Long-term impacts of sulfur mustard exposure on mental health, quality of life, and lung function

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To Nick and Artin

“Success is not how high you have climbed, but how you make a positive difference to the world.”

—Roy T. Bennett

My journey

From an e-mail to a doctoral thesis

At the end of my intern physicianship period in 2014, I got an e-mail from Fazil Moradi, who was researching anthropological aspect of the Anfal military operation against the Kurdish population in Kurdistan-Iraq. Fazil had observed an unusually severe nocturnal cough in one of the host family members exposed to chemical weapons many years ago. He had asked me if I, as a physician, could help in any way. I began working on learning more about the long-term effects of chemical weapons, and it turns out there is a lot I still do not know. To help and support patients who have been exposed, I reached out to a colleague at Angered local hospital, who put me in touch with Dr. Lars-Olof Larsson. He helped me understand just how complex this issue is. We decided that the best way to get more information would be to conduct a field study in the areas where chemical weapons have been used. With the help of the Kurdistan Regional Government representative in Stockholm, we were able to meet with the minister of social affairs in the Kurdistan Regional Government who was on an official visit in Stockholm. They invited us to Kurdistan-Iraq to visit the affected areas and conduct a pre-study. During our visit, we conducted focus group discussions and individual interviews with survivors of exposure, as well as health and administration staff.

Observing exposed survivors' situations and hearing their dreadful stories were unbearable. This story was just one of many that we heard during our pre-study. After we visited Sheik Wasan and Balisan, on our way to the hotel, our car's fuel pump kept failing, and the staff suggested visiting a nearby cemetery "Warre", as they would fix the problem with the car. To our dismay, we discovered that during the Anfal and chemical attacks, a tractor with a trolley had picked up the chemically injured people from attacked villages to transport them to the nearby hospital but was stopped at a military checkpoint, where they were sent back to their villages without medical assistance or treatment. As night fell and it began to rain, they were stranded at the roadside, and all 34 persons died from their injuries and were buried there, far away from their homes.

The survivors we interviewed told us about the ongoing health effects they suffered from years after the attacks. They also spoke about their challenges in accessing adequate healthcare, education, and employment opportunities due to their chemical exposure complications. It became clear to us that the issue of chemical warfare effects were not just a historical event but a continuing problem for the exposed people of Kurdistan. The pre-study helped me to identify the knowledge gaps and the need for more research and awareness of the long-term effects of chemical warfare agents on survivors.

Upon my return to Sweden, I recognized the challenges of translating my observations into a research question that could be perceived as clinically relevant in Sweden and convince people that the issue of chemical warfare agents was not just a thing of the past but had devastating effects on survivors. It created the need for greater research on and awareness of their long-term effects. Despite the invaluable support of esteemed professionals like Dr. Lars-Olof Larsson and Dr. Kristian Svenberg during my pre-doctoral phase, when I met Prof. Anna-Carin Olin, my research question evolved, and I became a registered doctoral student. Sweden's limited knowledge, understanding, and clinical research made these tasks demanding and time-consuming. Finding funding for my research was also challenging because my research did not have any perceived clinical relevance in Sweden. Partly, the research elements announced did not match my studies, and it was difficult to locate exposed survivors who had resettled in Sweden.

In addition to the hindrances mentioned above that I faced, there were other challenges regarding the issue. An important lesson from our pre-study was that the survivors of chemical weapon attacks wish to be more than just studied as research subjects. Instead, they desire their stories to be heard and shared with others. Another lesson was that the chemical bombing of Halabja was politicized and polarized. These issues made working with SM-exposure issues, especially in Halabja, a sensitive topic.

Therefore, to face the challenges, I approached the issue without preconceived prejudices, with an open mind, engaged with strong and different competencies in the research group, and took advantage of their knowledge and perspectives. To meet the survivors' wishes, I intended to explore the issue more meaningfully through qualitative and quantitative methods with

anthropological inquiry. In doing so, we sought to shed light on the long-lasting effects of these attacks and give a humanistic, scientific voice to survivors' ongoing misery and suffering. By conducting a study on the effects of chemical warfare on gender disparities, specifically examining how it affects men and women differently, we highlighted how the gender differences should be addressed differently since the women were targeted for direct and indirect impacts of the use of chemical weapons.

Furthermore, navigating the complexities and sensitivities of health problems of individuals exposed to SM required a delicate balance between preserving integrity and impartiality while respecting the topic's sensitivity. In my position as a researcher, I have tried to remain impartial to maintain the credibility of my research. At the same time, I have maintained transparency in my research methodology and data analysis, ensuring the reproducibility of my findings.

The issue's sensitivity could have influenced my qualitative research. However, the results were a consensus among the research team. I have ensured that my research is carried out respectfully and ethically in a more professional, less emotional routine with a scientific human approach.

The journey which began with an e-mail ended in a doctoral thesis thanks to many engaged people, especially my main supervisor, Dr. Bledar Daka!

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ABSTRACT

Sulfur mustard is a highly harmful blistering chemical warfare agent with an alkylation ability that can affect multiple organs (skin, eyes and lungs) in the short and long term. Sulfur mustard's long-term biopsychosocial effects have not been sufficiently studied. This thesis aims to explore and describe such effects on individuals exposed to sulfur mustard and compare them with unexposed individuals in Sweden and Kurdistan-Iraq.

For Studies I and II, individuals exposed to sulfur mustard in Halabja, Kurdistan-Iraq were interviewed in 2016. For Studies III and IV, exposed individuals originally from Kurdistan but now living in Sweden were recruited and compared with unexposed Kurdish-Swedish individuals. In Study III, the Montgomery and Asberg Depression Rating Scale was used to collect mental health data, while, the quality of life was evaluated using the RAND Short Form Health Survey 36-Item. In Study IV, impulse oscillometry, multiple breath washout, and the diffusing capacity of the lungs for carbon monoxide were used to evaluate lung function.

Systematic text condensation was deployed to analyze the interviews in Study I, while the content analysis approach was employed in Study II. For Studies III and IV, group comparisons were carried out using the Mann-Whitney U-test, independent t-test, or Fisher's exact test, depending on the type of variables.

The narrative findings in Study I showed that individuals exposed to sulfur mustard had poor access to sustainable healthcare in Kurdistan-Iraq. They were stigmatized and socially abandoned because of the label "Chemically exposed survivor". The narrative findings indicated development of "Chemical contamination anxiety" which caused fear and insecurity and limited their ability to start a family and be active in social and professional life. The gender-related effects of exposure in Study II showed that women experienced more psychosocial effects while men were worried about post-exposure complications e.g. disabilities and death.

Study III showed that individuals exposed to sulfur mustard had significantly poorer quality of life and more moderate depressive symptoms than those not exposed. Study IV revealed that individuals exposed to sulfur mustard had markedly worse small airways function than unexposed participants.

Overall, this thesis with its mixed-method approach showed an association between sulfur mustard exposure and significant long-term worse physical and mental symptoms, impaired quality of life, and lower lung function among individuals exposed to sulfur mustard than those unexposed. The thesis emphasizes the importance of a biopsychosocial model to address this group of patients' unique needs.

Keywords: Chemical Warfare Agent, Sulfur Mustard, Halabja, Quality of life, Mental health, Small airways dysfunction

SAMMANFATTNING PÅ SVENSKA

Senapsgas är ett mycket skadligt blåsbildande kemiskt stridsmedel med alkylerande förmåga, som kan påverka flera organ (hud, ögon och lungor) på kort och lång sikt. De långsiktiga biopsykosociala effekterna av senapsgas är inte tillräckligt studerade. Denna avhandling syftar till att utforska och beskriva sådana effekter på individer exponerade för senapsgas och jämföra med oexponerade individer i Sverige och Kurdistan-Irak.

I studie I och II intervjuades individer i 2016 som hade exponerats för senapsgas i Halabja, Kurdistan-Irak. För studier III och IV rekryterades exponerade individer ursprungligen från Kurdistan, som bodde i Sverige. Dessa deltagare jämfördes med oexponerade kurdiska-svenska individer. I Studie III användes Montgomery och Åsberg Depression Rating Scale för att samla in data om psykisk hälsa, medan livskvaliteten utvärderades med hjälp av RAND Short Form Health Survey 36-Item. I Studie IV, användes impulsoscillometri, kvävgasutsköljning och diffusionskapacitet för kolmonoxid för att utvärdera lungfunktionen.

Systematisk textkondensering användes för att analysera intervjuerna i studie I medan innehållsanalys approachen tillämpades i studie II. För studier III-IV utfördes gruppjämförelser med Mann-Whitney U-test, independent t-test, eller Fisher's exact test beroende på typen av variabler.

De narrativa fynden i studie I visade att individer som exponerades för senapsgas hade dålig tillgång till sjukvård i Kurdistan-Irak. De stigmatiserades och övergavs socialt på grund av etiketten "Kemiskt exponerad överlevande". Narrativa fynd indikerade utveckling av “Kemisk kontamineringsångest" som orsakade rädsla och osäkerhet och begränsade deras möjligheter att bilda familj, och vara aktiva i social- och yrkesliv. Genusrelaterade effekter av exponeringen i studie II visade att kvinnor upplevde betydande psykosociala effekter medan männen var mer oroliga för komplikationer efter exponering, t.ex. funktionsnedsättningar och dödsfall. Studie III visade att individer som exponerades för senapsgas hade statistiskt säkerställd sämre livskvalitet och måttlig depressiva symptom än de oexponerade deltagarna. Studie IV visade att individer som exponerades för senapsgas hade markant sämre små luftvägsfunktion än oexponerade deltagare.

Sammantaget visar denna avhandling med blandade metoder en association mellan senapsgasexponering och avsevärda långsiktiga sämre fysiska och psykiska symptom, lägre livskvalitet och sämre lungfunktion bland individer som exponerades för senapsgas än oexponerade deltagare. Avhandlingen betonar vikten av en biopsykosocial modell för att ta hand om de unika behoven hos denna speciella grupp av patienter.

CONTENTS

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Moradi Faraidoun**, Söderberg Mia, Moradi Fazil, Daka Bledar, Olin Anna-Carin, and Mona Lärstad: Health perspectives among Halabja's civilian survivors of sulfur mustard exposure with respiratory symptoms—a qualitative study. PLoS ONE. 2019;14(6)

II. **Moradi Faraidoun**, Moradi Fazil, Söderberg Mia, Daka Bledar, Olin Anna-Carin, and Mona Lärstad: Gendered lived experiences of marriage and family following exposure to chemical warfare agents: content analysis of qualitative interviews with survivors in Halabja, Kurdistan-Iraq. BMJ Open. 2020;10(10)

III. **Moradi Faraidoun**, Moradi Fazil, Li Ying, Olin Anna-Carin, and Daka Bledar The impact of sulfur mustard on quality of life and mental health in Kurdish survivors in Sweden, thirty years after exposure. Health and quality of life outcomes 2022;20(1):1-10

IV. **Moradi Faraidoun**, Kjellberg Sanna, Li Ying, Daka Bledar, and Olin Anna-Carin: Respiratory function 34 years after sulfur mustard exposure in survivors in Sweden. Submitted for publication.

