Critical Care, Critical Emissions: Applying life cycle assessment on intensive and perioperative care

Hemberg, Linn

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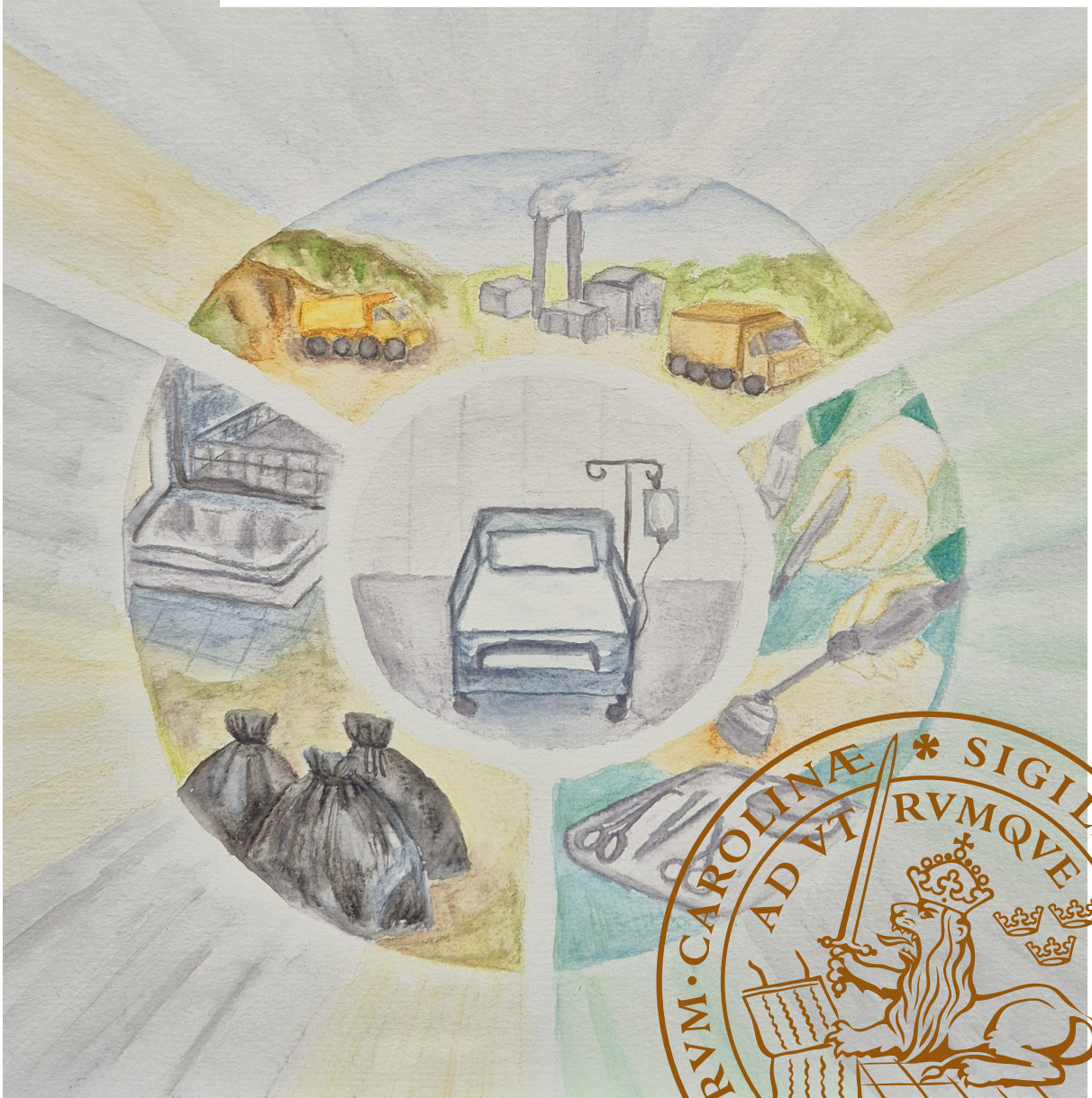
Applying life cycle assessment on intensive and perioperative care

LINN HEMBERG
AGENDA 2030 GRADUATE SCHOOL | FACULTY OF MEDICINE | LUND UNIVERSITY



LINN HEMBERG has carried out her doctoral studies at the Faculty of Medicine and the Agenda 2030 Graduate School at Lund University, ranked as the leading university in sustainability in 2026 (QS World University Ranking).

Her research combines environmental and medical science to assess the climate and environmental impact of intensive and perioperative care in Sweden. Life cycle assessment is used to compare the impact of single use and reusable products used in the intensive care unit and surgical theatres, as well as to find modifiable hot spots that can be targeted to reduce the overall climate impact of intensive care. This thesis also explores the use of life cycle assessment to compare environmental impacts of interventions assessed in clinical trials.

The overall aim of this thesis is to generate knowledge that benefits both individual patients as well as the general health of the population.

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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 30th of March 2026 at 09.00 at the Museum of Medical History, Helsingborg

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Associate Professor, National University of Singapore

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Abstract

Background. Climate change is the greatest threat to human health in the 21st century and healthcare contributes to approximately 5% of global greenhouse gas emissions. Intensive and perioperative care are particularly resource intensive. This thesis aimed to assess the climate and environmental impacts of perioperative and intensive care (Papers I–III) and to explore how environmental outcomes and associated uncertainties can be evaluated in a clinical trial context (Paper IV).

Methods. Life cycle assessment (LCA) was applied in all four papers to quantify environmental impacts across the life cycle of healthcare products and activities. Papers I and II combined LCA with life cycle costing to compare single-use, reusable, and mixed systems for laparoscopic surgery and central venous catheter (CVC) insertions in a Swedish setting, and the impact on resource use, climate change, ecosystem quality and human health was assessed. Paper III applied LCA to estimate the total climate impact per inpatient day in a Swedish intensive care unit (ICU). In Paper IV, LCA was applied to compare the impact of an intervention and comparator in a clinical trial assessing fluid administration on 18 environmental outcomes, climate impact (kg CO_2eq) was the primary outcome. Group differences were analysed using a general linear model and a hierarchical mixed-effects model that incorporated LCA uncertainty.

Results. Reusable trocar systems and CVC insertion kits had 45–95% lower impact than the single-use alternatives on all environmental impact categories and was about half as expensive. The median climate impact of one ICU inpatient day was estimated at 30 kg CO_2eq, increasing to 126 kg CO_2eq with a high-impact energy mix. In Paper IV, results were consistent for most outcomes, with minimal differences between the statistical approaches.

Conclusions. In Sweden, replacing single-use items with reusable alternatives offers the greatest potential to reduce the climate impact of intensive and perioperative care, while renewable energy remains essential as a mitigating strategy globally. Simpler statistical approaches appear sufficient for evaluating environmental outcomes in clinical trials.

Key words: sustainable healthcare, life cycle assessment, intensive care, perioperative care, climate impact, environmental impacts

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MADE IN SWEDEN

Dedication

To seven-year-old me, that wanted to learn everything there is to know, and to my teacher Elisabet who ignited a spark of curiosity and thirst for knowledge that has been ever growing and unquenchable since first grade.

Table of Contents

Populärvetenskaplig sammanfattning

Klimatförändringarna är nutidens största hot mot människors hälsa. Samtidigt står sjukvården för cirka 5 procent av de globala utsläppen av växthusgaser och därför kan klimatkrisen ses som en sjukvårdskris.

Intensivvård och kirurgi är särskilt resurskrävande både vad gäller materialanvändning och energiförbrukning. Syftet med denna avhandling var att undersöka klimat- och miljöpåverkan från kirurgi och intensivvård, samt att utforska hur miljöeffekter och dess osäkerheter kan utvärderas inom ramen för en klinisk studie. Genomgående har klimatpåverkan (kg CO2eq), alltså utsläpp av växthusgaser varit i fokus.

En metod kallad livscykelanalys (LCA) användes för att modellera och beräkna klimat- och miljöpåverkan genom hela livscykel för olika produkter och interventioner. LCA användes för att jämföra påverkan på resursanvändning, klimatförändringar, ekosystem och mänsklig hälsa av att använda engångs- och flergångsprodukter. Dels jämfördes engångs- och flergångsinstrument för titthålskirurgi, dels engångs- och flergångsinstrument som används inom intensivvården vid inläggning av centrala ven katetrar. LCA användes också för att uppskatta den totala klimatpåverkan av att vårda en patient på en svensk intensivvårdsavdelning under ett dygn. LCA användes även för att beräkna och jämföra påverkan på 18 olika miljöpåverkanskategorier för två behandlingsalternativ som jämförts i en klinisk studie. Syftet var att testa och jämföra två statistiska metoder för att avgöra om det fanns en skillnad mellan grupperna. Skillnad mellan grupperna analyserades därför med en enklare statistisk metod, och därefter med en mer avancerad metod som även tog hänsyn till osäkerheter i LCA-modellen.

Sammantaget så hade flergångsprodukterna 45–95% lägre klimat- och miljöpåverkan än motsvarande engångsprodukter. Dessutom var flergångsalternativen betydligt billigare. Den genomsnittliga klimatpåverkan från ett vårddygn på en svensk intensivvårdsavdelning uppskattades till 30 kg CO2eq, och ökade till 126 kg CO2eq vid användning av fossila energikällor. De olika statistiska analysmetoderna visade på i stort sett samma skillnader mellan de två grupperna i den kliniska studien för de flesta av miljöpåverkanskategorierna, oavsett om osäkerheter i LCA-modellen inkluderades eller inte.

I Sverige finns en stor potential att minska klimatpåverkan från kirurgi och intensivvård genom att ersätta engångsprodukter med flergångsalternativ. Samtidigt är tillgång till förnybar energi avgörande för att minska vårdens klimatpåverkan globalt. Resultaten tyder också på att en enklare statistisk metod kan räcka för att utvärdera miljöeffekter och associerade osäkerheter i kliniska studier.

Abbreviations

API	Active pharmaceutical ingredient
CFC	Chlorofluorocarbon
CVC	Central venous catheter
CI	Confidence interval
DCB	Dichlorobenzene
GHG	Greenhouse gases
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
ICU	Intensive care unit
ISO	International Organization for Standardization
HVAC	Heat ventilation and air conditioning
LCA	Life cycle assessment
LCC	Life cycle costing
LCI	Life cycle inventory
LCIA	Life cycle impact assessment
LMIC	Low- and middle-income countries
PM	Particulate Matter
SDG	Sustainable development goals
SE	Standard error
TEG	Triethylene glycol
UV	Ultraviolet
WHO	World Health Organization

Abstract

Background: Climate change is the greatest threat to human health in the 21st century and healthcare contribute to approximately 5% of global greenhouse gas emissions. Intensive and perioperative care are particularly resource intensive. This thesis aimed to assess the climate and environmental impacts of perioperative and intensive care (Papers I–III) and to explore how environmental outcomes and associated uncertainties can be evaluated in a clinical trial context (Paper IV).

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List of Papers

Papers included in this thesis

This thesis includes the following four original papers:

Paper I **Boberg L.**, Singh J., Montgomery A., and Bentzer P. Environmental impact of single use, reusable, and mixed trocar systems used for laparoscopic cholecystectomies as Epub. *PLOS ONE.* 2022. 17(7):e0271601. DOI: 10.1371/journal.pone.0271601.

Paper II **Hemberg, L.**, Wessberg, N., Leire, C., and Bentzer P. Environmental impact of single use and reusable items in central venous catheter insertion kits: a life cycle assessment. *Intensive Care Med*. 2023. 49(6):662–664. DOI: 10.1007/s00134-023-07078-9

Paper III **Hemberg, L**., Singh, J. and Bentzer, P. A process-based life cycle assessment of the climate impact of a Swedish intensive care unit. *Sci Rep.* 2025. 15:19435. DOI: 10.1038/s41598-025-02789-z

Paper IV **Hemberg, L.**, Olsen M.H., Lindén A., Petersen J.J., Möller P.W., Jakobsen J.C., Christensen R., Bentzer P. Assessing uncertainty of environmental outcomes in a clinical trial: An applied example, using data from the protocolized REDUction of non-resuscitation fluid versus usual care in SEptic shock patients (REDUSE) Feasibility Trial. [manuscript]

Other publications

Bentzer P, Lindén A, Olsen MH, Lilja G, Fisher J, Sjövall F, Kander T, Lengquist M, Samuelsson L, Undén J, Palmnäs E, Oras J, Cronhjort M, Balintescu A, Lind A, Ahlström B, Meirik M, Savilampi J, Pekkarinen P, Berggren A, Oscarsson N, Said M, Castegren M, Faria S, **Hemberg L**, Linder A, Lipcsey M, Skrifvars MB, Wise MP, Nielsen N, Jakobsen JC. Protocolized REDUction of Non-Resuscitation Fluids in SEptic Shock Patients. A Protocol for the REDUSE Randomized Clinical Trial. *Acta Anaesthesiol Scand*. 2025. 69(7):e70095. DOI: 10.1111/aas.70095.

Petersen JJ, **Hemberg L**, Thabane L, Hopewell S, Chan AW, Hróbjartsson A, Mathiesen O, Kandasamy S, Siegfried N, Williamson PR, Fox L, Kamp CB, Hoffmann JM, Brorson S, Jakobsen JC, Bentzer P. Reporting of environmental outcomes in randomised clinical trials: a protocol for a scoping review. *BMJ Open*. 2025. 15(9):e101709. DOI: 10.1136/bmjopen-2025-101709.

Petersen JJ, **Hemberg L**, Thabane L, Hopewell S, Chan AW, Hróbjartsson A, Mathiesen O, Kandasamy S, Siegfried N, Williamson PR, Fox L, Kamp CB, Hoffmann JM, Brorson S, Boutron I, McGain F, McAlister S, Mutengu L, Slutzman J, Sherman JD, Bentzer P, Jakobsen JC. Protocol for development of SPIRIT and CONSORT extensions for reporting climate and environmental outcomes in randomised trials (SPIRIT-ICE and CONSORT-ICE). *BMJ Open*. 2025. 15(9):e106708. DOI: 10.1136/bmjopen-2025-106708.

Bentzer P, Talbot A, **Hemberg L**. Sustainability in anaesthesia and intensive care - an obligation to turn danger into opportunity. *Eur J Anaesthesiol*. 2023. 40(10):721–723. DOI: 10.1097/EJA.0000000000001842.

Hemberg L. Engångsprodukternas era är över. *Uppdukat*. 2024. 3:30–32.

Petersen JJ, **Hemberg L**, Thabane L, Hopewell S, Chan AW, Hróbjartsson A, Mathiesen O, Sergeant M, Kandasamy S, Siegfried N, Williamson PR, Fox L, Kamp CB, Hoffmann JM, Brorson S, Bentzer P, Jakobsen JC. Integrating environmental outcomes in randomised clinical trials: a call to action. *Lancet*. 2025. 405(10477):446–448. DOI: 10.1016/S0140-6736(24)02666-7.

Hemberg L. Healthy Planet Healthy People?, in Through the kaleidoscope of sustainability – 25 essays, ed. Gunneflo, M. 2025. Lund University. p.188–191

Hemberg L, Juul Petersen J, Hróbjartsson A, Mathiesen O, Barkholt Kamp C, Brorson S, Jakobsen JC, Bentzer P. Klimatpåverkan bör ingå som effektmål i framtidens kliniska prövningar. *Läkartidningen*. 2025.

Hemberg L. Mångdubbelt större klimatpåverkan från laparoskopiska portar. *Svensk Kirurgi*. 2025. 83:124–125.

Preface[1]

First do no harm…

… is the guiding principle of healthcare workers all over the world and in an era of climate crises, biodiversity loss and other environmental challenges it can be regarded as quite a paradox that healthcare, which is intended to do no harm account for about five percent of the global emission of greenhouse gases (GHG), contributing to said crisis, regarded as the single largest threat to human health in the 21st century.

Up until now, or at least a few decades ago, the resource demanding activities of healthcare has been justified by the aim of saving lives. This raises a fundamental question – how do we reconcile the conflicting goals of high-quality individual care for all human beings with the collective need for a sustainable use of the planet's resources?

Not only do high-quality care in developed countries disproportionally drive emissions of GHG, but the need for better care globally would require an even higher demand of resources, increasing global environmental harm. Here in lies a clear conflict, to ensure equitable access to high-quality healthcare globally, the environmental pressures would likely be exacerbated unless profound systemic changes are made. The question is then how such change can be achieved?

[1] This preface has been adapted from the author's contribution to the book *Through the kaleidoscope of sustainability – 25 essays,* written by the PhD students and alumni in the Agenda 2030 Graduate School, Lund University.

Aims

The purpose of this thesis has been to broaden health care's guiding principle of "first do no harm", expanding it beyond the individual patients to guide actions that help save the planet, a prerequisite for life and the health and wellbeing of present and future generations.

The aim was to assess the climate and environmental impacts from perioperative and intensive care, to identifying modifiable elements that can be targeted to reduce the overall climate and environmental impacts from healthcare activities, and to contribute to the methodological development needed to provide such insights.

Specific aims

The specific aim in Paper

I. was to estimate and compare the environmental and economic impacts of using single use and reusable trocars in laparoscopic surgery
II. was to estimate and compare the environmental and economic impacts of using single use and reusable items in central venous catheter (CVC) insertion kits
III. was to estimate the total climate impact of Swedish intensive care and to identify modifiable elements
IV. was to explore how different types of uncertainties in clinical trial LCAs could be assessed.

Introduction

Healthy planet, healthy people

In 2009 a framework that defines safe limits for human pressure on nine critical environmental processes needed for enabling a stable and resilient earth system was developed, called the planetary boundaries (1). Already then three out of nine boundaries were crossed, and today seven out of nine boundaries have been transgressed (**Figure 1**). For each boundary crossed, the risk for large-scale abrupt or irreversible environmental changes increases, leading to an increased risk of adverse effects on human health and ecosystems (2). The nine boundaries are interrelated, and the transgression of one boundary has the potential to create a ripple effect on the other boundaries (2).

The transgression of the planetary boundaries marks the end of the Holocene, the time era which has described the earth system and its environment since the end of the last ice age about 10 000 years ago. Instead, we are entering the Anthropocene, an era which is characterized by the impact human activity has on the earth and our surrounding environment (1).

Although the boundaries can't be considered in isolation from one another, climate change is probably the boundary which people are most familiar with. The environmental mechanism of climate change, or global warming, is explained by the greenhouse effect. In principle the amount of incoming solar radiation and the energy leaving the earth's atmosphere through reflection or as infrared radiation should be in balance. However, GHGs absorb the infrared radiation and traps it in the atmosphere, causing an imbalance of radiation entering and leaving the atmosphere. This explains why the temperature increase with a higher content of atmospheric GHGs (3). The increased concentration of GHGs in the atmosphere, superseding the internationally agreed limit set in the 2015 Paris Agreement, could lead to extreme impacts on the earth system and human health (2).

In fact, climate change already adversely affects human health (4), the rise of atmospheric and ocean temperatures has led to an increased frequency of weather-based natural disasters such as droughts, floods and wildfires, increased frequency of heat waves, changes in infectious disease vectors and negative impact on agriculture crop yields (5-7). Climate change is associated with an increased risk for several diseases such as acute infection-related respiratory and intestinal diseases,

exacerbation of pre-existing pulmonary lesions, heat-related dehydration, cerebral insults, myocardial infarctions, and acute kidney dagame during heat waves (8). The World Health Organization (WHO) has estimated that climate change will lead to about 250 000 additional deaths annually between year 2030 and 2050 (9).

