions were added: ***How much do problems regarding [domain] make you worry about the future***, and ***To what extent do problems within [domain] affect your quality of life?*** Finally, questions from Alcohol Use Disorder Identification Test-Concise (AUDIT-C), KATZ-ADL index, Work Ability Index (WAI) and one question about the ability to walk for six minutes were added. However, almost all questions from the WAI proved to have response scales in the wrong format and thus were excluded from analyses. One question regarding previous intensive care was added in the questionnaire, considering this was an exclusion criterion for the control group.

The number of questions attracted some interest in the second part of **PAPER I**. However, previous local experience from oncology on similar questionnaires had shown a high response rate despite numerous questions. For example, Alsadius et al. used the methodology on patients with prostate cancer and received a response rate in their patient group of 89% using a questionnaire with 164 questions.[79] We decided not to exclude any issues at this stage, knowing that a future reduction was part of the strategy.

3.1.2 PART 2 | THE QUANTITATIVE PART

Of the 518 ICU survivors and 231 controls participating, 395 ICU survivors and 197 controls returned a completed questionnaire, resulting in 76.2% and 85.3% return rates, respectively. The priming of eligible participants by sending an introductory information letter before making the first phone call may be one of many factors responsible for the relatively high response rate considering the number of questions. However, a recently conducted RCT on pre-notification letters failed to show any significant effect on response rate.[80] The study was, however, a nested study within a systematic review and lacked power. Further, response rates in both groups were just above 40%. Several studies have attempted to evaluate the impact of the number of questions in survey studies, with diverging results. Beebe et al. tested two versions of a questionnaire on bowel disease in an American population aged 25-65.[81] They found no difference in response rates between the two-page version with 18 questions (response rate 44.6%) and the four-page version with 35 questions (response rate 48.4%).

Contrasting to these findings are those from Ettridge et al., testing the perception of two different online versions of a questionnaire on HRQOL for women with breast cancer.[82] The number of questions was dynamic, but the group with a minimal set of questions received a maximum of 127 questions, while the group with the extended set received a maximum of 230 questions. There was no measurable difference in perceptions toward the two questionnaires. However, the qualitative analysis showed that while there was a tendency to favour the lesser workload completing the minimal set, there was also a tendency to favour the comprehensiveness of the extended set, with the explicit advantage of fewer gaps in content.

The results from **PAPER I** could be interpreted either way; considering the amount of over 300 questions, response rates in both groups were almost surprisingly good. On a speculative note, the adequacy of the content may be a factor in at least the ICU survivor group. However, we do not know whether response rates could have been even higher with fewer questions.

The most frequent reason for declining participation among ICU survivors was family members refusing to participate. In contrast, the primary reason among controls was a lack of time. Although we created a comprehensive list of reasons for declining participation with the purpose of further analysing these results, in the end, people who decline participation almost just as often decline to reason about why, and further analysis would be highly skewed.

Infection/sepsis was the most common admission diagnosis for the ICU survivors, accounting for 27.8%, followed by trauma at 13.4% and respiratory failure at 10.9%. The median SAPS 3 score was 59, with a range of 16 to 100, and the median length of stay in the ICU was 5.6 days, with a range of 3.0 to 78.6 days. Most ICU survivors (78.5%) required mechanical ventilation for a median of 4.0 days (range 0-74 days). The distribution of the primary diagnosis groups was relatively similar among ICU survivors and interviewees.

3.1.2.1 Demographics and characteristics

There were no age or gender differences between the ICU survivors and the control group, indicating a successful matching. There were no differences in educational level. The ICU survivors had a higher prevalence of comorbidities than the control group, with significant differences found in 13 out of 22 conditions. The implication of these two last findings forms the basis of **PAPER II**.

3.1.2.2 Comparison between the two groups

The ICU survivors differed significantly in responses to most questions across all domains compared with the control group (Table 3.1.2.2; Tables S1-S13).

In all, responses from the ICU survivor group was significantly worse in over three quarters of questions, compared with the non-ICU-treated control group. However, as can be seen in Table 3.1.2.2, large variations can be seen across the different domains. Perhaps most surprising is the finding that the domain on cognitive dysfunction contained the proportionally *fewest* amount of questions differing between the groups. Findings in our domain on cognitive dysfunction will be further discussed in section 3.3.1, but the results, contrasting primarily with those of Pandharipande et al., may reflect on their more extensive cognitive evaluation, but alternatively on their lack of a comparison with a control group.[34]

3.1.2.3 Lost to follow-up

Compared to the subset of ICU survivors who returned the questionnaire, the 123 ICU survivors lost to follow-up were markedly younger, with a median age of 52 years (range 18-92). There were no difference in sex (36.7% females). They had a median ICU length of stay of 7.3 days (range 3-27), thus longer than the average among the participants. Similar to the participants, the most common admission diagnosis was infection/sepsis (20.3%) with trauma (16.1%) and respiratory failure (13.6%) as the second and third most common. Median SAPS3 score was 57.3 (range 23-110), and 35.8% had been mechanically ventilated for a median of 7.2 days (range 1-26).

To summarise the comparison between the lost to follow-up subset and the participants, the lost to follow-up subset was younger, equally ill upon admission, and had a longer average stay than the participants. There was no overrepresentation of patients with psychiatric disease, but no further analysis of trauma patients have been done. However, caution should be exercised in interpreting the lost to follow-up subset, as there may not be any advanced interpretation beyond the lower participation rate of younger people in surveys.

Table 3.1.2.2 Number of issues per domain with significantly worse outcome in the ICU survivor group compared to the non-ICU-treated control group.

Cognition	14 of 31 (45%)
Fatigue	12 of 14 (86%)
Physical health	26 of 26 (100%)
Pain	16 of 18 (89%)
Mental health	18 of 21 (86%)
ADL	13 of 13 (100%)
Sleep	7 of 11 (64%)
Appetite & Alcohol use	6 of 11 (55%)
Sexual health	9 of 11 (82%)
Sensory functions	14 of 18 (78%)
Gastrointestinal functions	7 of 8 (88%)
Urinary tract functions	3 of 8 (38%)
Work life	8 of 8 (100%)

3.2 PAPER II

The easiest way to follow the findings in **PAPER II** is to remember the model:

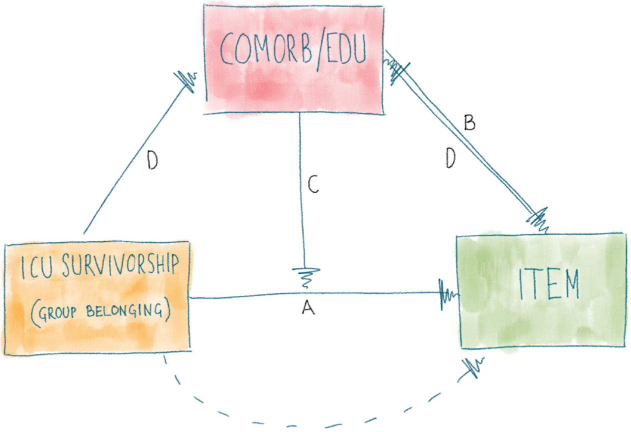


Figure 3.2 Schematic figure of the two models (equal models for comorbidity and educational level, respectively). **Arrows A & B** represent associations tested for. **Arrow C** represent a moderation effect of the third-variable on the relationship between ICU survivorship and the item tested. **Arrows D** and **dotted arrow** represent a distorted association (collider bias).

3.2.1 Bivariable analysis

The initial analysis identified a significant difference in quality of life between ICU survivors and non-ICU-treated controls in a majority (78%) of items. Responses to all, or almost all, questions differed in the domains of Fatigue, Physical health, Pain, Mental health, ADL, Gastro-intestinal functions, and Work life (Tables S1-S13).

3.2.2 The effect of comorbidity

After introducing comorbidity into the multi-variable model, the following could be seen: A significant effect from ICU survivorship on the issue tested remained in 139 of the 218 questions (Tables S1-S13; Legend A & B).

In more than half (58%) of these 139 questions, comorbidity had no effect (Tables S1-S13; Legend A). In the remaining 59 questions, the association with ICU survivorship existed simultaneously with an association with comorbidity (Tables S1-S13; Legend B). Thus, comorbidity did not remove the association with ICU survivorship; rather, the analysis shows that there is room for multiple explanations of a phenomenon.

Regarding the separate association of comorbidity, parallel to the association of ICU survivorship, large differences could be seen across domains: Sexual health and Sensory functions showed a parallel association between comorbidity and the issue tested in a majority of issues; 5 of 6 questions and 10 of 13 questions, respectively. Conversely, none of the questions in the domains of Cognition and Fatigue had a significant parallel association between comorbidity and the issue tested.

Moderation, or effect modification, of comorbidity on the association between ICU survivorship and the issue tested was found in six questions (Tables S1-S13; Legend C & D).

This finding is essential, as it means that in our sample, comorbidity alone has a minimal effect on the relationship between intensive care and its outcome. Given that comorbidity may have an effect in parallel to that of ICU survivorship, as shown in the previous paragraph, comorbidity as a variable cannot be considered an alternative explanation for our findings in **PAPER I**, only a complementary. It also speaks toward including multiple variables in future analyses regarding comorbidity, not in the form of multi-variable analysis, but in models taking the interdependency of variables into account, thus better mimicking reality and raising the explanatory power of the analyses.

In 25 questions, there was no longer any significant effect from ICU survivorship after introducing comorbidity as a moderator (Tables S1-S13; Legend E & F). This could, at least partially, be interpreted as if the initially seen significant effect in the bivariable was too weak to remain in a more complex model.

Summarising the role of comorbidity on the issues we tested in our sample of ICU survivors, it seems that although a higher comorbidity burden was seen in the ICU survivor group, this difference at most had a parallel effect on about 40% of the issues, rather than reducing the effect of ICU survivorship, illustrating how careful one has to be with too broad general statements regarding the behaviour of comorbidity. Interpreting our results, it is thus important to note that they do not negate findings indicating some effect from chronic disease on quality of life after intensive care, as shown in several studies.[83 84 85] However, had we found a moderation effect of comorbidity in most questions, the conclusions of **PAPER II** would have been that comorbidity explains *why* ICU survivors have a lower quality of life than that of a non-ICU-treated control group, as sometimes alluded to.[61] An additional implication of these findings is that a randomised control group from the public may still be suitable as a control group for trials, despite having significantly less comorbidity.

3.2.3 The effect of educational level

The model using educational level as a moderator showed that the significance of ICU survivorship remained in 139 questions (Tables S1-S13; Legend A & B).
Educational level was not significantly associated with the issue tested in 113 of these 139 questions (Tables S1-S13; Legend A). In 26 of the 139 questions, the association between ICU survivorship and the item tested remained significant simultaneously, with a significant association between educational level and the item (Tables S1-S13; Legend B).

In these questions, the domains in which the proportionally highest number of associations remained significant after introducing educational level into the model were Cognition (18 of 18 questions still with a significant difference between groups), Appetite & Alcohol use (6 of 6 questions), Pain (17 of 18 questions), Sensory functions (14 of 15 questions) and Fatigue (11 of 12 questions).

Educational level moderated the association between ICU survivorship and the issue tested in 32 questions (Tables S1-S13; Legend C & D); 11 questions in the domains of Physical health, seven in ADL and occasional questions in other domains. In addition, a few questions with non-significance in the bivariable analysis showed a moderation effect from educational level. However, since the association between ICU survivorship and the item tested was non-significant, these items are reported as non-significant.

These findings are interesting. The moderation of the effect on ADL issues by educational level indicates that in the ICU survivor group, a higher educational level is associated with a lesser degree of ADL issues, while in the non-ICU-treated control group, there was no difference across educational levels.

The results in the cluster regarding physical health are somewhat similar; the higher the education, the lesser the physical health issues, while no such difference was seen in the control group. Reasons for this difference should be further studied, but examples of theoretical explanations are that knowledge about rehabilitation, or the availability of rehabilitation itself, is higher in the educated subgroup.

When considering the results of **PAPER II**, it is essential to remember that these are separate analyses on an item-per-item basis. Thus, it would be precarious to draw conclusions in the style of *Comorbidity is/is not…*, even on a domain level. Instead, these findings emphasise the diversity in behaviour, statistical and clinical, that different issues express. Further, this study only tests the role of moderator variables. Hypothetically, these variables could function as mediators, at least comorbidity, or confounders, in the word's modern, more proper, definition. However, as mediators or confounders, most combinations of variables become clinically implausible when extracting a single item and reasoning about the chronological relationships.

> *The most important interpretation of* PAPER II *is that significant differences in the number of comorbidities between ICU survivors and a non-ICU-treated population do not explain differences in quality of life.*

3.3 PAPER III

As will be seen in a domain-by-domain walkthrough of the results, although there were many similarities between the two groups, there are important differences at a clinical level. The most important difference is that the ICU survivor group, when compared to the control group, seems to emphasise the overall issues when relating to quality of life rather than focusing on everyday issues, perhaps representing a reprioritisation or recalibration as part of a response shift.

There are two main statistical findings in **PAPER III**. First, the study shows that, with few exceptions, the $Question_{QoL}$ of all domains loads in one and only one dimension. That is, not all issues are related to an effect on quality of life in our sample. Second, our analysis shows that about half of the domains show a different pattern regarding the correlation to quality of life in ICU survivors versus non-ICU-treated controls.

First, all domains converged for a solution, qualifying all domains for further analyses (Tables S1-S13).