ABBREVIATIONS

AX: Area of reactance
BMI: Body Mass Index
CWAs: Chemical Warfare Agents
COPD: Chronic Obstructive Pulmonary Disease
DNA: DeoxyriboNucleic Acid
DLCO: Diffusing capacity of the lung for carbon monoxide
FDR: Frequency dependence of resistance
IOS: Impulse oscillometry
KRG: Kurdistan Regional Government
LCI: Lung clearance index
MBW: Multiple breath washout
MADRS-S: Montgomery and Asberg Depression Rating Scale-Self-rating
OPCW: Organization for the Prohibition of Chemical Weapons
PTSD: Post-Traumatic Stress Disorder
QoL: Quality of Life
PCS: Physical Component Summary
PTSD: Post-Traumatic Stress Disorder
MCS: Mental Component Summary
RNA: Ribonucleic acid
R5: Resistance at 5 Hz
R20: Resistance at 20 Hz
SAD: Small airways dysfunction
S_{acin}: Ventilation inhomogeneity in the entrance to the acinar airway zone
S_{cond}: Ventilation inhomogeneity in the conducting airways zone
SF-36: RAND 36-Item Short Form Health Survey
SM: Sulfur mustard

INTRODUCTION

Chemical Warfare Agents (CWAs) rank among the most brutal weapons of mass destruction. The fact that they are easy and cheap to produce makes them an attractive choice for small terrorist groups to inflict massive loss of human lives. Sulfur mustard (SM) is the most commonly used CWA and poses an immense threat to human health and security. The Organization for the Prohibition of Chemical Weapons (OPCW) has defined a chemical weapon as "a chemical used to cause intentional death or injury through its toxic properties"; even ammunition, devices, and other equipment specially designed to weaponize toxic chemicals and their precursors also fall under the definition of chemical weapons.

Exposure to this agent not only causes physical injuries and mental harm but can also have severe, long-term effects on individuals' biopsychosocial conditions. These have not been well studied. However, the long-term effects can significantly impact the exposed individual's overall well-being. Therefore, this thesis comprises mixed methods: qualitative research to examine patterns, social and individual living conditions, gender-based disparities in lived experiences, and reflections regarding exposure to SM and quantitative research to determine disparities, effects, and associations statistically among exposed and unexposed individuals. Both methods support comprehending the full spectrum of how chemical weapons impact on exposed individuals' biopsychosocial situation.

CHEMICALS AS WARFARE AGENTS THROUGHOUT HISTORY

Throughout history, humans have not hesitated to resort to any means to achieve military goals or eliminate the enemy quickly. Hunters in southern Africa during the Late Stone Age (10,000 BCE) used toxins and chemicals such as the poisoned arrow to enhance their effectiveness in hunting(1) and soldiers in India used toxic fumes as weapons of mass destruction against the enemy around 2000 BCE(2).

In the years around World War I, CWAs were rapidly modernized. Soon, many industrialized countries gained access to new knowledge to produce various types of more lethal and advanced CWAs(3). Despite the global ban according to the Hague Convention in 1899 and the Geneva Protocol of 1925 (4, 5), chemical weapons have been used in many international, civil, and regional conflicts(6-12). Examples are World Wars I and II, Italy using sulfur mustard against Ethiopia, Japan employing it against China, Germany heavily attacked the French town of Armentieres with SM in 1917, and Poland utilizing it against Germany during the 1930s(12). It was also used during the Iran-Iraq war (8) including genocidal violence against the Kurdish population in Kurdistan-Iraq in the late 1980s (9), in the Syrian civil war in 2013 (11) and even in terrorist attacks, e.g., Tokyo 1995(10). Another example is the chemical poisoning with Novichok in Salisbury, UK, in 2018(13). In addition, industrial chemical accidents and environmental disasters have occurred, e.g. in Bhopal, India, in 1984(14) and the chlorine spill in South Carolina, USA, in 2005(15). The easy access to knowledge of CWAs' production, the increased global threat from international and regional wars, and the actions of terrorists show that CWAs still shadow human security.

Parallel to the development and use of CWAs, there have been various measures to limit their use or at least minimize their harmful effects. One of the first written descriptions is the "Laws of Manu", a Hindu treaty on statecraft (400 BCE) that regulates the use of toxins and chemicals in war(16). Since modern treaties(4, 5) did not prevent the use of CWAs the OPCW was formed, and most states ratified the Chemical Weapons Convention in the1990s(17, 18). The convention has classified CWAs in different groups (Fig.1). Consequently, the OPCW has established a list of recognized CWAs under the name "Controlled substances list". However, this list is far from containing all toxic chemical substances that can be used as lethal chemical warfare agents. Thus, this list is occasionally updated based on chemical incidents and the evaluation of these chemicals' potential risk as CWAs. Despite this, the use of chemical weapons in the Syrian civil war indicates a legal vacuum regarding the route of responsibility and its form of punishment.

While significant steps have been taken to minimize production, more needs to be done to prevent use and to hold perpetrators accountable.

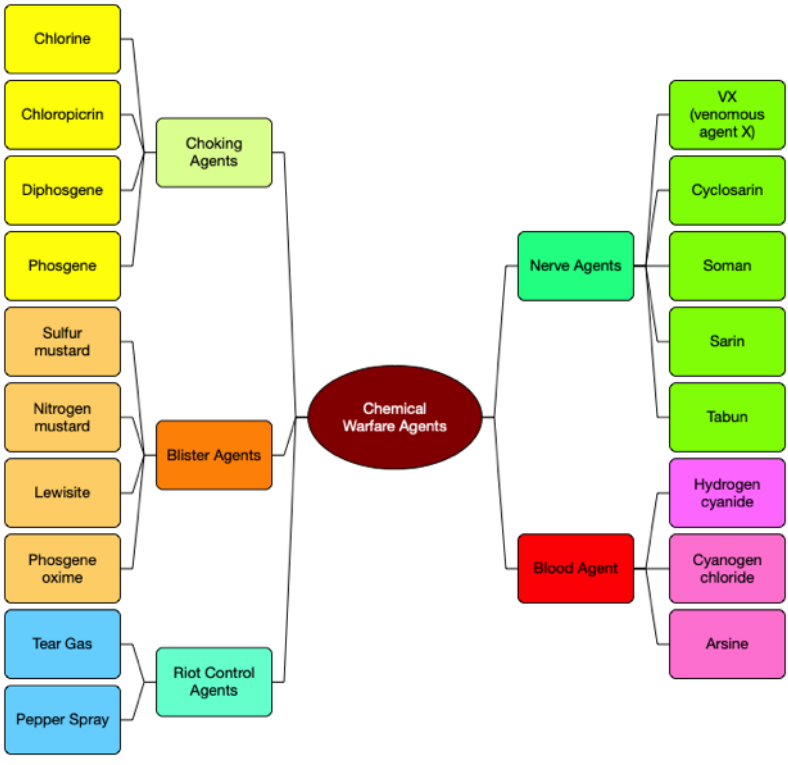

***Figure 1**. Classification of chemical warfare agents in the Chemical Weapons Convention by the Organisation for the Prohibition of Chemical Weapons. 2023.*

The chemical attacks against the Kurdish people

The Anfal campaign, known as the Genocide in Iraq, was a military operation conducted by the Iraqi government in the late 1980s against the Kurdish population(19). Consisting of eight conventional and chemical attacks(19, 20), it targeted the Kurdish Autonomous Region of Iraq (Fig. 2). The campaign's name derives from a chapter in the Quran and means "spoil of war". It resulted in widespread destruction and loss of life(19).

Study conducted in the past have verified use of SM and sarin gases targeting the Iraqi Kurdish population(21). Several locations were attacked with CWAs in 1987-1988, some of them several times. In the city of Halabja alone there were up to 5,000 immediate deaths and several thousand survivors with severe injuries and restrictions(19, 20, 22).

The department of the Ministry of Martyrs and Anfal Affairs within the Kurdistan Regional Government (KRG) was established in 2006 to manage this issue and support the survivors. The survivors who are believed to have enduring post exposure health complaints, are referred to the Ministry of Martyrs and Anfal Affairs. Their registration as CWAs-exposed survivors is a long and complicated process as recognition means getting a life annuity and other economic and social benefits. The individuals thus referred meet a foreign medical board consisting of various specialists, e.g. pulmonologist, ophthalmologist, dermatologist and local staffs of the above-mentioned department. In accordance with and based on exposure history, clinical symptoms, physical status, and laboratory and radiological investigations, the survivor is rated on a disability scale, i.e., easy, mild, moderate and severe. An internal report from the Ministry of Martyrs and Anfal Affairs in the KRG reveals that thousands of individuals exposed to CWAs in Kurdistan-Iraq are suffering from various physical symptoms.

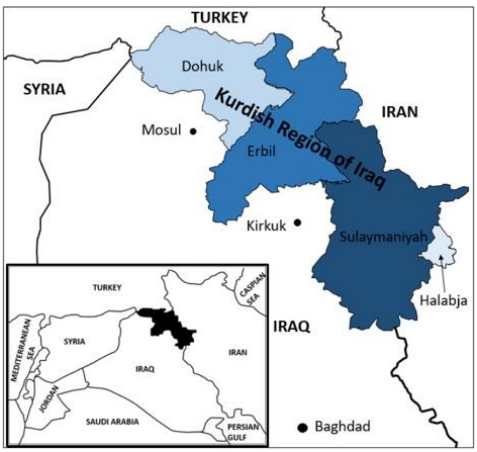

Figure 2. *Administrative map of Kurdistan-Iraq. Source: H. Mohammed et al Transportation Research Interdisciplinary Perspectives 2 (2019).*

SULFUR MUSTARD

Sulfur mustard (bis(2-chloroethyl) sulfide) was synthesized for the first time in 1822(23). In 1860, the SM vesicant properties were observed, and SM of higher purity was produced in 1886(23). In the early 20th century, German chemists investigated the military use of SM(23). It was given the name yperite when it was used in a military operation during WWI in Ypres in Belgium(24). Exposure to SM which is also called mustard gas or HD(23), is associated with a low mortality of around 3% but high morbidity(12). It affects several organs, such as airways, skin, eyes, blood and nervous system, with long-term biopsychosocial impacts(6, 25-28).

The mechanism of how SM causes short- and long-term multiple organ damage is not fully understood. There is no specific antidote or treatment for damage after exposure(23). Also, clinical diagnosis with conventional pulmonary function testing of survivors has been challenging (29).

Understanding the exact mechanisms behind SM-related symptoms is fundamental for developing treatment and care. On the other hand, the availability of specific biomarkers and appropriate investigation technique are crucial for early diagnosis and the prevention of deterioration due to lung diseases. Consequently, at present, the early detection of pulmonary complications is limited.

POTENTIAL MECHANISMS OF ACTION FOR SULFUR MUSTARD

The SM-related multiple organ damage in the short- and long-term indicates the different biological mechanisms of action. There are some hypotheses regarding these pathways (Fig. 3). The lipophilic property of SM facilitates its rapid absorption into tissues and cells through direct contact with skin, inhalation, and ingestion(30). When SM is triggered within the body, it generates a highly reactive, cyclic sulfonium ion. This ion possesses the ability to bind with numerous biological molecules, with functional groups, e.g., sulfhydryl, carboxyl, and aliphatic amino(31). These biomolecular interactions overlap and result in DNA damage, dysfunctional proteins, oxidative stress, inflammatory response, apoptosis, and cell death(12, 23, 32). The SM alkylation of the sulfhydryl group of cysteine and binding to glutathione lead to reducing its content in the cell and subsequently increasing free radicals. This leads to cell membrane damage, necrosis, and cell death(33-35). This mechanism of action is probably attributed to the short effects of SM(36).