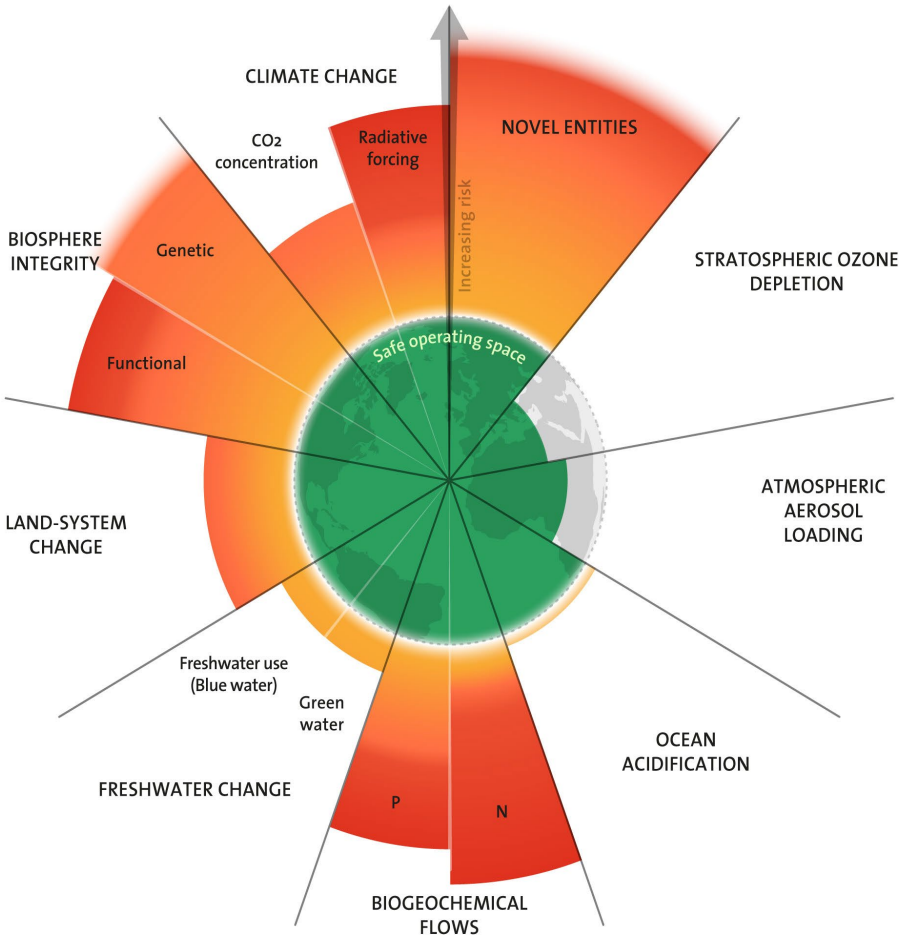

Figure 1. The 2025 update to the planetary boundaries.
The planetary boundaries that define safe limits for human pressure on the earth system. Two boundaries remain within a safe operating space (green) while seven boundaries have been transgressed (orange/red). Credit: Azote for Stockholm Resilience Centre, based on analysis in Sakschewski and Caesar et al. 2025 (10).

Healthcare's climate impact

Climate change is the greatest threat to human health in the 21st century. And whilst the guiding principle of healthcare is do no harm, healthcare activities account for almost 5% of the global net emissions of GHG (11), ranging from 4% to 10% of national GHG emissions (12-16). About 70% of the total emissions can be attributed to indirect emissions that origin primarily from the healthcare supply chain and about 30% can be attributed to direct emissions that is related to healthcare operational emissions, transports, and energy consumption (11). As a response to the climate crisis and the realisations of healthcare's own contribution to the global emission of GHG, voices have been raised by both healthcare professionals and patients to find sustainable healthcare pathways (17, 18). The number of studies that assess climate and environmentally friendly healthcare pathways has increased exponentially over the last couple of decades.

Life cycle assessment (LCA)

LCA is a popular method used to estimate the environmental impact of a product or system. The idea of LCA was conceived in the 1960's as part of the environmental movement and the recognition of humans' excessive use of non-renewable resources. But it wasn't until the 1990s that the method got real traction within the scientific community, culminating with the International Organization for Standardization's (ISO) release of the ISO14040 and ISO14044 standards by the end of that decade (19). Today the application and reporting of LCA is guided by an updated version of the standards established by ISO in 2006 (20, 21). LCA is a method that quantify environmental impacts of a product or system, by including the needed exchanges between the biosphere and technosphere throughout all life cycle phases: raw material extraction; production; use phase; waste management; and all transportation (19) (**Figure 2**).

Figure 2. LCA schematic
The exchange pathways between the biosphere (green) and technosphere (brown) throughout all life cycle phases: raw material extraction, production, transportation, use, and waste management.

Information on impacts from different materials and processes is commonly collected from large databases (22). Products or systems are modelled in special software developed for LCA, using data from the databases. The software then summarises the environmental impacts from the model. Beside climate impact, LCA can be used to estimate the impact on a range of categories such as impact from air pollution, impacts connected to resource use, and impact on ecosystems.

Healthcare LCAs

The number of studies using LCA to estimate the environmental impact of healthcare activities has increased rapidly during the last decade. From early 2000 until 2010 only a couple of articles were published each year. Today almost 400 articles have been reported in the HealthcareLCA Database, an online repository of published, peer reviewed healthcare LCAs (23). Most studies included in the database is on medical equipment and products, representing 35%, or on procedures, medical interventions and investigations, representing 30% (**Figure 3**).

Most of the studies used a cradle to grave approach, meaning that impacts throughout the entire life cycle was included in the analyses, from raw material extraction to waste management.

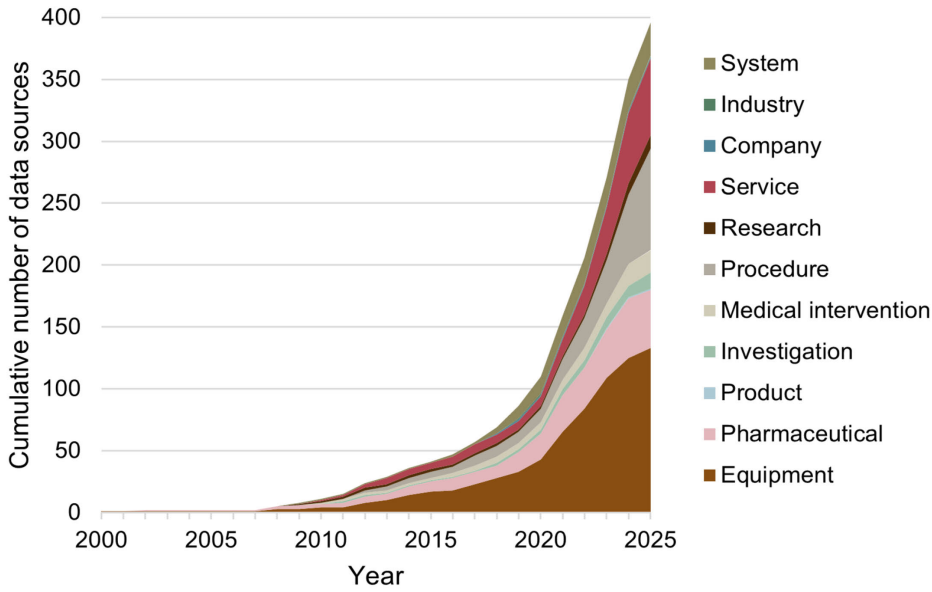

Figure 3. Cumulative data sources within the HealthcareLCA database
This chart summarizes the cumulative number of data sources that are currently included in the HealthcareLCA database and breaks them down into different categories. Credit: HealthcareLCA, 2021 (24).

High-resource healthcare

Intensive and perioperative care are two of the most resource intensive medical specialties at the hospital due to their excessive use of disposables, requirement of sterilised instruments and the units' high energy demand to run heat ventilation and air conditioning (HVAC) and all electronic equipment and lighting.

The high resource turnover in these units and interest of their environmental impact is also reflected in the number of published articles focusing on these two specialties, representing about 35% of the total amount of published articles included in the HealthcareLCA database (23).

LCA studies on medical equipment and products used in intensive care include studies on, laryngoscopes (25, 26), laryngeal mask airways (25, 27), CVC insertion kits (28), anaesthetic drug trays (29, 30), and pulse oximeters (31). LCA studies on intensive care interventions include an assessment of the climate impact of treating patient with septic shock (32), and an assessment of the environmental impact of open versus closed endotracheal suctioning in invasively ventilated critically ill patients (33).

LCA studies on medical equipment and products used in perioperative care include studies on laparoscopic instruments (34, 35), endotracheal tubes (36), instruments

for robotic surgery (37), and cardiopulmonary bypass devices (38). LCA studies on surgical interventions include assessments of cardiac surgery (39, 40), carpal tunnel release (41), liver transplantation (42), and care pathways for anastomotic leaks (43). There is also a study which estimated the total climate impact from surgery in Canada, USA and the United Kingdom (44).

Clinical trial LCAs

For clinical trials, LCA has primarily been used to estimate the climate impact of the trials themselves and the trial related activities (45, 46). A few clinical trials have also included environmental impacts as outcomes (47, 48). Since comparative LCAs are increasingly applied in medicine, a need for future clinical trials to compare not only clinical outcomes, but also the environmental impacts of the interventions have been raised (49). There is currently a project registered with the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network that aim to develop extensions for the Recommendations for Interventional Trials 2025 (SPIRIT 2025) and Consolidated Standards of Reporting Trials 2025 (CONSORT 2025) that include climate and environmental impacts as outcomes when reporting the result of a clinical trial (50, 51). The extensions are called SPIRIT-Implementing Climate and Environmental outcomes in clinical trials (SPIRIT-ICE) and CONSORT-ICE.

Uncertainties in healthcare LCAs

Information on the impacts from different material and process is available in large databases. The impacts of materials and processes in these databases are often given with a measure of uncertainty. For example, the climate impact from transporting a certain weight by lorry in Europe has been calculated for different vehicles, loads, and fuels, allowing the estimated average climate effect per kilometre, and the associated variation, to be entered into the database. The uncertainty of the environmental impacts of the entire system can then be assessed using Monte Carlo simulations, which utilizes randomly sampled data for all identified materials and processes in the system to generate a point estimate with a 95% reference interval. Monte Carlo simulations have been the most common way of estimating the uncertainty of LCA results across scientific fields, and several LCA software tools have Monte Carlo simulations as a built-in feature (52).

In a clinical trial setting, LCA data is a combination of database data with known uncertainties and independent data collected during the trial for which uncertainties are unknown. There is currently no consensus on how the difference between environmental impacts in such context should be assessed, and the subject has received surprisingly little attention. This is perhaps because many environmental

scientists regard LCA as a method to explore systems and to identify hotspots rather than to assess the differences between different processes.

When comparing different processes, one school of thought is that inferential statistics, as is commonly used in medicine, can be used to compare Monte Carlo simulation data from the two systems (53-55). In contrast, some argue that such an approach is flawed because it violates the requirement of independent observations and because the P value will be inflated by an increased number of Monte Carlo simulations without additional data entering the system (56).

Rationale for this thesis

With climate change being the greatest threat to human health in the 21st century and the transgression of seven out of nine planetary boundaries, the rational and aim of this thesis has been to identify modifiable elements that can be targeted to reduce the climate and overall environmental impact from healthcare. This thesis has focused on the resource intensive specialties intensive an perioperative care, and the results are intended for clinicians, personnel working with procurement of medical equipment, and for policy makers. The aim was also to explore how uncertainties in the LCA model can be assessed in a clinical trial context, to be able to contribute to the methodological development needed for the inclusion of environmental impacts as outcomes in clinical trials.

Environmental impacts beyond climate change

As outlined in the introduction human life on earth is threatened not only by climate change but by the transgression of several planetary boundaries. Most impact categories assessed in LCA are related to the boundaries in the planetary boundary framework (**Figure 4**). Below follows a short description of the most common environmental impacts assessed with LCA and how they affect human health.

Categories with a direct effect on human health

Fine particulate matter formation

The environmental mechanism of fine particulate matter formation refers to a change in the ambient concentration of particulate matter (PM) after the emission of precursor substances, most common are Ammonia (NH_3), Nitrogen Oxides (NO_x), and Sulphur Dioxides (SO_2) (57).

Fine particulate matter formation refers to the emission of household and ambient air pollutants which is harmful to human health. Ambient air pollution caused over 4 million deaths in 2019 (58) and was estimated to cause over 100 million lost years of healthy life in 2015 (59). Exposure to PM is also associated with chronic and acute respiratory diseases, lung cancer, diabetes and adverse birth outcomes (57). It has further been shown that exposure to ambient air pollution before admission to intensive care prolong the duration of artificial ventilations in intensive care patients (60). The emission of fine particulate matter has negative effects also from a planetary health perspective since it leads to crop damage and forest degradation as well as reinforces both global warming and acidification (1).

Toxicity

The environmental mechanism of toxicity is divided into four steps. First the increase in chemical concentration in a given environment is estimated. Then the bioavailability of that chemical is quantified. The amount of available chemicals is then related to the effect on the ecosystem, and lastly the effect on ecosystem is translated into impact on human health or in terms of changed biodiversity over time

and space (57). The emission of chemicals into the environment or from chemical ingredients used in products released in the production phase, during use, or as part of the waste management process adversely affect human health by increasing the risk of both carcinogenic and non-carcinogenic diseases, and through its negative effect on terrestrial, freshwater, marine, and aerial ecosystem (57).

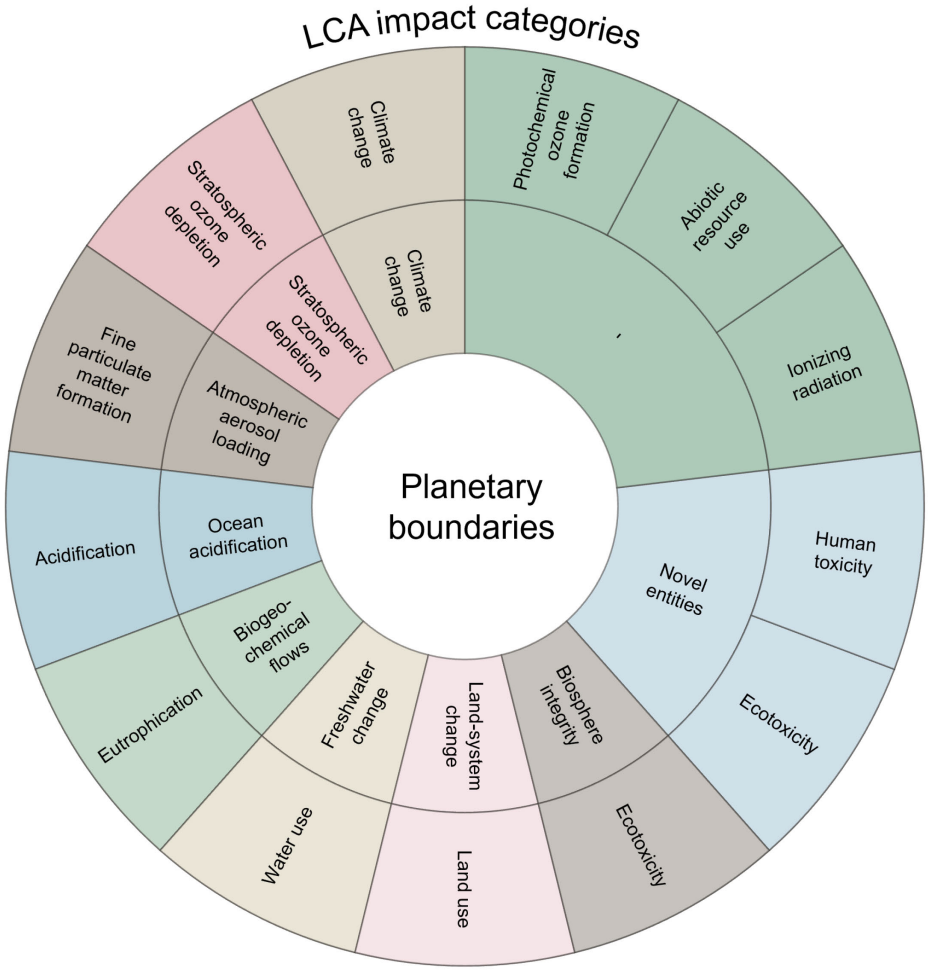

Figure 4. Connection between planetary boundaries and impact categories assessed in LCA. The connection between the planetary boundaries (inner circle) and environmental impact categories assessed in LCA (outer circle).

Photochemical ozone formation

The environmental mechanism of photochemical ozone formation is complex since there are an abundance of different substances that affects it. Briefly, the compounds are formed as secondary contaminants by the oxidisation of primary contaminants such as volatile organic compounds (VOC), non-methane VOC (NMVOC), or carbon monoxide (CO) in the presence of nitrogen oxides (NO_x) (57).

The reactive nature with photochemically generated pollutants causes organic molecules to oxides in exposed surfaces in the vegetation and on man-made surfaces. When ozone and other reactive oxygen compounds which are formed in the process is inhaled it has a negative effect on human health since it harms the tissues in the respiratory tracts, causing respiratory diseases (57).

Stratospheric ozone depletion

The environmental mechanism behind stratospheric ozone depletion is that the ozone is destroyed by the emissions of chemicals, primarily chlorofluorocarbons (CFC) which are used as refrigerants, foam blowing agents, solvents, and halons which are used as fire extinguishing agents. Since ozone absorbs UV radiation, the depletion of stratospheric ozone reduces the atmosphere's ability to absorb the incoming UV radiation. The main concern is the increased exposure to UV-B which impact on human health are suspected to increase the risk of skin cancer, cataracts, sun burns and immune system diseases (57).

Abiotic resource use

Abiotic resources are natural resources with a functional value to society, such as fossil fuels, minerals and metals. The environmental mechanisms of abiotic resource use are connected to the energy consumption and cost of the raw material extraction. It is assumed that easily accessible and cheap resources are extracted first, leaving future generations with low value resources that are harder to extract, increasing the energy requirements and cost per kg extracted material (57). The most prominent health issue with abiotic resource use is the impact that fossil resources used as fuels cause through the combustion process and the emitted air pollutions (57).

Ionising radiation

The environmental mechanism of ionising radiation refers to the emission of a radionuclide, most often from the use of nuclear power (57). It has adverse effect on human health since it increases the risk of cancer and hereditary diseases (61).

Categories with an indirect effect on human health

Eutrophication

The environmental mechanism of eutrophication refers to the degrading condition of aquatic environments because of the enrichment of nutrient salts, which primarily has to do with humans' increased use of compounds containing either phosphorus (P) or nitrogen (N), such as in the manufacturing of fertilizers used in food production (1). Eutrophication primarily effects the planetary health since human activity led emissions of P and N perturb the global cycles of these elements, reducing the resilience of the earth system (1). The degradation of water quality, the altered composition of species, and in the long term the transition of lakes into swamps, grasslands and forests also has a negative effect on human health due to the decreased access to freshwater and its negative effect on fishery (57).

Acidification

The environmental mechanism of acidification is connected to the ecosystems' capacity to neutralise acid. Acidification occurs naturally over time but increases with man-made input of hydrogen ions to the soil and freshwater aquatic ecosystems. The main source is air-borne emissions from gases that release hydrogen when degraded in the atmosphere or after deposition to soil and water. The main compounds contributing to terrestrial and freshwater acidification is sulphur oxides (SO_x) and nitrogen oxides (NO_x). The main effect of acidification is forest declines and acidic lakes. (57). Ocean acidification rather occurs as a result of the increase in CO_2 emissions since the addition of CO_2 to the ocean increases the acidity of the surface water (1). The ocean serves as a CO_2 sink, removing roughly 25% of human CO_2 emission from the atmosphere. The planetary boundary for ocean acidification was recently transgressed, the trend is worsening and the oceans' capacity to hold CO_2 is limited (2), meaning that acidification and global warming negatively reinforce each other (1). Ocean acidification therefore mainly affects human health through its reinforcement of global warming.

Water use

The environmental mechanisms driving water use include factors such as different types of water use, the source of water, water availability, and status of watersheds. Although water is a renewable resource, the availability of water is limited, meaning that water consumption upstream will lead to water deprivation for downstream users (57). Only 1% of water from precipitation is used by humans. Despite the abundance of water, bad management and highly populated areas have led to water scarcity in many areas around the world. Water availability and climate change also negatively reinforce each other. The global manipulation of freshwater effects ecological abilities such as natural carbon capture and storage, climate regulation, as well as undermining the resilience of local ecosystems (1). In turn, climate change

cause both droughts and floods which negatively affect human health through for example changes in infectious disease vectors (57).

Land use

The environmental mechanism for land use is the physical and chemical effect that land transformation and land occupation have on the soil surface disposition and on altered species composition and reduced habitat sizes (57). Soil is a finite resource and the competition between resource users drives a continuous change in land use. The expansion of croplands, pastures, urban areas and other human land-use-intensive activities that are needed for food, fibre, settlement, and transport infrastructure comes at the cost of biodiversity loss and adverse impact on human quality of life (1, 57).

Methods

This section first describes the framework and foundation of LCA together with general methodological choices consistent throughout all papers. Then methods used to assess uncertainties are described. Lastly, details on the application of LCA in the respective papers is presented.

Life cycle assessment

LCA is the central method applied in all four papers. LCA is a quantitative method used to measure the environmental impact of a product or system, throughout its entire life. It is an iterative method comprised by four steps, (i) goal and scope, (ii) life cycle inventory (LCI), (iii) life cycle impact assessment (LCIA), and (iv) interpretation of results (20, 21). **Figure 5** illustrates the general framework of an LCA.

In the first two studies, we combined LCA with life cycle costing (LCC) to considers the financial costs of the analysed systems alongside their environmental impacts. LCC follows the same four steps as an LCA and include both direct and hidden costs associated with the product or system throughout the life cycle (62).