3.3.1 Cognition (Table S1)

With a three-factor solution in Cognition, the $Cognition_{QoL}$ did not load strongly enough in any dimension, in either of the groups. Thus no quality of life dimension was found. There are several possible explanations for this finding. First, the sample size affects factor loadings, and a larger sample size can stabilise factor loadings and might have been able to show a correlation, given that such a correlation exists. However, the sample size in the Cognition domain was large, with an average of 304 responses in the ICU survivor group and should be sufficient to show an existing correlation. Another possible explanation would be that neither group actually correlates their issues to an effect on quality of life. With a mean age of around 65 years, mild cognitive problems may perhaps be coped with as age-related. An additional explanation is regarding the ability to relate to, and measure, quality of life at all when having a cognitive dysfunction. On one end of the cognitive dysfunction spectrum, patients with Alzheimer's disease rank their HRQOL significantly higher than their caregivers.[86] On the other end, both patients and caregivers have been shown to lack the ability to identify existing mild cognitive dysfunction in Parkinson's disease.[87] Finally, it should be noted that we have used a strong threshold of 0.60. This avoids type I errors in sequential **PAPER IV**, where the lower confidence level will be used as a threshold.

Both groups shared similar language difficulties (***Difficulties finishing sentences***; ***Losing the thread easily***). However, the ICU survivor group singled out issues related to memory and language into a second dimension (***Don't remember what you said***; ***Don't remember what you have done***; ***Think you have done something but you haven't***), while the non-ICU-treated control group's language dimension still included these memory-related issues. Finally, compared to the non-ICU-treated control group, the ICU survivor group had a dimension primarily dominated by executive abilities issues (***Difficulties taking the initiative***; ***Difficulties prioritising***; ***Difficulties concentrating***; ***Difficulties finding alternative solutions***).

3.3.2 Fatigue (Table S2)

Comparing the groups in the two-factor dimensionality shows that the ICU survivor group exhibited much fewer issues correlating together with the $\mathit{Fatigue}_{QoL}$ item in a quality of life dimension ($\mathit{Fatigue}^{QoL}$; 3 vs 12). While the non-ICU-treated control group linked nearly all issues with quality of life, only issues impacting social life, such as tiredness affecting work or social activities, were correlated together with the $\mathit{Fatigue}_{QoL}$ item in the ICU survivor group. In the ICU survivor group, two issues – feeling tired from reading and from watching TV – constituted a separate dimension, whereas, in the non-ICU-treated control group, these issues were part of the $\mathit{Fatigue}^{QoL}$ dimension. That a relatively healthy control group, supposedly with low levels of fatigue, correlates most fatigue issues to quality of life may not be surprising. The reverse finding in the ICU survivor group should not be interpreted as a low prevalence of fatigue in this group but rather probably a matter of coping strategies. Several studies have pointed to the prevalence of severe fatigue after intensive care. Morel et al. evaluated 351 ICU survivors between six months and five years after ICU discharge, similar to our sample, and found more than half affected.[88] However, an association with quality of life was not saught-after. Our findings suggest that the ICU survivor group focused more on the broader impact of fatigue than the day-to-day symptoms compared to the control group since our model relativises the issues between the groups.

3.3.3 Physical health (Table S3)

The four-factor dimensionality between the two groups in physical health showed no major differences, with both groups having very few items correlating together with the $\mathit{Physical\ health}_{QoL}$ item in an $\mathit{Physical\ health}^{QoL}$ dimension. Both groups showed that general physical health and future worries about physical health were correlated with quality of life. However, the ICU survivor group showed an additional correlation between limitations of activities and quality of life, once again perhaps emphasising a shift in focus from minor concerns to the broader perspective.

3.3.4 Pain (Table S4)

A four-dimension solution was retrieved for the pain domain. In both groups, pain that prevented planned activities affected quality of life, which was the only issue related to quality of life in the non-ICU-treated control group. The ICU survivor group had an additional issue related to quality of life, ***Worrying about pain***, that did not load in the $\textit{Pain}^{QoL}$ dimension in the control group. Both groups shared a dimension related to pain and sleep, such as using painkillers to sleep better and difficulty sleeping due to pain, but these issues were not correlated quality of life.

3.3.5 Mental health (Table S5)

The two groups differed significantly in the three-dimension solution for the Mental health domain and how they relate these issues to quality of life. In particular, the ICU survivor group had multiple issues related to a low mood state that correlated together with the $\textit{Mental health}_{QoL}$ item (e.g., feeling depressed, anxious, hopeless, and with low self-esteem), whereas no issues were found to constitute a $\textit{Mental health}^{QoL}$ dimension in the control group. This may be an effect of the relativism incorporated into the MG-EFA or that the construct of $\textit{Mental health}^{QoL}$ is different between the two groups. However, it is essential to note that the loading of the $\textit{Mental health}_{QoL}$ item in the control group was 0.55, thus at least moderate. The groups had similar patterns in the other two dimensions, with one dimension containing issues related to short-temperedness and impatience, and another dimension containing issues related to the ability to find enjoyment and optimism.

3.3.6 ADL (Table S6)

A three-dimension solution was retrieved for the ADL domain. In the ICU survivor group, a third of issues loaded strongly in an $\textit{ADL}^{QoL}$. This included avoiding taking public transport, help shopping, cooking, and with housework, and finally, worrying about daily activities. The non-quality of life dimension in this group was primarily composed of more intimate issues, such as help showering, getting dressed and visiting the toilet. In contrast, no issues in the non-ICU-treated control group were found to be correlated together with $\textit{ADL}_{QoL}$ item, despite most issues having a strong loading. As in the Mental health domain, this must be interpreted in the light of the relativism incorporated in an MG-EFA. Also similar to the *Mental health*$_{QoL}$ item, the loading of the *ADL*$_{QoL}$ item was still 0.55 and 0.53 in the two dimensions for the control group. Thus, with less stringent criteria, all ADL issues in the control group would be considered correlated with quality of life.

3.3.7 Sleep (Table S7)

In the three-dimension solution of the Sleep domain, the ICU survivor group had only one issue significantly correlated together with the *Sleep*$_{QoL}$ item – sleep-related worries. In contrast, no issue was found to be loading in a *Sleep*^{QoL} in the control group. Instead, sleep-related worries were associated with this group's need for sleeping pills.

Our finding aligns with other studies of sleep-related problems in ICU survivors and quality of life. A prospective multi-centre cohort study found that although ICU survivors had more sleep-related issues post-ICU than a randomised sample of regional controls, these issues only weakly correlated to HRQOL measured with SF-36.[89] A partial explanation may be the minimal change in the prevalence of sleep-related issues post-ICU compared to pre-ICU in the study.

3.3.8 Appetite & Alcohol use (Table S8)

First, note that this domain contains two *Question*$_{QoL}$ items; one *Appetite*$_{QoL}$ and one *Alcohol use*$_{QoL}$. A three-dimension solution was retrieved for the domain on appetite and alcohol use. Both groups were found to have a similar pattern regarding quality of life, with the *Appetite*$_{QoL}$ and *Alcohol use*$_{QoL}$ items correlating together with the issue of future worries regarding both appetite and alcohol use. However, only the ICU survivor group had poor appetite included in the *Appetite*^{QoL} dimension.

3.3.9 Sexual health (Table S9)

A two-dimension solution was retrieved for the Sexual health domain, in which the two groups showed similarity across all dimensions except for the issue of surgical scars affecting sex life, which correlated together with the *Sexual health*$_{QoL}$ item only in the ICU survivor group. Both groups had the issue of worries about sex life loading in the *Sexual health*^{QoL}. Furthermore, a dimension consisting of sex drive, sexual activity, sex life, and orgasm constituted the second, non-QOL dimension in both groups.

3.3.10 Sensory functions (Table S10)

A three-dimension solution was retrieved for the Sensory functions domain. The two groups exhibited notable differences in their correlation of sound- and hearing-related issues together with the *Sensory functions*$_{QoL}$ item. The non-ICU-treated control group correlated several such issues together with the *Sensory functions*$_{QoL}$ item, while in the ICU survivor group, only ***Reduced hearing limiting social life*** correlated together with *Question*$_{QoL}$. Conversely, the ICU survivor group loaded various issues related to voice and throat problems and reduced taste and smell in the *Question*^{QoL} dimension, issues that did not load in *Question*^{QoL} in the non-ICU-treated control group.

3.3.11 Gastrointestinal functions (Table S11)

A two-dimension solution was retrieved for the gastrointestinal domain, with similar, unsurprising findings regarding quality of life; social life limitations from bowel problems and worrying about bowel problems loaded in the *Gastrointestinal functions*^{QoL} dimension in both groups. In addition, bowel leakage was also correlated together with the *Gastrointestinal functions*$_{QoL}$ item in the ICU survivor group.

3.3.12 Urinary tract functions (Table S12)

A two-dimension solution was retrieved for the Urinary tract functions domain, with some differences in the groups' relation to *Urinary tract functions*$_{QoL}$. While both groups reported urinary urgency as an issue, only the non-ICU-treated control group correlated it together with *Urinary tract functions*$_{QoL}$. In contrast, the ICU survivor group correlated socially limiting issues together with the *Urinary tract functions*$_{QoL}$ item, such as difficulties feeling the need to urinate and urinary problems restricting social activities.

3.3.13 Work life (Table S13)

Note that this domain contains two *Question*$_{QoL}$; one *Work problems*$_{QoL}$ and one *Financial problems*$_{QoL}$. The best model fit was found with a two-dimension solution for the Work life domain. Although the two groups had mainly similar dimensionality, the relationship to *Work life*$_{QoL}$ differed. Both groups included questions about worries related to future work, work capacity, and finances in the same dimension, but only the ICU survivor group loaded these in a *Work life*^{QoL} dimension. In fact, no dimension at all correlated together with neither *Question*$_{QoL}$ in the control group. Finally, both groups included issues related to work capacities, such as self-assessed work capacity, ability to work in the future, and physical/mental work demands in the same dimension.

3.4 PAPER IV

3.4.1 Bivariable analysis

The initial bivariable analysis showed 64 items with a lower confidence level correlation of ≥ 0.50, but one item, ***Tiredness affecting work,*** was excluded based on low covariance totalling 63 items for further analysis.

3.4.2 Unidimensional model and construct validity

The CFA showed that the unidimensional fit of the model was good, with all fit measures (RMSEA, CFI, TLI, and SRMR) being above their thresholds, with only one exception (Table 3.4.2a):

Table 3.4.2a Fit measures for unidimensional model

	RMSEA	CFI	TLI	SRMR	CR	AVE
Cognition	0,072	0,963	0,952	0,038	0,95	0,57
Fatigue	0,066	0,963	0,949	0,033	0,93	0,61
Physical health	0,061	0,994	0,982	0,015	0,86	0,60
Pain	0,037	0,994	0,988	0,022	0,90	0,60
Mental health	0,087	0,960	0,941	0,027	0,94	0,68
ADL	0,000	1,000	1,000	0,005	0,84	0,57
Sleep	-	-	-	-	0,78	0,64
Appetite	0,000	1,000	1,000	0,000	0,86	0,67
Alcohol use	-	-	-	-	0,86	0,75
Sexual health	-	-	-	-	0,71	0,55
Sensory functions	-	-	-	-	0,75	0,60
Gastrointestinal functions	0,000	1,000	1,000	0,000	0,79	0,65
Urinary tract functions	-	-	-	-	0,79	0,65
Work life	0,000	1,000	1,000	0,000	0,80	0,57

The Mental health domain showed excellent to good fit in all indices apart from RMSEA. However, with a value of 0.087, the fit can still be considered good to acceptable, considering that RMSEA is more stringent than the other indices and the strength of the other indices in this domain.

All 14 domains showed a CR above 0.70, indicating good construct reliability. As a subgroup of construct validity, convergent validity was good, as indicated by AVE over 0.50. The interpretation is that the 14 domains are homogeneous and measure the same concept on a domain-per-domain basis. Finally, discriminant validity was shown in all correlation pairs with one exception (between *Cognition*^{QoL} and *Fatigue*^{QoL}) (Table 3.4.2b).

Table 3.4.2b Correlation pairs between domains

Cognition	(0.77)											
Fatigue	0,79	(0.78)										
Physical health	0,46	0,70	(0.77)									
Pain	0,39	0,58	0,69	(0.78)								
Mental health	0,61	0,67	0,60	0,57	(0.83)							
ADL	0,44	0,59	0,75	0,60	0,58	(0.77)						
Sleep	0,50	0,62	0,56	0,59	0,66	0,55	(0.81)					
Appetite	0,31	0,49	0,45	0,41	0,47	0,48	0,44	(0.82)				
Sex life	0,22	0,36	0,40	0,42	0,40	0,41	0,33	0,23	(0.77)			
Sensory functions	0,47	0,56	0,50	0,52	0,52	0,49	0,51	0,47	0,29	(0.78)		
Gastrointestinal functions	0,24	0,35	0,42	0,43	0,40	0,40	0,45	0,38	0,37	0,41	(0.79)	
Urinary tract functions	0,14	0,18	0,37	0,30	0,31	0,33	0,52	0,26	0,25	0,35	0,58	(0.81)

This indicates that our domains genuinely measure different areas of post-ICU quality of life apart from *Cognition*^{QoL} and *Fatigue*^{QoL}, where the questions seem to measure related constructs, if not the same. The link between cognition and fatigue in general, without our quality of life aspect, has been studied in various populations, mainly non-related to intensive care, with mixed results. However, in a systemic review and meta-analysis of 16 studies on acquired brain injuries, Dillon et al. found only weak associations between cognition and fatigue, apart from an association between tasks that require continuous attention and fatigue.[90] It should be noted that the diagnoses studied were precisely those we excluded from our sample.