Furthermore, the reaction of SM with DNA/RNA induces DNA damage through DNA alkylation, intra- or inter-strand cross-links, and disturbing the normal function of cell division, with, subsequently, severe injury and possibly cell death(37). The formation of double-strand breakage results in defects of the DNA repair pathway, e.g., poly (ADP-ribose) polymerase (PARP-1). It also results in hyperactivation of this repair pathway and depletion of nicotine adenine dinucleotide depletion (NAD+), in other words, deprivation of energy causing genotoxicity and mutation(38-41). Upregulation of apoptosis-related genes, specifically p53, following SM-induced damage in keratinocytes and pulmonary epithelial with increased risk of respiratory cancer tracts, supports this belief that SM-induced DNA damage is probably part of SM mechanisms of action(42).

Another mechanism might be the SM-mediated alkylation of proteins with functional groups, e.g., sulfhydryl and amino causing enzyme inhibition. This disturbs the cell metabolism resulting in cell damage, death, and release of cell contents(43). The last step initiates the inflammatory response by

increasing the production of interleukin (IL)-1α, 1-β, IL-8, granulocyte-monocyte colony-stimulating factor, monocyte-activating protein-1 (MAP-1), and TNF-α(40).

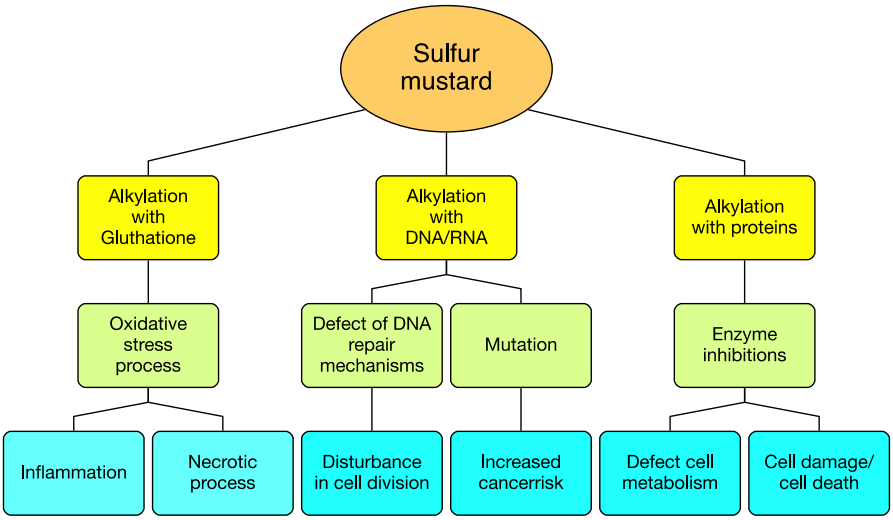

Figure 3. *Schematic illustration of potential mechanisms of action for sulfur mustard.*

The hypothesis is that the inflammation process is thought to be attributed to delayed lung complications, probably a consequence of the release of pro-inflammatory and inflammatory mediators. This release is due to the initiation of the oxidative stress process by releasing toxic mediators such as reactive oxygen species. They facilitate the accumulation of inflammatory cells, e.g., cyclooxygenase-2 (COX-2) and 12-lipoxygenase (12-LO), and the underproduction of protective substances, including so-called surfactants(44-47).

Despite indications of neuropsychiatric illnesses due to exposure to SM, the pathophysiological aspects have not been thoroughly studied in SM-exposed survivors. It is generally over time that the neuropsychiatric symptoms become apparent(48, 49). This might be explained by the fact that vesicant agent causes damage after passing the brain barrier and entering the brain. Furthermore, previous studies on SM or its analogue and in survivors with

war-related PTSD revealed brain impacts both structurally and functionally(50, 51). Reduced level of serum melatonin (a hormone that performs a crucial function in facilitating sleep) is also shown in SM-exposed survivors(51).

The severe traumatic event exposed individuals go through, if not treated promptly after exposure to a CWAs, can result in persistent PTSD and enduring psychosomatic problems, including ongoing pain, depression, and anxiety. Moreover, numerous studies have documented that the presence of mental illnesses and symptoms in individuals exposed to SM is linked to neuronal damage in the nervous system(6, 28). A follow-up of 44 individuals exposed to a compound containing SM and Lewisite in China in 2003 showed significant autonomic and neurocognitive dysfunction(52). This was attributed to the direct consequences of the brain damage probably caused by the mixture of SM/Lewisite. Long-term cognitive ability could potentially be affected by brain “abnormalities” in individuals exposed to SM(50, 53). Although a traumatic event related to CWA exposure is considered a significant contributor to mental illness, the biological effect of SM cannot be ignored and requires further investigation.

HEALTH EFFECTS DUE TO EXPOSURE TO SULFUR MUSTARD

Following exposure to SM, generally, there is a several hours' long, symptom-free interval(23). The duration of the free interval, the development of symptoms, and the severity of injury largely depend on multiple factors, i.e., the dose, duration, and nature of SM exposure, even climate temperature, age, and protective clothing(54). The dermal, ocular, respiratory, and haematological systems are thought to be the most impacted organs after SM exposure(12, 23). The ocular system is the organ most sensitive to SM exposure but the skin is the most extensive exposed organ. This means that the respiratory tract is the major impacted organ in the long term.

PHYSICAL COMPLAINTS

Systemic toxicity is probably related to the high dose of SM exposure(55). In the literature, the systematic symptoms are thought to be similar to those caused by radio- or chemotherapy. Headache, nausea, vomiting, and loss of appetite are associated with exposure to a low dose of SM; however, exposure to a higher dose gives more severe gastrointestinal tract symptoms, as well as diarrhea, fever, and bone marrow impact such as leucopoenia and cachexia. There have been reports of cases where the central nervous system has been severely stimulated, leading to convulsions.

The ocular organ, the warm and moist atmosphere of the eyes make the ocular organ the most sensitive and the first to show signs and symptoms after exposure to SM(55). After exposure, the SM-exposed survivors reported symptoms such as eyes burning, sensations of tearing, conjunctivitis, and a feeling of grittiness under the eyelid, corneal oedema, sensitivity to light (photophobia), severe blepharospasm (eyelid twitching), and even more severe issues such as corneal damage, ulceration, and perforation(56). Many survivors reported temporary blindness within hours or days after exposure. A previous study revealed the manifestation of ocular symptoms 50 years after exposure to SM(57).

Dermatological symptoms are experienced by almost all of those exposed to SM(55). Itching and erythema are the most acute symptoms to be developed. Severe erythema followed by blister formation and ulceration of dermal structures is one of several dermatological symptoms(58). The development of blisters has been reported in the survivors several weeks after SM exposure. The severity of delayed respiratory complications has been reported to be associated with the development of the severity of the initial dermatological symptoms(55). The long-term dermatological problems of hypopigmentation and hyperpigmentation are perceived as an aesthetic problem for the exposure survivors, especially the women(59, 60). Otherwise, long-term dry skin with persistent pruritis and burning are inevitable for survivors.

Respiratory symptoms are the dominant effects of SM exposure in the short and long term(55). Depending on the factors mentioned above, the exposed individual may experience various symptoms that affect their upper respiratory tract within hours. These symptoms may include irritation of the nasal mucosa, burning sensation in the throat, hoarseness, sneezing, coughing, lacrimation, rhinorrhoea, loss of smell and taste, hacking cough, acute tracheobronchitis, oedema in the upper and lower airways, and ulcerations(55).

The delayed respiratory effects are reported by more than 80% of SM survivors. They deteriorate continuously and are severe health challenges for SM-exposed survivors(25, 54, 61). Lung complications are thought to be the main cause of death in SM survivors post exposure(62).

Radiological investigations have shown different kinds of lung damage, including air trapping, bronchiectasis, mosaic parenchymal attenuation, irregular and dilated major airways, bronchial wall thickening, and lung fibrosis(48, 63, 64). The occurrence of cancer is reported among workers at SM production facilities and storage sites(65, 66). Iranian SM-exposed survivors with bronchiectasis and lung fibrosis were shown to have a significantly higher risk of developing lung cancers 40 years post exposure(64). Studies have shown that many individuals who have been exposed to SM have experienced significant symptoms such as recurring pneumonia, chronic bronchitis, COPD, cryptogenic organizing pneumonia,

bronchiolitis obliterans, and even emphysema(48, 67). Bronchiolitis obliterans is, however, the major long-term consequence(68, 69).

Spirometry tests have revealed restrictive, obstructive, or normal results in SM-exposed survivors(44, 70, 71). However, spirometry has failed to measure the function of small airways (airways with an internal diameter <2 mm) until onset of clinical symptoms(72, 73). Though, disease in this lung region, "small airways dysfunction (SAD)", is reported to be a major pathological incident in asthma and COPD(49) and is described as existing across all severities in these diseases(72). Thus, SAD has not previously been studied thoroughly in individuals exposed to SM. Therefore, we used different non-invasive techniques to assess airways in SM-exposed survivors compared to unexposed individuals.

PSYCHOLOGICAL COMPLAINTS

Being exposed to SM can be quite distressing, just like any other unexpected stressor. However, it can cause symptoms of distress that are beyond usual human experience, potentially leading to trauma and mental illness. Following SM exposure, the survivors have reported acute stress disorder, acute helplessness to protect oneself and family, anxiety, loss of perceived safety, shock, insomnia, feeling desperate, and crisis(74).

The long-term negative mental health effects after exposure to CWAs attacks are apparent in individuals exposed to SM but they have not been studied in depth compared to physical effects. The neuropsychiatric health sequelae have been even less explored(28, 75, 76). Mental onset 2-3 decades after exposure to SM may be manifest in hostility, anxiety, obsessive-compulsive behavior, somatization, depression, and PTSD, and also as inability to resume normal living due to reduced health(77).

Depression is a main cause of mental illness in the world and is widespread among SM survivors(78). Psychosocial factors play a crucial role in the development of depression. The crisis reaction is an example of psychosocial components that is suspected to increase the risk of developing depression later in life. Thus hormonal imbalances in the monoamine systems, the

pituitary-hypothalamus-adrenal axis(79, 80), as well as the occurrence of neurodegenerative processes, are reported as biological vulnerabilities for the occurrence and extension of depression(81). Depression causes a diversity of symptoms including impaired physical and emotional well-being, e.g., feelings of sadness, loss of interest in activities and surroundings. Feelings of guilt and failure exist side by side with pessimism and suicidal thoughts. The ability to function at work and at home is reduced(82).

Despite the right to social security and social benefits and access to the highest quality of long-term care services in Iran, 12 % of the survivors still had moderate to severe and 48 % mild symptoms from lungs, skin, and eyes up to 4 decades after exposure to SM(29). Furthermore, another study revealed that 60% of Iranian survivors of CWA exposure suffered from mental illnesses up to 3 decades post exposure(83).

The long-term physical and psychological illnesses gradually impacts other aspects of a survivor's life. Consequently, survivors face biopsychosocial challenges such as physical incapacities, mental illness, social isolation due to stigmatization, and reduced socioeconomic independence(26, 84).

Understanding the patients' perception of their own complaints and experience is an essential contributor to effective health outcomes. The biopsychosocial model is a theoretical framework for grasping the interconnections between physical complaints, psychological burdens, and socioeconomic circumstances, and how they collectively influence various dimensions of individuals' QoL(85).