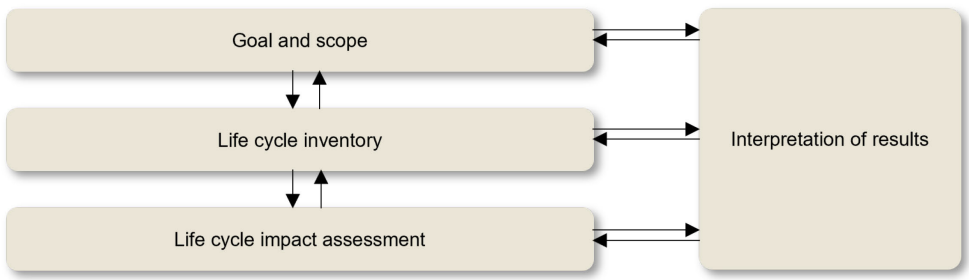

Figure 5. LCA framework
Schematic presentation of the four steps in an LCA: goal and scope; life cycle inventory; life cycle impact assessment; and interpretation. Adapted from the framework in ISO 14040 (20).

Goal and scope

The first step of an LCA is to elaborately define and describe the goal and scope of the study. The goal definition should contain a description of the intended application of the results as well as for what context and which audience the results are intended for (63). The scope of the LCA is then outlined to determine what should be assessed and what the system boundaries for the analysis are. The scope definition should further describe the functional unit and reference flows to be used in the LCA. Functional unit is defined based on the qualitative and quantitative aspects that a product or system needs to meet, which is especially important when different systems are compared. The functional unit can be derived by asking the questions: what? where? how much? for how long? and how well? The reference flows are then what is used to define how much of a product or system that is needed to fulfil the functional unit (63). The goal and scope is described separately for each paper.

Life cycle inventory (LCI)

The second step of an LCA is to conduct an inventory of all material and processes needed to model the studied system based on the system boundaries (64). Hospital staff and manufacturers was consulted in all four papers to collect real-world data concerning materials, production processes, mode of transport, usage, potential laundry and sterilization, and waste management.

The LCA software SimaPro was used to create the LCA models in all papers, using material and process data from the ecoinvent database (65) (**Table 1**).

Table 1. Software and database versions used in Paper I-IV
Version of SimaPro software and the ecoinvent databased used in the respective papers.

	Paper I	Paper II	Paper III	Paper IV
SimaPro	9.1.1.1	9.2.0.2	9.2.0.2	10.2.0.3
Ecoinvent	3.6	3.6	3.6	3.10

The ecoinvent database cover tens of thousands of materials and processes with information regarding their associated emissions. A schematic example on the interaction between biosphere and technosphere with associated emissions is provided in **Figure 6**.

An attributional, process-based LCA approach was used in all four papers, meaning that the models were based on physical material and process flows.

In **Paper I** and **Paper II** the weight of products was measured on site at the hospitals using a scale with ± 1 g precision. In **Paper III** and **Paper IV** KERN KB-N, KB 6500-1N balance, ± 0.1 g precision scale was used.

Transportation distances were estimated using Google Maps, assuming use of the fastest route in **Paper I**, **Paper II**, and **Paper III**.

The energy mix used to model energy consumption in the primary analyses in all four papers was specific for Sweden and consisted of approximately 40% nuclear power, 40% hydro power, 10% wind power, and 10% thermal power (66).

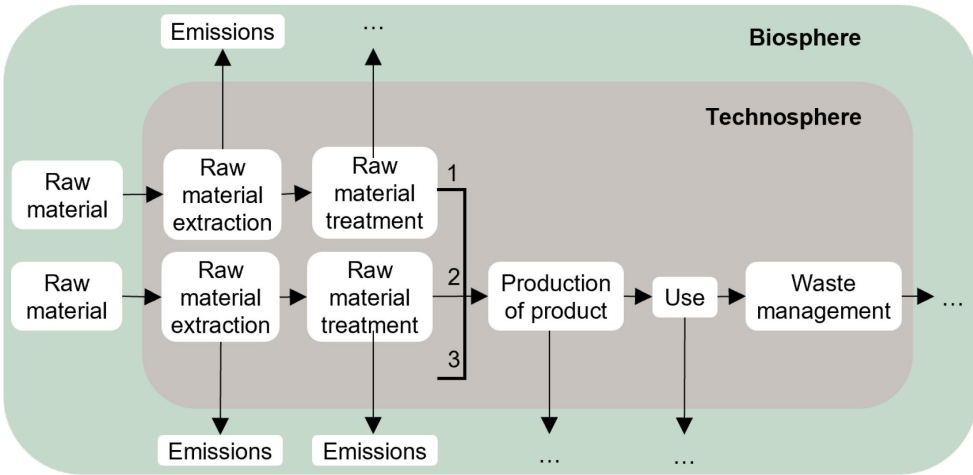

Figure 6. Interaction between biosphere and technosphere
A schematic figure showing on the exchanges between the biosphere and technosphere for each material and process throughout the life cycle.

Data management

Excel was used to file and organise all collected real-world data including weight, units, materials, production processes, information regarding the use, potential laundry and sterilisation, and sources of information. The material and processes selected in the ecoinvent database to create the model was stored in the same file together with any assumptions made to be able to replicate the model.

Life cycle impact assessment (LCIA)

The impact assessment is the third step of an LCA, and it is a largely automated process conducted in the LCA software to characterise the impact from all material and process flows identified during the inventory into one or more impact categories (57). Impact categories are either estimated at midpoint, meaning the absolute value of emissions, or at endpoint, meaning the downstream effect that these emissions have. A schematic example of the characterisation process is provided in **Figure 7**.

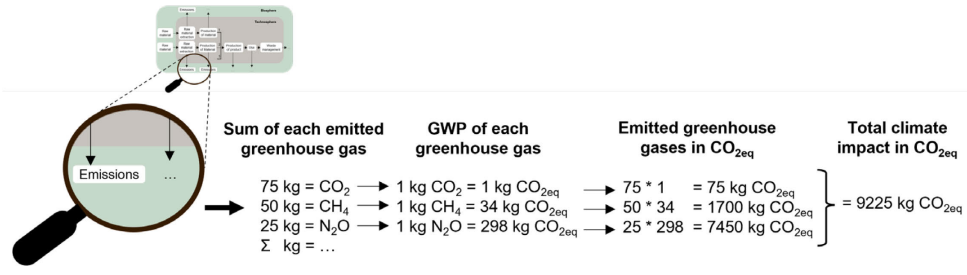

Figure 7. Example of the characterization process.
The amount of emitted GHG is characterised based on the global warming potential (GWP) of each GHG relative to that of 1 kg of carbon dioxide (CO_2), summarised and expressed as carbon dioxide equivalents (CO_{2eq}). CH_4 = methane. N_2O = Nitrous oxide. GWP based on the ReCiPe 2016 Midpoint (H) LCIA method (61).

In **Paper I** and **Paper II**, the IMPACT 2002+ LCIA method was used to assess the climate and environmental impact on fifteen impact categories at midpoint, presented as their downstream effect on four endpoints (**Figure 8**, **Table 2**) (67).

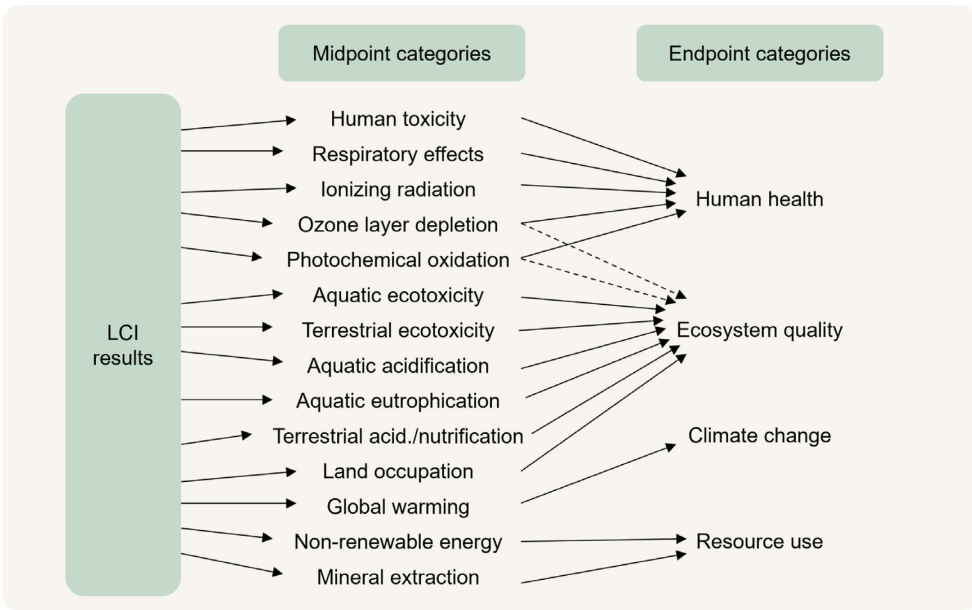

Figure 8. Impact pathways in IMPACT 2002 + LCIA method.
Impact categories and pathways, linking LCI via midpoint categories to endpoint categories covered by the IMPACT 2002+ LCIA method. Dashed lines represent uncertain pathways. Credit: Jolliet et al. 2003 (67), reproduced and adapted with permission from Springer Nature.

In **Paper III** and **Paper IV**, the ReCiPe 2016 Midpoint (H) LCIA method (61) was used to assess and present the climate and environmental impacts on eighteen impact categories at midpoint (**Table 2**), with global warming as the primary outcome.

Table 2. Midpoint impact categories covered by IMPACT 2002 + and ReCiPe 2016 Midpoint (H)
Impact categories, LCIA method(s), characterisation factor(s) and unit(s).

Impact category	LCIA method	Characterisation factor	Unit
Climate change/ Global warming	IMPACT 2002+	The ratio of the cumulated radiative forcing over 100 years of a given GHG to that of carbon dioxide (CO_2)	kg CO_2-eq
	ReCiPe 2016		
Eutrophication	IMPACT 2002+	Eutrophication potential of emissions into P-limited water relative to phosphate (PO_4)	kg PO_4 P-lim.
	ReCiPe 2016 [a]	Impact on freshwater ecosystems relative to that of phosphorus (P) and on marine ecosystem relative to nitrogen (N)	kg P-eq / kg N-eq
Ecotoxicity	IMPACT 2002+[b]	Toxicity of a chemical emitted into soil and water relative to triethylene glycol (TEG)	kg TEG soil kg TEG water
	ReCiPe 2016 [c]	Toxicity of a chemical emitted into ecosystems relative to 1,4-dichlorobenzene (DCB)	1,4-DCB
Human toxicity	IMPACT 2002+[d]	Human toxicity of an emission relative to chloroethylene (C_2H_3Cl) emitted into air	kg C_2H_3Cl eq
	ReCiPe 2016 [d]	Human toxicity of a chemical emitted into the ecosystem relative to 1,4-dichlorobenzene	1,4-DCB
Acidification	IMPACT 2002+	Acidification potential of an emitted substance relative to Sulphur Dioxide (SO_2)	SO_2 eq
	ReCiPe 2016		
Photochemical ozone formation	IMPACT 2002+	Ozone formation potential of an emission relative to ethylene (C_2H_4) emitted into air	kg C_2H_4 eq
	ReCiPe 2016 [e]	Ozone formation potential of an emission relative to nitrogen oxides (NO_x)	NO_x eq
Fine particulate matter formation	IMPACT 2002+	Formation of PM with a particle diameter of 2.5 microns or less	PM2.5 eq
	ReCiPe 2016		
Stratospheric ozone depletion	IMPACT 2002+	Ozone depletion potential of a certain chemical relative to that of chlorofluorocarbons (CFCs)	kg CFC-11 eq
	ReCiPe 2016		
Abiotic resource use, minerals and metals	IMPACT 2002+	The inherent properties of a resources as well as its consumption in relation to its availability relative to energy content (MJ) or copper (Cu)	MJ surplus
	ReCiPe 2016		kg Cu eq
Abiotic resource use, fossil fuels	IMPACT 2002+	The potential of a certain fossil fuel resource to carry energy	MJ Primary
	ReCiPe 2016		Kg oil-eq
Ionising radiation	IMPACT 2002+	Ionising radiation potential relative to that of either Cobalt-60 (Co-60) or Carbon-14 (C-14)	Bq C-14 eq
	ReCiPe 2016		kBq Co-60 eq
Water use	ReCiPe 2016	m^3 of water consumed per m^3 of water extracted	m^3
Land use	ReCiPe 2016	Species loss caused by transformation of natural land to used land, including the time it takes to back-transform it to natural land	m2*yr eq

[a] reported as two categories for marine and freshwater eutrophication respectively. [b] reported as two categories for soil and water ecosystems respectively. [c] reported as three categories for terrestrial, freshwater and marine ecosystems respectively. [d] reported as two categories for carcinogenic and non-carcinogenic human toxicity respectively. [e] reported as two categories for impact on human health and terrestrial ecosystems respectively.

Interpretation

The fourth step of an LCA is the interpretation of the results from the three previous steps taken together and analysed in the light of uncertainties and the assumptions that have been made and documented during the studies (68). A common aspect of the interpretation is contribution analyses, which are used to assess different life cycle phases relative contribution to the total impact of the product or system analysed. Contribution analyses were used in **Paper I**, **Paper II**, and **Paper III**.

Uncertainties and statistics

LCA is not exempted from uncertainties, and two main sources of uncertainty in LCA are model uncertainty and parameter uncertainty. Model uncertainties are connected to the assumptions made by the researchers upon which the model is built. Parameter uncertainties are associated with the input data used to create the model (52).

Model uncertainty

To handle model uncertainties, sensitivity analyses was used to test the robustness of the results in **Paper I**, **Paper II**, and **Paper III**. The sensitivity analyses in each paper are described later but an example of a sensitivity analysis which was used in all three papers was a change from a Swedish, low-climate-impact, energy mix to a high-climate-impact energy mix which is primarily based on fossil energy sources such as hard coal, lignite or oil. Many countries use energy mixes with a higher climate impact than Sweden and the change in the model let us assess the robustness and the impact that such change had on our results.

Parameter uncertainty

Monte Carlo simulations were used to assess parameter uncertainties in the process and material data used to create the LCA models. As described earlier Monte Carlos simulation is an uncertainty propagation method which model calculation repetitions (iterations) based on the probability distribution of each included input parameter (52). The probability distribution is, if possible, based on the variation in sample data and otherwise on a simplified standard procedure used by the ecoinvent database (69).

Monte Carlo simulations were performed in **Paper I**, **Paper II**, and **Paper III** to simulate the median with a 95% reference interval (2.5 – 97.5 percentiles), using 1000 iterations for each reference flow and impact category.

In **Paper I** and **Paper II** dependent (paired) Monte Carlo simulations was used to assess the certainty of differences between the compared reference flows, presented as the median difference with a 95% reference interval (2.5 – 97.5 percentiles). Reference intervals that did not cross zero were considered to reflect a true difference between the compared systems.

In **Paper IV** Monte Carlo simulations were used to randomly sample data within the uncertainty range for each data point in the LCA model to provide 100 repeated measures per patient and outcome to be used in a mixed-effects model, described in further detail in the next section about clinical uncertainty.

All Monte Carlo simulations were performed using the SimaPro software.

Clinical uncertainty

The LCAs in the **Paper I**, **Paper II**, and **Paper III** focused on products or processes and then Monte Carlo simulations were appropriate to use to assess the uncertainty in the input parameters used to model the products and processes. In **Paper IV**, rather than only looking at products or processes we compared the environmental impact of interventions in a clinical trial. In such setting some of the input parameters will be based on clinical data, for which inferential statistics are more appropriate. Thus, we explored two different statistical approaches to assess differences in environmental impacts between a specific intervention and a control comparator. We analysed trial data using a general linear model to compare groups, in which only the uncertainty in the intervention effect was included in the analysis, meaning using the point estimate per patient and outcome provided by the LCIA. In comparison, we used a hierarchical (mixed effects) model to compare groups in which the uncertainty in the clinical intervention and the uncertainty of the environmental parameters in the LCA models were included, utilising Monte Carlo simulations (**Figure 9**). The statistical approaches are described in detail later in this chapter.

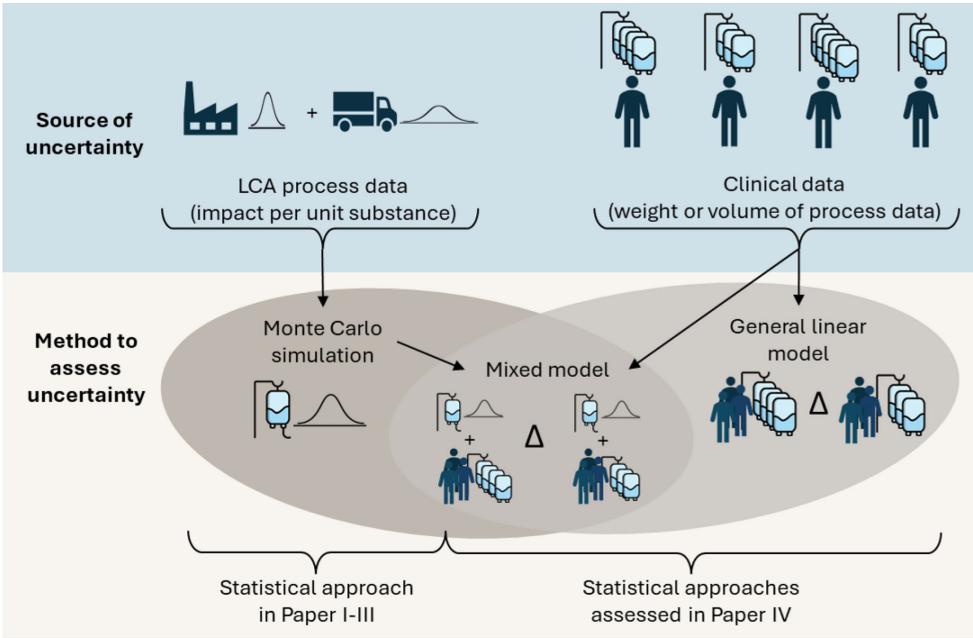

Figure 9. Schematic figure presenting sources of uncertainty and statistical approaches. Environmental parameter uncertainty from LCA assessed with Monte Carlo simulation (Paper I-III), and clinical uncertainty from intervention effect assessed with a general linear model or a combination of environmental parameter and clinical uncertainties assessed using a mixed model (Paper IV).

LCA applied in in Paper I

Goal and scope

We assessed the environmental impacts of three trocar systems used for laparoscopic cholecystectomies at three hospitals in Southern Sweden. For one procedure four trocars are needed, two small and two large (**Figure 10**).

One system consisted only of reusable trocars (Landskrona Hospital), one system was a mix of reusable and single use trocars (Helsingborg Hospital) and one system consisted only of single use trocars (Skåne University Hospital, Lund).

Landskrona Hospital was used as the index hospital in the analysis, meaning that all hospital related data, such as product storage information, the model of autoclave and washer disinfector, and waste treatment practice was collected from this institution. At Landskrona Hospital one large reusable trocar is used approximately 500 times during its lifetime, thus 500 laparoscopic cholecystectomies were used as

the functional unit in the LCA. The small trocars could be used up to 100 times during its lifetime.

Thus, the reference flow for 500 procedures were:

- 2 large and 10 small reusable trocars for the reusable system
- 1000 large and 1000 small single use trocars in the single use system
- 1 large and 10 small reusable trocars, and 500 large single use trocars in the mixed system

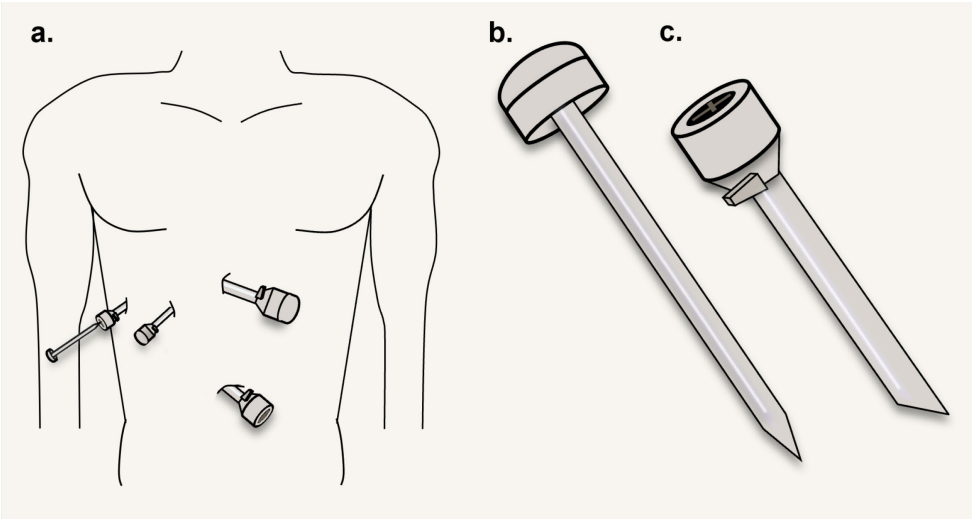

Figure 10. Trocars used for laparoscopic cholecystectomies.
(a) Placement of trocars for the procedure. Each trocar consists of (b) an obturator and (c) a cannula.