3.4.3 Multidimensional models

The multidimensional assessment of $[Domains]^{QoL}$ showed a good model-data fit according to RMSEA and SRMR, but CFI and TLI were not satisfactory. There are various ways in which the model can be respecified to fit the data better, but a sensitivity analysis found that although CFI would reach an acceptable level, the increased complexity of the model tells us that the unidimensional model should be chosen. Equally important, the unidimensional model is the model best described by our theory.

Similarly, the second-order model did not achieve a better fit than the first-order, unidimensional fit. A bifactor model could not be fitted without removing some of the domains. Thus, the potential bifactor model would be too far from our theory.

> *So what does this all mean? In our sample, ICU survivors have no general quality of life factor, i.e., no single, over-arching quality of life-construct. Rather, the structure of quality of life is best described as separate, domain-specific subsets of quality of life.*

JOAN MIRÓ
would paint a dreamlike landscape of his native Catalonia, with whimsical shapes and bold colors that convey a sense of playfulness and freedom, to express the joy of being alive after a close brush with death.

CONCLUDING THOUGHTS

This doctoral thesis shows the path from an idea almost all the way to a usable questionnaire on quality of life and burden of disease after intensive care. The research project has blended qualitative and quantitative methodologies, starting with a mixture of clinical experience, reflections and previous research experience in a different medical speciality. Some important points need to be made:

First, there are differences between ICU survivors and those not treated in intensive care. In a plethora of studies showing an affected life on follow-up after intensive care, a minority have used a non-ICU-treated control group. Even if all issues were to be explained by pre-ICU factors, there still are differences between these two groups. **Papers I, II**, and **III** have attempted to explore and explain at least a small part of these. Through them, we have discovered differences in areas previously unknown, reduced at least some alternative explanations for them, and found that some differences between ICU survivors and non-ICU-treated controls exist even on a conceptual level regarding quality of life.

Second, we do not have any subgroup analyses. The project could have dwelled on subgroup analyses after **paper I**. However, we took a different path, simply focusing on those aspects of our findings moving the process toward a finished questionnaire. Relevant subgroups in intensive care are more difficult to define than one may initially think, but once a finished questionnaire exists, there certainly are ideas to explore. Potentially, the questionnaire could be divided into core questions with condition-specific additions.

Third, as in all studies, generalisability has to be discussed. As already noted, our findings should not be extrapolated to patients having spent a shorter time in the ICU than 72 hours. At the early stages of the project, we hypothesised that 72 hours was an arbitrary but plausible threshold to filter out "noise" in the form of, for example, patients admitted only for post-operative supervision. It has been shown since that ICU length of stay as a marker for post-ICU issues is blunt, with, for example, a low ability to predict the onset of new physical disability.[91]
Furthermore, the results are not generalisable to patients typical for a neurointensive care unit since most patients with these diagnoses were excluded.

Fourth, this is one of only a few attempts at creating a follow-up questionnaire specifically for ICU survivors, and one of even fewer to compare with a non-ICU-treated control group. We chose to create an absolute majority of questions based on the stories of ICU survivors, thus closely mimicking the philosophy of the PROM "movement". By the time the first study was planned, the use of Delphi panels was not as common as today, thus, this was never a methodology we considered. The chosen methodology has been proven valuable and relevant in multiple studies, and the initial inclusion of all questions, no matter how unusual, in addition to using saturation for sample size, should ensure that a majority of issues experienced by ICU survivors were included in the provisional questionnaire. Furthermore, since a family member accompanied multiple ICU survivors, their viewpoints as stakeholders have been at least partially included. Using a Delphi panel methodology could have added important perspectives that were seemingly non-significant for ICU survivors but valuable for healthcare providers. At the same time, the conventional methodology in Delphi panels with voting of which issues to include conflicts with our chosen methodology.

Finally, this doctoral thesis is not an attempt to create a new framework or theory about quality of life. Our findings apply to our sample of ICU survivors and are, because of reliable data, externally generalisable to somewhat similar groups. Caution must be taken before overly extrapolating the findings to groups farther from our sample's characteristics. However, the results of **PAPERS III** and **IV** illustrate the carefulness one needs to take before labelling all post-ICU issues as quality of life issues, and that the structure and content of the quality of life of our ICU survivors may differ from that of ours.

MARK ROTHKO
would paint a canvas of deep, saturated colors blending together to convey a sense of emotional transcendence, using large, sweeping brushstrokes and an interplay of light and shadow to create a contemplative atmosphere.

ETHICAL CONSIDERATIONS

THE studies in this doctoral thesis are all built upon the two data collections in **PAPER I** – the qualitative interviews and the use of the initial provisional questionnaire in a sample of ICU survivors and a non-ICU-treated control group.

The *Regional Research Ethics Committee of Gothenburg*, Sweden, approved the data collections on February 26, 2015 (Ref 017-15) and February 23, 2016 (Ref 011-16). The second part of **PAPER I** is registered on clinicaltrials.gov (Ref. NCT 02767180).

Due to the nature of the research area, both the interviews and the questionnaires required personal, sensitive information in several areas to be gathered. The following precautionary steps were taken to protect participants from recognition:

- Interview recordings were encrypted and stored on a central server at the University of Gothenburg.
- All interviewees were coded. The code key was encrypted and safely stored.
- All personal data were handled in accordance with Personuppgiftslagen (1998:204).

- The database used in the second part of **PAPER I** was password protected and located on a central server at the University of Gothenburg.

- Questionnaires did not contain the participants' names.

- Identification of individual patients in resulting publications is not possible. Data has not been made publicly accessible.

Several other precautionary measures were taken to ensure an overall high ethical standard:

- As previously reported in Methodology, we had reason to choose an interviewer with domain knowledge. I participated in the survivors' routine visits to the post-ICU clinic to build trust. Not until after the regular visit was the survivor asked about participation. The survivor was given a chance to return home and further consider participation. However, all asked survivors agreed directly. Although this could signify them not daring to decline, their enthusiasm speaks the opposite. The survivor was allowed to choose a location for the interview. All but two chose the post-ICU clinic. They were allowed to be accompanied by a family member, something about one-third of the participants took advantage of.

- We added a chapter at the very end of the questionnaire regarding the questionnaire itself. Participants were encouraged to specify questions deemed too sensitive or that negatively affected them in any way. Less than ten questions were mentioned, with only one mentioned more than once – ***Har du känt dig långsam i tanken ("trög i tanken") den senaste månaden?,*** with a wording that was perceived as derogatory. Apart from occasional comments regarding the questionnaire length, no other negative feelings were feedbacked. Finally, fewer than five participants simply did not answer any questions about sexual health, possibly because of their sensitive nature.

- Although previous experience from the group regarding similar research within oncology indicated that most patients were happy to participate, there was still a risk that re-living a period such as an ICU stay would evoke unpleasant memories. This was also a concern from the

> Ethical Committee. As per recommendations, support from our social services was available to those in need. No such help was ultimately needed.

On a more personal note, there are two questions I regret omitting from the questionnaire – suicidal thoughts and whether it was all worth it. None of these issues was brought up in the interview phase, thus should preferably not be added according to our methodology. Nonetheless, it would have been highly interesting to evaluate the responses. We could have added them, but previous experience indicated potential friction in the ethical approval process. A few studies using the EQ-5D may hint at our likely results: The structure of EQ-5D makes it possible to gain a negative value, thus indicating a so-called State worse than death (SWD). Using data from a Swedish cross-sectional survey study on pain in an elderly population (mean age 76,2 years), Bernfort et al. found that although SWD according to the EQ-5D was present in almost 2% of the over 6000 responders, this finding correlated poorly with the participants' own opinion.[92] A control question showed that nearly half of the responders in the SWD group were fairly happy or happy and at least quite satisfied with life. In a study analysing data from Singapore, Canada, Thailand, The Netherlands and China, Gandhi et al. found that although values above 0 correlated well with health state, values below 0 correlated poorly with health state, thus questioning EQ-5D's ability to measure SWD.[93]

In our quantitative phase in **PAPER I**, we decided a priori to include survivors incapable of speaking for themselves, provided they had caregivers willing to function as proxies. It may be plausible to argue that SWD or at least states with very low quality of life could exist in occasional ICU survivors with severe disabilities. However, since these survivors would need their proxy to interpret their feelings and thoughts, those two questions would have been speculative at best, rendering them useless. Regarding the plausibility mentioned above in this last group of patients, it must be noted that ICU physicians' ability to estimate the quality of life of ICU survivors,[94] and physicians' general ability to estimate the quality of life of people with disability,[95] is misaligned with reality. This was tellingly forgotten by me above.

HIERONYMUS BOSCH would paint an otherworldly landscape teeming with grotesque, demonic creatures to express his profound fascination and fear of the afterlife, using thick, dramatic brushstrokes and eerie, muted colors that suggest the murky, uncertain nature of the hereafter.

FUTURE PERSPECTIVES

From ICU, they emerge,
Survivors with stories to tell,
Their insights bring hope.

ChatGPT[96]

FOR natural reasons, this chapter contains personal, speculative, reflections and, at best, anecdotal findings. While developing a new measurement tool, one may easily turn naïve and long for quick global acceptance and usage. However, numerous steps remain.

Further validation etc.

First, no matter how advanced the reduction process has been, several steps remain in the development of the questionnaire. For example, showing test-retest reliability, cross-culture, and criterion validity is common, as is of course formal translation into relevant languages. Furthermore, it should be used alongside SF-36 and EQ-5D to facilitate comparisons between the different questionnaires. To further both strengthen the predictive validity and gain more insight, longitudinal multi-centre studies must be conducted using the questionnaire.

As a research tool

A questionnaire specific to evaluating quality of life and burden of disease after intensive care may be used as an outcome measure in clinical trials. With the multitude of domains in our questionnaire, examples of outcomes could be scores in Cognition and Mental health domains when evaluating new sedatives or sedation policies, scores in the Physical health domain when evaluating early mobilisation, or scores in the Work life domain when evaluating long-term follow-up. It must be noted that there is no reason to claim that this questionnaire would necessarily be the best instrument to assess these domains. For example, there are batteries of cognitive tests that a neuropsychologist could use that are better suited. However, our questionnaire may be a pragmatic, validated solution in a research setting, with proven high compliance among ICU survivors.

What about the burden of disease?

The results of this doctoral thesis give a certain amount of understanding regarding the structure of quality of life in our sample of ICU survivors. But what about the issues still troubling our ICU survivors, although unrelated to quality of life? A future step would be to continue to explore these and add a set of issues not affecting quality of life, but still in need of attention in the form of, for example, therapy, help with insurance companies or contact with a primary care healthcare provider. The fact that not everything is quality of life, as shown in **PAPER III**, should not let us ignore the fact that there might be several issues in which a post-ICU clinic could guide the survivor forward.

Use in primary care

I received some three or four phone calls during the course of the second part of **PAPER I**, in which survivors or their family members asked permission to use the questionnaire when visiting their primary care physician. Reflecting on these conversations, it seemed as if they hoped the questionnaire could function as a tool to overcome a communication mismatch between them and their healthcare provider. They explicitly said that the questionnaire described their problems so well that they planned to simply hand it over and say ***Here, read it, this is me***. A few phone calls out of hundreds of participants is, of course, a minuscule, non-significant proportion of the participants. However, it still adds to the notion that these survivors may have trouble communicating their problems. It seemed as if the questionnaire gave them a language. My anecdotal finding aligns with those of Zilahi et al. and Hauschildt et al., where primary care rarely received any information regarding intensive care stay apart from that given by the survivors and their family members.

After finalising the questionnaire, different ways of visualising the results must be considered. To maximise understanding, this needs to be done not just on a group level but, even more importantly, on an individual level. We need to find a way to let the questionnaire facilitate a discussion between the survivor and their healthcare provider, be it physicians, physiotherapists, nurses etc., about the everyday issues experienced by that particular survivor.

Pre-ICU status

The academic holy grail for any researcher in this niche of intensive care outcome research is to find a way to collect accurate pre-admission data – accurate in the sense of collected from the patient, before admission. Currently, solutions have been either to use proxies or to let patients recollect their pre-ICU status after admission or even after discharge. While these methods have their merits, they also have limitations. It is not that these methods are utterly inadequate, but they have their flaws. Regarding the use of proxies, most often family members, results diverge.[97 98 99] While some have shown a sufficiently good concordance, others have shown that certain domains lack agreement and are inconsistent. On the other hand, letting the patients themselves try to remember their pre-ICU status opens up for recall bias. The nature of intensive care may prevent this type of information in perpetuity, but who said one should stop searching for the grail?

A caregiver questionnaire

All intensivists are used to having demanding conversations with the family members and caregivers of ICU patients. However, during the interview phase, several aspects of having a loved one in the ICU occurred that I had previously not thought of, evoking further questions. Central in these aspects is shame. First, what happens with your future relationship when you, out of pure love and mercy, have wished for your loved one to die, if only briefly? Second, what happens with a relationship in which your loved one returns home after months in the hospital but with severe personality changes? Third, what happens if love fades away, but your partner can no longer handle even the simplest aspects of ADL? Fourth, what happens in a relationship when your loved one returns home but simply cannot remember their feelings for you, as in some of our ICU survivors? Finally, what happens after a year or two when you start to grow tired of having the same discussions over and over again, of symptoms never improving, and memories never fading?

These are all issues brought up by close family members, even with the ICU survivor being present during the interviews. They remain unanswered but evoke curiosity and indicate a need for a questionnaire on the potential burdens of being a caregiver. Not to end on such a dismal tone, it must be noted that the absolute majority of interviewees and their family members expressed a strengthening of their relationship.

EDVARD MUNCH
would paint the desolation of surviving illness in a new light, with colors as vibrant as they are haunting, to illustrate the relief of overcoming death's embrace. He would use thick, visible brushstrokes that exude emotion and texture, as well as bold and contrasting colors that heighten the sensation of the painting's subject matter.