The World Health Organization characterizes QoL as a subjective assessment of how individuals see themselves within their cultural and value framework, considering their ambitions, anticipations, and worries(86). This definition pays more attention to people's subjective perceptions of the important features of their complex multidimensional well-being concepts. This including their physical, material, social, and emotional well-being, as well as their intertwined interactions in life. Therefore, it is difficult to define and measure QoL, and its subjectivity makes its interpretation even more challenging. There are several definitions of QoL as well as several different measuring methods, and thus no single definition or method is

comprehensive. We explored the QoL in survivors by applying the RAND Short Form Health Survey 36 (SF-36) questionnaire(87, 88).

However, diagnosis of mental illnesses is often based on patients' anamneses and no validated blood tests or objective methods exist for evaluating mental health. We used the Montgomery and Asberg Depression Rating Scale (MADRS-S), a mental health questionnaire to assess depressive symptoms. A self-reporting version of MADRS is often used in Scandinavian clinical practice as a complementary instrument for measuring the severity of depressive symptoms(89).

GENDER-DIFFERENCE EFFECTS

During wars, military operations, and chemical weapons attacks, women and children have been the most vulnerable victims, being hit the hardest and paying a disproportionate price. However, knowledge regarding gender differences impact due to exposure to SM is very scarce and has not been studied thoroughly. Existing data does however indicate long-term gender differences after exposure to a CWAs(90, 91). A study conducted in Iran found noticeable gender differences in the severity of post-exposure physical injuries related to SM exposure; while exposed men had a higher incidence of eye lesions, exposed women had a higher severity of skin lesions(29).

Moreover, it has been shown that pregnant women and their foetuses are particularly vulnerable to chemical exposure, which can lead to the development of abnormalities and congenital disabilities and the potential to disturb sex hormones and trigger an assortment of physiological and anatomical abnormalities in the male reproductive system following exposure. More research is necessary to understand the impact of these alterations on the fertility of individuals who have survived SM exposure (92-95). Currently, no research has been conducted on the effects of SM on the reproductive system of women.

In addition to the biological effects, women exposed to a CWAs are psychosocially affected in the long term. Research on the lasting effects of chemical disaster and other traumatic events, e.g., terror attacks, has revealed

that mental illnesses and adjustment disorders were more frequent in exposed women than men(96-98). In the case of chemical attacks, victims may also face social stigmatization and discrimination, which probably affect men and women differently.

Overall, exposure to SM can have unique and harmful effects on women and men biologically and psychosocially. Therefore, more research is needed to understand the gender-specific effects of SM fully. This thesis explores and elaborates on the gender perspective through a qualitative content analysis of interview material and quantitative measurement of health outcomes. It uses the RAND SF-36 to measure the quality of life and the MADRS-S to assess mental illness.

THE CWAs-EXPOSED SURVIVORS AND THE PRIMARY HEALTHCARE CLINICAL CONTEXT

The survivors of CWAs face a range of challenges that require a holistic approach over time. That is why primary healthcare, with its comprehensive and inclusive medical, psychological, and rehabilitation approach, can be a lifeline for these patients. It is an essential first point of contact that can coordinate specialist care and improve patients' QoL. In line with the biopsychosocial model, primary care physicians can fully grasp the complex interactions involved and offer multidisciplinary solutions. It is believed that primary healthcare is a vital component in a compassionate and inclusive healthcare strategy, and it should be readily available to all survivors of CWAs. However, some of this patient group might need more advanced specialist care.

Table 1. *Overview of the studies included in this thesis.*

Paper	Title	Aim	Methods and analysis approaches/ statistical methods	Study population	Data collecting techniques
I	Health perspectives among Halabja's civilian survivors of sulfur mustard exposure with respiratory symptoms—a qualitative study	To explore lived experiences and major concerns related to sulfur mustard exposure	Qualitative; Systematic text condensation	Sulfur mustard exposed survivors in Kurdistan Iraq N=16	Semi-structured interviews
II	Gendered lived experiences of marriage and family following exposure to chemical warfare agents: content analysis of qualitative interviews with survivors in Halabja, Kurdistan-Iraq	To study genus perspective about sulfur mustard effects	Qualitative; Content analysis	Sulfur mustard exposed survivors in Kurdistan Iraq N=16	Semi-structured interviews
III	The impact of sulfur mustard on quality of life and mental health in Kurdish survivors in Sweden, thirty years after exposure.	To evaluate and compare quality of life and mental health among sulfur mustard exposed vs unexposed individuals	Quantitative; Descriptive statistics Mann-Whitney u test. Independent t-test, Fisher's exact test. Mediation analysis	Sulfur mustard exposed survivors and unexposed individuals in Sweden N=48	Interview based questionnaire; -Rand Short Form Health Survey (SF-36) - MADRS-S
IV	Respiratory function 34 years after sulfur mustard exposure in survivors in Sweden	To investigate lung function among sulfur mustard exposed vs unexposed individuals	Quantitative; Descriptive statistics Mann-Whitney u test	Sulfur mustard exposed survivors and unexposed individuals in Sweden N=30	-Impulse oscillometry -Nitrogen Multiple breath washout -Diffusing capacity of the lung for carbon monoxide

AIM

GENERAL AIM

The overarching objective of this thesis has been to describe and explore long-term biopsychosocial problems: lived experiences, major concerns related to sulfur mustard exposure in exposed individuals and how exposure affects existential conditions, everyday social life, and gender relations. Furthermore, this thesis aimed to study the long-term impacts of sulfur mustard exposure on mental health, quality of life, and small airways function.

SPECIFIC AIMS

I. To explore major post-exposure health concerns in Halabja's civilian survivors of chemical warfare agents with long-term respiratory symptoms.

II. To explore the lasting effects of chemical warfare agents on marriage and family building among civilian survivors in the city of Halabja.

III. To assess and evaluate the quality of life and mental health condition of Kurdish sulfur mustard survivors resettled in Sweden and compare with an unexposed Kurdish group in Sweden.

IV. To evaluate and compare small airways function between individuals previously exposed to SM and unexposed individuals in Sweden.

PARTICIPANTS AND METHODS

PARTICIPANTS

Kurdistan-Iraq

The SM-exposed participants in this thesis are Kurdish individuals who survived the chemical attacks in Kurdish regions during the Anfal military operation in the late 1980s. These individuals are registered in a database managed by the Ministry of Martyrs and Anfal Affairs, and they are given a disability scale based on physical illnesses such as lungs, eyes, and skin complaints. The author of this thesis conducted a field pre-study in Kurdistan-Iraq in 2015, visiting affected areas and conducting group discussions with survivors to learn more about the exposure issues.

The individuals exposed to SM and participating in Studies I and II were selected from a database provided by the Bureau of the Ministry of Martyrs and Anfal Affairs in Halabja. This region has the highest concentration of survivors of chemical warfare agents exposure. A purposive approach was applied to collecting data from a heterogeneous group with different demographic variables, e.g. sex, age, marital status, education level. A prespecified inclusion criterion was the existence of respiratory symptoms as a sign of exposure to SM. The potential participants were contacted by telephone, and data was collected until data saturation was reached with 16 interviews in 2016. The Halabja Chemical Victims' Society and Halabja Glory Organization played a role in organizing the recruitment of participants.

Sweden

Regarding the participants included in Studies III and IV in Sweden, they were recruited among Kurdish individuals who had moved to Sweden as refugees due to political instabilities in the Middle East, particularly in the Kurdistan regions in the last 3 decades. Their exposure to CWAs made these individuals perceptible to us as a "hard to reach" population. A snowballing

approach was used as a purposive sampling method, along with other traditional sampling techniques, to identify and enlist potential participants. For the studies in Sweden, the SM-exposed participants were compared to SM-unexposed participants recruited among the first generation of the Kurdish-Swedish population. The participants were selected based on specific criteria, such as ethnicity, age, and sex. The SM-exposed participants were individuals who had survived the chemical attacks in the Kurdistan regions of Iraq and Iran in the late 1980s, had physical symptoms developed at the time of SM exposure, and were between 30 and 80 years old. The SM-unexposed participants were Kurdish-Swedish individuals with no history of SM exposure and were also between 30 and 80 years old.

It is worth noting that there is no database of CWAs-exposed individuals in Sweden and no evidence-based laboratory tests exist to confirm long-term exposure, making it challenging to determine the exposure to SM. Therefore, exposure history was determined based on participants' lived experiences, memories, and narratives. The data was collected for Papers III in 2018 and IV in 2019 and 2022, respectively.

METHODS

Qualitative (Papers I & II) and quantitative (Papers III & IV) methods are used in this thesis, with different data collection techniques, management, and statistical analysis approaches (Table 1) described in detail below.

STUDIES BASED ON QUALITATIVE METHODS

A qualitative research method (I-II) was used to examine thoroughly patterns in social and individual living conditions, as well as lived experiences and thoughts. To collect data, interview technique was applied, which is widely recognized for identifying issues of high importance to the individuals being interviewed(99). This approach allowed us to gain a comprehensive

understanding of the challenges faced by CWA survivors. Open-ended questions about participants' biopsychosocial challenges following exposure were asked. This technique provided a mutual opportunity for the interviewer to collect complete data and for the participants to discuss their major concerns openly.

STUDIES BASED ON QUANTITATIVE METHODS

The quantitative research used statistical methods to investigate the possible differences, impacts, and relationships between individuals who have been exposed to SM and those who have not. In Paper III we used two well-validated questionnaires: the SF-36 V.1 (87, 88) to assess QoL and the MADRS-S to study mental health in SM-exposed versus unexposed groups (89). The data from SM-exposed participants was collected through individual interviews while the data from unexposed participants was self-reported. For Paper IV we used different non-invasive techniques to assess lung function in SM-exposed survivors compared with unexposed individuals.

HEALTH MEASUREMENTS

QUALITY OF LIFE

The SF-36 is a 36-item instrument to survey health status and QoL(87). Since its development in 1992, the SF-36 questionnaire has been used to measure an individual's overall quality of life. Its results have been helpful in shaping public health policy and influencing policymakers(87, 88). The questionnaire is comprised of 36 questions which can be used to explore how physical and mental illnesses affect social and professional life. Based on these questions, eight scaled scores are generated (vitality, physical functioning, bodily pain, general health, physical role functioning, emotional role functioning, social functioning, and mental health). Moreover, the subscales are summarized into two main components: Physical Component Summary (PCS), which includes physical functioning, physical role functioning, general health, and bodily pain, and Mental Component Summary (MCS), which includes vitality, social

functioning, emotional role functioning, and mental health. Higher scores indicate a better possible perception of QoL.

SEVERITY OF DEPRESSIVE SYMPTOMS

The MADRS is a mental health questionnaire designed in 1979 by British and Swedish researchers(89). A self-rating version of MADRS is often used in clinical practice as a complementary instrument to measure the severity and diagnosis of depression and follow up the treatment(100). The MADRS-S comprises nine subscales covering the following symptoms: 1. Reported sadness 2. Inner tension 3. Reduced sleep 4. Reduced appetite 5. Concentration difficulties 6. Lassitude 7. Inability to feel 8. Pessimistic thoughts 9. Suicidal thoughts. Each subscale rating is from 0 to 6, and the overall MADRS-S ranges from 0 to 54. A higher MADRS-S score indicates more depressive symptoms. The severity of depression following overall MADRS-S scores is: No depression: 0-12 points. Mild depression: 13-19 points. Moderate depression: 20-34 points. Severe depression: ≥ 35 points(101).