System boundaries for both single use and reusable trocars were set to include raw material and fibre production, for both the production of trocars and the production of their packaging. Waste scenarios and energy savings due to the recycling of packaging materials were included in the assessment. Similarly, transports from the manufacturer to the hospital and from hospital to waste management facilities were included.

In the sterilization process, trocars in the reusable system represented 2% of a fully loaded autoclave and about 8% of a fully loaded washer-disinfector, and model inputs were allocated based on the trocars share of a fully loaded machine. In the mixed system the reusable trocars represented 1.5% of a fully loaded autoclave and around 6% of a fully loaded washer-disinfector.

Inventory

Transport from the manufacturers in Ireland, Great Britain, the Netherlands and Germany, to Landskrona hospital in Sweden was modelled as a lorry weighing 16–32 metric tons with a Euro Class 5 engine for road transport and transport by boat was modelled as freight by sea on ferry.

The individual trocar package for new trocars was modelled based on data from the manufacturer of the trocars in the reusable trocar system. The sterilization wrap, used in the sterilization process and for the storage of the reusable trocars in between surgeries was modelled based on information from Landskrona hospital.

Based on information from Getinge AB, the manufacturer of the sterilization machines, the sterilization process was modelled with water from well (tap water), deionized water, detergent (alkylbenzene sulfonate), and average wastewater treatment for Europe.

For waste treatment, all trocars were assumed to be incinerated whereas paper and plastics from instrument packaging and sterilization wraps were assumed to be recycled.

Sensitivity analyses

As reusable trocars can break and have a shorter lifetime, or, in some cases be used more than 500 times two sensitivity analyses were performed where the functional unit was changed to 250 and 750 surgeries.

Data on some of the plastic materials was neither provided by the manufacturer nor included in the ecoinvent database. To assess the impact of our assumptions concerning these materials we performed two sensitivity analyses in which all plastic materials were changed to either polycarbonate or high-density polyethylene.

One of the manufacturers had air freight as an alternative and we therefore performed a sensitivity analysis using air freight as main mode of transportation.

To assess a situation in which the machines were not fully loaded two sensitivity analyses was performed in which we increased the allocation by two and five times the allocation in the primary analysis.

To test the model's sensitivity to the choice of electricity mix in the sterilization process two sensitivity analyses were performed. One with a high-climate-impact electricity mix exemplified by country specific data for Poland (76% hard coal and lignite, 14% renewable, 8% thermal gas, 2% nuclear) and one with a European average electricity mix (39% fossil fuel, 35% renewable energy, 26% nuclear) (65, 70).

LCA applied in Paper II

Goal and scope

We compared single use and reusable items used for CVC insertions, including scissor, needle holder, haemostatic forceps, bowl, gown and drape.

The functional unit for comparison was set to one CVC insertion and input data was primarily gathered from Helsingborg Hospital in southern Sweden. Three CVC kits were included in the analysis. The first kit consisted of both reusable instruments and textiles, the second kit of reusable instruments and single use textiles, and the third kit consisted of both single use instruments and textiles (**Figure 11**).

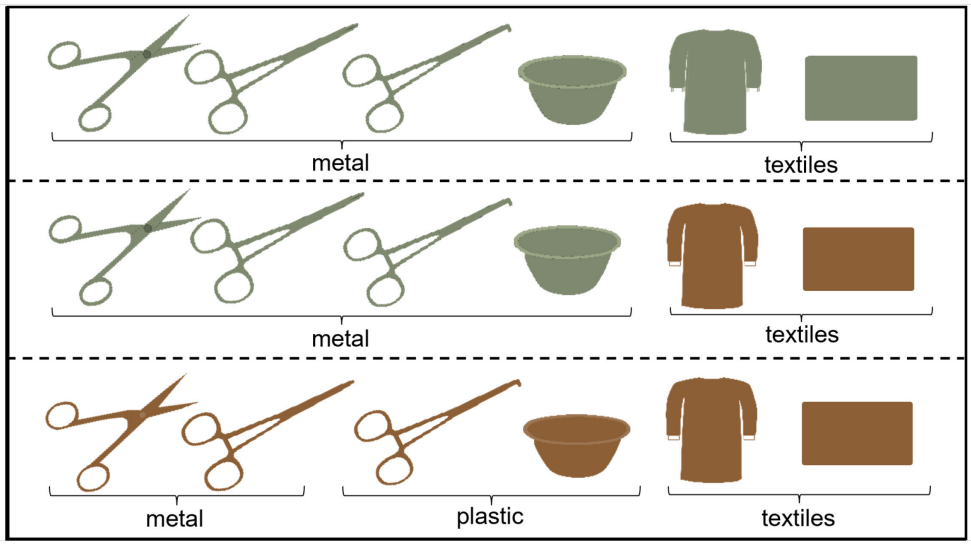

Figure 11 The CVC kits
The instruments (scissors, needle holder, haemostatic forceps, bowl) and the textiles (gown and drape) in the kit containing reusable metal items and reusable textiles (green), the kit containing reusable metal items and single use textiles (green / brown), and the kit containing single use metal and plastic items and single use textiles (brown).

In clinical practice, several additional items are used for CVC insertion but for the purpose of this analysis we only included items for which both single use and reusable alternatives were available.

The lifespan of reusable metal items was assumed to be 300 uses, based on information provided by the staff at Helsingborg Hospital. The reusable metal bowl

included in the set is virtually indestructible but for the purposes of the analysis it was assumed to have the same life span as the other reusable metal objects. The lifespan of the reusable sterile surgical gown and reusable sterile surgical drape were assumed to have a life span of 70 cycles based on information from the hospital's textile and laundry service.

LCC was performed to assess the direct financial costs of each system. The financial comparison, like the environmental assessment, only included the items that differ between the three kits. Costs for purchase and disposal of the items were included in the analysis and for the reusable items costs of laundry and sterilization was also included. Since repair of reusable instruments occurs after approximately 100-750 cycles (28, 71) repair costs were assumed to be negligible and therefore excluded from the analysis.

Inventory

The single use instruments and textiles as well as the reusable instruments were modelled based on information provided by the suppliers.

After use, the reusable scissors, needle holder, haemostatic forceps, and bowl were prewashed and transported to the sterile technical unit for subsequent sterilization. Energy and water consumption in the sterilization process was modelled based on information provided by the manufacturer of the autoclave and washer disinfector. Allocations in the sterilisation process was made based on that the reusable items used for one CVC insertion takes up 1.7% of the space in the autoclave and 6.7% of the space in the washer disinfector.

Since Helsingborg Hospital does not use any sterile reusable textiles, the model was based on information collected from the neighbouring county, Region Västra Götaland. Data concerning the energy and water consumption in the laundry process was obtained from the closest laundry capable of washing sterile textiles, located in Alingsås, Sweden. Transport to the laundry facility and back to Helsingborg Hospital was included in the analysis.

Waste treatment was modelled as incineration, including transport from Helsingborg hospital to the local waste disposal facility.

Sensitivity analyses

As single use scissors made from metal has previously been suggested to have a higher impact than comparable single use scissors made from plastic (71), we performed a sensitivity analysis to test the results robustness when using a single use scissor and needle holder made from plastic instead of metal.

To test the model's sensitivity to the choice of electricity mix in the sterilization and laundry process of the reusable metal items and textiles, two sensitivity analyses were performed. One with a high-climate-impact electricity mix exemplified by country specific data for Poland and one with a European average electricity mix (65, 70).

We performed a sensitivity analysis where the reusable metal items were sterilized at a remote location, using the same distance as for the transportation of textiles to the laundry facility, 520km.

We performed a sensitivity analysis in which we increased the allocation of water and electricity used in the sterilization process by 50% to simulate a model which includes standby time and accessory loads (72, 73).

We performed a sensitivity analysis where the reusable surgical textiles were modelled using a 50/50 cotton-polyester blend as this is an alternative to the 100% polyester used in our primary analysis.

In previous LCAs possible reuses of reusable metal instruments have varied between 300 and 3500 reuses (28, 71, 74) and possible reuses of surgical textiles has varied between 50-127 reuses (75), we therefor performed a sensitivity analysis that simulated 3500 reuses of metal instruments and 127 reuses of surgical textiles. We performed a second analysis with 100 reuses of metal instruments and 25 reuses of surgical textiles to model a scenario where items get misplaced. For these scenarios sensitivity analyses was performed also for the LCC.

Finally, we performed a sensitivity analysis to test the LCC results robustness to fluctuations in electricity prices, increasing the price per kWh 5-fold.

LCA applied in Paper III

Goal and scope

The aim was to estimate the climate impact per inpatient day of an ICU in Sweden. An additional aim was to identify modifiable elements that healthcare professionals and administrative staff can target to reduce the climate impact of intensive care.

The analysis included single use items, reusable instruments and textiles, pharmaceuticals and fluids, medical gases, diagnostic imaging, and energy consumption for HVAC, electronic equipment, and lighting. Patient food services were excluded from the analysis since ICU patients in Sweden rarely eat solid food and instead receive enteral or intravenous nutrition. Active Pharmaceutical Ingredients (APIs) were excluded from the primary analysis. See **Figure 12** for system boundaries.

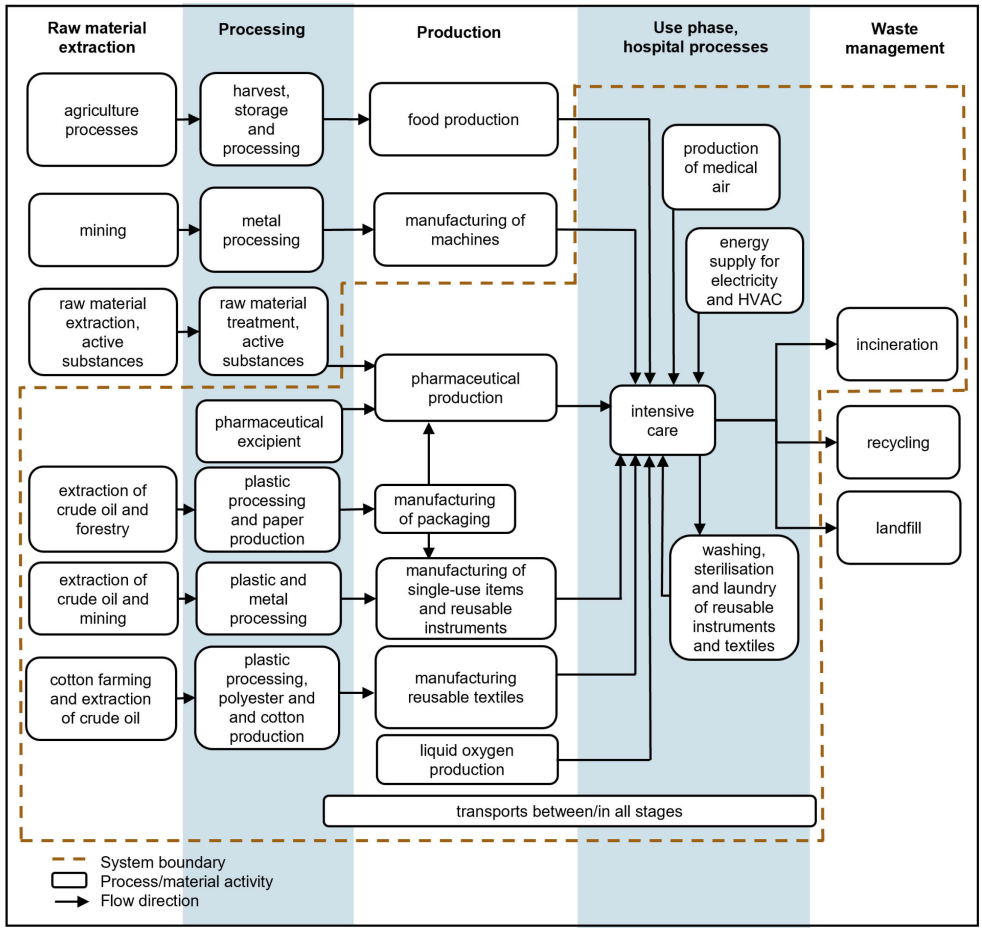

Figure 12. System boundaries for the LCA in Paper III
System boundaries showing material and processes included (within the dashed lines) and excluded (outside the dashed lines) in the analysis. Arrows show on physical flow directions.

Inventory

Input data were collected from January 1 to December 31, 2022, from the ICU at Helsingborg Hospital in southern Sweden. Information on patient demographics was retrieved from the Swedish Intensive Care Registry (76).

Quantities of single use items, reusable instruments, and pharmaceuticals and fluids were retrieved from procurement records. Materials and production processes were assumed to be identical to those for similar products for items without such information. Only the primary material and associated processes of each item or service were included in the analysis. Thus, if a product's weight could be attributed primarily to a certain type of plastic, we included only that plastic in our inventory.

Data needed to model the sterilisation process of reusable items was provided by the sterile technical unit at the hospital.

Quantities of reusable textiles were based on data from the unit's administrative records and physical inventory in the unit's storage. Data needed to model the production of textiles as well as the laundry process was provided by the hospital's textile and laundry service.

Waste generated at the ICU is generally treated as hazardous waste and incinerated and all waste management was therefore modelled as municipal incineration.

Inventory of medical gas consumption was based on the number of hours of each included respiratory support mode (76), and data needed to model the production of medical gases was provided by the hospital's engineers.

Data on the unit's energy consumption for electricity and HVAC was also provided by hospital engineers. The energy consumption for electronic equipment and lighting was modelled with an average Swedish electricity mix (66). The same electricity mix was used to model the sterilisation and laundry process of reusable textiles and instruments. The energy requirement for HVAC was modelled as Swedish cogeneration with biogas (biowaste, sewage sludge) (65).

The type and number of diagnostic imaging procedures were retrieved from the unit's administrative records, and the data needed to model diagnostic imaging were based on a previous study (77), adapted to a Swedish setting.

Sensitivity analyses

We performed a sensitivity analysis to assess the impact of using high-climate-impact energy sources. A Polish electricity mix (65) was used to model the unit's electricity consumption for electronic equipment and lighting, liquid oxygen production, diagnostic imaging, and the sterilisation and laundry of reusable textiles and instruments. Polish cogeneration with hard coal (65) was used to model the energy requirement for HVAC in this analysis.

Because the climate impact of pharmaceuticals that are used in the ICU is complex, laborious to model, and rarely known, we excluded them from our primary analysis. To assess the effects of this omission, we performed a sensitivity analysis using previously published data on the climate impact of commonly used APIs (78).

LCA applied in Paper IV

Input data

We used input data from the protocolized REDUction of non-resuscitation fluid versus usual care in SEptic shock patients (REDUSE) Feasibility Trial. It was an investigator-initiated, multicentre, parallel-group randomized trial which included sepsis patients between March 7 and September 13, 2022. The trial compared protocolized reduction of non-resuscitation fluids (intervention) to usual care (control) during the first three days after inclusion (79). The trial included a total of 98 patients, of which 49 were allocated to the intervention, and 49 were allocated to usual care. Fluid data was available for 44 and 48 participants in the intervention and control group, respectively, and these data were used in the LCA.

Goal and scope

The functional unit for the assessment was the total volume of intravenous solutions of sodium chloride, Ringer-acetate and glucose solutions given per patient during the first 3 days in the ICU after inclusion in the trial. The analysis included 0.9% sodium chloride, Ringer-acetate, and glucose solutions (25g, 50g, 100g, 200g, and 300g/L), including packaging. All other types of fluids and materials was outside the boundaries of this LCA (**Figure 13**).

Inventory

Real-life data on material and processes was collected from hospitals and manufacturers. We modelled 1 ml of each fluid including packaging modelled as the weight of packaging per ml fluid, to be able to create a model for each patient included in the trial.

Statistical analyses Paper IV

Prior to the analysis of data, we published a statistical analysis plan (Appendix). Analyses were performed in SAS Studio (v. 9.4) (80).

Analysis of environmental effects in the two groups using conventional medical statistics

For each patient, we used the point estimate for respective outcome as calculated in the LCIA. We analysed each of the 18 continuous outcomes using a general linear

model adjusted for site (six levels) as a fixed effect factor, which is common for multicentre clinical trials. For each outcome, the model included: the follow-up score as the dependent variable and treatment group as the primary independent variable, while adjusting for clinical site as a categorical factor. Estimated between-group differences is reported as the contrast between the predicted (adjusted) group means, expressed as least squares means (also known as marginal means). For each outcome, we present the adjusted mean for each group with standard error (SE), the adjusted mean difference, the corresponding 95% confidence interval (CI), and the two-sided p-value.

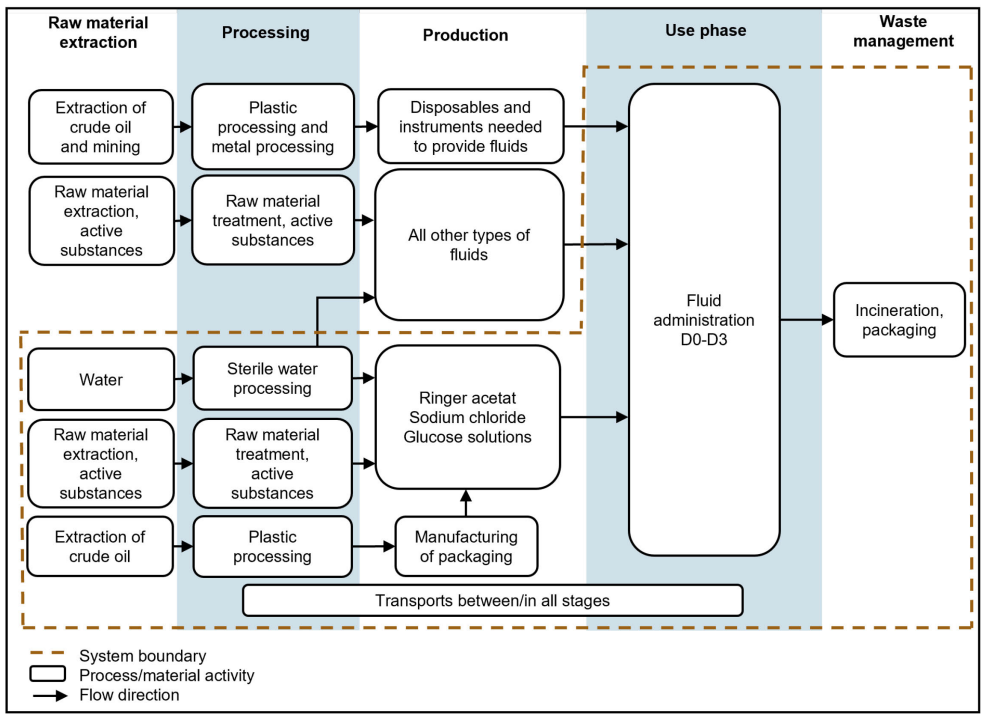

Figure 13. System boundaries for the LCA in Paper IV.
System boundaries showing material and processes included (within the dashed lines) and excluded (outside the dashed lines) in the analysis. Arrows show on physical flow directions.

Analysis of environmental effects in the two groups using a mixed model

To incorporate the uncertainty of the LCA alongside the uncertainty of the intervention effect, we analysed the Monte Carlo–generated repeated datasets within a mixed-effects framework. The outcomes were analysed using a linear mixed-effects model to compare the experimental intervention with the control comparator while explicitly accounting for uncertainty arising from the LCA. For

each participant, 100 Monte Carlo–derived LCA realizations were available and treated as repeated observations. The model included treatment group and study site as fixed effects, with a participant-specific random intercept to account for within-participant correlation. Repeated Monte Carlo samples were modelled within participants using a compound symmetry covariance structure, reflecting equal correlation across LCA realisations for a given individual. Models were estimated using restricted maximum likelihood (REML), and inference for fixed effects was based on the Kenward–Roger small-sample degrees-of-freedom approximation.

Adjusted group means and between-group differences were obtained from model-based least squares means, with corresponding 95% CI. The primary estimand was the adjusted mean difference in environmental impact between intervention and control groups. For each outcome, we present the adjusted mean for each group with SE, the adjusted mean difference, the corresponding 95% CI, and the two-sided p-value.

Comparison of the two statistical approaches

To evaluate the effect of the two statistical approaches on the resulting treatment effect, we compared whether the adjusted mean differences differed across methods. Each of the 18 outcomes yielded two independent sets of estimates: one from the conventional general linear model and one from the mixed-effects model. These estimates were compared using the adjusted mean difference between groups with 95% CI and two-sided p-values to enable direct comparison. Following the general framework described by Altman & Bland, comparisons focused on whether the two treatment effect estimates differ beyond what would be expected from their respective uncertainties (81). Concordant estimates – similar point estimates with overlapping confidence intervals – support robustness of the main effect independent of the method used. Conversely, meaningful divergence between the two estimates (e.g., non-overlapping confidence intervals or relevant shifts in magnitude) indicate that incorporating LCA-related uncertainty affects inference. The results for the comparison between methods are expressed as adjusted group differences derived from the marginal (least squares) means to ensure interpretability and comparability across modelling approaches.