ACKNOWLEDGEMENTS

The following are just some of those whom I wish to thank:

» My fantastic main supervisor – **Stefan Lundin** – for ideas, laughs, and an often unreasonably strong, and sometimes uncalled-for, support. Whether in Gothenburg, Brussels, London, or elsewhere, you bring energy, you bring knowledge, and you bring joy. Thank you.

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Ann-Charlotte, I would still know nothing about possessive agents without you, and my world would be a duller place. Most importantly, without you, this idea would have never been formed out of the vagueness that existed before.
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Elias. I would have been done years ago without you. You took a concept, lifted it to new levels, and forced me to read, read and read. Endless are the nights when I have gone to bed more stupid than when I woke up. For that, I owe you. A lot.

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- My wonderful children, **Anine** and **Francis**. I did this beside you while you were asleep, I did this secretly while you were eating, and I did it openly when you wanted to play. We did this together. I love you!

ELSA BESKOW
would illustrate the joy of newfound life after being ill, by depicting an enchanted garden filled with blooming flowers, playful fairies, and curious woodland creatures, all captured in a whimsical and delicate watercolor style.

REFERENCES

1 Nightingale, F.
Notes on Hospitals
Chapter 9
https://archive.org/details/notesonhospital01nighgoog/page/n6/mode/2up (2023-04-18)

2 Lassen, H.
The Epidemic of Poliomyelitis in Copenhagen, 1952
Proc R Soc Med • 1954 • 47(1) 67-71

3 Ibsen, B.
From anaesthesia to anaesthesiology. Personal experiences in Copenhagen during the past 25 years. Chapter V The polio epidemic
Acta Anaesthesiol Scand • 1975 • Suppl 61: 21-28

4 Ibsen, B.
The Anaesthetist's Viewpoint on the Treatment of Respiratory Complications in Poliomyelitis During the Epidemic in Copenhagen, 1952
Proc R Soc Med • 1954 • 47(1) 72-74

5 Berthelsen, P.G. & Cronqvist, M.
The First Intensive Care Unit in the World: Copenhagen 1953
Acta Anaesthesiol Scand • 2003 • 47(10) 1190-1195

6 The Ebart family
[Personal communication]
2023-04-14

7 Cullen, D.J. & Briggs, B.A.
Survival and Follow-Up Results of Critically Ill Intensive Care Patients
Crit Care Med • 1973 • 1(2) 114

8 Aristotle
Nicomachean Ethics
Book I Chapter 2 • ~340-330 B.C.E.
https://www.gutenberg.org/files/8438/8438-h/8438-h.htm#chap10 (2023-04-15)

9 Epicurus
Sovran Maxims
Doctrine 3 • ~300 B.C.E.
https://epicurus.net/en/principal.html (2023-04-15)

10 Augustin
Confessions
Book X • 397-398 C.E.
https://www.gutenberg.org/files/3296/3296-h/3296-h.htm#link2H_4_0010 (2023-04-15)

11 Boethius
The Consolation of Philosophy
Book III • 524 C.E.
https://www.gutenberg.org/files/14328/14328-h/14328-h.htm#Page_150 (2023-04-15)

12 John Locke
Second Treatise Of Government
Two Treatises of Government; Chapter II, Sec 6 • 1689
https://www.gutenberg.org/files/7370/7370-h/7370-h.htm#CHAPTER_II (2023-04-15)

13 Jean-Jacques Rosseau
The Social Contract
Book I, Chapter VI • 1762
https://www.gutenberg.org/files/46333/46333-h/46333-h.htm#CHAPTER_VI (2023-04-15)

14 Jeremy Bentham
An Introduction to the Principles of Morals and Legislation
Chapter I,II • 1789
https://oll.libertyfund.org/title/bentham-an-introduction-to-the-principles-of-morals-and-legislation#lf0175_label_007 (2023-04-15)

15 John-Stuart Mill
Utilitarianism
Chapter 2 "What Utilitarianism Is" • 1863https://www.gutenberg.org/files/11224/11224-h/11224-h.htm#CHAPTER_II (2023-04-15)

16 Dept. of Social Welfare, State of New York
A Study of the Medical Needs of Recipients of Old Age Assistance in New York City in 1934
Lyon Publishing • 1937 • Albany, NY

17 Kossman, C.
Nomenclature and Criteria for the Diagnosis of Cardiovascular Diseases
Circulation • 1964 • 30 321-325

18 Harvey, R.M. et al.
Philosophy of the New York Heart Association Regarding Assessment of Cardiovascular Function
Circulation • 1982 • 66(1) 249

19 Karnofsky, D.A. et al. (1948)
The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma: With Particular Reference to Bronchogenic Carcinoma
Cancer • 1948 • 1(4) 634-656

20 Katz, S.
Multidisciplinary Study of Illness in Aged Persons. I. Methods and Preliminary Results
J Chronic Dis • 1958 • 7(4) 332-345

21 Katz, S.
Multidisciplinary Studies of Illness in Aged Persons. Ii. A New Classification of Functional Status in Activities of Daily Living
J Chronic Dis • 1959 • 9(1) 55-62

22 Mahoney, F. et al.
Rehabilitation of Chronically Ill Patients: The Influence of Complications on the Final Goal
Southern Medical Journal • 1958 • 51(5) 605-609.

23 Moskowitz, E. & Mccann, C.
Classification of Disability in the Chronically Ill and Aging
J Chronic Dis • 1957 • 5(3) 342-346

24 World Health Organisation
Constitution of the World Health Organization
https://www.who.int/about/governance/constitution (2023-04-15)

25 Campbell A. et al.
The Quality of American Life: Perceptions, Evaluations, and Satisfactions
Russel Sage Foundation, New York • 1976

26 Andrews, F.M. & Withey, S.B.
Developing Measures of Perceived Life Quality: Results From Several National Surveys
Social Indicators Research • 1974 • 1(1) 1-26

27 Eisenberg, H.S. & Goldenberg, I.S.
A measurement of quality of survival of breast cancer patients.
In Clinical Evaluation in Breast Cancer. (Hayward, J.L. [ed.]& Bulbrook, R.D. [ed.] • 1966 • London:Academic Press

28 Retan, J.W. & Lewis, H.Y.
Repeated Dialysis of Indigent Patients for Chronic Renal Failure
Annals of Internal Medicine • 1966 • 64(2) 284-292

29 Priestman, T.J. & Baum, M.
Evaluation of Quality of Life in Patients Receiving Treatment for Advanced Breast Cancer
Lancet • 1976 1(7965) 899-900

30 Bergner, M. et al.
The Sickness Impact Profile: Development and Final Revision of a Health Status Measure
Medical Care • 1981 • 19(8) 787-805

31 Hunt, S.M. et al.
Measuring Health Status: A New Tool for Clinicians and Epidemiologists
J R Coll Gen Pract ◆ 1985 ◆ 35(273) 185-188

32 Patrick, D.L. et al.
Quality of Life Following Intensive Care
Journal of General Internal Medicine ◆ 1988 ◆ 3(3) 218-223

33 Ware, J.E. & Sherbourne, C.D.
The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual Framework and Item Selection
Medical Care ◆ 1992 ◆ 30(6) 473-483

34 EuroQoL Group
EuroQoL – A New Facility for the Measurement of Health-Related Quality of Life
Health Policy ◆ 1990 ◆ 16(3) 199-208

35 Myhren, H. et al.
Posttraumatic Stress, Anxiety and Depression Symptoms in Patients During the First Year Post Intensive Care Unit Discharge
Crit Care ◆ 2010 ◆ 14(1) R14

36 Pandharipande, P.P. et al.
Long-Term Cognitive Impairment After Critical Illness
New England Journal of Medicine ◆ 2013 ◆ 369(14) 1306-1316

37 Herridge, M.S. et al.
Functional Disability 5 Years After Acute Respiratory Distress Syndrome
New England Journal of Medicine ◆ 2011 ◆ 364(14) 1293-1304

38 Hodgson, C.L. et al.
Predictors of Return to Work in Survivors of Critical Illness
Journal of Critical Care ◆ 2018 ◆ 48 21-25

39 Ulvik, A. et al.
Sexual Function in ICU Survivors More Than 3 Years After Major Trauma
Intensive Care Med ◆ 2008 ◆ 34(3) 447-453

40 Koster-Brouwer, M.E. et al.
Occurrence and Risk Factors of Chronic Pain After Critical Illness
Critical Care Medicine ◆ 2020 ◆ 48(5) 680-687

41 Alexopoulou, C. et al.
Sleep Quality in Survivors of Critical Illness
Sleep Breath ◆ 2019 ◆ 23(2) 463-471

42 Needham, D.M. et al.
Improving Long-Term Outcomes After Discharge From Intensive Care Unit: Report From a Stakeholders' Conference
Crit Care Med ◆ 2012 ◆ 40(2) 502-509

43 Needham, D.M.
[Personal communication]
2020-04-22

44 Mackillop, E. & Sheard, S.
Quantifying Life: Understanding the History of Quality-Adjusted Life-Years (QALYS)
Soc Sci Med • 2018 • 211 359-366

45 Dunberger, G. et al.
Self-Reported Symptoms of Faecal Incontinence Among Long-Term Gynaecological Cancer Survivors and Population-Based Controls
European Journal of Cancer • 2010 • 46(3) 606-615

46 Bergmark, K. et al.
Vaginal Changes and Sexuality in Women With a History of Cervical Cancer
New England Journal of Medicine • 1999 • 340(18) 1383-1389

47 Mata, G.V.
Quality of Life: A Tool for Decision-Making in the ICU. Spanish Group for the Epidemiological Analysis of Critical Patients (PAEEC)
Intensive Care Med • 1994 • 20(4) 251-252

48 Capuzzo, M. et al.
Analysis of Quality of Life. Development of an Evaluation Instrument
Anaesthesia • 1997 • 63(5) 149-157

49 Chrispin, P.S. et al.
Short Form 36 in the Intensive Care Unit: Assessment of Acceptability, Reliability and Validity of the Questionnaire
Anaesthesia • 1997 • 52(1) 15-23

50 Ridley, S.A. & Wallace, P.G.
Quality of Life After Intensive Care
Anaesthesia • 1990 • 45(10) 808-813

51 Needham, D.M. et al.
Improving Long-Term Outcomes After Discharge From Intensive Care Unit: Report From a Stakeholders' Conference.
Critical Care Medicine • 2012 • 40(2) 502-509

52 Badia, X. et al.
Measuring Health and Health State Preferences Among Critically Ill Patients
Intensive Care Medicine • 1996 • 22(12) 1379-1384

53 Angus, D.C. et al.
Surviving Intensive Care: A Report From the 2002 Brussels Roundtable
Intensive Care Medicine • 2003 • 29(3) 368-377

54 Lim, W.C. et al.
Conceptualizing and Measuring Health-Related Quality of Life in Critical Care
Journal of Critical Care • 2016 • 31(1) 183-193

55 Bergmark, K. et al.
Patient-Rating of Distressful Symptoms After Treatment for Early Cervical Cancer
Acta Obstet Gynecol Scand • 2002 • 81(5) 443-450

56 EORTC quality of life group
Quality of Life Group Guidelines for Developing Questionnaire Modules
2011

57 Glaser, B. & Strauss, A.
The Discovery of Grounded Theory: Strategies for Qualitative Research
Mill Valley, CA: Sociology Press • 1967

58 Van Rijnsoever, F.J.
(I Can't Get No) Saturation: A Simulation and Guidelines for Sample Sizes in Qualitative Research
PLoS One • 2017 • 12(7) e0181689

59 Steineck, G. et al.
Symptom Documentation in Cancer Survivors as a Basis for Therapy Modifications
Acta Oncol • 2002 • 41(3) 244-252

60 Patrick, D.L. et al.
Content Validity – Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR Pro Good Research Practices Task Force Report: Part 2 – Assessing Respondent Understanding
Value Health • 2011 • 14(8) 978-988

61 Sjöberg, F. et al.
Letter to the Editor
Crit Care • 2021 • 25(1) 255

62 Feinstein, A.R.
The Pre-Therapeutic Classification of Co-Morbidity in Chronic Disease
J Chronic Dis • 1970 • 23(7) 455-468

63 Sax, F.L. & Charlson, M.E.
Medical Patients At High Risk for Catastrophic Deterioration
Critical Care Medicine • 1987 • 15(5) 510-515

64 Charlson, M.E. et al.
A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation
J Chronic Dis • 1987 • 40(5) 373-383

65 Jones, J.R.A. et al.
Socioeconomic Position and Health Outcomes Following Critical Illness: A Systematic Review
Crit Care Med • 2019 • 47(6) e512-e521

66 Darin-Mattsson, A. et al.
Different Indicators of Socioeconomic Status and Their Relative Importance as Determinants of Health in Old Age
Int J Equity Health • 2017 • 16(1) 173

67 Galobardes, B. et al.
Indicators of Socioeconomic Position (Part 1)
J Epidemiol Community Health • 2006 • 60(1) 7-12

68 Yusuf, S. et al.
Modifiable Risk Factors, Cardiovascular Disease, and Mortality in 155 722 Individuals From 21 High-Income, Middle-Income, and Low-Income Countries (Pure): A Prospective Cohort Study
The Lancet • 2020 • 395(10226)

69 Hernán, M.A. & Robins, J.M
Causal Inference: What If
Boca Raton: Chapman & Hall/CRC • 2020

70 Howard, J.S. et al.
Response Shift Theory: An Application for Health-Related Quality of Life in Rehabilitation Research and Practice
J Allied Health • 2011 • 40(1) 31-38

71 Hofhuis, J.G. et al.
Conceptual Issues Specifically Related to Health-Related Quality of Life in Critically Ill Patients
Crit Care • 2009 • 13(1) 118