PULMONARY FUNCTION TESTS

The investigation of airways (Fig. 4) was assessed by applying Impulse oscillometry (IOS) (CareFusion, Germany) and using a Jaeger Master Screen system according to current guidelines(102). IOS is a non-invasive pulmonary function test that uses sound waves to measure the resistance to the normal air movement in and out of the lungs when one is breathing at rest and provides information on the lung airways' mechanical properties (resistance and reactance). The procedure of the investigation is explained elsewhere(103). The reported variables included are: resistance at 5 and 20 Hz (R5 and R20, respectively) and their difference as a measure of small airways resistance (i.e., R5-R20), called frequency dependence of resistance (FDR),(104) and area of reactance (AX), which is an indicator of the "stiffness" of the small airways.

The multiple breath washout with nitrogen (N_2MBW) was used to evaluate the uniformity of gas distribution in the lungs(105). N_2MBW (EcoMedics, Switzerland) was carried out using the ExhalyzerD device with the software Spiroware 3.3.1. By breathing 100% oxygen, nitrogen was washed out from the lung. The ExhalyzerD is validated according to current guidelines for inert gas washout tests(105). Reported outcomes included: (i) lung clearance index

(LCI) as a measure of global lung ventilation inhomogeneity, (ii) ventilation inhomogeneity in the conducting airways (Scond), (iii) and at the entrance to the acinar airway zone (Sacin)(105).

The diffusing capacity of the lung for carbon monoxide (DLCO) measures the gas exchange capacity in the lung across the alveolar-capillary interface (106). DLCO was performed using the single breath method with a Jaeger Master Screen system (CareFusion, Germany). The test procedure was carried out according to the guidelines for the method(107). Reported outcomes were alveolar volume (VA), DLCO, and their ratio (DLCO/VA).

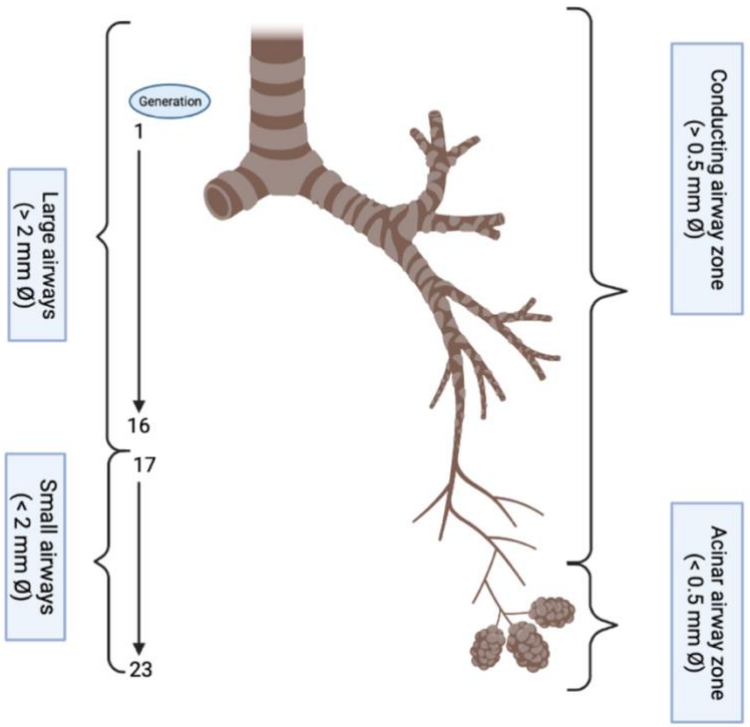

Figure 4. *A schematic illustration of the bronchial tree (large airways, small airways, conducting zones, and acinar zones in terms of size and number of airway generations). Created with BioRender.com*

ETHICAL CONSIDERATIONS

The Regional Ethical Review Board at the University of Gothenburg approved all studies included in this thesis (reference number 599-17). Furthermore, data collection permission was obtained for Studies I and II from the Ethical Committee of the College of Medicine at the University of Sulaimani in Kurdistan-Iraq (reference number 7/23/1751). The studies conducted adhered to the ethical guidelines of the Declaration of Helsinki regarding medical research involving human subjects.

The participants included in all studies in this thesis received oral and written information in Kurdish- Sorani language about the study. They were informed that participating was voluntary and that they could withdraw at any time without explanation or consequence. Their integrity is highly prioritized, the data is reported at the group level, and their contact information is anonymized.

In Kurdistan-Iraq as per the local context, the act of signing documents has been linked to their bureaucratic purpose, leading to a sense of scepticism towards written consent. Hence, verbal informed consent was sought instead. However, written consent was obtained when the participants received a copy of their transcript interview and commented on it before submission.

They were fully informed about the potential risks and benefits of participating. The researcher who conducted the interviews and collected data was a physician and specialist in Family Medicine and was fully aware of the potential risks that participants may face during the study, such as emotional distress, confidentiality breaches, and stigma. Therefore, all necessary measures were taken to ensure that participants' rights were fully respected and that their privacy and confidentiality were protected throughout the process.

In case of any emotional distress, preparations were made to refer the participant to a medical clinic for further assistance. Participation in qualitative studies allowed individuals to express their concerns regarding post-exposure fear and related issues. It is rare for females exposed to CWAs

to discuss their lived experiences outside a research context within the community. Participating in a qualitative study provides a platform for individuals to express their concerns, leading to a better understanding of the individuals' subject matter and making their experiences and thoughts more visible.

The gender factor of the interviewer might have hindered female interviewees from sharing key personal stories, but the fact that the interviewer was also a medical practitioner may have reduced this barrier since participants tended to have confidence in doctors(108).

DATA MANAGEMENT AND STATISTICAL ANALYSIS

DATA MANAGEMENT AND ANALYSIS

PAPERS I&II

The audio-recorded interviews were transcribed verbatim and translated into English by an authorized translator. The data was later validated, and the first author anonymized it before being distributed to the other authors. The first author kept the codes confidentially.

In Paper I, we used systematic text condensation inspired by Giorgi's phenomenological analysis, applying a thematic cross-case analysis(109). This approach, without further colouring the participants' assertions, emphasizes their experiences and perspectives. The procedure followed several steps, including: 1. the studying of the interviews to get a preliminary overview; 2. the coding process by classifying the material into meaningful units that represented previously selected themes inspired by the WHO definition of health and QOL; 3. condensing the selected codes and producing the appropriate citations; 4. the process was achieved by presenting the first author's descriptions and concepts and refining them within the research group.

For Paper II, we employed a qualitative content analysis approach that involved integrating anthropological inquiry to gain a more comprehensive understanding of both the manifest and latent content of the data(110). By studying interpretations within their social-historical context, we aimed to go beyond individual narratives, particularly from participants who seldom discuss their lived experiences openly.

The research group members studied the interviews to obtain a preliminary overview. The first author coded the data closely with the second author and the research group discussed the codes suggested before condensation. Later, the citations were produced, the categories were created, and manifest and latent content was discussed within the research group. We used the computer software NVivo (QSR International Pty Ltd, V.10) to sort the quotations(111). The results were reported following the Consolidated

Criteria for Reporting Qualitative Research (COREQ) 32-item checklist(112).

STATISTICAL ANALYSIS

PAPERS III & IV

We applied an independent T-test, or Fisher's exact test, depending on the type of variables, to compare the demographic variables between groups, i.e., sex, age, BMI, education achievement, employment, and marital status.

Furthermore, for all between-group comparisons of the outcome measures, the Mann-Whitney U test was used as skewed distribution, including the RAND SF-36 and MADRS-S scores and overall mean MADRS-S and PCS and MCS in Paper III, and in Paper IV, IOS, N_2MBW, and DLCO variables outcomes, and the z-scores. Calculations of z-scores were made based on Global Lung Function Initiative reference equations for DLCO(113) and based on two locally collected healthy control cohorts for IOS (n=158) and N_2MBW (n=400), respectively(114). Limits of normality were defined as >1.96 and <1.96 z-score.

In Paper III, we conduct mediation analysis to separate the exposure's direct and indirect effect on PCS, MCS, and MADRS-S, through indirect pathway of the employment and education, using package "mediation" in R. The statistical analyses were carried out using IBM SPSS 27 and R 4.0.2.

RESULTS

Papers I and II

The material used in Studies I and II involved 16 interviews in person, with individuals exposed to CWAs and having a mean age of 45.5 years, and with 62% of them being female. Table 2 highlights their demographic characteristics. Of the participants, 69% reported having skin lesions as a manifestation of SM exposure at the time. Furthermore, only 50% were married, 56% had primary or lower education, and only 31% had any occupation.

Table 2. *Summary of demographic variables.*

Variables	Total n (%)	Male n (%)	Female n (%)
Mean age (range), yrs.	45.5 (34–67)	44.7 (34–67)	46.8 (35–61)
Sex	16 (100)	6 (38)	10 (62)
Marital status			
Married	8 (50)	6 (100)	2 (20)
Single	4 (25)	0 (0)	4 (40)
Divorced	3 (19)	0 (0)	3 (30)
Widow	1 (6)	0 (0)	1 (10)
Education			
Elementary school or lower	9 (56)	3 (50)	6 (60)
High school	4 (25)	2 (33)	2 (20)
University studies	3 (19)	1 (17)	2 (20)
Occupation			
Employed	5 (31)	3 (50)	2 (20)
Tobacco consumption			
Non-smoker	15 (94)	6 (100)	9 (90)
Former smoker	1 (6)	0 (0)	1 (10)
Children			
No	4 (25)	0 (0)	4 (40)
Yes	12 (75)	6 (100)	6 (60)

Paper I

The current study utilized a sample size of 16 participants who were interviewed in person to investigate the effects of SM exposure. Table 2 provides key demographic information about the study participants, revealing that 69% of them experienced skin injury at the time of the incident, strongly suggesting exposure to SM and associated with long-term respiratory symptoms.

The study participants expressed different concerns related to the exposure about their general health, quality of life, and access to healthcare services.

Through analysis of the data collected, 14 distinct themes emerged, which were classified into three overarching categories: (1) General health, (2) Quality of life, and (3) Access to healthcare services. Figure 5 provides a detailed overview of these themes.

One of the most notable findings was the prevalence of depressive symptoms in nearly two-thirds of the participants and a high incidence of suicidal ideation in more than one-third of the participants.

A biopsychosocial illustration has been created to demonstrate the interactions between these components in SM-exposed participants (Fig.6).