Results

Paper I

We compared environmental impacts of using single use and reusable trocars for laparoscopic cholecystectomies.

LCIA results

The reusable system had the lowest impact on all endpoint categories, whereas the single use system had the highest impact on all endpoints (**Table 3**).

Table 3. LCIA endpoint category results in Paper I

Environmental impact of the single use, mixed and reusable trocar systems used for 500 laparoscopic cholecystectomies on the endpoint categories resource use, climate change, ecosystem quality, and human health.

Endpoint category	Unit	Single use system	Mixed system	Reusable system
Resource use	MJ primary	8,015	7,573	2,870
Climate change	kg CO_2 eq	564	508	118
Ecosystem quality	PDF*m2*yr	168	135	93
Human health	DALY	0.00034	0.0003	0.0001

Compared to the single-use system, the reusable system had a 64% lower impact on resource use [median difference (Δ) 5,160 MJ primary (95%-reference interval: 4,400–5,770)], a 79% lower impact on climate change [Δ 446 kg CO 2 eq (413–483)], a 45% lower impact on ecosystem quality [Δ 79 PDF/m^2*yr (24–112)], and a 71% lower impact on human health [Δ 2.4x10 DALY/person/yr (1.3x10-4-7-4x10-5)].

Each life cycle phase's contribution to the respective system's impact on all endpoints is presented in **Figure 14**. Briefly, the production of trocars and their packaging contributed by 70–95% of the impact on the resource use and human health endpoints for all product systems. Similarly, production were the largest contributor to the climate change endpoint for all product systems, representing 60–70% of the total impact. The production phase represented 90% of the single use system's impact, 65% of the mixed system's impact, and 35% of the reusable system's impact on the ecosystem quality endpoint. The sterilization process contributed to 35% of the mixed system's impact and 65% of the reusable system's impact on the ecosystem quality endpoint.

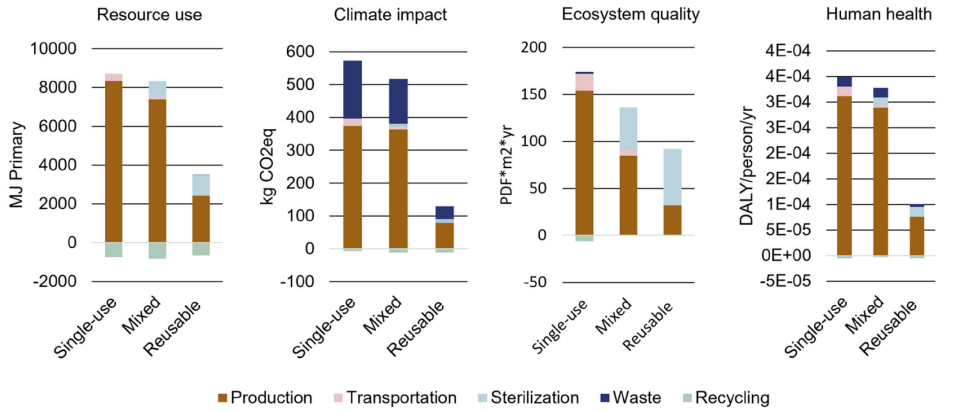

Figure 14. Contribution analysis for endpoint category results in Paper I.
The contribution from production, transportation, sterilization, waste, and recycling to the product systems' total impact on each endpoint category.

LCC results

The result of the LCC showed that the cost for the single use trocar system was 37,567 euros for 500 procedures, which is about twice as expensive as the financial costs for the reusable and mixed trocar systems (**Table 4**).

Table 4. LCC results in Paper I
Total cost for the single use, mixed, and reusable trocar systems used for 500 procedures, for the primary analysis and the four sensitivity analyses.

	Single use system	Mixed system	Reusable system
Primary analysis	37,567 €	18,560 €	17,359 €
250 procedures	18,783 €	10,624 €	10,643 €
750 procedures	56,350 €	27,663 €	24,076 €
2-times allocation in sterilization process	37,567 € [a]	22,400 €	19,692 €
5-times allocation in sterilization process	37,567 € [a]	29,398 €	26,690 €

[a] Based on the primary analysis since sterilization is not part of the single-use trocar system's life cycle.

The purchase cost was the major cost for all systems. Purchase represented over 99% of the total cost of the single use system, 73% of the total cost of the mixed trocar system, of which most could be referred to the purchase of single use trocars, and 63% of the total cost of the reusable trocar system, of which most could be referred to the purchase of single use membranes. For the reusable and mixed trocar

systems labour costs and the allocated costs of purchase and service of the autoclaves and washer-disinfectors contributed by 8-15% of the total cost

Sensitivity analyses

The single use trocar system continued to be the most expensive trocar system in all sensitivity analyses (**Table 4**).

The larger impact of the single use system on climate change and on human health compared to the reusable system remained in all sensitivity analyses. In contrast, the difference between these two systems regarding effects on the resource endpoint was no longer apparent when using a high-climate-impact electricity mix in the sterilization process (**Figure 15**).

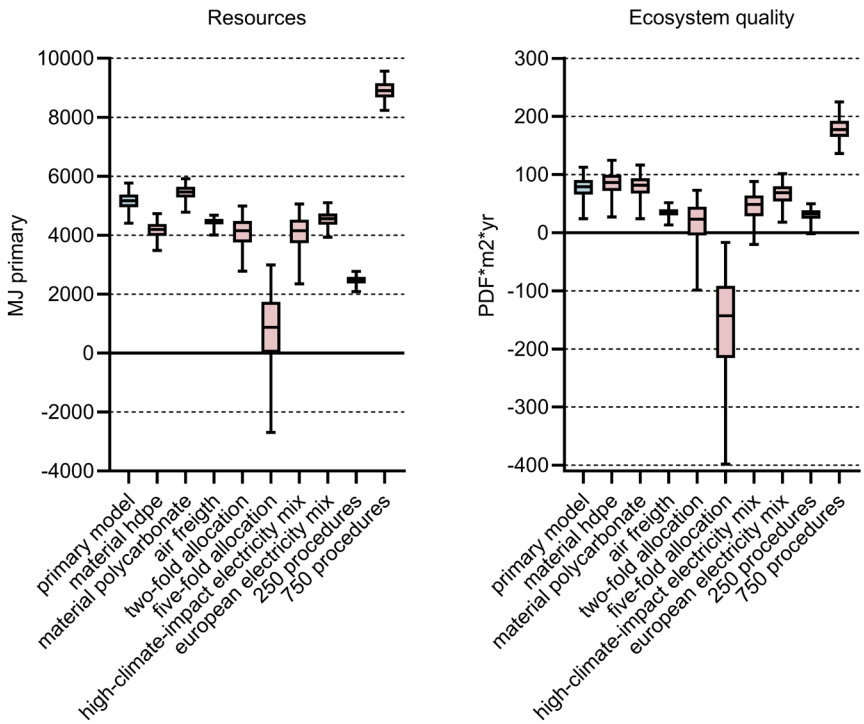

Figure 15. Median difference between the single-use and reusable trocar systems in the primary and sensitivity analyses.

The median differences of primary analysis (blue) compared to sensitivity analyses (pink) Data are presented as median and the 2.5th to 97.5th percentiles. There is a difference between the two alternatives if the 2.5th percentile is ≥ 0 or the 97.5th percentile is ≤ 0. A positive value indicate that the single-use system had a higher impact.

Similarly, there were no difference between these systems on the ecosystem quality endpoint when using a high-climate-impact electricity mix in the sterilization process, reduced number of reuses, or with an increased allocation in the sterilization process. With a five-fold allocation in the sterilization process the reusable system got a higher impact than the single use system on the ecosystem quality endpoint (**Figure 15**).

The larger impact of the mixed system on climate change, human health and resource use compared to the reusable system remained in all sensitivity analyses. There was however no difference between the impact of the mixed system and reusable system on the ecosystem quality endpoint when using an increased allocation in the sterilization process.

Paper II

We compared environmental impacts of using single use and reusable items and sterile textiles in kits used for CVC insertions.

LCIA results

The CVC kit with reusable items and textile had the lowest impact on all endpoint categories, whereas the single use kit had the highest impact on all endpoints (**Table 5**).

Table 5. LCIA results in Paper II.
Environmental impact of the single use, mixed and reusable CVC kits used for one procedure on the endpoint categories resource use, climate change, ecosystem quality, and human health.

Endpoint category	Unit	Single use kit	Mixed kit	Reusable kit
Resource use	MJ primary	41	34	14
Climate change	kg CO_2 eq	2.3	1.7	0.2
Ecosystem quality	PDF*m2*yr	3.5	0.9	0.5
Human health	DALY	6x10-6	1,6x10-6	3.1x10-7

Compared to the single use kit, the kit with reusable instruments and reusable textiles had a 65% lower impact on resource use [Δ: 27 MJ primary (19–33)], a 90% lower impact on climate change [Δ: 2.1 kg- CO_2eq (1.9–2.5)], an 85% lower impact on ecosystem quality [Δ: 3 PDF*m2*yr (1.6–4.5)], and a 95% lower impact on human health [Δ: 5.8×10^{-6} DALY/person/yr (4.8×10^{-6}-7.1×10^{-6})].

Each life cycle phase's contribution to the respective system's impact is reported in detail in **Figure 16**. The production phase contributed the most to the total impact

from the single use and the mixed kit on all endpoints. Sterilization and laundry contributed the most to the total impact from the reusable kit on the resource use and ecosystem quality endpoints, all life cycle phases could be attributed about the same share of the reusable kit's total impact on climate change and human health.

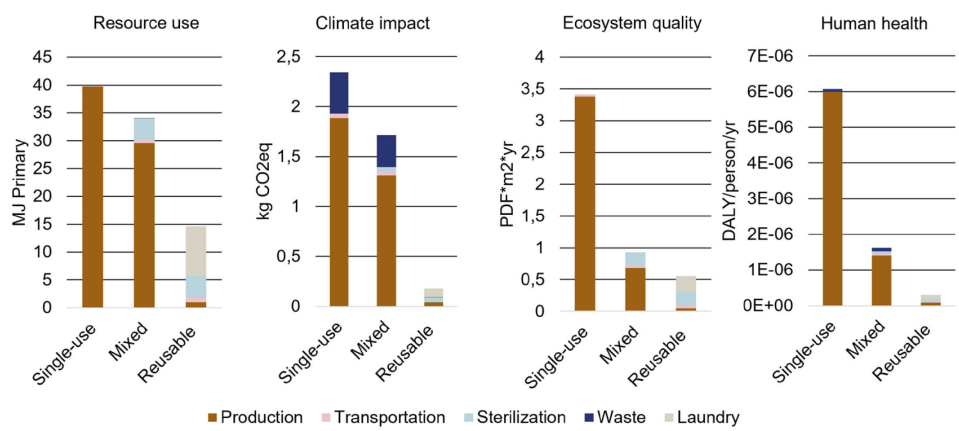

Figure 16 Contribution analysis for endpoint category results in Paper II.
The contribution from production, transportation, sterilization, waste, and laundry to the CVC kits' total impact on each endpoint category.

LCC results

The single use kit and mixed kit had similar costs and were about 60% more expensive compared to the reusable kit (**Table 6**).

Table 6. LCC results
Cost comparison. Total cost for each of the kits for the primary model and sensitivity analyses.

	Single use kit	Mixed kit	Reusable kit
Primary model	9.2 €	9.1 €	5.7 €
100 / 25 reuses of reusable items and textiles	9.2 €	10.1 €	6.7 €
3500 / 127 reuses of reusable items and textiles	9.2 €	8.6 €	5.2 €
5-fold electricity price	9.2 €	9.3 €	6.1 €

Conversion of the prices in Swedish krona to Euro was based on exchange rates on the 30th of mars 2022 (1sek = €0.097).

Sensitivity analyses

The lower impact of the reusable kit on all endpoints compared to the single use kit and the mixed kit remained in all sensitivity analyses.

The sensitivity analyses in the LCC showed that the reusable kit continued to be the cheapest in all sensitivity analyses. The mixed kit was more expensive than the single use kit when using fewer number of reuses or when using a 5-fold electricity price (**Table 6**).

Paper III

We estimated the total climate impact per inpatient day from an intensive care unit in southern Sweden, including energy requirement, single use products, reusable items and textiles, pharmaceuticals, and medical gases.

Demographics

The ICU at Helsingborg Hospital cares primarily for adult medical and surgical patients and has 4 treatment rooms with 8 beds. In 2022, 539 patients were treated for 1779 inpatient days. Thus, 0.056% (1/1779) of all items and resources that were included in the analysis were allocated to one inpatient day. Patient characteristics and treatment intensity are presented in **Table 7**.

Table 7. Patient characteristics and treatment intensity at the Helsingborg Hospital ICU, 2022.
Data are presented as median and interquartile range (IQR) or n (%) as appropriate.

Number of admissions	539	
Number of patients	495	
Number of inpatient days	1,779	
Postoperative patients	66	(12.2%)
Length of ICU stay in hours	34	(15–87)
Number of patients receiving invasive ventilation	270	(50%)
Total time with invasive ventilation (h)	22,506	
Number of patients receiving non-invasive ventilation	101	(19%)
Total time with non-invasive ventilation (h)	2,421	
Number of patients receiving high-flow oxygen	108	(20%)
Total time with high-flow oxygen (h)	10,248	
Number of patients receiving CRRT	41	(8%)
Total time with CRRT (h)	3,679	

CRRT = continuous renal replacement therapy.

Inventory

A total of 98 types of single use items and 13 types of reusable instruments were included in the analysis. A total of 0.6 washer-disinfector runs in the ICU were attributed to each inpatient day to wash reusable instruments. A total of 0.09 washer-disinfector runs and 0.009 autoclave runs in the sterilisation unit were attributed to each inpatient day. A total of 10 types of reusable textiles were included in the

analysis, and 5.4 kg of textiles was attributed to each inpatient day. The laundry of textiles required 43 litres of water and wastewater treatment, 111 km of transport, and 7.1 kWh of electricity per inpatient day. A total of 45 pharmaceutical products and fluids were included in the analysis. The main excipient in most products was ultrapure water.

Medical air was produced on site at the hospital, and liquid oxygen was produced off-site in Sweden and delivered to the hospital by lorry. An average of 5.8 hours of high-flow oxygen therapy (8641 litres of medical air, 8641 litres of oxygen), 1.4 hours of non-invasive ventilator treatment (735 litres of medical air, 490 litres of oxygen), and 12.6 hours of invasive ventilator treatment (4554 litres of medical air, 3036 litres of oxygen) were attributed to each inpatient day.

The ICU's HVAC consumed an average of 74.1 kWh per inpatient day, and electronic equipment and lighting consumed an average of 48.6 kWh per inpatient day.

An average of 0.12 CTs, 0.02 MRIs, 0.51 X-rays, and 0.02 ultrasound examinations were ordered by the ICU and performed by the Department of Radiology per inpatient day.

LCIA results

The median climate impact from one inpatient day was 30 kg CO_2eq (95%-reference interval: 27–31) (**Table 8**).

Table 8. Climate impact per inpatient day for the primary and sensitivity analyses in Paper III. Primary analysis with low-climate-impact energy sources. Sensitivity analysis with high-climate-impact energy sources. Result presented as median, 95% reference interval, percentage of the total climate impact in each analysis, and the increased impact between the primary and sensitivity analyses.

Categories	Primary analysis (low-climate-impact energy sources)		Sensitivity analysis (high-climate-impact energy sources)		Increase in climate impact
	kg CO_2eq per inpatient day	% of total	kg CO_2eq per inpatient day	% of total	
Single use items	19 (18–20)	63%	19 (18–20)	15%	-
Electricity	3 (2.3–3.9)	10%	50 (37–67)	39%	+1567%
HVAC	2.5 (2–3)	9%	16 (14–20)	13%	+540%
Pharmaceuticals and fluids	1.9 (1.7–2.2)	7%	1.9 (1.7–2.2)	2%	-
Medical gases	1.5 (1.2–1.9)	5%	24 (18–33)	19%	+1500%
Reusable textiles	0.78 (0.7–0.9)	3%	7.7 (5.7–10)	6%	+887%
Diagnostic imaging [a]	0.63	2%	2.5	2%	+297%
Reusable instruments	0.5 (0.4–0.6)	2%	5.1 (3.9–6.8)	4%	+920%
Total [b]	30 (27–31)		126.5 (103–154)		+322%

[a] Results adapted from a previous study [15], no uncertainty is available. [b] Uncertainty range does not cover diagnostic imaging.

The contribution analysis showed that single use items represented 63% of the total impact, followed by the energy consumption for electric equipment and lighting (10%) and HVAC (9%), pharmaceuticals and fluids (7%), medical gases (5%), reusable textiles (3%), diagnostic imaging (2%), and reusable instruments (2%) (**Figure 17**, **Table 8**). The contribution analysis showed that most of the single use items' climate impact was generated by 5 items. Aprons accounted for 14% of the single use items' total climate impact, followed by gloves and syringes accounting for 12% each, woven gauze 11%, and wash wipes 8% (**Figure 17**).

The production of liquid oxygen represented nearly all the impact from medical gases, of which over 70% was used for high-flow oxygen therapy. The production of packaging represented nearly all impact of pharmaceuticals and fluids.

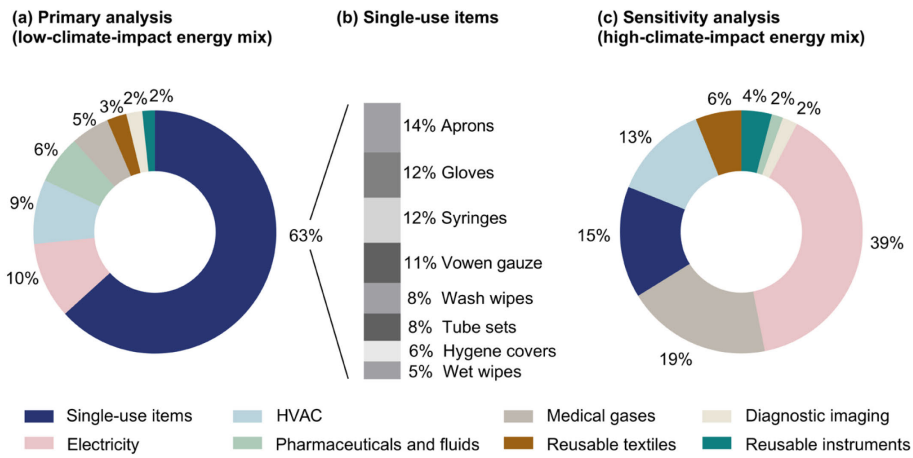

Figure 17. Contribution analysis for the primary and sensitivity analyses in Paper III
Contribution analysis showing the impact from various activities in the ICU, based on results from the (a) primary analysis using a low-climate-impact energy mix, including (b) the single use items that contributed to ≥ 5% of the total impact from single use items, and the (c) sensitivity analysis using a high-climate-impact energy mix in the model. HVAC = heat, ventilation, and air conditioning.

Sensitivity analyses

Our sensitivity analysis using a high-climate-impact energy mix increased the climate impact by 322% compared to the primary analysis, to a median of 126.5 kg CO_2eq (103-154) per inpatient day (**Table 8**). This increase could primarily be explained by an increased impact from electricity, HVAC, and medical gases.

To assess the effects of excluding APIs in our primary analysis, we performed a sensitivity analysis using previously published data on the climate impact of 12

common APIs used in the ICU. The analysis only marginally increased the climate impact per inpatient day, by 0.05 kg CO_2eq or 0.1%.

Paper IV

We estimated the climate and environmental impacts of two treatments compared in a clinical trial and compared two statistical approaches to assess the difference between the treatment groups.

Life cycle inventory

The intervention group received a median of 2,326 ml (IQR: 1,340 – 4,039) of fluid per patient and the control group received a median of 5,531 ml (IQR: 3,977 – 7,374) of fluid per patient, in the first three days after inclusion (**Table 9**). The median of sodium chloride, Ringer-acetate, and the glucose solutions administered per patient to the intervention and control group, as well as the median difference between the groups are presented in **Table 9**.

Table 9. Intervention data included in the LCA.
Data are presented as median (IQR).