72 Shannon, C.E.A
Mathematical Theory of Communication
The Bell system technical journal • 1948 • 130(10) 379-423

73 Zinbarg, R.E. et al.
Cronbach's alpha, Revelle's beta, and Mcdonald's omega: Their Relations With Each Other and Two Alternative Conceptualizations of Reliability
Psychometrika • 2005 • 70(1) 123-133

74 Enders, C.K. & Bandalos, D.L.
The Relative Performance of Full Information Maximum Likelihood Estimation for Missing Data in Structural Equation Models
Structural equation modeling • 2001 • 8(3) 430-457

75 Hennink, M. & Kaiser, B.N.
Sample Sizes for Saturation in Qualitative Research: A Systematic Review of Empirical Tests
Soc Sci Med • 2022 • 292 114523

76 Ogden, J. & Cornwell, D.
The Role of Topic, Interviewee and Question in Predicting Rich Interview Data in the Field of Health Research
Sociol Health Illn • 2010 • 32(7) 1059-1071

77 https://icuregswe.org
Search criteria "General ICU"+"At least 72 hours"+"18 years old or older".
It is not possible to retrieve median ICU length of stay after filtering on minimum length of stay

78 König, C. et al.
What Matters Most to Sepsis Survivors: A Qualitative Analysis to Identify Specific Health-Related Quality of Life Domains
Qual Life Res • 2019 • 28(3) 637-647

79 Alsadius, D. et al.
Patient-Reported Gastrointestinal Symptoms Among Long-Term Survivors After Radiation Therapy for Prostate Cancer
Radiother Oncol ◆ *2014* ◆ *112(2) 237-243*

80 Woolf, B. & Edwards, P.
Does Pre-Notification Increase Questionnaire Response Rates: A Randomised Controlled Trial Nested Within a Systematic Review
BMC Med Res Methodol ◆ *2021* ◆ *21(1) 259*

81 Beebe, T.J. et al.
Shortening a Survey and Using Alternative Forms of Prenotification: Impact on Response Rate and Quality
BMC Med Res Methodol ◆ *2010* ◆ *10 50*

82 Ettridge, K. et al.
A Randomised Online Experimental Study to Compare Responses to Brief and Extended Surveys of Health-Related Quality of Life and Psychosocial Outcomes Among Women With Breast Cancer
Qual Life Res ◆ *2021* ◆ *30(2) 407-423*

83 Erbs, G.C. et al.
Comorbidities Might Condition the Recovery of Quality of Life in Survivors of Sepsis
J Intensive Care Med ◆ *2019* ◆ *34(4) 337-343*

84 Langerud, A.K. et al.
Health-Related Quality of Life in Intensive Care Survivors: Associations With Social Support, Comorbidity, and Pain Interference
PLoS One ◆ *2018* ◆ *13(6) e0199656*

85 Griffith, D.M. et al.
Determinants of Health-Related Quality of Life After ICU: Importance of Patient Demographics, Previous Comorbidity, and Severity of Illness
Crit Care Med ◆ *2018* ◆ *46(4) 594-601*

86 Felekoğlu, E. et al.
Investigation of the Factors Affecting Quality of Life in Patients With Mild to Moderate Alzheimer's Disease in Terms of Patients and Caregivers
Medicina (Kaunas) ◆ *2021* ◆ *57(10) 1067*

87 Copeland, J.N. et al.
Accuracy of Patient and Care Partner Identification of Cognitive Impairments in Parkinson's Disease-Mild Cognitive Impairment
Mov Disord ◆ *2016* ◆ *31(5) 693-698*

88 Morel, J. et al.
Prevalence of Self-Reported Fatigue in Intensive Care Unit Survivors 6 Months-5 Years After Discharge
Sci Rep ◆ *2022* ◆ *12(1) 5631*

89 Orwelius, L. et al.
Prevalence of Sleep Disturbances and Long-Term Reduced Health-Related Quality of Life After Critical Care: A Prospective Multicenter Cohort Study
Crit Care ◆ *2008* ◆ *12(4) R97*

90 Dillon, A. et al.
Is There Evidence for a Relationship Between Cognitive Impairment and Fatigue After Acquired Brain Injury: A Systematic Review and Meta-Analysis
Disabil Rehabil • 2022 • 1-14

91 Milton, A. et al.
ICU Discharge Screening for Prediction of New-Onset Physical Disability-a Multinational Cohort Stud
Acta Anaesthesiol Scand • 2020 • 64(6) 789-797

92 Bernfort, L. et al.
People in States Worse Than Dead According to the EQ-5D UK Value Set: Would They Rather be Dead
Qual Life Res • 2018 • 27(7) 1827-1833

93 Gandhi, M. et al.
Valuation of Health States Considered to be Worse Than Death-an Analysis of Composite Time Trade-Off Data From 5 EQ-5D-5L Valuation Studies
Value Health • 2019 • 22(3) 370-376

94 Detsky, M.E. et al.
Patients' Perceptions and ICU Clinicians Predictions of Quality of Life Following Critical Illness
J Crit Care • 2018 • 48 352-356

95 Iezzoni, L.I. et al.
Physicians' Perceptions of People With Disability and Their Health Care
Health Aff (Millwood) • 2021 • 40(2) 297-306

96 ChatGPT
Prompted "Please write a haiku about the future when finally having a good way of measuring quality of life in survivors of intensive care."
https://chat.openai.com • 2023-03-17

97 Gosset, A.T. et al.
Patients' Primary Activities Prior to Critical Illness: How Well Do Clinicians Know Them and How Likely Are Patients to Return to Them
Crit Care • 2018 • 22(1) 340

98 Gluck, S. et al.
Wide Disagreement Between Alternative Assessments of Premorbid Physical Activity: Subjective Patient and Surrogate Reports and Objective Smartphone Data.
Crit Care Med • 2017 45(10) e1036-e1042

99 Dinglas, V.D. et al.
Quality of Life Before Intensive Care Using EQ-5D: Patient Versus Proxy Responses
Crit Care Med • 2013 • 41(1) 9-14

SALVADOR DALI
would paint a desolate, barren landscape, depicting a world without the vitality of life or the beauty of nature. The colors would be muted, almost colorless, as if drained of all energy, except for a single object in the foreground, an egg, which would be painted with brilliant, vivid colors, symbolizing the potential for new life, growth, and renewal.

APPENDIX

The papers in this doctoral thesis contain vast amounts of data, a natural effect considering the number of analyses performed, often on over 200 questions. Therefore, when creating this appendix, I have chosen to present the most important findings in a schematic way rather than reproducing thousands of data points. Hopefully, this helps a general discussion and sparks curiosity.

Legend for tables S1-S13

Mwu	Mann-Whitney U test in paper I
Bivar.	Bivariable analysis in paper II
Comorb.	Model with comorbidity as moderator
Edu.	Model with educational level as moderator

ICU vs. Controls	Groups in MG-EFA in paper III
1st, 2nd…	Dimensions in domain

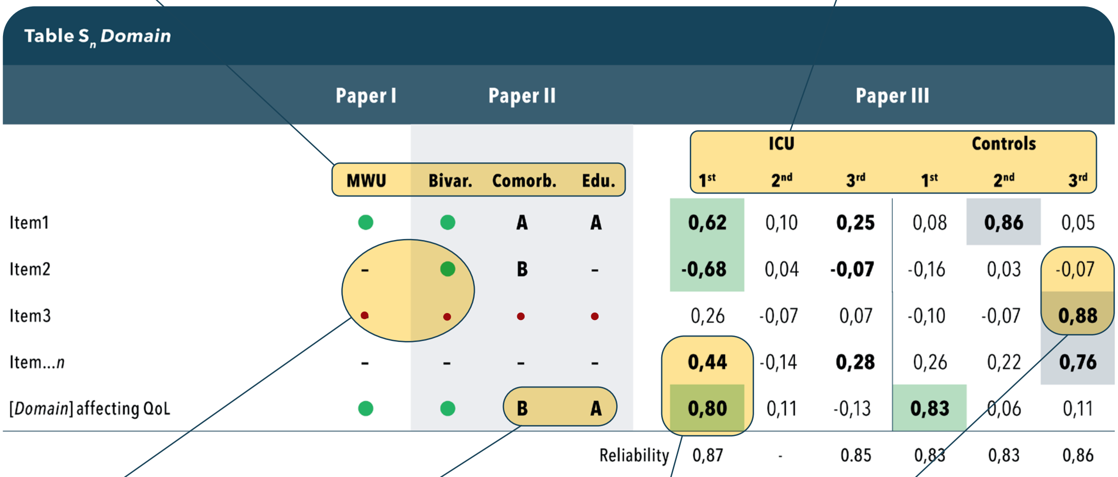


Table S_n *Domain*

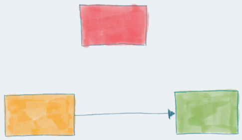
	Paper I	Paper II			Paper III					
					ICU			Controls		
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Item1	●	●	**A**	**A**	**0,62**	0,10	**0,25**	0,08	**0,86**	0,05
Item2	-	●	**B**	-	**-0,68**	0,04	**-0,07**	-0,16	0,03	-0,07
Item3	•	•	•	•	0,26	-0,07	0,07	-0,10	-0,07	**0,88**
Item…*n*	-	-	-	-	**0,44**	-0,14	**0,28**	0,26	0,22	**0,76**
[*Domain*] affecting QoL	●	●	**B**	**A**	**0,80**	0,11	-0,13	**0,83**	0,06	0,11
				Reliability	0,87	-	0.85	0,83	0,83	0,86

A-G	See opposite page

●	Significant
•	Non-significant
-	N/A. Reasons may vary (e.g., data type or assumptions)

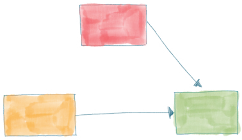
Value	Correlation coefficient ("loading"), non-significant
Value, bold	Correlation coefficient ("loading"), significant
Value, bold, in green	At or above threshold | QOL-dimension
Value, bold, in blue	At or above threshold | Non-QOL dimension

Guide for model in paper II | Tables S1-S13



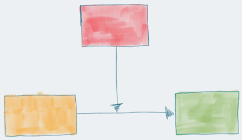
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



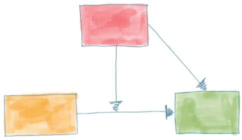
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



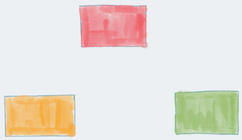
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



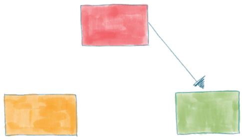
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



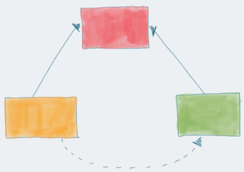
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

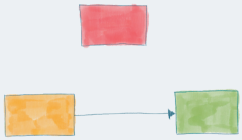
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QoL-dimension
⬜ Non-QoL dimension

Table S1 Cognition. Summarised results from paper I, II, and III.

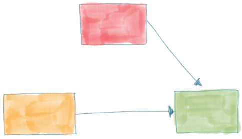
	Paper I	Paper II			Paper III					
					ICU			Controls		
	MWU	Bivar.	Comorb.	Edu.	1st	2nd	3rd	1st	2nd	3rd
Difficulties finding words	•	•	•	•	**0.79**	0.01	0.00	**0.44**	0.25	0.08
Difficulties finishing sentences	●	●	**E**	**A**	**0.87**	0.01	0.02	**0.65**	0.14	-0.01
Losing the thread easily	●	●	**A**	**A**	**0.70**	0.16	0.06	**0.75**	0.03	-0.01
Don't remember what you have said	●	●	**E**	**A**	0.10	**0.68**	0.04	**0.78**	0.00	-0.07
Don't remember what you have done	●	●	**E**	**A**	-0.13	**0.88**	0.02	**0.83**	-0.05	-0.22
Think you have done something but you haven't	●	●	**E**	**A**	0.17	**0.69**	-0.03	**0.64**	0.11	-0.15
Forgotten what you were going to get	•	●	**E**	**A**	0.10	**0.32**	**0.36**	0.21	**0.45**	-0.04
Need to be reminded to do an activity	●	●	**A**	**A**	0.03	**0.52**	**0.33**	0.25	**0.38**	0.12
Difficulties thinking clearly	●	●	**A**	**A**	**0.41**	-0.02	**0.51**	**0.46**	**0.34**	0.11
Need for memos	•	•	•	•	0.10	0.16	**0.40**	0.03	**0.67**	-0.18
Difficulties remembering names	•	•	•	•	**0.34**	0.08	**0.28**	**-0.27**	**0.84**	0.01
Difficulties remembering general knowledge	•	•	•	•	0.18	0.22	**0.43**	0.17	**0.64**	-0.08
Difficulties remembering what you have read	•	•	•	•	0.24	0.02	**0.59**	0.05	**0.80**	-0.02
Difficulties remembering previous TV-episode	•	●	**E**	**A**	0.03	**0.45**	**0.36**	0.04	**0.48**	**0.31**
Difficulties learning new things	•	•	**G**	**G**	0.18	0.11	**0.58**	-0.03	**0.60**	**0.45**
Difficulties remembering numbers	•	•	•	•	0.03	0.20	**0.53**	-0.12	**0.80**	0.01
Difficulties being on time	•	•	**G**	•	0.08	**0.30**	**0.35**	**0.66**	-0.02	0.02
Missed a scheduled meeting	•	●	**E**	**A**	0.02	**0.39**	0.23	0.09	0.17	-0.23
Mistaken which day of the week	●	●	**A**	**A**	-0.04	**0.41**	**0.37**	**0.60**	0.02	0.22
Forgotten where you have put something	•	•	•	•	-0.02	**0.39**	**0.40**	-0.02	**0.70**	-0.10
Need to double-check things	•	•	•	•	-0.02	0.13	**0.48**	0.04	**0.51**	0.02
Difficulties finding your way around	•	•	•	•	-0.01	0.22	**0.38**	0.16	**0.33**	**0.26**
Someone said that you have memory problems	●	●	**A**	**A**	-0.13	**0.52**	**0.39**	**0.43**	0.19	-0.03
Worrying about having memory problems	•	●	**A**	**A**	0.19	**0.29**	**0.39**	**0.50**	0.00	**0.56**
Difficulties taking initiatives	●	●	**A**	**A**	0.01	**-0.34**	**0.91**	**0.34**	0.13	**0.46**
Difficulties prioritising	•	•	**G**	•	-0.05	**-0.30**	**0.86**	**0.29**	**0.40**	0.19
Difficulties concentrating	●	●	**A**	**A**	**0.24**	-0.21	**0.79**	**0.31**	**0.44**	0.17
Difficulties finding alternative solutions	●	●	**A**	**A**	-0.08	0.03	**0.75**	**0.53**	0.13	**0.30**
Time spent reading	•	•	•	**C**	0.12	0.00	-0.22	-0.09	-0.06	0.02
[*Domain*] affecting QoL	●	●	**C**	**A**	**0.37**	0.04	**0.49**	**0.39**	0.21	**0.43**
Future [*domain*] worries	●	●	**C**	**A**	**0.29**	-0.01	**0.49**	**0.48**	-0.02	**0.67**
Reliability					0.88	0.88	0.89	0.85	0.87	-