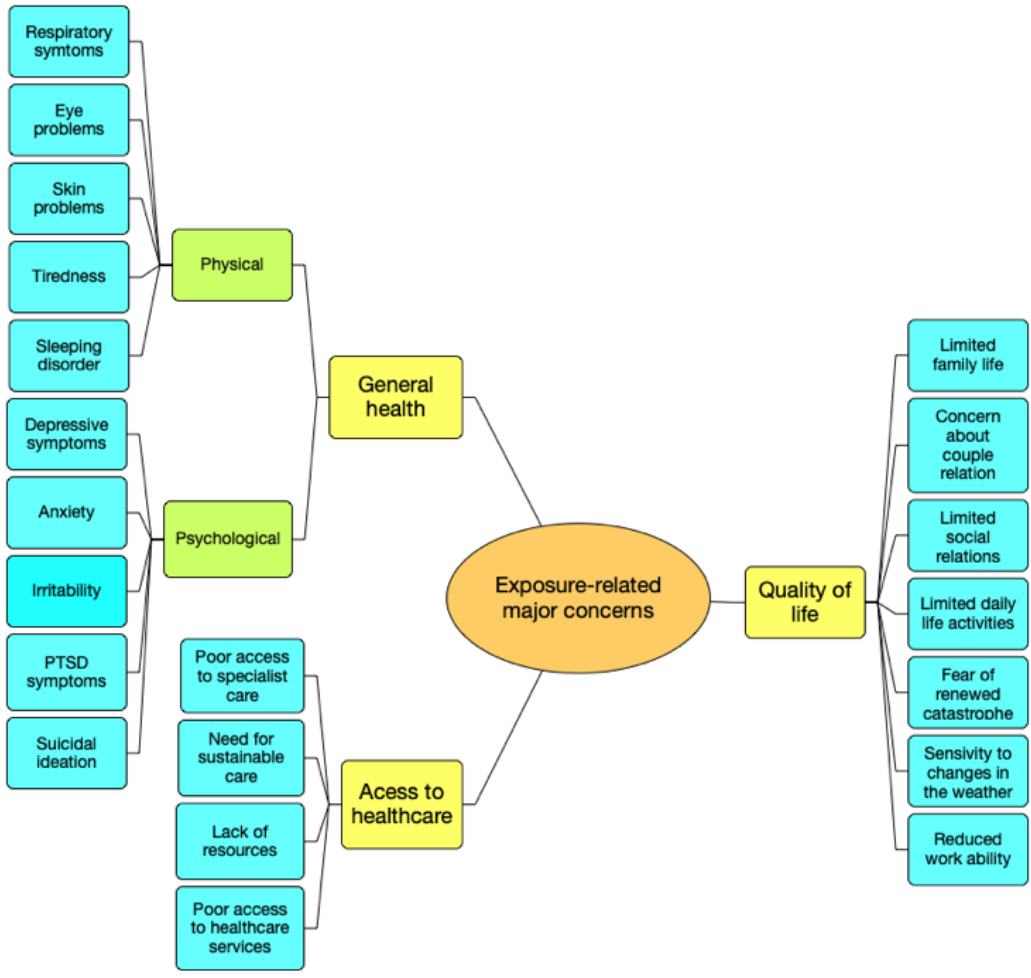

Figure 5. *Major concerns related to exposure among SM-exposed participants.*

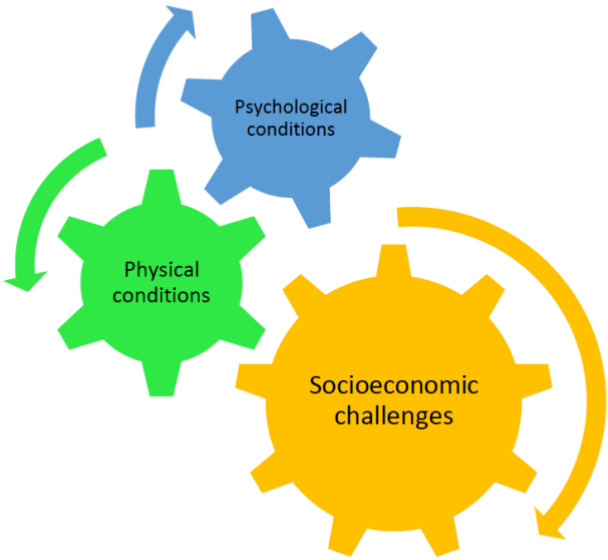

Figure 6. *The biopsychosocial illustration in SM-exposed participants shows the complexity of survivors' somatic and mental complaints and the development of socioeconomic challenges and their intertwined interactions.*

Paper II

The narrative findings indicated that people exposed to SM express different gender concerns about their relationships, family life, and social interactions. After analyzing these concerns, we have identified two main categories of manifest content issues: social isolation and uncertainty about marriage. The individuals' underlying emotions can be summed up as latent uncertainty about marriage (to get married or not to get married), which significantly impacts their personal and professional lives (Fig. 7).

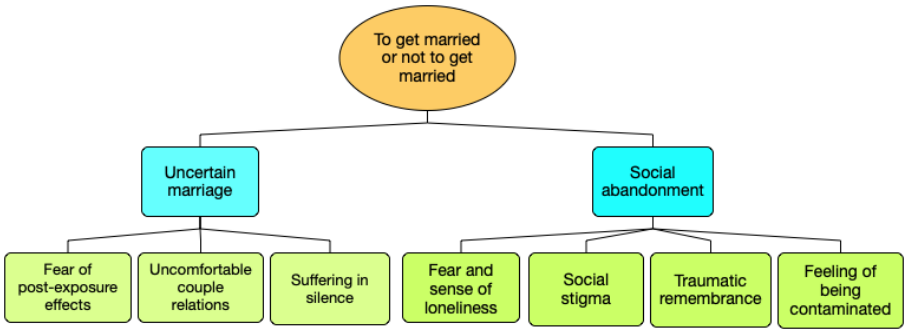

Figure 7. *Manifest and latent content analysis.*

Figure 8 demonstrates how exposure to SM affects men and women differently. Female survivors faced more challenges in getting married, and uncertainty about their marriage. The exposed males on the other hand felt anxiety and were uncertain about building a family and were fearful of complications such as disabilities and death.

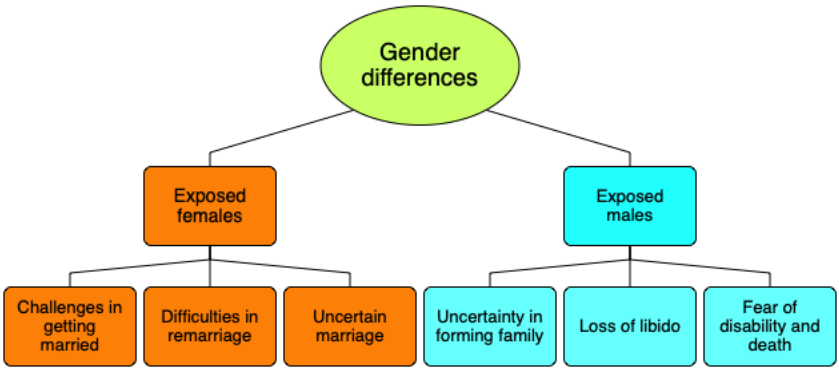

Figure 8*. Gender difference impacts of SM exposure.*

PAPER III

The study analyzed data from a total of 48 participants, divided into two groups: the exposed group had 18 participants (mean age 51.3 ± 8.2 years, 50% women), while the unexposed group had 30 participants (mean age 48.7 ± 10.3 years, 47% women). Table 3 provides a more detailed overview of both groups' demographic, socioeconomic, and exposure variables with regard to the nature of SM. It is worth noting that there were no significant differences in sex, age, BMI, or marital status between the two groups. However, higher unemployment and lower education levels were found in the exposed group compared to the unexposed group. Additionally, 61% (11 participants) in the exposed group reported primary SM exposure.

Table 3. *Participants' sociodemographic and route of sulfur mustard exposure characteristics (n = 48).*

	Unexposed (n = 30)	**Exposed (n = 18)**	**P value**
Sex, Women, n (%)	14 (47)	9 (50)	0.53
Age (years)			.0.37
Mean±SD	48.7 ± 10.3	51.3 ± 8.2	
Median (Min-Max)	51.5 (32–67)	51.5 (30–66)	
Height (cm)			0.49
Mean±SD	169 ± 7	167 ± 13	
Median (Min-Max)	169(157–180)	170 (145–189)	
Body mass index (kg/m^2)			0.64
Mean±SD	27.4 ± 3.9	27.2 ± 3.1	
Median (Min-Max)	26.5(22.8–39)	25.9 (23–33)	
Educational achievement, n (%)			**0.02**
≤ Primary	1 (3)	16 (33)	
High school	12 (40)	7 (39)	
≥ University	17 (57)	5 (28)	
Employment status, n (%)			**0.01**
Unemployed	4 (13)	9 (50)	
Marital status, n (%)			0.58
Married	22 (73)	12 (67)	
Single	1 (3)	2 (11)	
Divorced	7 (23)	4 (22)	
Type of exposure, n (%)			
Primary		11 (61)	
Secondary		7 (39)	

Figure 9 shows that individuals exposed to the SM had significantly worse outcome for RAND SF-36 than those not exposed and this was observed

across all eight measurements of the RAND SF-36 variables. Similarly, Figure 10 illustrates that the exposed group scored significantly higher on all nine measurements of the MADRS-S variables and overall mean scores compared to the unexposed group. The results revealed significantly more moderate depressive symptoms and lower QoL components; PCS and MCS, respectively, among the exposed group compared to the unexposed group (Fig. 11). Within the exposed group, the participants reported lower scores for MCS than PCS, indicating worse mental well-being than physical one.

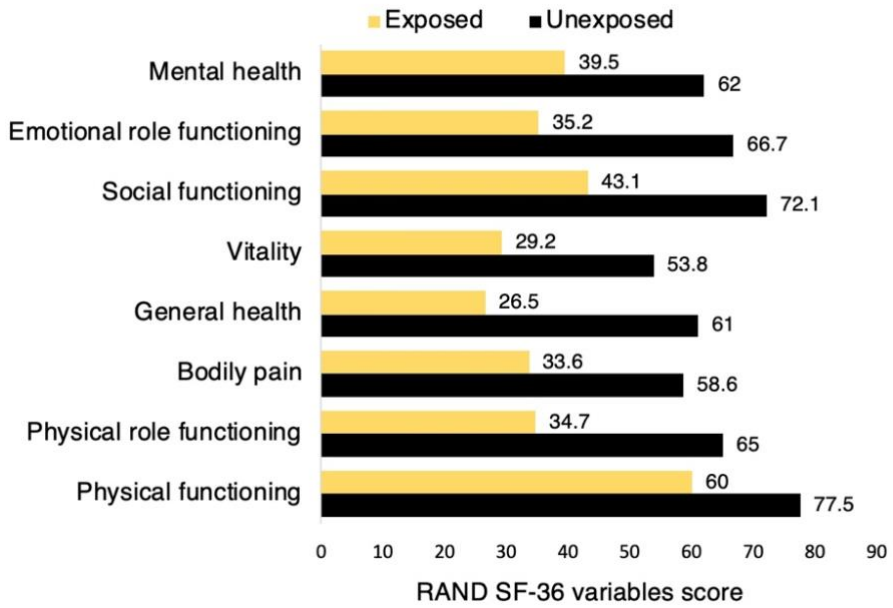

Figure 9. *Descriptive statistics on RAND Short Form Health Survey 36-items in the exposed (n=18) and unexposed (n=30) groups. All group comparisons are significant ($p<0.05$). Mann-Whitney U test was used for between-group comparisons. Higher score indicates a better quality of life.*