Volume (ml)	Intervention (N=44)	Control (N=48)	Difference between medians
Ringer-acetat	950 (140 ; 2000)	1,000 (217 ; 2,478)	50 (77 ; 478)
Sodium chloride 9g/L	685 (271 ; 1356)	1,342 (620 ; 2,295)	658 (349 ; 939)
Glucose 25g/L		0 (0 ; 0)	0 (0 ; 0)
Glucose 50g/L	162 (0 ; 346)	427 (0 ; 1,204)	265 (0 ; 858)
Glucose 100g/L	0 (0 ; 0)	1,540 (0 ; 2,568)	1,540 (0 ; 2,568)
Glucose 200g/L	0 (0 ; 137)	0 (0 ; 0)	0 (0 ; 137)
Glucose 300g/L	0 (0 ; 0)	0 (0 ; 0)	0 (0 ; 0)
Total amount of fluids first 3 days after inclusion	2,326 (1,340 ; 4,039)	5,531 (3,977 ; 7,374)	3,205 (2,638 ; 3,336)

Life cycle impact assessment

When using a general linear model, the marginal mean for the primary outcome, global warming, was 2.71 kg CO_2eq per patient (SE: ± 0.38) in the intervention group and 6.15 kg CO_2eq per patient (± 0.37) in the control group, with a mean difference of 3.45 kg CO_2eq per patient (95% CI: 2.50 to 4.39, P= <.0001) (**Figure 18**).

When using a mixed model, the marginal mean was 2.72 kg CO_2eq per patient (± 0.38) in the intervention group and 6.14 kg CO_2eq per patient (± 0.38) in the control group, with a mean difference of 3.42 kg CO_2eq per patient (95% CI: 2.47 to 4.37, P= <.0001) (**Figure 18**).

Results for the exploratory outcomes are presented in **Table 10**.

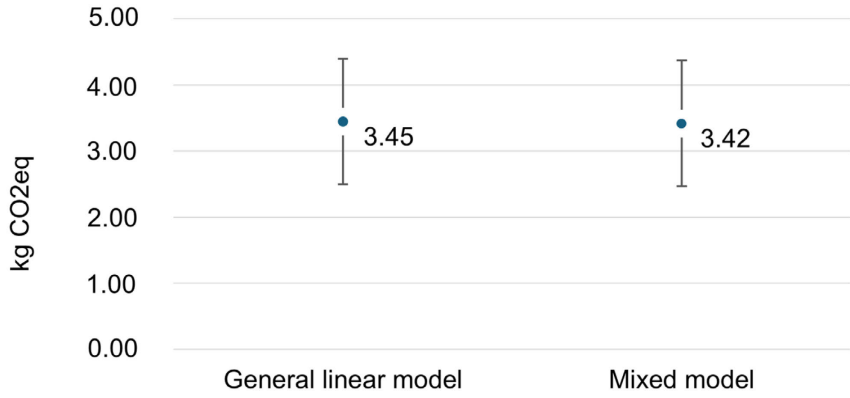

Figure 18. Difference between groups using the two statistical approaches compared in Paper IV
Marginal mean difference per patient between the control group and the intervention group with 95% CI on the global warming outcome using a general linear model and a mixed model.

Comparison between statistical methods

The adjusted mean difference between the methods was 0.03 kg CO_2eq per patient (95% CI: -1.45 to 1.51), meaning that the outcome of the models was similar, with almost no difference in results regardless of which method was used (**Table 10**).

The results were concordant also for 14 of the exploratory outcomes: fine particulate matter formation, fossil resource scarcity, freshwater ecotoxicity, freshwater eutrophication, human carcinogenic toxicity, human non-carcinogenic toxicity, ionizing radiation, land use, marine ecotoxicity, marine eutrophication, mineral resource scarcity, ozone formation ecosystem, terrestrial acidification, and terrestrial ecotoxicity (**Table 10**).

For the exploratory outcomes stratospheric ozone depletion, ozone formation human health, and water consumption the mixed model did not converge, meaning that only results from the general linear model was provided and no comparison between methods could be made (**Table 10**),

Table 10. Outcomes using a general linear model and a mixed model in Paper IV

Adjusted mean for each group and standard error (SE), adjusted mean difference and corresponding 95% CI, and the two-sided p-value using the general linear model and the mixed model. Comparison between approaches presented as adjusted group differences with the corresponding 95% CI.

	General linear model				Mixed model				Contrast between model
	Intervention: Mean (SE)	Control: Mean (SE)	Difference (95%CI)	P-value	Intervention: Mean (SE)	Control: Mean (SE)	Difference (95%CI)	P-value	Difference between differences (95%CI)
Primary outcome									
Global warming (kg CO_2 eq)	2.71 (0.38)	6.15 (0.37)	3.45 (2.5 – 4.39)	< .0001*	2.72 (0.38)	6.14 (0.38)	3.42 (2.47 – 4 .37)	< .0001*	0.027 (-1.45 – 1.51)
Exploratory outcomes									
Fine particulate matter formation ($PM_{2.5}$ eq)	0.0035 (0.0005)	0.0081 (0.0005)	0.0046 (0.0034 – 0.0058)	< .0001*	0.0035 (0.0005)	0.0081 (0.0005)	0.0046 (0.0033 – 0.0058)	< .0001*	0 (-0.002 – 0.002)
Fossil resource scarcity (kg oil eq)	1.07 (0.14)	2.39 (0.14)	1.32 (0.96 – 1.68)	< .0001*	1.08 (0.15)	2.34 (0.15)	1.26 (0.87 – 1.64)	< .0001*	0.07 (-0.52 – 0.65)
Freshwater ecotoxicity (kg 1.4-DCB eq)	0.12 (0.02)	0.27 (0.02)	0.15 (0.11 – 0.19)	< .0001*	0.13 (0.02)	0.2 (0.027)	0.15 (0.1 – 0.2)	< .0001*	0 (-0.07 – 0.07)
Freshwater eutrophication (kg P eq)	0.0013 (0.0002)	0.0029 (0.0002)	0.0016 (0.0011 – 0.002)	< .0001*	0.0014 (0.0002)	0.0031 (0.0002)	0.0017 (0.0012 – 0.0023)	< .0001*	0 (-0.001 – 0.001)
Human carcinogenic toxicity (kg 1.4-DCB eq)	0.47 (0.07)	1.04 (0.06)	0.57 (0.41 – 0.74)	< .0001*	0.37 (0.15)	0.94 (0.15)	0.57 (0.2 – 0.95)	0.0032*	0 (-0.45 – 0.45)
Human non-carcinogenic toxicity (kg 1.4-DCB eq)	2.6 (0.36)	5.78 (0.36)	3.18 (2.27 – 4.09)	< .0001*	-86 (125)	-83 (124)	2.78 (-310 – 316)	0.9859	0.4 (-345 – 346)
Ionizing radiation (kBq Co-60 eq)	0.18 (0.02)	0.39 (0.02)	0.21 (0.15 – 0.27)	< .0001*	-1.5 (6.1)	5.8 (6.1)	7.3 (-8 – 22.6)	0.346	7.1 (-24 – 9.8)
Land use (m^2/a crop eq)	0.15 (0.03)	0.52 (0.03)	0.37 (0.29 – 0.45)	< .0001*	0.15 (0.03)	0.52 (0.03)	0.37 (0.28 – 0.45)	< .0001*	0.003 (-0.13 – 0.13)
Marine ecotoxicity (kg 1.4-DCB eq)	0.19 (0.03)	0.43 (0.03)	0.23 (0.16 – 0.3)	< .0001*	0.2 (0.03)	0.43 (0.03)	0.23 (0.16 – 0.3)	< .0001*	0.001 (-0.109 – 0.106)
Marine eutrophication (kg N eq)	0.0003 (0.0001)	0.0011 (0.0001)	0.0008 (0.0006 – 0.001)	< .0001*	0.0003 (0.0001)	0.0011 (0.0001)	0.0008 (0.0006 – 0.001)	< .0001*	0 (0 – 0)
Mineral resource scarcity (kg Cu eq)	0.009 (0.001)	0.021 (0.001)	0.011 (0.008 – 0.015)	< .0001*	0.009 (0.001)	0.021 (0.001)	0.011 (0.008 – 0.015)	< .0001*	0 (-0.005 – 0.005)

[a] mixed model could not generate results. Abbreviations: SE = Standard Error; CI = confidence interval. * = P < 0.05

Table 10 (continuation). Outcomes using a general linear model and a mixed model in Paper IV

Ozone formation, human health (kg NO_x eq)	0.006 (0.001)	0.013 (0.001)	0.007 (0.005 – 0.009)	< .0001*	- [a]	- [a]	- [a]		- [a]
Ozone formation, terrestrial ecosystem (kg NO_x eq)	0.006 (0.001)	0.014 (0.001)	0.008 (0.006 – 0.01)	< .0001*	0.006 (0.001)	0.014 (0.001)	0.008 (0.006 – 0.01)	< .0001*	0 (0 – 0)
Stratospheric ozone depletion (kg CFC-11 eq)	1.06E-06 (2.1E-07)	3.3E-06 (2.1E-07)	2.3E-06 (1.7E-06 – 2.8E-06)	< .0001*	- [a]	- [a]	- [a]		- [a]
Terrestrial acidification (kg SO_2 eq)	0.0074 (0.0011)	0.0174 (0.0011)	0.0099 (0.0073 – 0.0126)	< .0001*	0.0075 (0.0011)	0.0174 (0.0011)	0.0099 (0.0072 – 0.0126)	< .0001*	0 (-0.004 – 0.004)
Terrestrial ecotoxicity (kg 1.4-DCB eq)	62 (9)	128 (9)	66 (43 – 88)	< .0001*	63 (9)	127 (9)	64 (41 – 87)	< .0001*	1.6 (-34 – 37)
Water consumption (m^3)	0.025 (0.004)	0.06 (0.004)	0.036 (0.027 – 0.045)	< .0001*	- [a]	- [a]	- [a]		- [a]

[a] mixed model could not generate results.

Ethical considerations

In **Paper I**, **Paper II**, and **Paper III**, no personal data was used and therefore applications to the ethical review board were not required. In **Paper IV**, we used anonymised data from the REDUSE-feasibility trial including information on study site and fluid volumes given to each of the enrolled patients. The original trial protocol was approved by the Swedish ethics review authority (#2020-06594, 08 August 2021) and followed the ethical standards of the 1964 Helsinki declaration and its later amendments.

Although no personal data was used in **Paper I**, **Paper II**, and **Paper III** there are other important ethical consideration that has been considered throughout the conduct and writing of the included papers and this thesis. One aspect has to do with the balancing of the clinical effects on the patient level and the indirect effects that the clinical decisions have on public health in terms of environmental impacts. In a situation in which the clinical effect on the patient level does not differ between compared interventions or products, the choice with the lowest climate- and environmental impact should be chosen. As an example, in both **Paper I** and **Paper II**, no evidence was found that supported the use of either single use or reusable items. With the reusable alternatives having both lower environmental impacts as well as financial costs the ethical choice would be to use reusable instruments in a setting comparable to the one modelled in the two papers. However, in a situation in which an intervention has a beneficial effect on a patient level and detrimental effect on public heath a potential ethical conflict arises. This potential conflict is compounded by the fact that the clinical effect on a patient level is often relatively certain whereas environmental effects on public health are less certain.

Another ethical conflict can arise if LCA results that compare two systems show on environmentally beneficial results for both systems but for different impact categories. The results in **Paper I**, **Paper II**, and **Paper IV**, which was comparative LCAs, show on concordant results across impact categories, favouring the use of the reusable systems and of the intervention. An example of how a conflict can arise would be if one system is favourable in terms of climate impact whereas the compared system is favourable in terms of water use. To add another layer of complexity to this conflict, different geographical areas might be affected differently by the same type of impact. Healthcare systems in Western countries, as major contributors to GHG emissions, have a moral responsibility to consider the global consequences of their practices. Many products that are used in high income

countries are produced in low- and middle-income countries (LMIC), that are both disproportionally affected by climate change as well as more vulnerable to other types of environmental hazards such as water scarcity or the emission of toxic pollutants near manufacturing sites. Future medical advancements in wealthier nations should not come at the cost of the health and well-being of poorer communities. Healthcare interventions, particularly those with substantial environmental footprints, risk exacerbating existing inequalities by disproportionately harming vulnerable populations and fostering an unjust allocation of healthcare resources.

Prioritizing interventions that reduce GHG emissions often aligns with more efficient resource use, addressing both environmental and social justice concerns. Although that might be true in most cases, environmental impacts beyond climate change should not be neglected without proper consideration of what the different contexts are throughout the life cycle of the system or product assessed in the LCA, and how these contexts might be affected differently.

Discussion

Compared to other environmental assessments

The results from **Paper I** and **Paper II** suggest that using reusable instruments and textiles are both environmentally and financially beneficial.

The finding that the single use trocar system and CVC kit had higher environmental impacts compared to that of the reusable alternatives aligns with a growing body of literature suggesting that the environmental impact of reusable products used perioperatively is lower than that of single use alternatives. Reusable scissors (71), laryngeal masks (27), laryngoscope blades and handles (26), laparotomy pads (82), anaesthetic drug trays (30), gowns and drapes (75), and sharps containers (83) have all been suggested to have a lower environmental impact compared to single use alternatives.

The results of both the environmental and financial assessment in **Paper I** further align with the results from an early economic an environmental comparison between single use and reusable instruments for laparoscopic cholecystectomies (84), as well as a recent study that estimated the environmental impact of single use and hybrid trocars (35).

However, there are studies in which reusable instruments have been suggested to have larger environmental impacts than their single use alternatives. Sets of instruments for spinal fusion surgery (85) and CVC insertions (28) with reusable components have been suggested to have greater environmental impacts than their single use alternatives. In both studies this result could be explained by factors related to the sterilization process. In one of the studies the reusable alternative included long transportation distances between each surgery and the sterilization facility (85), and in the other study high-climate-impact energy sources was used to model the electricity consumption (28). Although reusable options have lower environmental impacts than their single use alternatives in most settings, it is important to note that results cannot be generalized without careful consideration of the local context upon which the model is based.

In contrast to the study where reusable CVC insertion kits were shown to have a larger environmental impact than the single use alternative (28), we found that the reusable kit was associated with a lower climate impact than the single use and mixed kits in **Paper II**. This is mainly explained by the inclusion of sterile textiles

in our analysis, but the low-climate-impact electricity mix and lower energy use in our primary analysis also contributed to the reversed results. In our sensitivity analysis using an average European electricity mix, the climate impact of the reusable kit approached that of the reusable kit in the previous study (28).

A major finding in **Paper II** was that the change from single use to reusable textiles during CVC insertions dramatically reduced the environmental impact on the resource use and climate change endpoints. The textile production represented about 65% of the total climate impact for the single use and mixed kits. Reusable sterile textile has previously been shown to have a lower climate impact compared to single use alternatives (75), highlighting an area which could be targeted to reduce the environmental impact of not only CVC insertions, but also of other procedures requiring sterile textiles

In **Paper III** the principal finding was that one inpatient day at an ICU in Sweden had a climate impact of 30 kg CO_2 eq. Over 60% of the total climate impact could be attributed to using single use items, followed by the energy consumption for electric equipment, lighting, and HVAC (roughly 20%). A sensitivity analysis showed that a high-climate-impact energy mix increased the climate impact by 322% to 126.5 kg CO_2 eq.

Our results suggest that the total climate impact of an inpatient day at a Swedish ICU is much lower than the 88 kg and 178 kg CO_2 eq that have been reported for treating septic patients at an ICU in Australian and the US, respectively (32), and lower than the 138 kg CO_2 eq that has been reported per inpatient day for treating medical ICU patients in the US (86). As suggested by our sensitivity analysis with a high-climate-impact energy mix, the difference in results is explained by the fact that Sweden mainly uses a low-climate-impact energy mix. Our sensitivity analysis showed that energy consumption and single use items contributed approximately to 80% and 15% of the total climate impact, respectively, when using a high-climate-impact energy mix. This aligns with the contribution reported for treating septic patients in Australian and the US (32). In contrast, the relative contribution of energy was lower in the medical ICU in the US, at 30%, and that of single use items was higher, at roughly 30% (86). A hybrid LCA approach and the inclusion of the production of electronic equipment, staff travel, and patient food within the system boundaries could explain the differing results of the latter study.

Methodological considerations

System boundaries and generalizability

Setting the goal and scope is the first step of an LCA and one of the key aspects is to define the system boundaries for the analysis, meaning that decisions on what to include and exclude from the analysis must be made (63, 87).

As an example, only the trocars and their packaging was included in **Paper I**, excluding all other instruments and materials needed to perform the surgery from the analysis. The impact of the surgery would therefore be much higher than the impact that we presented in our paper. This is showcased by comparing our LCA to the study where single use and hybrid trocars were assessed. While the relative differences between the single use systems and hybrid or reusable systems are similar in the two studies, the magnitude of the difference in absolute figures was up to 5 times as high in the previous study (35). They included complementary instruments such as the storage tray, longer transportation distances, and a different source of electricity which is most likely the reason why the impact in absolute figures were higher than in our study.

An LCA is a model that will never truly reflect reality, different system boundaries in studies assessing similar products or systems are thus a consequence of the natural variation in the real world. The system boundaries used in **Paper III** is a great example of this. Patient characteristics and the type of care that is delivered by an ICU differ between countries and even across ICUs within a country, which naturally leads to a limitation of the results' external validity. In contrast to Swedish ICUs where oral feeding is unusual, it might be common in other settings. In the hybrid LCA on the medical ICU in the US, patient food contributed to more than 10% of the total climate impact (86). In such settings, mitigating strategies targeting impacts associated with food preparation as well as hospital food waste are warranted (88).

Taken together, the above emphasize the need to consider both scope and local context when interpreting LCA results and illustrates that modelling parameters are of great importance in the assessment of the absolute effect of any given process.

Data collection and allocation

In the second step of an LCA, the inventory phase, the sources of data and the method used to allocate multifunctional processes will affect the results (64). Multifunctional processes are processes used within a system which is utilised by other systems as well. Taking the sterilisation process in **Paper II** as an example. Besides the instruments in the reusable CVC kit, the autoclave and washer disinfector are used to sterilise other products as well. Meaning that we needed to allocate the share of the total amount of water and energy used by the machines for the sterilization of the CVC kit. Allocation can be made in multiple ways. The allocation should if possible be made based on causal physical relationships between processes and emissions. However, it can often be hard to establish the exact relationships, and then representative parameters can be used instead, such as allocating based on volume or weight (87). In **Paper II** allocation was based on the loading capacity of the respective machines. Using information on how many program-runs it would take to sterilize the instruments in the reusable CVC kit used during a year for the procedure assessed in our study and dividing it by the total

number of program-runs performed by the autoclave and washer disinfector during the same year, further divided by the number of CVC insertions performed during the year, made it possible to allocate the amount of water and electricity needed to sterilise the instruments in one reusable CVC kit. In the study by McGain et al. (28), the autoclaves and washer–disinfectors had different loading capacities meaning that they used a different allocation and that the share of the total amount of water and electricity used in the sterilisation process differed between the studies.

The sterilisation process in **Paper II** can also be used as an example on the influence that data sources have on the results. We used consumption data provided by the manufacturer for the washer-disinfector and autoclave, meaning that standby time and test runs was excluded from our analysis. These components were included in the previous study on CVC insertion kits since they used site-specific data (28) and the implication of this was that the sterilisation process generated a higher climate impact in their analysis compared to ours.

Another example of how the source of information may influence the results can be showcased by **Paper I**. Due to the lack of information on regional and hospital specific wastewater treatment, we used an average European process. Since the average wastewater treatment in Europe can be assumed to have a different composition of pollutants compared to the wastewater treatment used by Swedish hospitals, the accuracy of the results can thus be questioned.

Allocation is not only affected by the assumption made by the LCA practitioner, but it is also affected by the selected database. The ecoinvent databases has four different system models, or allocation approaches available. The first three approaches are attributional, meaning that impact of a product or system is estimated in isolation from the surrounding technosphere (87, 89). The first approach includes recyclable material and is called allocation at point of substitution (APOS), meaning that any burden or credits from recycling is shared between the producer and subsequent user. The second and third approach is cut-off approaches where the impact from primary production of materials always is allocated to the primary user of a material and if any material is recycled, the primary producer does not receive any credit for the provision of this material. Meaning that recyclable materials are available burden-free to recycling processes and that recycled materials only generate impacts from the recycling processes at the end of the life cycle (69, 89, 90). The fourth approach is a consequential approach, where multifunctional processes in contrast to the attributional approaches is handled by system expansion, meaning that a products or system's consequence on the surrounding technosphere is considered (87). We used an attributional approach in all four papers, since we were interested in knowing what impact that could be attributed to the assessed products and systems. In **Paper I**, the benefit of recycling was included in the assessment whereas a cut-off approach was used in **Paper II**, **Paper III**, and **Paper IV**. The change between the first and second paper had to do with a better understanding of what the implication of using the different system models were. I

initially thought that to be able to model recycling the APOS approach had to be used. Later on, I realised that the selected allocation approach only dictated who were given credits and burdens of recycled content. Since no recycled material was used in the production phase in either of the studies, and only packaging was modelled with recycling at end of life, the cut-off approach was deemed more appropriate for the latter studies.