Guide for model in paper II | Tables S1-S13



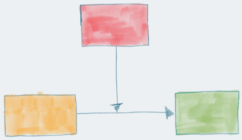
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



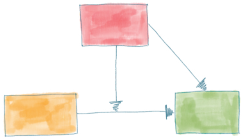
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

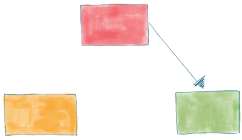


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

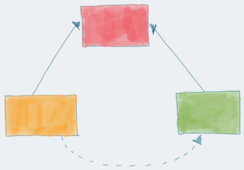
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

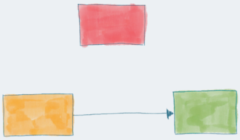
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QOL-dimension
⬜ Non-QOL dimension

Table S2 Fatigue. Summarised results from paper I, II, and III.

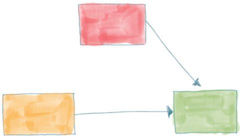
	Paper I	Paper II			Paper III			
					ICU		Controls	
	MWU	Bivar.	Comorb.	Edu.	1st	2nd	1st	2nd
Need for daytime rest	●	●	C	A	0,23	**0,53**	**0,65**	0,08
Tough getting started doing things	●	●	A	A	**0,30**	**0,51**	**0,68**	-0,08
Difficulties finishing things due to feeling exhausted	●	●	A	A	**0,32**	**0,54**	**0,85**	-0,01
Difficulties doing things under pressure	●	●	A	A	**0,56**	**0,34**	**0,82**	0,08
Difficulties multitasking due to feeling exhausted	●	●	A	A	**0,48**	**0,34**	**0,91**	0,08
Tired from reading	●	●	A	A	**0,86**	-0,02	**0,81**	0,12
Tired from watching TV	●	●	A	A	**0,79**	0,00	**0,80**	0,00
Tired from conversation between more than two people	●	●	A	A	**0,56**	**0,26**	**0,85**	-0,03
Fallen asleep when reading	•	•	•	•	**0,38**	0,07	**0,45**	**0,35**
Fallen asleep during a conversation	•	•	•	•	**0,28**	-0,01	**0,52**	0,18
Tiredness affecting work	●	●	A	C	-0,03	**0,90**	**0,88**	0,14
Tiredness limiting social activities	●	●	A	A	-0,01	**0,86**	**0,78**	-0,20
[*Domain*] affecting QoL	●	●	A	A	0,04	**0,88**	**0,92**	**-0,37**
Future [*domain*] worries	●	●	A	A	**0,30**	**0,56**	**0,80**	-0,19
				Reliability	0.83	0,92	0,96	-

Guide for model in paper II | Tables S1-S13



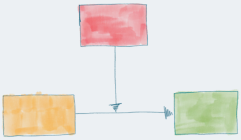
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



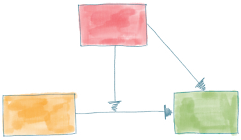
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



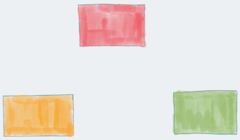
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



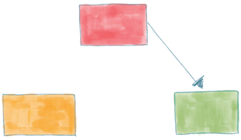
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



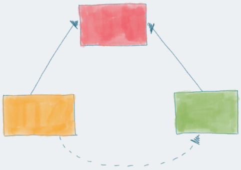
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

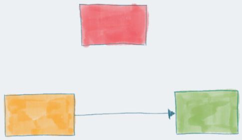
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

●	Significant
•	Non-significant
-	N/A
🟩	QoL-dimension
⬜	Non-QoL dimension

Table S3 Physical health. Summarised results from paper I, II, and III.

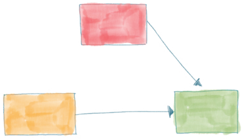
	Paper I	**Paper II**			**Paper III**							
					ICU				**Controls**			
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**4th**	**1st**	**2nd**	**3rd**	**4th**
Physical health in general	●	●	**A**	**D**	0,01	0,00	**0,79**	0,00	0,06	0,02	**0,74**	-0,10
Reduced feeling in face	●	●	**A**	**A**	0,29	0,12	0,05	**0,34**	**0,41**	**0,27**	-0,04	0,23
Arm weakness	●	●	**A**	**D**	**0,52**	-0,10	**0,42**	0,16	**0,36**	**0,26**	0,23	0,03
Reduced feeling in arms	●	●	**A**	**A**	**0,67**	0,03	0,03	**0,33**	**0,93**	0,03	-0,12	-0,03
Reduced feeling in hands/fingers	●	●	**A**	**A**	**0,69**	0,11	-0,03	**0,26**	**0,69**	0,20	-0,06	0,01
Raynaud's in fingers	●	●	**A**	**A**	**0,44**	0,21	0,06	**0,32**	**0,36**	0,23	0,08	-0,09
Difficulties extending your wrist	-	●	**A**	**A**	**0,57**	0,00	-0,02	0,20	0,17	0,13	-0,16	0,21
Difficulties lifting lightweight objects	●	●	**B**	**A**	**0,88**	0,03	-0,04	-0,02	0,08	**0,86**	0,03	-0,03
Difficulties turning on taps/opening jars	●	●	**A**	**A**	**0,86**	-0,07	0,04	-0,06	-0,08	**0,90**	0,02	0,03
Difficulties using hands	●	●	**A**	**C**	**0,80**	0,05	0,02	-0,08	**0,25**	**0,27**	0,02	0,19
Leg weakness	●	●	**A**	**D**	0,12	**0,49**	**0,33**	-0,05	0,05	0,19	**0,46**	**0,29**
Reduced feeling in legs	●	●	**A**	**A**	0,13	**0,83**	-0,14	0,08	**0,76**	-0,16	0,09	0,06
Reduced feeling in feet/toes	●	●	**A**	**A**	-0,07	**0,90**	-0,08	0,08	**0,67**	-0,23	0,06	0,03
Restless legs	●	●	**B**	**A**	0,01	**0,33**	**0,23**	**0,27**	**0,31**	0,05	**0,26**	-0,08
Dizziness when standing up	●	●	**B**	**A**	0,13	0,12	**0,33**	0,07	0,13	0,17	0,15	0,23
Losing balance easily	●	●	**B**	**D**	**0,30**	**0,34**	**0,24**	-0,15	0,13	0,02	0,12	**0,65**
Difficulties climbing stairs	●	●	**B**	**D**	0,04	**0,43**	**0,40**	**-0,27**	-0,13	0,02	**0,48**	**0,61**
Unsteady gait	●	●	**B**	**D**	**0,26**	**0,63**	0,04	-0,23	0,13	-0,01	0,03	**0,78**
Legs feeling heavy	●	●	**B**	**D**	-0,02	**0,63**	0,17	-0,06	0,10	0,02	0,14	**0,57**
Swollen legs/ankles	●	●	**B**	**A**	-0,11	**0,46**	0,13	0,04	0,12	-0,08	**0,26**	0,10
Raynaud's in toes	●	●	**B**	**A**	-0,12	**0,73**	0,11	0,13	**0,31**	-0,07	0,22	-0,03
Foot drop	-	●	**B**	**A**	0,09	**0,67**	-0,20	-0,03	0,04	0,00	-0,18	**0,72**
Contractures	●	●	**B**	**B**	0,16	**0,40**	0,23	-0,04	-0,01	0,21	**0,36**	**0,30**
Periods of heavy sweating	●	●	**F**	**C**	0,14	0,01	**0,32**	**0,38**	0,02	0,08	0,23	0,18
Able to walk six minutes	-	●	**B**	**A**	0,09	0,18	**0,24**	**-0,44**	-0,18	-0,12	-0,04	**0,70**
Walking longer than 1 km	-	●	**B**	**B**	-0,05	0,18	**0,36**	**-0,43**	-0,04	-0,10	0,21	**0,36**
Shortness of breath limiting physical activities	●	●	**B**	**D**	-0,01	-0,02	**0,75**	-0,17	-0,03	-0,04	**0,57**	0,14
Physically active >30 min	●	●	**B**	**D**	-0,02	0,01	**-0,50**	**0,29**	0,01	0,08	**-0,42**	-0,01
[*Domain*] affecting QoL	●	●	**B**	**B**	0,00	0,13	**0,76**	0,03	-0,01	0,01	**0,86**	0,01
Future [*domain*] worries	●	●	**B**	**A**	0,03	0,09	**0,72**	0,08	**0,16**	-0,01	**0,80**	0,02
				Reliability	0,89	0,87	0,85	-	0,82	0.85	0,88	0,80

Guide for model in paper II | Tables S1-S13



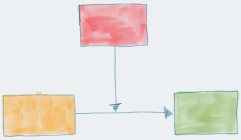
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



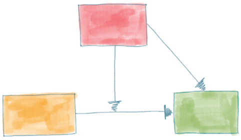
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

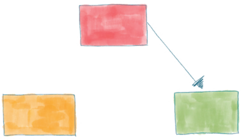


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

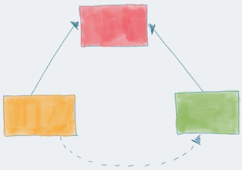
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

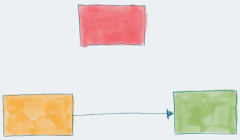
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

🟢 Significant
🔴 Non-significant
- N/A
🟩 QOL-dimension
⬜ Non-QOL dimension

Table S4 Pain. Summarised results from paper I, II, and III.

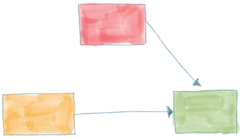
	Paper I	**Paper II**			**Paper III**							
					ICU				**Controls**			
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**4th**	**1st**	**2nd**	**3rd**	**4th**
Headaches	•	•	•	•	**0,26**	**0,29**	0,02	-0,14	0,18	**0,26**	**0,24**	-0,10
Finding normal touch bothersome	●	●	**A**	**A**	**0,27**	**0,28**	0,07	0,15	-0,03	0,14	**0,38**	-0,19
General body pain	●	●	**B**	**A**	**0,34**	**0,48**	0,03	-0,05	0,19	**0,52**	0,19	0,07
Shoulder pain	●	●	**A**	**A**	**0,86**	0,00	-0,03	-0,21	**0,49**	-0,07	**0,58**	0,01
Arm pain	•	●	**E**	**A**	**0,81**	-0,03	0,08	0,09	**0,57**	0,07	**0,43**	0,05
Hand pain	●	●	**A**	**B**	**0,37**	0,23	0,08	**0,28**	**0,47**	**0,36**	-0,04	-0,03
Back pain	●	●	**F**	**A**	0,14	**0,55**	0,00	-0,14	0,06	**0,31**	0,02	**0,33**
Chest pain	●	●	**B**	**A**	**0,43**	0,26	-0,05	-0,01	0,00	**0,34**	0,02	-0,08
Abdominal pain	●	●	**A**	**A**	0,10	**0,34**	0,04	-0,07	-0,07	0,18	**0,30**	-0,03
Leg pain	●	●	**B**	**B**	0,06	**0,64**	-0,01	**0,39**	-0,16	**0,68**	0,02	0,02
Foot pain	●	●	**A**	**A**	-0,05	**0,61**	-0,02	**0,41**	-0,23	**0,35**	0,17	0,00
Uses of painkillers	-	●	**F**	**C**	0,10	0,07	**0,46**	**-0,32**	-0,05	**0,31**	0,08	0,22
Pain stopping planned activity	●	●	**B**	**A**	0,05	**0,66**	0,12	0,00	-0,06	0,11	0,14	**0,68**
Painkillers to manage ADL	●	●	**B**	**A**	-0,04	0,08	**0,79**	-0,21	0,02	**0,41**	0,22	0,27
Painkillers for sufficient sleep	●	●	**B**	**A**	-0,01	**-0,36**	**0,91**	-0,01	-0,08	0,05	**0,79**	-0,01
Pain makes going to sleep difficult	●	●	**B**	**A**	0,08	0,03	**0,75**	0,18	0,10	0,08	**0,67**	0,09
Woken by pain	●	●	**B**	**A**	0,15	0,24	**0,46**	0,10	-0,01	-0,08	**0,52**	**0,47**
[*Domain*] affecting QoL	●	●	**B**	**A**	-0,04	**0,78**	0,15	-0,03	0,08	**0,34**	-0,01	**0,69**
Future [*domain*] worries	●	●	**B**	**A**	-0,05	**0,76**	0,11	0,03	0,00	**0,67**	-0,02	**0,29**
				Reliability	0,81	0,85	0,87	-	-	0.77	0.75	0.72

Guide for model in paper II | Tables S1-S13



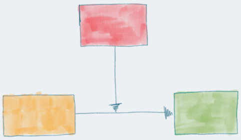
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



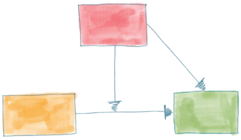
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



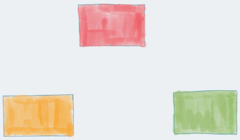
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



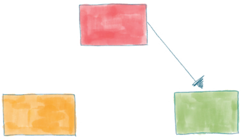
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



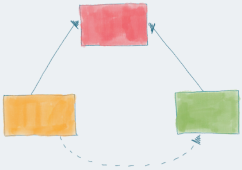
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

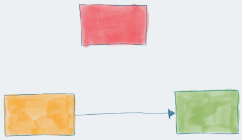
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

●	Significant
●	Non-significant
-	N/A
🟩	QOL-dimension
⬜	Non-QOL dimension

Table S5 Mental health. Summarised results from paper I, II, and III.