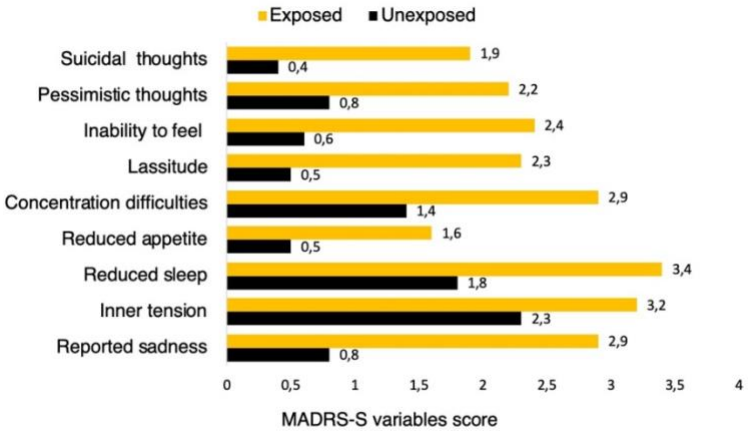

Figure 10. *Descriptive statistics on Montgomery-Åsberg Depression Rating Scale (MADRS-S) variables in the exposed (n=18) and unexposed (n=30) groups. All group comparisons are significant (p<0.05). Mann-Whitney U test was used for between-group comparisons. Higher score indicates more depressive symptoms.*

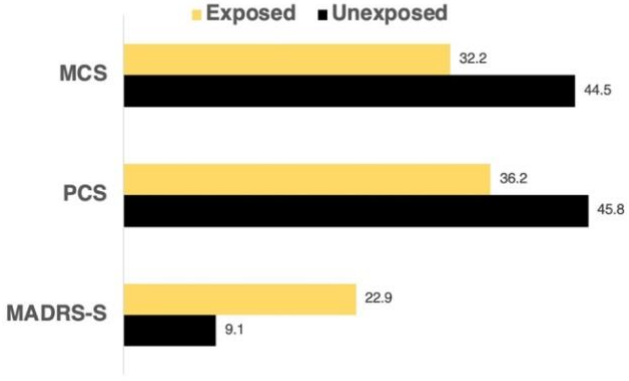

Figure 11. *Descriptive statistics on overall Mean Montgomery-Åsberg Depression Rating Scale (MADRS-S) and Overall mean Physical Component Summary (PCS), Mental Component Summary (MCS) in the exposed (n=18) and unexposed groups (n=30). Higher score in MADRS-S indicates more depressive symptoms. Lower score in PCS and MCS indicate lower QoL. All group comparisons are significant (p<0.05). Mann-Whitney U test was used for between-group comparisons.*

PAPER IV

Sociodemographic variables and the nature of exposure of the participants are summarized in Table 4. The data collected from 30 participants, SM-exposed (n=15, mean age 53± 8 years, 33% women) and unexposed participants (n=15, mean age 53± 7 years, 33% women) from Kurdish individuals resident in Sweden, was included in Study IV.

Table 4. *Characteristics of the study population.*

	Unexposed (n = 15)	Exposed (n = 15)	P value
Sex, Women, n (%)	5 (33%)	5 (33%)	
Age (years)			0.86
Mean±SD	53 ± 7	53± 8	
Median (Min-Max)	54 (43–69)	54 (35–70)	
Height (cm)			0.49
Mean±SD	169 ± 7	167± 3	
Median (Min-Max)	169(157–180)	170 (145–189)	
Body mass index (kg/m^2)			0.46
Mean±SD	28 ± 2	29± 4	
Median (Min-Max)	28 (25–31)	30 (23–40)	
Smoking history			
Current/Ex/Never	0/0/0	1/0/0	
Type of exposure, n (%)			
Primary		10 (67%)	
Secondary		5 (33%)	

Figure 12 demonstrates statistically significant differences between SM-exposed and SM-unexposed group for small airways specific variables $FDR_{(Z)}$ (P=.029) and $Sacin_{(Z)}$ (P=.033), indicating a lower small airways function in SM-exposed participants than unexposed participants. Likewise, the exposed group demonstrated significantly increased LCI(Z) (P=.002), indicating abnormal global ventilation inhomogeneity.

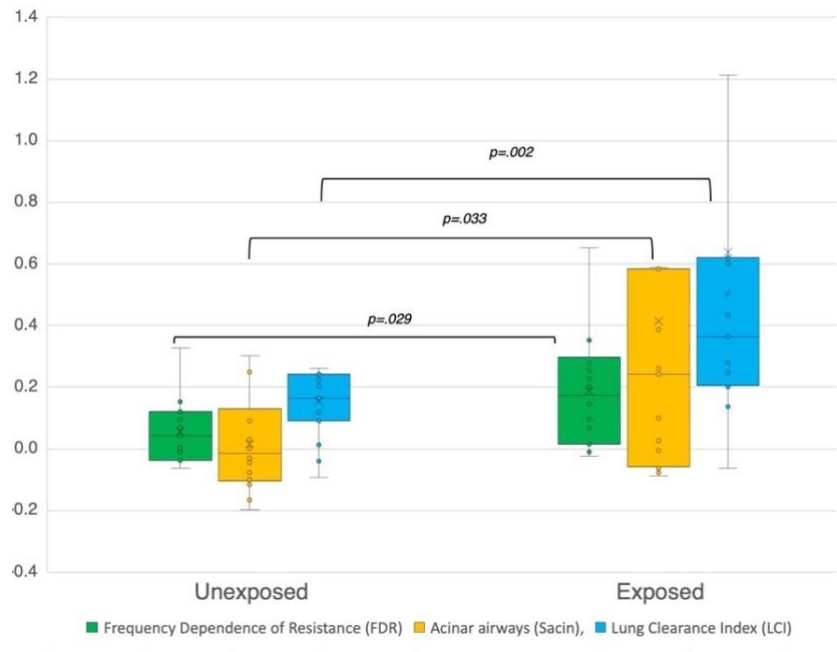

Figure 12. *Z-score outcomes for FDR in 14 exposed versus 15 control, Sacin, and LCI in 15 exposed versus 14 unexposed participants. Mann-Whitney U test used for between-group comparisons.*

Furthermore, as illustrated in Figure 13, there were nine participants (64%) in SM-exposed group with abnormal values in FDR, AX, and Sacin variables; five participants with abnormal values for both FDR and AX, two participants

showed abnormalities for AX and Sacin, and two participants had abnormalities for all three variables mentioned. Overall, 13 out of 15 participants in the SM-exposed group had some abnormal result. In unexposed participants, no abnormal value was found for the same participant by both IOS and N_2MBW variables; however, one (7%) participant showed abnormality for DFR and AX, and 7 out of 15 had some abnormal result. No statistically significant differences were found between the groups' DLOC parameters.

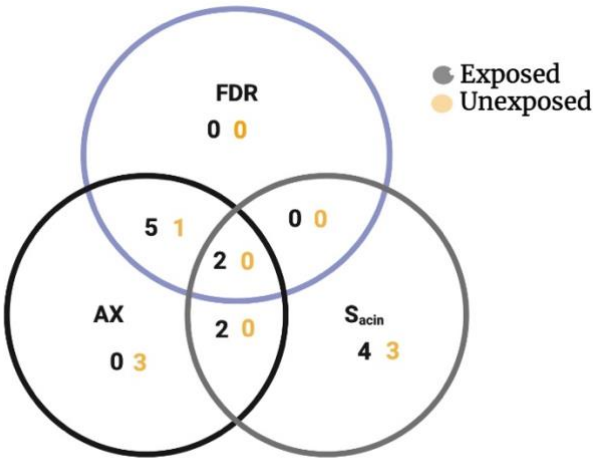

Figure 13. *The number in each circle shows participants with abnormal values in SM-exposed and unexposed groups with different outcomes; IOS (14 participants in exposed group and 15 in unexposed) or N2 MBW (15 participants in exposed group and 14 in unexposed group) for FDR, AX, and Sacin separately or in combination. FDR=frequency dependence of resistance; AX=area of reactance; Sacin= the acinar airway zone. Created with BioRender.com*

DISCUSSION

The overall findings of this thesis reveal an association between exposure to SM and lifelong impaired physical, psychological and quality of life, as well as worse lung function in exposed participants compared to unexposed participants.

The multiple physical and mental illnesses and development of "chemical contamination anxiety" in SM-exposed persons in Study I and sense of social abandonment and stigmatization in Study II are reflected in SM-exposed persons' impaired QoL and higher occurrence of depressive symptoms compared to the unexposed individuals in Study III. Furthermore, fatigue and reduced workability in Studies I and III are confirmed in SM-exposed persons' lower lung function than in unexposed individuals in Study IV.

Qualitative studies

The narrative findings of Studies I and II show that SM-exposed participants experienced poor access to primary care services and little specialist contact, partly due to a shortage of knowledge and limited access to specialist care and partly because of financial problems and mutual mistrust between SM-exposed patients and health staff. This might explain why the SM-exposed participants continuously see how their physical and psychological well-beings decline, negatively impacting their socioeconomic situations, an apparent biopsychosocial challenge (Figures 5 and 6).

The stamp of "Chemical exposed survivor" had an overwhelming impact on their social life. Also, the lack of public knowledge regarding SM-related post-exposure symptoms has gradually resulted in feelings of stigmatization and social isolation since productive post-exposure coughing is perceived by the community as infectious, that is, as tuberculosis.

On the other hand, it is crucial to note that this stamp has played a vital role in fostering a strong sense of identity among those exposed to chemicals. This shared identity serves as a powerful tool to resist discrimination, as previously discussed in Studies I and II. It suggests a strong fellowship among those with existential concerns, common memory, and resilience.

It is probable that the post-exposure physical and psychological complaints, poor access to sustainable healthcare services, and unanswered questions regarding the post-exposures' health-related concerns have resulted in the development of what is called "Chemical Contamination Anxiety" (CCA), a strong physical and psychological reaction and a sense of fear and uncertainty. People with CCA may find it difficult to engage fully in their family, social, professional lives, and have low beliefs in the future which can be frustrating and isolating (I). The community, especially the clinical healthcare staff in somatic disease, has a merely physiological focus and medication solution for this group of patients. Narrative findings from Studies I and II reveal that those exposed to SM reported a lack of understanding from healthcare professionals and employers regarding the prolonged effects of exposure. This lack of comprehension can worsen the situation for SM victims who struggle to communicate the limitations on their social and work lives as a result of the exposure. These results align with similar findings from other studies conducted on Iranian SM-exposed veterans(26).

In contrast to a conventional weapon, e.g., a bullet that can be removed from the body, the exposed participants think that the unseen SM has become part of their bodies and altered them. They feel that that their bodies have been contaminated. This might explain their belief in the teratogenic effects of SM, and these effects are passed on to their children (Fig.7). These concerns further complicate the CCA, leading to an overarching sense of uncertainty that influences all decisions related to starting a family and having children. The SM-exposed participants' lived experiences and narrative findings indicate that the exposure adversely affects the survivors' experiences and relations to family building, with gender difference impacts (II). Furthermore, the female survivors had more obstacles to getting married, facing difficulties in getting remarriage, were uncertain about their marriage, and were living under socioeconomic vulnerabilities compared to male survivors (Fig. 8). However, the exposed male suffers in silence with fear of post-exposure complications, e.g., disabilities and death, and has anxiety over forming a family (II).

However, it was not possible to show gender differences with quantitative health surveys in SM-exposed participants in Sweden (III). This might be attributed to the low number of participants. Thus SM-exposed participants

in Sweden enjoy an equal individual mode of existence and gender equality in the community. However, a previous study showed gender differences in term of physical injuries among Iranian individuals exposed to SM(29).