The choice of LCIA method

Two LCIA methods was used to characterise the impact of the products and systems analysed in the respective papers in this thesis. We used IMPACT 2002+ in **Paper I** and **Paper II**, presenting results at endpoint. In **Paper III** and **Paper IV**, ReCiPe 2016 Midpoint (H) was used, and results were presented at midpoint. The reason for using IMPACT 2002+ in the first two papers had to do with its geographical representativeness for Europe. We changed to ReCiPe 2016 which has a global coverage since IMPACT 2002+ became out of date, and due to the realisation that Sweden was only the setting in which the use phase and waste management took place, whereas most of the raw material extraction, production and transportation was located outside of not only Sweden but also outside of Europe.

The selection of LCIA method will influence the results. Different impact assessment methods compile data and characterize midpoint and endpoint categories differently, using different characterisation factors and different units (57). The characterization process was exemplified in **Figure 7** (p.33). A study which assessed the uncertainty caused by the selection of LCIA method found that for most impact categories, the maximum value was 10,000 times higher than the minimum value depending on which LCIA method that was used. The only category which got consistent results across LCIA methods was global warming (91). There are several reasons for this discrepancy. First, the associated characterisations values, or emissions, of a certain substance vary substantially across methods. Second, different methods have different coverage, meaning that the number of substances covered by the LCIA methods differ. Although the characterisation factors were the same across methods for global warming, the coverage differed in terms of how many substances the different methods covered for each GHG, resulting in different GWP for the same GHG across LCIA methods (91).

As previously stated, LCA is merely a model of reality, and the assumptions made in the goal and scope phase often lead to some sort of simplifications, due to how system boundaries are set and how allocation has been made. The characterisation process in the LCIA add to this simplification since no LCIA method cover all substances available in the inventory databases (91). Using endpoints often add another abstraction step to the process, when midpoints are characterised into endpoints. As a brief reminder, midpoint is impact in terms of the quantity of emissions whereas endpoint is the damage that these emissions cause (57). The

amount of information kept throughout an LCA therefore decreases with each step throughout the life cycle (**Figure 19**).

The question is then, why we should present endpoint impact, when a lot of information seems to be lost in the process. The main reason is due to its interpretability by non-LCA practitioners (92). Take stratospheric ozone depletion, by IMPACT 2002+, as an example. At midpoint the impact is presented as kg of chlorofluorocarbon equivalents (kg CFC-11 eq) which to most people doesn't mean much in terms of understanding the consequence of the impact. However, when further characterised into the human health endpoint, it is measured in disease-adjusted-life-years (DALY), which is easier to interpret by decision makers and, in the context of healthcare, clinicians. Reporting environmental impacts in units only known to sustainability-experts is meaningless unless the absolute impact is translated to equivalents and put into a context which clinicians and healthcare staff can understand (93). This is probably one of the reasons for why most health care LCAs choose to report climate impact, it is commonly known and easy to compare to everyday life activities such as driving a car or flying roundtrips between two cities.

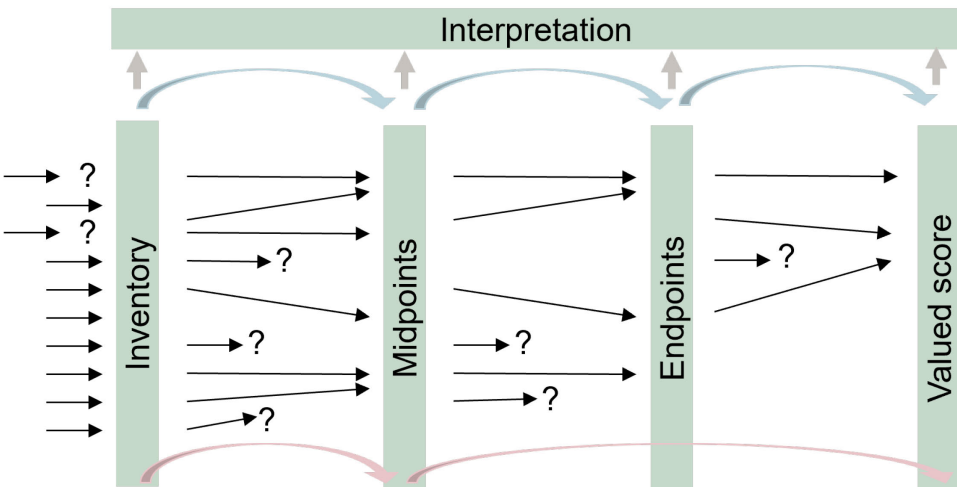

Figure 19. Schematic presentation of information loss throughout the steps in an LCA. Basic differences between the midpoint (pink swinging arrows) and the endpoint approach (blue swinging arrows). The small arrows represent added information in a cause-effect framework. The question marks indicate information that was available but could not be further modelled, such as unmeasured emissions, unconsidered types of releases, and substances where characterisation factors, midpoint or endpoint models have still to be established. Credit: Bare JC et al. 2000 (92), reproduced and adapted with permission from Springer Nature.

Normalisation and weighting

In **Figure 19**, the last step is called valued score, since the figure is reproduced from an old figure, one could instead talk about normalisation and weighting of results. These are optional steps in an LCA (57). Normalisation is a process where all impact categories are put on a common scale to be able to compare the size of impact across impact categories. The impacts are thus compared to a reference system, for example a country or an industrial sector. Meaning that the impact is presented as share of total impact by the reference system rather than in absolute values. Weighting is taking normalisation one step further, prioritising the different impact categories by applying different or equal weights to each category (57). While normalisation is useful to be able to provide an impression of the relative magnitude of the environmental impact from each category, weighted results are more useful for communicating results in a way that prioritise underlying ethical values. It should be noted that weighting is purely subjective, based on the choice of an individual or a group of individuals (57).

Normalisation and weighting were not applied in any of the papers included in this thesis. We thought that the information given by presenting endpoint results in **Paper I** and **Paper II** provided enough, and interpretable, information without being further normalised. In **Paper III** and **Paper IV**, the primary outcome was global warming which, as recently stated, already is a well-known unit also outside the LCA and environmental science communities. Thus, further characterisation, normalisation and weighting was deemed unnecessary especially due to the potential loss of information and increased abstraction that each step potentially contribute to.

Uncertainties in healthcare LCAs

As described in the method section, there are two main types of uncertainties in an LCA, model uncertainty and parameter uncertainty. Model uncertainty, is best handled by sensitivity analyses and this has commonly been used within healthcare LCA. About 40% of all studies included in the HealthcareLCA Database use some sort of sensitivity or scenario analysis (23).

Parameter uncertainty on the other hand has rarely been assessed in healthcare LCAs. Monte Carlo simulation is the most common method to assess uncertainty of LCA results but only a few healthcare LCAs has utilised it to assess the environmental parameter uncertainty of their results (28, 31, 38, 94-97). We used Monte Carlo simulations in all four papers.

In **Paper I** and **Paper II** we extended the use of Monte Carlo simulations to assess the certainty of difference between the product systems, utilising paired Monte Carlo simulations. We presented results as the median difference with a 95%

reference interval. This enabled us to provide an estimate of the precision that suggested that differences between the systems were robust in both studies since none of the reference intervals crossed zero in the primary analyses. The reference interval did however cross zero in some of the comparisons in the sensitivity analyses in **Paper I** (**Figure 15**, p.50). This type of comparison, using paired Monte Carlo simulations, has to my knowledge not been done in any other healthcare LCA. An alternative approach which is similar to paired Monte Carlo simulations is discernibility analysis, then the difference is presented as the share of iterations in a Monte Carlo simulation were one product or system gets a higher impact than the compared alternative (98). Discernability analysis was used in an LCA that compared single use and reprocessing of face masks during the Covid-19 pandemic (94).

Uncertainties in clinical trial LCAs

In **Paper IV** we wanted to explore how LCA uncertainties can be assessed when interventions in a clinical trial are compared. Then the intervention effect adds another layer of uncertainty to the LCA. In clinical trial analyses, measurement error is typically not explicitly modelled under the assumption that such errors are similar between treatment groups and therefore cancel out in comparative analyses. One could argue that ignoring uncertainties in environmental parameters when applying standard statistical methods to LCA results is similar to this practice. However, this argument only holds if the underlying LCA models are identical between groups. In **Paper IV**, although the same types of fluid were modelled for both treatment groups, differences in administered volumes resulted in different LCA models for each patient. Under such conditions, uncertainties in environmental parameters may affect the groups differently. This distinction aligns with LCA methodological guidance emphasising that uncertainty should be explicitly addressed when model configurations differ between compared alternatives (52) and provides a rationale for assessing environmental parameter uncertainty rather than assuming equivalence.

In **Paper IV**, the differences between groups were similar even when the uncertainty in the LCA model was included in the analysis. That the mixed model did not converge for three of the exploratory outcomes illustrated that the added complexity of this approach may result in loss of robustness. Since the added complexity of the mixed model did not meaningfully influence the point estimates and conclusions for most impact categories, a general linear model which are less complex, more robust and more familiar to trialist and medical statisticians appear appropriate to use when differences in environmental impact between interventions are assessed.

The 95% CI did however increase for the difference between the intervention and control group for two of the exploratory outcomes in the mixed model compared to the general linear model. This suggests that for some outcomes, large uncertainties in environmental parameters may influence statistical power and alter results. For

such outcomes the mixed model approach offered additional information compared to the general linear model, which might be useful for clinicians and decision makers.

Strengths and limitations

The main strength in all four papers, especially in **Paper I** and **Paper II** that compared single use and reusable products, was that our LCA models were based on products and processes used in clinical practice, meaning that we can suppose clinical equipoise.

In **Paper III** another key strength is that we performed an exclusively process-based LCA and we included pharmaceuticals, fluids, and diagnostic imaging, which are components of ICU care that have not been considered in previously. We gained novel insights into the relative contributions of these components, which represented 8% of the total climate impact per inpatient day. The contribution is sizable and that these components represent potential targets for climate impact mitigation efforts.

The prepublication of the statistical analysis plan for **Paper IV** is a strength. As described earlier only a few clinical trials has included environmental impacts as outcomes. The exploration of statistical approaches in **Paper IV** contributes with insights important for the methodological development required for the inclusion of environmental outcomes in clinical trials, and insights on how to systematically assess the certainty in clinical trial LCAs.

A limitation in all four papers concerns data management and the potential of systematic errors. I am the only one in the author groups with experience of performing LCA in SimaPro, meaning that the LCA model in SimaPro has not been validated by someone else. To the best of my ability, the risk of introducing systematic errors when creating the LCA models has been mitigated by using a built-in-feature in SimaPro that allow you to trace the status for each modelled product including the statuses: none, temporary; draft; to be revised; to be reviewed; and finished, meaning that each model aspect has been checked at least six times.

Another limitation concerns the scope of the analyses and the selected system boundaries. In **Paper I** and **Paper II**, we only included one or some of the products needed to perform the procedures, meaning that the relative difference between the single use and reusable alternatives would be a lot smaller if all other material and processes needed to perform the procedures were included. In **Paper III**, we only included single use items of which more than 1000 had been ordered during the year, meaning that we might have overlooked heavy items with a potentially high climate impact, of which few were procured. In **Paper IV** we only included the

fluids and their packaging. An important consideration in trial-based LCAs is the potential health effects of the intervention. If an intervention leads to reduced ICU or hospital length of stay, the resulting environmental benefits could be substantial. Excluding inpatient bed days from the system boundaries in **Paper IV** is thus a limitation, in terms of estimating the true environmental difference between interventions but also in assessing how uncertainty propagates through more comprehensive healthcare LCAs. Including ICU or hospital stay in **Paper IV** would also have increased the proportion of the LCA model shared between treatment groups. Under such circumstances, the relative influence of uncertainty in environmental parameters on between-group differences would likely be reduced. The exclusion of intervention-related health effects is therefore a limitation not only of the LCA results themselves but also of the comparison between statistical approaches.

It should be acknowledged that Sweden, a high income country, was used as setting in all four papers. The results' generalisability to LMIC are therefore limited, necessitating additional studies to assess hotspots that could be targeted for adaptation and mitigation in such countries.

Sustainability is three-fold, including environment, economic and social sustainability. This thesis has focused mainly on the environmental aspects, and to some extent the economic aspects of sustainability. Social sustainability is however not covered in this thesis and that presents a potential limitation connected to the exclusion of LMIC since much of the production of medical items are located in these countries, where work and living conditions often are characterized by high levels of informal employment, poor occupational safety, and significant economic vulnerability.

Mitigation strategies

Based on the results in **Paper I**, **Paper II**, and **Paper III**, Swedish healthcare and healthcare systems similar to that in Sweden should focus on reducing the use of single use items to mitigate climate and environmental impacts form intensive and perioperative care. In **paper III**, the results showed that five products contributed to about 60% of the total impact from single use items. These items included aprons, gloves, woven gauze, syringes, and wash wipes. This finding aligned with results from a previous study that estimated the climate impact from disposables used at an ICU in the Netherlands (99). Collectively, the results suggest that such products constitute robust targets for climate impact mitigation strategies.

Notably, a previous report indicates that non-sterile gloves are overused and misused up to 40% of the time, leading to unnecessary use of resources and an increased risk of cross-contamination (100). Thus, educating staff about the benefits

of adhering to recommendations on proper glove use is an opportunity to reduce both the environmental impacts and the risk of cross-contamination (100).

Reducing the use of single use items could also be achieved by switching to reusable alternatives with similar clinical performance whenever available. In **Paper II** reusable textiles was found to have approximately one-sixth of the climate impact compared to the single use option. We are unaware of any evidence that show on clinical benefits with either single use or reusable aprons, meaning that considerable reductions in climate impact could be achieved by replacing single use aprons with reusable aprons, without compromising the quality of care. Other mitigating strategies to reduce climate impact is to extend the use of infusion sets from four to seven days, which can be safely done without jeopardizing patient safety (101). Between 12-44% of pathology tests are performed without clinical indication (102), meaning that adhering to the principle of testing wisely would lead to both climate impact reductions as well as reducing the risk of negative health effects and financial cost (103, 104).

The foremost opportunity for countries that are dependent on high-climate-impact energy sources is to accelerate the transition to renewable energy alternatives. Reducing the overall energy consumption by limiting the number of hours that electronic equipment is on standby, upgrading old equipment to newer more energy-efficient models, and restricting the use of equipment with high energy requirements whenever possible is also an important strategy for mitigating climate impact in these countries, as well as for countries using low-climate-impact energy sources.

Clinical trials are the cornerstone of healthcare, providing evidence on which interventions and pharmaceuticals that should be given to a patient to generate the best potential outcome and to reduce the risk for adverse side effects or potentially death. With considerable improvements within medical research, an increased level of standard care, and technological developments only marginal benefits might be seen in new treatments. As a consequence, non-inferiority trials have become a common practice, where the aim is to show that a new treatment is not worse than the existing one rather than showing on superiority (105). A lot of clinical trials thus show on similar clinical outcomes across treatment options. In such settings, including environmental outcomes as part of the clinical trials represents a great opportunity to provide additional information for decisionmakers to choose treatment options wisely both in terms of patient safety and in terms of environmental impact.

Future research

Which environmental impact categories to include in an LCA should generally depend on geographical, temporal, and technical considerations (57), meaning that one must consider what and where raw materials are extracted, which production processes that are used and where the production is located as well as what and where emissions connected to use and waste management take place. In addition, it has been argued that the selection of an impact category should depend on its relevance for health care and human health (93). In the second chapter in this thesis, different impact categories, their relation to the planetary boundaries, and their effect on human health was presented. Future research should explore which impact categories that should be assessed in healthcare LCAs based on their geographical, temporal, and technological relevance as well as their relevance for human health, and explore potential human health trade-offs. One option would be to explore the planetary boundary framework as a potential tool to support impact category selection in healthcare LCA, choosing impact categories based on the level of transgression and the potential detrimental effect that each boundary has or might lead to.

One of the limitations with this thesis is that all four paper are in a high-income country setting. Future studies should assess environmental impacts form intensive and perioperative care in LMIC countries, to be able to show on the environmental impacts of and to find modifiable hotspots from these units in such countries.

In trials where the intervention and control rely on substantially different materials or processes compared to the trial used for input in **Paper IV**, LCA model uncertainty may play a larger role. Materials and processes in LCA databases are associated with different levels of uncertainty meaning that the magnitude and structure of uncertainty can vary substantially across product systems and impact categories (61). The two statistical approaches evaluated in **Paper IV** might yield less concordant results when input from other trials are used. It is therefore imperative that the effect of LCA model uncertainty on environmental impact results in clinical trials is assessed in more data sets to test the robustness of our results. It has previously been argued that there is need for literature that provide guidance on how LCA uncertainties should be handled in different contexts, to support practitioners to implement uncertainty analyses regardless of their level of expertise (106). Demonstrating when simpler statistical approaches is sufficient and when more complex modelling are warranted, could offer guidance for researchers and decision-makers seeking to balance methodological rigor with analytical feasibility. The process of generating the data to be analysed in the mixed model in **Paper IV** was time consuming and alternative, less complex and more time efficient approaches should also be explored. Artificial Intelligence and automated processes to be used in the generation of environmental parameter uncertainty data is a potential area for future research to explore.

Conclusion

In Sweden, the main opportunity to reduce the climate and environmental impacts from intensive and perioperative care is to limit the use of single use items. In **Paper III** single use items was found to represent over 60% of the total climate impact from intensive care. The results in **Paper I** and **Paper II** provided concrete examples of the benefit of using reusable items, the use of reusable alternatives were shown to offer robust opportunities to reduce the environmental impacts compared to using single use options, even when sterilisation and laundry in between uses was accounted for.

In countries which are dependent on high-climate-impact energy sources, transitioning to low-climate-impact energy sources or lowering the energy consumption is the foremost opportunity to reduce the climate impact of intensive care.

The inclusion of environmental outcomes in clinical trials is unavoidable, and we need to make sure that clinical trials provide information on the climate and environmental impact of assessed interventions that can be provided to clinicians and decision makers. Although further studies are required to assess robustness of the results in **Paper IV**, particularly when underlying LCA models differ substantially between treatment groups, our results suggest that the more complex mixed model were less robust and that a parsimonious two-group analysis using aggregated data appear sufficient for most environmental outcomes in trial data similar to ours, making uncertainty analyses of environmental clinical trial data simpler and more accessible to trialists and researchers.

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Appendix

STATISTICAL ANALYSIS PLAN

Assessing uncertainty of environmental outcomes in a clinical trial:

An applied example, using data from the protocolized REDUction of non-resuscitation fluid versus usual care in SEptic shock patients (REDUSE) Feasibility Trial

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Administrative Information

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INTRODUCTION

Rationale for this study

The environmental impacts of products or processes have been estimated using the Life Cycle Assessment (LCA) methodology for over 30 years (1). LCA is a quantitative method that summarises the environmental impact from processes and materials used within a system, from cradle to grave (2). Information on impacts from materials and production processes is commonly collected from large databases. The researcher surveys the system to get input data such as materials, weights, production processes, and transportation distances, which are used to calculate the associated environmental impacts using data from these databases (2). The impacts of materials and processes in the databases are given with a measure of uncertainty. For example, the climate impact from transporting a certain weight by lorry in Europe has been calculated for different vehicles, loads, and fuels, allowing the estimated average climate effect per kilometre, and the associated variation, to be entered into the database. The uncertainty of the environmental impact of the entire system can then be assessed using a Monte Carlo simulation, which utilizes randomly sampled data for all identified processes in the system to generate a point estimate with a 95% reference interval. Monte Carlo simulations have been the most common way of estimating the uncertainty of LCA results across scientific fields, and several LCA software tools have Monte Carlo simulations as a built-in feature (3).

Comparative LCAs are increasingly applied in medicine, and we envision that future clinical trials will compare not only clinical outcomes, but also the environmental impacts of the interventions (4). However, there is currently no consensus on how to assess the difference between environmental impacts, and the subject has received surprisingly little attention. This is perhaps because many environmental scientists regard LCA as a method to explore systems and to identify hotspots rather than to assess the differences between different processes. When comparing processes, one school of thought is that inferential statistics, as is commonly used in medicine, can be used to compare Monte Carlo simulation data from the two systems (5-7). In contrast, some argue that such an approach is flawed because it violates the requirement of independent observations and because the P value will be inflated by increased number of Monte Carlo simulations without additional data entering the system (8). In a clinical trial setting, LCA data will be a combination of database data with known uncertainties and independent data collected during the trial. For example, in a trial assessing two strategies for administering fluid, the environmental impact per litre of fluid is known before the trial commences, but the effect of the interventions on the volume of fluid at the patient level is unknown and independent.

In this analysis, we will explore two statistical approaches to assess environmental impacts of interventions in clinal trials. We will analyse trial data using conventional medical statistics, in which only the uncertainty in the intervention effect is included in the analysis. In addition, we will use a mixed model in which both the uncertainty in the clinical intervention and the underlying uncertainty in the life cycle impact for each patient are assessed. For this purpose, we will use input data from the REDUction of non-resuscitation fluid in SEptic shock (REDUSE) Feasibility Trial (9).