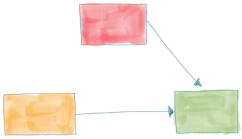
	Paper I	**Paper II**			**Paper III**					
						ICU			**Controls**	
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Crying easily	●	●	**A**	**A**	**0,27**	**0,25**	0,18	**0,48**	0,06	0,03
Feeling short-tempered	●	●	**A**	**A**	**0,92**	-0,01	0,06	**0,98**	0,00	**0,32**
Loosing patience easily	●	●	**A**	**A**	**0,88**	0,04	0,03	**0,95**	-0,01	**0,26**
Difficulties feeling warmth towards family members	•	●	**E**	**A**	**0,41**	**0,29**	-0,05	**0,43**	0,19	-0,11
Difficulties unwinding	●	●	**E**	**A**	**0,23**	**0,51**	-0,03	**0,50**	**0,36**	0,01
Worrying about little things	●	●	**A**	**B**	**0,26**	**0,59**	-0,02	**0,67**	0,18	0,05
Feeling low-spirited	●	●	**A**	**A**	**0,15**	**0,77**	-0,06	**0,57**	0,39	-0,01
Feeling depressed	●	●	**B**	**A**	0,00	**0,89**	-0,07	**0,52**	**0,40**	-0,01
Periods of anxiety	●	●	**A**	**A**	-0,01	**0,86**	**0,15**	**0,18**	**0,67**	0,00
Panic attacs	●	●	**A**	**A**	0,03	**0,57**	**0,26**	-0,19	**0,70**	0,02
Feelings of hopelessness	●	●	**A**	**C**	0,04	**0,80**	0,02	-0,01	**0,83**	-0,04
Feelings of life being meaningless	●	●	**B**	**A**	0,08	**0,76**	-0,01	0,17	**0,71**	0,05
Cannot stop worrying about being ill	●	●	**F**	**A**	0,01	**0,60**	0,03	**0,29**	0,25	-0,08
Low self-confidence	●	●	**A**	**A**	-0,06	**0,80**	-0,01	**0,33**	**0,45**	-0,02
Low self-esteem	●	●	**A**	**A**	-0,04	**0,83**	0,05	**0,48**	0,39	-0,01
Able to laugh at things	•	•	•	•	0,00	**-0,50**	**0,61**	0,00	0,20	**0,87**
Able to look forward to things	●	●	**F**	**B**	0,00	**-0,57**	**0,65**	**-0,19**	0,00	**0,72**
Difficulties talking about your illness to family/close friends	•	•	•	•	0,03	**0,49**	0,06	**0,17**	0,11	**-0,29**
Feeling that others think you talk too much about your illness	●	●	**A**	**A**	**0,28**	**0,25**	0,18	**0,32**	0,01	0,05
Counselling (pre-ICU vs "previously")	-	•	•	•	-0,12	**0,39**	0,08	**0,32**	0,05	-0,03
[*Domain*] affecting QoL	●	●	**A**	**A**	0,07	**0,72**	0,04	**0,55**	0,18	-0,11
Future [*domain*] worries	●	●	**A**	**C**	-0,05	**0,84**	0,09	**0,35**	0,34	-0,13
				Reliability	0.91	0,94	0.83	0,85	0,85	0.79

Guide for model in paper II | Tables S1-S13



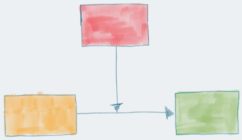
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



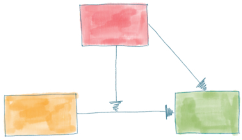
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

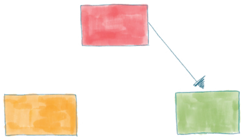


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

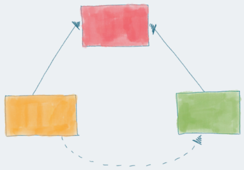
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

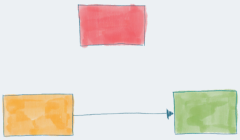
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
● Non-significant
- N/A
🟩 QOL-dimension
▨ Non-QOL dimension

Table S6 ADL. Summarised results from paper I, II, and III.

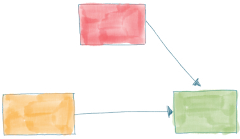
	Paper I	**Paper II**			**Paper III**			
					ICU		**Controls**	
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**1st**	**2nd**
Home care	-	●	**B**	**A**	**0,55**	0,22	0,14	**0,96**
Personal assistant	-	•	•	•	**0,46**	**0,28**	**0,97**	0,16
Help showering	-	●	**B**	**D**	**0,79**	**0,41**	**0,83**	**0,52**
Help getting dressed	●	●	**A**	**B**	**0,90**	**0,28**	**0,88**	**0,66**
Help moving between chair and bed	●	●	**A**	**A**	**0,89**	**0,32**	**0,99**	**0,29**
Support sitting up	●	●	**A**	**D**	0,10	**0,49**	**0,99**	**0,33**
Help visiting the toilet	●	●	**A**	**A**	**0,88**	0,15	**0,97**	0,16
Help with shopping	●	●	**A**	**D**	**0,51**	**0,65**	**0,60**	**0,92**
Help with cooking	●	●	**B**	**D**	**0,54**	**0,62**	**0,63**	**0,89**
Help with housework	●	●	**B**	**D**	**0,52**	**0,65**	**0,64**	**0,83**
Help with medication	●	●	**B**	**D**	**0,41**	**0,44**	0,12	**0,85**
Avoided travelling in a car	●	●	**E**	**A**	0,09	**0,25**	0,10	**0,26**
Avoided taking public transport	●	●	**A**	**A**	0,10	**0,60**	**0,83**	**0,33**
Help managing bills	●	●	**A**	**D**	**0,41**	**0,49**	0,10	**0,95**
[*Domain*] affecting QoL	●	●	**D**	**B**	**0,33**	**0,88**	**0,53**	**0,55**
Future [*domain*] worries	●	●	**B**	**B**	0,18	**0,85**	**0,43**	**0,79**
				Reliability	0,92	0,85	0,95	0,93

Guide for model in paper II | Tables S1-S13



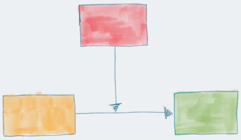
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



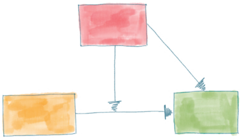
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



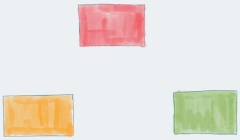
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



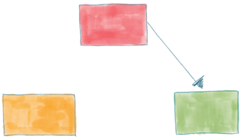
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



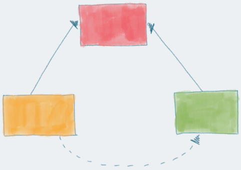
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

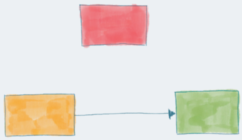
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

●	Significant
•	Non-significant
-	N/A
🟩	QoL-dimension
▨	Non-QoL dimension

Table S7 Sleep. Summarised results from paper I, II, and III.

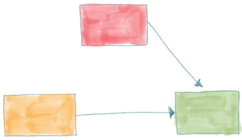
	Paper I	**Paper II**			**Paper III**					
						ICU			**Controls**	
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Need for daytime nap	●	●	**B**	**A**	0,05	0,09	0,22	**0,92**	0,00	-0,40
Difficulties going to sleep	●	●	**A**	**A**	0,16	0,00	**0,58**	-0,02	**0,31**	**0,43**
Need for sleeping pills	●	●	**B**	**B**	-0,15	0,27	0,25	0,00	-0,31	**0,72**
Anxiety before going to sleep	●	●	**A**	**C**	0,12	**0,60**	0,12	-0,06	0,07	**0,53**
Difficulties going back to sleep	•	•	•	•	**0,36**	-0,02	**0,44**	-0,01	**0,77**	0,01
Night-time worrying	•	•	•	•	0,20	0,04	0,00	0,16	**0,71**	0,00
Nightmares	●	●	**A**	**A**	0,00	**0,92**	-0,18	**0,37**	0,18	0,04
Nightly sweats disturbing sleep	•	•	•	•	0,04	**0,37**	0,12	**0,46**	0,19	0,00
Heart palpitations disturbing sleep	•	●	**E**	**A**	-0,02	**0,59**	0,00	**0,44**	-0,24	0,23
[*Domain*] affecting QoL	●	●	**A**	**A**	0,04	0,03	**0,77**	0,07	**0,39**	**0,47**
Future [*domain*] worries	●	●	**F**	**A**	-0,02	0,14	**0,71**	**0,30**	0,01	**0,66**
				Reliability	-	0.73	0.81	-	0.75	0.63

Guide for model in paper II | Tables S1-S13



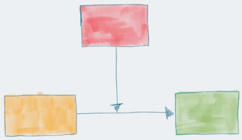
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



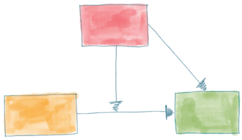
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

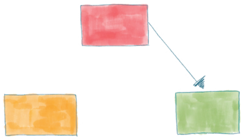


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

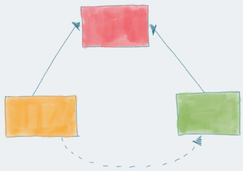
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

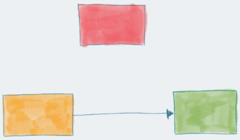
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
● Non-significant
\- N/A
🟩 QoL-dimension
⬜ Non-QoL dimension

Table S8 Appetite & Alcohol use. Summarised results from paper I, II, and III.

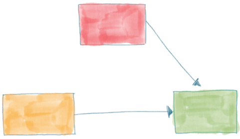
	Paper I	Paper II			Paper III					
					ICU			Controls		
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Bothersome thirst	●	●	**B**	**B**	**0,29**	-0,11	0,10	**0,57**	-0,03	0,03
Difficulties chewing	●	●	**B**	**B**	**0,55**	-0,01	0,05	**0,24**	**0,27**	0,14
Sugar cravings	•	•	•	•	0,10	**-0,27**	**0,34**	0,03	**0,24**	-0,07
Poor appetite	●	●	**B**	**A**	**0,80**	0,09	-0,02	**0,97**	0,01	-0,03
Alcohol, how often	●	●	**B**	**B**	-0,02	**0,66**	-0,13	-0,20	-0,03	**0,25**
Alcohol, glasses on a typical day	•	•	•	•	0,02	**0,76**	0,10	-0,14	0,02	**0,34**
Alcohol, how often 6 or more glasses	•	•	•	•	**0,15**	**0,81**	0,01	-0,03	0,00	**0,28**
Appetite affecting QoL	●	●	**A**	**A**	**0,89**	-0,02	0,06	**0,29**	**0,77**	0,01
Worrying about appetite	●	●	**A**	**A**	**0,78**	0,02	-0,04	-0,01	**1,00**	-0,06
Alcohol affecting QoL	•	•	•	•	0,00	0,01	**0,94**	0,01	**0,41**	**0,71**
Worrying about alcohol	•	•	•	•	-0,01	0,16	**0,71**	-0,01	-0,01	**0,90**
				Reliability	0,86	0,79	0.84	–	0.94	0.85

Guide for model in paper II | Tables S1-S13



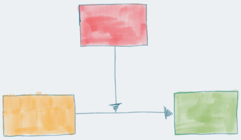
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



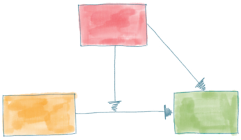
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



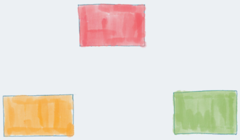
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



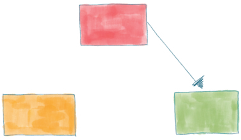
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



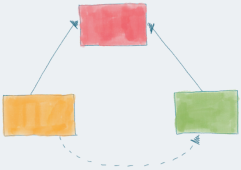
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

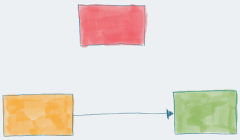
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

●	Significant
•	Non-significant
-	N/A
🟩	QoL-dimension
▨	Non-QoL dimension

Table S9 **Sexual health.** Summarised results from paper I, II, and III.