Quantitative studies

The prolonged mental illnesses, e.g., moderate depressive symptoms, shown in Study III are characteristic of the narrative findings of Study I. The authorities in the KRG did not directly relate mental illnesses to exposure, resulting in these conditions being insufficiently addressed both medically and socially. The complexities in distinguishing and diagnosis of mental illnesses may be a plausible explanation. Likewise, delayed effects of SM such as the manifestation of neuropsychiatric symptoms can only be observed in the long run. Nevertheless, SM-related DNA damage(50), and prolonged and widespread mental illness among SM-exposed survivors means that possible biological effects of exposure beyond the psychological trauma-related ones of SM exposure cannot be ruled out.

Moreover, Study III showed a significantly more impaired QoL in SM-exposed participants than in the unexposed individuals. The perception of QoL might be affected by diverse factors. In our study, we statistically analyzed the impacts of other factors such as employment and education on the outcomes of Study III. However, the findings indicate that exposure to SM had the greatest direct influence on physical and mental well-being and the level of depressive symptoms experienced (III). The impaired QoL can be attributed to a combination of long-term physical and mental complaints (28, 82) (Fig. 5), which might influence the SM-exposed individuals' capabilities to complete an education, get employment, or work, due to reduced workability affecting the perception of QoL (Fig. 6).

The findings of Study IV, presented in Figures 12 and 13, uncover the presence of SAD and lower lung function in individuals who have been exposed to SM are similar to previous studies conducted on SM-exposed individuals 10-15 years post exposure (63, 69), suggesting N_2MBW and IOS as complementary techniques in assessing SAD in individuals exposed to SM. A previous study demonstrated that SM-exposed individuals ran a risk of developing respiratory symptoms up to 3 decades post exposure(57). Moreover, it appears that SM exposure has different impacts on small

airways, which could potentially clarify why clinical respiratory issues tend to develop gradually in survivors of SM exposure. It is noteworthy that small airways are typically the less noticeable portion of the lungs, and SAD can often go undetected by spirometry test until the appearance of severe clinical symptoms. The SM-delayed respiratory symptoms which affect the majority of SM-exposed survivors deteriorate continuously(25, 48, 54), and are thought to be a key factor behind sleep disturbances, persistent fatigue, deterioration in workability, and social stigmatization. And, finally, they negatively affecting QoL and mental health(115-118). The possibility to detect the SM-exposed individuals at risk for developing respiratory diseases as well as regular follow-up and treatment can prevent, postpone or at least minimize lung damage and might promote mental health and improve QoL.

METHODOLOGICAL DISCUSSION – STRENGTHS AND LIMITATIONS

This is the first thesis in Sweden and Kurdistan-Iraq that focuses on overall SM survivors' long-term lung function, mental health, exposure-related health concerns, and quality of life.

The recruitment process for the study faced certain limitations due to the exposed group being a "hidden population". One such limitation was the possibility that individuals who had suffered severe or simple SM exposure might not have been willing to participate in the study. However, a snowballing approach and other traditional sampling techniques were implemented to reduce sampling bias, which improved the prospects of identifying and recruiting potential participants in Studies III and IV.

Another challenge was the lack of a comprehensive database of CWA-exposed individuals in Sweden and the absence of laboratory tests to confirm exposure history. This posed a threat to the validity of the study's findings. Nevertheless, a purposive sampling approach, accounting for different demographic variables including physical injuries at the time of exposure, was implemented to ensure that a varied group of participants was selected. This subsequently strengthened the internal validity of the study.

Additionally, the inclusion of both SM-exposed and SM-unexposed individuals enabled a comparison of the effects of exposure to SM, thus strengthening the study's external validity. Overall, despite the limitations, the recruitment process employed several techniques to ensure that a robust sample was obtained, which would facilitate a thorough investigation of the study's research questions.

Applying the interview technique made it possible to collect complete data of interest since the technique is recognized for identifying issues of high priority for interviewed individuals(99).

Two common approaches for data analysis in qualitative research are systematic text condensation and content analysis. The first one with inspiration from Giorgi's phenomenological manner, is widely used within the medical field(109, 119, 120). This approach is a great way to data analysis because it is organized and systematic, which helps identify themes and patterns in data. The use of systematic text condensation in Study I allowed for an overall description and exploration, which was the aim of the study. However, it might have oversimplified or overlooked nuances in the data. While content analysis lacks an underlying theory, it can still provide valuable insights by uncovering hidden patterns and themes, in addition to the more apparent ones. This can help researchers gain new insights into the data.

On the other hand, phenomenology was an alternative approach that could allow for in-depth exploration and understanding of individual experiences. However, it is highly dependent on researchers' personal knowledge and interpretations.

One limitation is that the survivors in Halabja were exposed to different CWAs, i.e., SM and sarin. Therefore, the possibility of overlapping and synergistic effects cannot be excluded. To minimize this concern, we had a prespecified criterion in Studies I and II to have respiratory symptoms as a delayed effect of SM. Likewise, the narrative outcomes in Studies I and II might have been affected by their cumulative traumatic experiences from a war-ravaged environment. However, based on the symptoms observed, it seems probable that the cause was chemical attacks. Thus, unlike structured questionnaire surveys, there is no universally agreed-upon format for reporting or analyzing narrative data. Therefore, we further investigated the

major findings of Study I: QoL, mental health, and respiratory condition in SM-exposed participants in retrospective cohort Studies III and IV, with the advantage of standardizing the outcomes and comparison with unexposed participants.

The reliability and validity of MADRS have been established to assess the severity of depression in adults, including inpatients and outpatients(101). However, MADRS validity in SM-exposed individuals has not been studied. Nevertheless, our results have been confirmed by other studies and MADRS remains a commonly-used complementary tool in clinical practice in Scandinavia(28, 83, 121).

The need has been discussed for a more comprehensive questionnaire (Mustard QoL) to cover other aspects of the exposure-related issue such as the uncertainties and fear. Due to a lack of Kurdish population-based algorithms, we applied to both SM-exposed and SM-unexposed groups standard (U.S.-derived) scoring algorithms in the User Manual for combining PCS and MCS(122). However, the outcomes of RAND SF-36 corresponded to other study(123).

A major strength of this thesis is using non-invasive pulmonary function tests (IOS, MBW, and DLCO) for the first time for assessing small airways in SM-exposed individuals (Study IV). These techniques hold many benefits, such as their ability to detect changes in various segments of small airways in early stages, ease of management, independence from the patient effort (MBW, IOS), and quickness (IOS and DLCO). However, their drawbacks include limited accessibility and established reference ranges.

However, we used z-scores based on references that might have caused an under-over classification of SAD. Nevertheless, there was a strong correlation between absolute measured values and z-scores in assessing abnormal values.

Studies III and IV are retrospective cohort studies of observational nature. Therefore, it is difficult to comment on the causality since they present a different level of evidence from randomized controlled trials. However, a randomized controlled trial with SM on humans is not ethically motivated. Thus, the mediation analysis showed significant exposure's direct effect on the outcomes in Study III. The thesis revealed a substantial level of

consistency in the findings obtained from both qualitative and quantitative studies.

Another strength of this thesis is the interdisciplinary research group that worked on this project. Also, combining qualitative and quantitative research methods allowed for more comprehensive insights. The data collection techniques were individual interviews, health survey questionnaires, and non-invasive pulmonary investigation tests. These techniques ensured the good quality and reliability of the data collected. Furthermore, the analysis approaches implemented employed systematic text condensation, content analysis, mediation, and statistical comparisons between exposed and unexposed participants, which helped to increase the credibility of the analytical approach and the data generated, and to create results of high validity.

GENERAL CONCLUSION

This thesis showed that exposure to SM was linked to long-term mental and physical health problems and impaired quality of life. These long-term health effects resulted in socioeconomic difficulties, social stigmatization, and psychosocial, gender-based disparities. In this thesis impaired function in airways was also observed in exposed individuals when compared with unexposed individuals.

These findings emphasize the need to increase knowledge among health staff and the community about long-term effects, and also the need for research and resources dedicated to addressing the gender-based disparities and specific needs of those impacted by exposure to SM.

SPECIFIC CONCLUSIONS

1. Paper I presented narrative findings that the SM-exposed participants still suffer from physical, mental and socioeconomical complications. The establishment of a comprehensive intervention programme is necessary, requiring collaboration from different disciplines such as medical, psychological, rehabilitative, educational, cultural, and social domains to address the issue at hand.

2. Paper II revealed that those who have been exposed to SM experience uncertainty when it comes to marriage and starting a family. It is important to recognize and address these gender differences to provide proper support and guidance for those affected.

3. Paper III showed that SM-exposed participants suffered significantly from an impaired quality of life and moderate depressive symptoms compared to unexposed participants. The recommendation is therefore that the healthcare system should prioritize enhancing the quality of life for survivors and for promptly identifying any mental health concerns that may arise.

4. Paper IV showed that exposure to SM can result in long-term damage to the small airways in most individuals in this study. It is unclear if these individuals are at risk of further deterioration and lung disease, but it would be valuable to investigate this further. Additionally, the use of two lung testing techniques, IOS and N_2MBW, can provide additional insights into detecting respiratory issues in survivors of SM exposure. Understanding and describing the remaining damage in the small airways is the initial step towards better treatment and follow-up care.

FUTURE PERSPECTIVES

In addition to their use as weapons of mass destruction, chemicals agents are produced and used worldwide with numerous industrial applications, making them a potential hazard in chemical industrial accidents that jeopardize human security. While much attention has been given to addressing the immediate physical consequences of chemical weapons, there remains a significant need to investigate thoroughly the long-term effects that may persist over time. These long-term effects can have devastating impact on biopsychosocial conditions, with gender differences in exposed individuals.

The suggestion is therefore to adopt a biopsychosocial model to improve the quality of life, promote mental health, and enhance the socioeconomic situations of this unique group of patients. Worth noting is that multi-modal rehabilitation programmes have improved the conditions of other patient groups with complex and multifaceted conditions(124).

The findings of Studies I and II in this thesis suggest that the biopsychosocial impact of exposure to chemical weapons has not been adequately researched. Further investigations are needed to explore and address the concerns of exposed survivors. This includes reducing chemical contamination anxiety, improving the understanding of gender differences, and elucidating the possible teratogenic, genetic, and carcinogenic effects of SM.

The presence of prolonged mental illness among individuals exposed to SM, as shown in Study III, calls for further clinical and laboratory studies in SM-exposed survivors. The aim would be to investigate SM's possible biological and nervous system effects, particularly in understanding delayed neuropsychiatric illness and long-term sequelae on the nerve system.

Study IV indicates that exposure to SM can also lead to long-term impairment in small airways. This is a concern because small airways dysfunction often goes undetected until more severe clinical symptoms manifest. Future studies need to explore small airways dysfunction in larger populations of individuals exposed to SM in order to clarify the condition's prevalence and verify the findings.

Research is crucial into (i) the mechanisms of action that make sulfur mustard toxic; (ii) what molecular targets or pathways can be used to develop effective countermeasures, including preventative measures and treatments; and (iii) better policies and regulations to prevent the production and use of chemical weapons. Furthermore, efforts must be made to raise awareness about the long-term effects of CWAs on survivors and their families. Education campaigns can be implemented to ensure that both the general public and healthcare professionals are aware of how to identify and address biopsychosocial complaints and economic difficulties related to CWAs, particularly in countries with a significant number of CWA survivors who are resettling.

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