Rationale for the SAP

This Statistical Analysis Plan (SAP) was finalized before the analysis of data to ensure transparency, objectivity, and reproducibility of the analyses. Pre-specifying the statistical methods minimizes the risk of data-driven decisions and selective reporting, thereby reducing

bias and enhancing the credibility of results. This aligns with ICH E9 guidance and international best practice, which emphasize that key analytic principles must be determined a priori (10). By defining in advance how primary and secondary outcomes will be analysed, the SAP provides confidence that conclusions are based on robust, pre-planned methods rather than post hoc choices influenced by observed data. To further strengthen transparency, the SAP also includes an anticipated manuscript outline in the form of mock-ups of figures and tables, presented in the expected order of appearance.

Objectives

To compare two approaches for assessing differences in environmental impact data using aggregated point estimates for environmental impact of each patient in a trial (conventional medical statistics), or, using a mixed model (based on 100 repeated samples for each individual and all outcomes) in which both the uncertainty of the LCA and the effect of the clinical intervention in each patient is assessed.

Hypothesis

The null hypothesis is that the two approaches to the comparison of clinical trial data will result in similar interpretations.

METHODS

Input data

The REDUSE feasibility trial was an investigator-initiated, multicentre, parallel-group randomized trial which included sepsis patients between 7 March and 13 September 2022. Adult patients (≥18 years of age) with septic shock (suspected/confirmed infection, plasma lactate>2 mmol/l and infusion of vasopressor to maintain MAP>65 mmHg after adequate fluid resuscitation) and ongoing vasopressor therapy were eligible for inclusion within 12 h of ICU admission. The exclusion criterion was suspected or confirmed pregnancy. The trial compared protocolized reduction of non-resuscitation fluids (intervention) to usual care (control). The trial included a total of 98 patients of which 49 were allocated to the intervention, and 49 were allocated to usual care (9). Fluid data was available for 44 and 48 participants in the intervention and control group, respectively and these data were used in this analysis.

Analysis - Life cycle assessment

Goal and scope

The functional unit for the assessment will be volume of sodium chloride, glucose and Ringer-acetate given to sepsis patients during the first three days in the ICU after inclusion in the trial. The analysis will include 0.9% sodium chloride, Ringer-acetate, and glucose solutions (25g, 50g, 100g, 200g, and 300g/L) given during the first three days (D0-D3) (suggested presentation in Table 1). In addition, the analysis will include packaging, modelled as weight of packaging per ml fluid administrated. All other types of fluids and materials will be outside the boundaries of this LCA (Figure 1).

Table 1. Intervention data included in the LCA

	Intervention (N=??)	**Control (N=??)**	**Difference between medians (95% CI)**
Volume Ringer-acetat	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume Sodium chloride 9g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume glucose 25g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume glucose 50g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume glucose 100g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume glucose 200g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Volume glucose 300g/L	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)
Total volume of fluids first 3 days after inclusion	xx (xx-xx)	xx (xx-xx)	xx (xx-xx)

Data are presented as median (IQR).

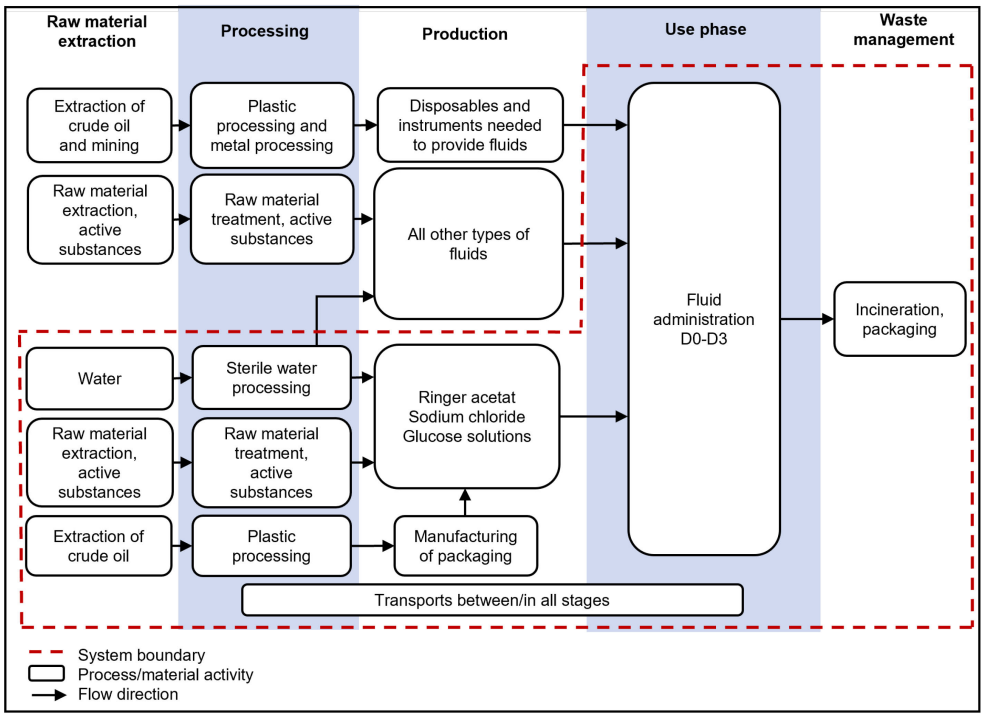

Figure 1. System boundary of the LCA.

Life cycle inventory

Real-life data on material and processes will be collected from hospitals and manufacturers to create a model for each patient included in the trial using the LCA software SimaPro v.10.2.0.3 (PRé Sustainability, Amersfoort, The Netherlands) and the ecoinvent 3.10 database (11). The database covers tens of thousands of materials and processes with information regarding their associated environmental impacts. The ecoinvent database provides an uncertainty range for each data point, which is based on variation in sample data when possible and otherwise based on a simplified standard procedure to estimate the uncertainty of data, based on a single source of information (12).

Life cycle impact assessment (LCIA) – environmental outcomes

Life cycle impact assessment will be used to estimate the environmental impact per patient on the 18 environmental outcomes, listed below. We will use the ReCiPe 2016 impact assessment method (13) to characterize the life cycle impact of the fluids provided to each patient. The point estimate per patient, is the sum of the impacts from all materials and processes used to model the volume of fluids administered to the patient. We will present data for the primary outcome in the main manuscript and other environmental outcomes will primarily be presented as Supplementary Material. All outcomes are continuous. Definitions and units for the different outcomes are presented in Table 2.

Primary outcome:

- Global warming (kg CO_2 eq)

Exploratory outcomes:

- Fine particulate matter formation ($PM_{2.5}$ eq)
- Fossil resource scarcity (kg oil eq)
- Freshwater ecotoxicity (kg 1.4-DCB eq)
- Freshwater eutrophication (kg P eq)
- Human carcinogenic toxicity (kg 1.4-DCB eq)
- Human non-carcinogenic toxicity (kg 1.4-DCB eq)
- Ionizing radiation (kBq Co-60 eq)
- Land use (m^2/a crop eq)
- Marine ecotoxicity (kg 1.4-DCB eq)
- Marine eutrophication (kg N eq)
- Mineral resource scarcity (kg Cu eq)
- Ozone formation - Human health (kg NO_x eq)
- Ozone formation - Terrestrial ecosystem (kg NO_x eq)
- Stratospheric ozone depletion (kg CFC-11 eq)
- Terrestrial acidification (kg SO_2 eq)
- Terrestrial ecotoxicity (kg 1.4-DCB eq)
- Water consumption (m^3)

Repeated measures - Monte Carlo simulations
Monte Carlo simulation will be used to randomly sample data within the uncertainty range for each data point in the LCA model to provide 100 repeated measures per patient and outcome.

Table 2. ReCiPe 2016+ life cycle impact assessment impact categories.

Impact category	Definition	Unit
Global warming	Global warming potential of carbon dioxide equivalents over a 100-year period	kg CO_2 eq
Fine particulate matter formation	Human population intake of fine particulate matter formation ($PM_{2.5}$), due to change in ambient concentration of $PM_{2.5}$ after the emission of different precursors, i.e. Ammonia, Nitrogen Oxides, Sulphur Dioxides, expressed as $PM_{2.5}$ equivalents.	$PM_{2.5}$ eq
Water use	m3 of water consumed per m3 of water extracted	m^3
Land use	The annual relative species loss caused by specific land use (i.e. annual crops, permanent crops, mosaic agriculture, forestry, urban land, pasture) types in human-made land covers, expressed as m2 of annual crop equivalents.	m^2/a crop eq
Fossil resource scarcity	The ratio between the higher heating value of different fossil resources and the energy content of crude oil, expressed as oil equivalents.	kg oil eq
Mineral resource scarcity	The decrease in ore resource concentration leading to an increase in the ore produced per kg of mineral resource extracted, expressed as copper equivalents	kg Cu eq
Ionizing radiation	The collective dose of ionizing radiation resulting from radionuclide emissions, expressed as cobalt-60 equivalents.	kBq Co-60 eq
Stratospheric ozone depletion	A decrease in stratospheric ozone concentration over an infinite time horizon, expressed as Trichlorofluoromethanes equivalents.	kg CFC-11 eq
Freshwater eutrophication	Increase in phosphorus (P) in freshwater	kg P eq
Marine eutrophication	Increase in Nitrogen (N) in marine water	Kg N eq

Terrestrial acidification	Change in acid deposition in natural soils, expressed as Sulphur Dioxide equivalents.	kg SO_2 eq
Photochemical ozone formation, ecosystem	Tropospheric ozone increase, expressed as nitrogen oxides (NOx) equivalents	kg NO_x eq
Photochemical ozone formation, human health	Human intake of ozone after being exposed to NOx or non-methane volatile organic compounds (NMVOC) emissions expressed as NOx equivalents.	kg NO_x eq
Human carcinogenic toxicity	Risk-increase of cancer disease incidence, expressed as 1,4-Dichlorobenzene equivalents.	kg 1.4-DCB eq
Human non-carcinogenic toxicity	Risk-increase of non-cancer disease incidence, expressed as 1,4-Dichlorobenzene equivalents.	kg 1.4-DCB eq
Terrestrial ecotoxicity	The fate and effect of chemical emissions, expressed as 1,4-Dichlorobenzene equivalents.	kg 1.4-DCB eq
Marine ecotoxicity	The fate and effect of chemical emissions, expressed as 1,4-Dichlorobenzene equivalents.	kg 1.4-DCB eq
Freshwater ecotoxicity	The fate and effect of chemical emissions, expressed as 1,4-Dichlorobenzene equivalents.	kg 1.4-DCB eq

Categories, definitions, and units adapted from Huijbregts et al. (13).

Statistical analyses

An overview of the two statistical approaches described below is presented in Figure 2. In this study, missing data are assumed to be Missing Completely At Random (MCAR) because of the secondary nature these findings and the few missing values arise solely from stochastic features of the Monte Carlo simulation process rather than from patient characteristics or outcome severity (14). Under MCAR, the probability of missingness is unrelated to both observed and unobserved data, making it the only missing-data mechanism that can be safely ignored without introducing bias. This aligns with published guidance that MCAR represents the rare situation in which likelihood-based mixed-effects models yield unbiased estimates without requiring imputation. Accordingly, the analysis proceeds using all available observations under a defensible MCAR assumption (14).

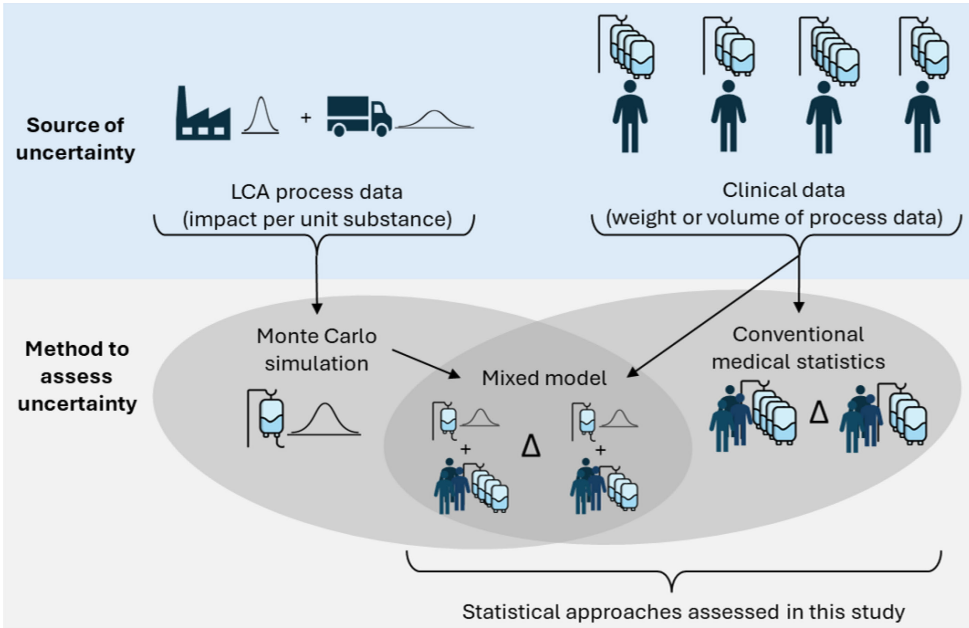

Figure 2. Schematic figure presenting the sources of uncertainty and statistical approaches

Analysis of environmental effects in the two groups using conventional medical statistics: For each patient we will use the point estimate for respective outcome as calculated in the LCIA. We will analyse each of the 18 continuous outcomes using general linear model while adjusting for site (n = 6). For each outcome, the model will include: the follow-up score as the dependent variable and treatment group as the primary independent variable, while adjusting for clinical site as a factor. Estimated between-group differences will be reported as the contrast between the predicted (adjusted) group means, expressed as Least Squares Means (also known as marginal means). For each outcome, we will present the adjusted mean for each group, the adjusted mean difference, the corresponding 95% confidence interval (CI), and the two-sided p-value.

Analysis of environmental effects in the two groups using a mixed model

To incorporate the uncertainty of the LCA alongside the uncertainty of the intervention effect, we will analyse the Monte Carlo–generated repeated datasets within a mixed-effects framework. Each of the 18 continuous outcomes will be modelled using a linear mixed-effects model with the repeated draws (100 samples per participant) as the dependent observations. The model will include a fixed effect for treatment group, a patient-specific random intercept to account for within-participant correlation across samples, and a fixed effect for clinical site. Models will be estimated by Restricted Maximum Likelihood (REML), applying the Kenward–Roger small-sample degrees-of-freedom approximation for inference on fixed effects, with the Satterthwaite method used where Kenward–Roger is not supported. The within-participant

residual covariance will be modelled parsimoniously, e.g. First order autoregressive (AR(1)), and the final structure will be selected using model fit criteria to avoid over-parameterisation.

Estimand and reporting. The primary estimand is the marginal (least squares) mean difference between groups, interpreted as the average treatment effect across the repeated-measure simulation window. Time (iteration index) will be included as a fixed effect to adjust for secular trends, but no group-by-time interaction will be estimated; a constant treatment effect across iterations is assumed. For each outcome, we will report adjusted marginal means for each group, the adjusted mean difference with 95% CIs, and two-sided p-values. This mixed-effects linear model framework appropriately accounts for within-patient clustering and for uncertainty propagated through repeated sampling. All outcomes are continuous and will be summarised using model-based marginal means with corresponding uncertainty estimates.

Comparison of the two statistical approaches

To evaluate the effect of the two statistical approaches on the resulting treatment effect, we will compare whether the adjusted mean differences differ across methods. As schematically illustrated in Figure 3, each of the 18 outcomes will yield two independent estimates: one from the conventional general linear model and one from the mixed-effects model. These estimates will be placed on a common scale (adjusted mean difference between groups with 95% confidence intervals and two-sided p-values) to enable direct comparison (suggested presentation in Table 3). The general linear model provides a single-patient, single-measurement estimate reflecting only between-patient variability, whereas the mixed-effects model incorporates additional uncertainty arising from the LCA process and its Monte Carlo simulations (100 iterations per participant), while adjusting for within-patient correlation.

Following the general framework described by Altman & Bland, comparisons will focus on whether the two treatment-effect estimates differ beyond what would be expected from their respective uncertainties (15). Concordant estimates - similar point estimates with overlapping confidence intervals - will support robustness of the main effect independent of the method used. Conversely, meaningful divergence between the two estimates (e.g., non-overlapping confidence intervals or relevant shifts in magnitude) will indicate that incorporating LCA-related uncertainty affects inference. All results will be expressed as adjusted group differences derived from marginal (least squares) means to ensure interpretability and comparability across modelling approaches.

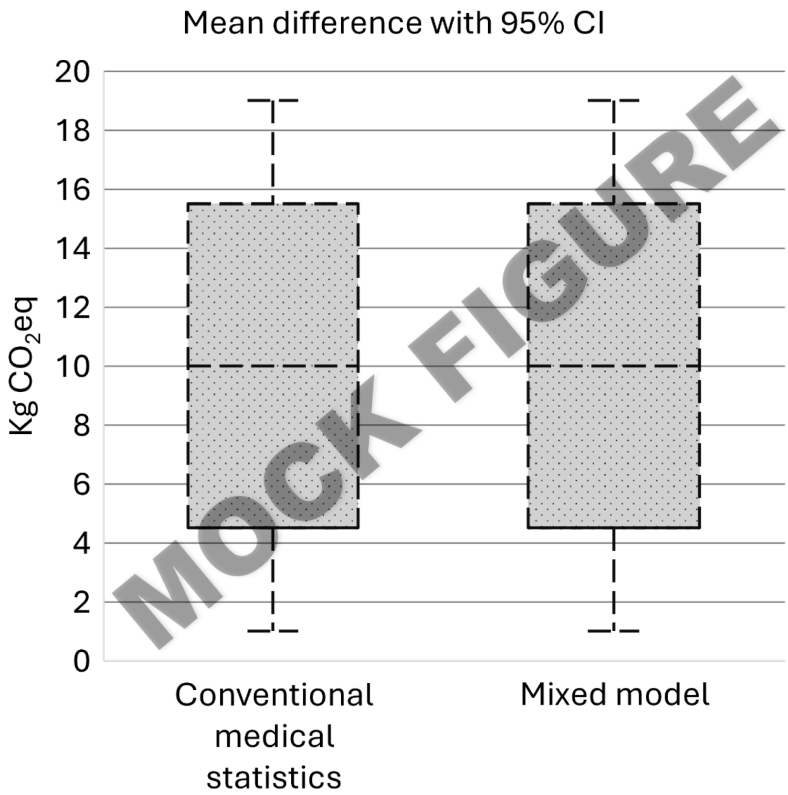

Figure 3: Schematic illustration of how the mean difference between groups and 95% CI on the climate impact endpoint using conventional medical statistics and mixed model will be presented.

Table 3: Outcomes using conventional statistics and a mixed model

	Conventional medical statistics			Mixed Model			Contrast between Models
	Intervention: Mean (SE)	**Control: Mean (SE)**	**Difference (95%CI)**	**Intervention: Mean (SE)**	**Control: Mean (SE)**	**Difference (95%CI)**	**Difference between differences (95%CI)**
Primary outcome							
Global warming (kg CO_2 eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Secondary outcomes							
Fine particulate matter formation ($PM_{2.5}$ eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Fossil resource scarcity (kg oil eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Freshwater ecotoxicity (kg 1.4-DCB eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Freshwater eutrophication (kg P eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Human carcinogenic toxicity (kg 1.4-DCB eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Human non-carcinogenic toxicity (kg 1.4-DCB eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Ionizing radiation (kBq Co-60 eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Land use (m^2/a crop eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Marine ecotoxicity (kg 1.4-DCB eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Marine eutrophication (kg N eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Mineral resource scarcity (kg Cu eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Ozone formation, human health (kg NO_x eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Ozone formation, ecosystem (kg NO_x eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Stratospheric ozone depletion (kg CFC-11 eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Terrestrial acidification (kg SO_2 eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Terrestrial ecotoxicity (kg 1.4-DCB eq)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)
Water consumption (m^3)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx-xx)

Discussion

The aim of this statistical analysis plan is to ensure transparency, objectivity, and reproducibility of the analyses. It describes the characteristics of the clinical trial that will be used as input data in the LCA. Assumptions and methodological choices concerning the LCA are described.

This statistical analysis plan has several strengths. It describes the planned methodology and analyses. The primary and secondary outcomes are defined, and states which results will be presented in the main manuscript. The statistical analyses as well as the comparison between the statistical approaches are described in detail to avoid data-driven analyses and risk of outcome reporting biases.

There are limitations with this study. For example, we will only use data from one clinical trial using one set of parameters in our LCA model. This may limit the generalizability of the results to other types of clinical trials in which uncertainties regarding the intervention effect as well as the processes and uncertainties in the underlying LCA models are different.

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Conflicts of Interest
Peter Bentzer, Linn Hemberg, Johanne Juul Petersen, Janus Christian Jakobsen, Per Werner Möller and Markus Harboe Olsen reports no conflicts of interest.

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