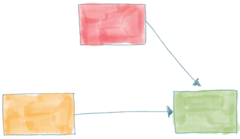
	Paper I	**Paper II**			**Paper III**			
					ICU		**Controls**	
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**1st**	**2nd**
Difficulties handling physical closeness from loved ones	●	●	**A**	**A**	-0,10	**0,24**	**-0,17**	**0,23**
Sex drive	●	●	**B**	**B**	**0,74**	**0,20**	**0,70**	0,07
Sexual activity	●	●	**B**	**B**	**0,89**	0,09	**0,91**	0,05
Sex life	●	●	**B**	**B**	**0,69**	**0,29**	**0,74**	**0,17**
Orgasm	●	●	**B**	**B**	**0,87**	0,00	**0,88**	0,00
Bothered by being naked in front of partner	•	•	**G**	**G**	0,05	**0,45**	-0,03	**0,36**
Surgical scars affecting sex life	●	●	**B**	**A**	0,09	**0,60**	-0,03	**0,31**
Lack of energy affecting sex life	●	●	**E**	**C**	**-0,15**	**0,36**	0,04	**0,50**
Pain during sex	●	•	**G**	**G**	-0,02	**0,30**	**-0,17**	0,11
[*Domain*] affecting QoL	●	●	**C**	**A**	**-0,17**	**0,73**	-0,04	**0,87**
Future [*domain*] worries	•	•	•	**G**	0,00	**0,63**	0,12	**0,78**
Vaginal dryness	-	•	•	•	-	-	-	-
Erectile dysfunction	-	•	•	•	-	-	-	-
				Reliability	0,90	0,78	0,90	0.75

Guide for model in paper II | Tables S1-S13



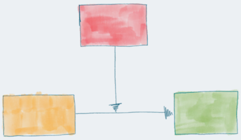
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



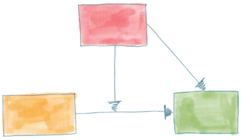
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



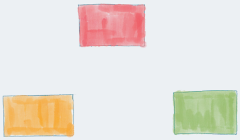
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



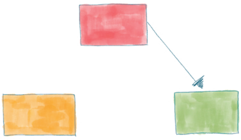
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



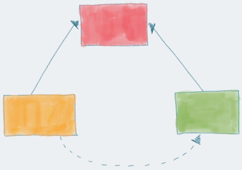
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

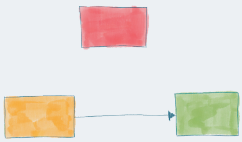
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QOL-dimension
▨ Non-QOL dimension

Table S10 Sensory functions. Summarised results from paper I, II, and III.

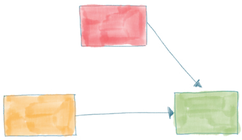
	Paper I	Paper II			Paper III					
					ICU			Controls		
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**3rd**	**1st**	**2nd**	**3rd**
Reduced taste	●	●	**A**	**A**	**0,62**	0,10	0,25	0,08	**0,86**	0,05
Reduced smell	•	•	•	•	**0,62**	-0,08	0,19	0,00	**0,75**	0,07
Reduced eyesight/vision	-	•	•	•	**-0,38**	0,04	-0,07	-0,16	-0,03	-0,07
Visual field	-	•	•	•	0,26	-0,07	0,07	-0,10	-0,07	-0,08
Colour vision	-	•	•	•	**0,42**	-0,22	**0,30**	0,04	0,03	0,01
Sensitive to bright light	-	•	•	•	**0,44**	-0,14	**0,28**	0,26	0,22	-0,16
Blurred vision	-	•	**G**	•	**0,29**	-0,02	-0,12	0,16	0,08	-0,02
Reduced hearing	-	●	**A**	**A**	**-0,38**	**0,78**	0,15	-0,21	-0,04	-0,05
Sound hypersensitivity	-	•	•	•	**0,34**	**-0,35**	**0,33**	0,14	-0,16	0,08
Poor hearing	-	●	**B**	**A**	**0,28**	**-0,66**	**-0,40**	**0,30**	0,07	-0,10
Sound hypersensitivity	•	•	•	•	**0,57**	**-0,37**	**0,37**	**0,72**	0,01	0,13
Difficulties hearing what people say	•	•	**G**	•	**0,55**	**-0,61**	**-0,35**	**0,71**	**0,27**	0,18
Reduced hearing limiting social life	•	•	•	•	**0,60**	**-0,36**	**-0,39**	**0,62**	0,22	0,07
Sound hypersensitivity limiting social life	●	•	•	•	**0,54**	-0,21	0,24	**0,74**	0,22	0,04
Tinnitus	●	●	**A**	**A**	0,21	**-0,28**	0,03	**0,79**	0,04	0,12
Mouth dryness	●	●	**B**	**B**	**0,52**	0,19	**0,28**	0,25	**0,58**	0,21
Mouth soreness	●	●	**B**	**B**	**0,61**	**0,28**	0,25	0,22	**0,39**	**0,28**
Hoarseness	●	●	**B**	**A**	**0,63**	0,13	0,23	0,08	**0,82**	0,15
Cracking voice	●	●	**B**	**A**	**0,68**	0,24	0,22	0,16	**0,77**	-0,05
Throat pain	●	●	**B**	**A**	**0,57**	0,26	-0,25	**0,34**	**0,30**	**0,48**
Throat feeling constricted	●	●	**B**	**B**	**0,61**	**0,30**	**-0,41**	0,19	0,10	**0,85**
Choking easily	●	●	**B**	**B**	**0,57**	**0,37**	**-0,44**	-0,01	0,04	**0,82**
Difficulties swallowing	●	●	**B**	**D**	**0,66**	**0,34**	-0,33	0,15	0,02	**0,84**
Throat problems limiting social life	●	●	**F**	**A**	**0,62**	**0,39**	-0,18	**0,35**	0,16	**0,74**
[*Domain*] affecting QoL	●	●	**B**	**A**	**0,80**	0,11	-0,13	**0,83**	0,06	0,11
Future [*domain*] worries	●	●	**F**	**A**	**0,63**	0,16	0,14	**0,77**	0,03	0,20
				Reliability	0,81	0,83	-	0,86	0,83	0,76

Guide for model in paper II | Tables S1-S13



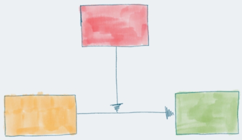
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



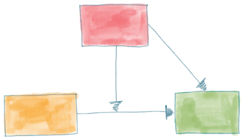
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

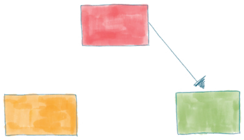


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

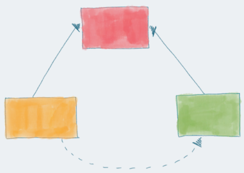
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

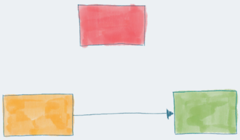
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QOL-dimension
⬜ Non-QOL dimension

Table S11 GI functions. Summarised results from paper I, II, and III.

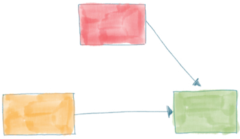
	Paper I	**Paper II**			**Paper III**			
					ICU		**Controls**	
	MWU	**Bivar.**	**Comorb.**	**Edu.**	**1st**	**2nd**	**1st**	**2nd**
Stoma	●	-	-	-	-	-	-	-
Constipation	•	●	**F**	**D**	**0,36**	**0,83**	-0,04	**0,44**
Diarrhoea	●	●	**A**	**C**	**0,44**	**-0,67**	**0,53**	0,12
Bowel urgency	●	●	**F**	**A**	**0,59**	**-0,50**	**0,81**	-0,01
Bowel leakage	●	●	**A**	**B**	**0,70**	-0,09	**0,58**	0,10
Bowel problems limiting social life	●	●	**A**	**A**	**0,76**	0,06	-0,01	**0,60**
[*Domain*] affecting QoL	●	●	**A**	**A**	**0,87**	0,11	0,23	**0,60**
Future [*domain*] worries	●	●	**B**	**A**	**0,84**	0,11	0,00	**0,96**
				Reliability	0,86	0.80	-	0,87

Guide for model in paper II | Tables S1-S13



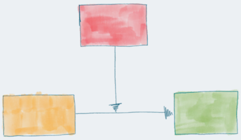
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



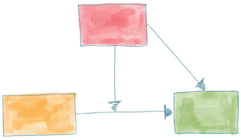
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



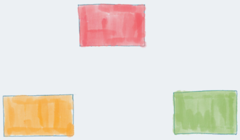
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



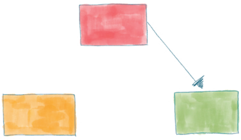
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



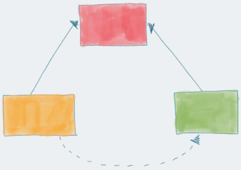
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

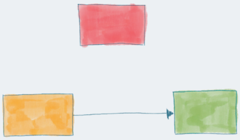
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QoL-dimension
⬜ Non-QoL dimension

Table S12 UT functions. Summarised results from paper I, II, and III.

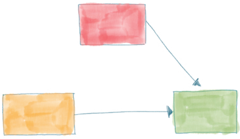
	Paper I	Paper II			Paper III			
					ICU		Controls	
	MWU	Bivar.	Comorb.	Edu.	1st	2nd	1st	2nd
Difficulties feeling the need to urinate	●	●	A	A	**0,63**	**-0,23**	0,16	**0,37**
Difficulties emptying the bladder	•	●	F	D	**0,41**	0,08	-0,03	**0,57**
Night-time emptying of bladder	•	•	•	•	0,08	0,35	-0,06	**0,41**
Urinary urgency	•	•	•	•	0,00	**0,95**	-0,02	**0,65**
Stress incontinence	•	•	•	•	**0,34**	**0,38**	0,08	**0,30**
Urinary problems limiting social activities	●	●	B	C	**0,66**	-0,04	**0,28**	0,00
[*Domain*] affecting QoL	●	●	F	A	**0,77**	0,07	0,01	**0,78**
Future [*domain*] worries	•	•	•	•	**0,86**	0,00	0,01	**0,58**
				Reliability	0,82	–	–	0.71

Guide for model in paper II | Tables S1-S13



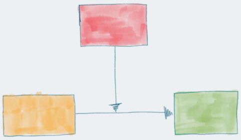
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



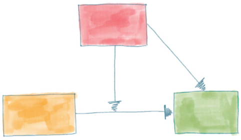
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



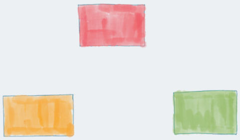
C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.



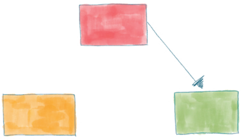
D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.



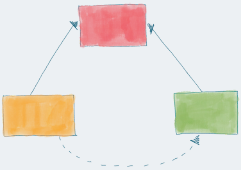
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

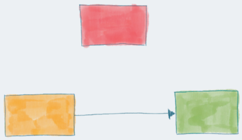
There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QoL-dimension
⬜ Non-QoL dimension

Table S13 Work life. Summarised results from paper I, II, and III.

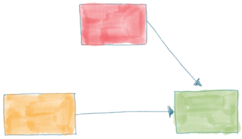
	Paper I	Paper II			Paper III			
					ICU		Controls	
	MWU	Bivar.	Comorb.	Edu.	1st	2nd	1st	2nd
Health reasons for stopping working	-	●	C	A	0,18	**0,38**	**0,40**	**0,30**
Self-assessed capacity to work	-	●	A	D	**-0,86**	-0,11	**-0,90**	0,04
Same type of work in 2 years' time	●	●	B	B	**-0,87**	0,05	**-0,74**	-0,01
Work capacity and physical demands	●	●	A	D	**0,89**	0,02	**0,92**	0,02
Work capacity and psychological demands	●	●	A	B	**0,87**	-0,01	**0,77**	-0,02
Work problems affecting QoL	●	●	A	A	0,09	**0,68**	**0,38**	**0,54**
Financial problems affecting QoL	●	●	A	A	0,17	**0,65**	**0,26**	**0,54**
Worries about working life	●	●	A	B	**-0,21**	**0,93**	-0,11	**0,88**
Worries about work capacity	●	●	A	A	0,00	**0,83**	0,17	**0,71**
Worries about finances	●	●	A	A	0,00	**0,83**	-0,01	**0,68**
				Reliability	0,91	0,93	0,91	0,79

Guide for model in paper II | Tables S1-S13



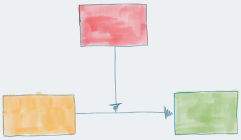
A

ICU survivorship is associated with the item.
The third-variable is not associated with the item.



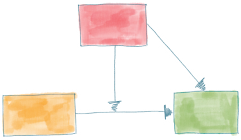
B

Both ICU survivorship as well as the
third-variable is associated with the item.
These two relationships are parallel to each other.



C

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is not associated with the item.

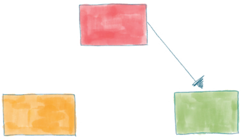


D

The third-variable functions as a moderator,
i.e., the difference between ICU survivors and controls
in the item varies with the degrees of the third-variable.
The third-variable is associated with the item.

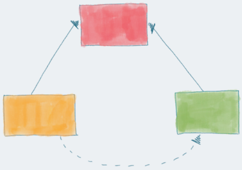
E

Neither ICU survivorship nor the third-variable
is associated with the item.



F

ICU survivorship is not associated with the item.
The third-variable is associated with the item.



G

There is a distorted association between ICU survivorship and the
item caused by the third-variable acting as a collider.

● Significant
• Non-significant
- N/A
🟩 QOL-dimension
▨ Non-QOL dimension