PRIMARY HYPERHIDROSIS
Prevalence and impacts for the individual

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To Ladan, Gabriel and Isabell

In medicine we ought to know the causes of sickness and health. And because health and sickness and their causes are sometimes manifest, and sometimes hidden and not to be comprehended except by the study of symptoms, we must also study the symptoms of health and disease.

Avicenna 973-1037 CE
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Abstract

Primary hyperhidrosis, excessive sweating, is a condition with unknown prevalence in many parts of the world. The disease debuts in adolescence and it affects men and women in equal proportions. A genetic background exists and the most common localisation on the body for excessive sweating is the axillary region. It is known that primary hyperhidrosis reduces quality of life and interferes with daily activities. Affected individuals often hide their sweating problems and the disease may lead to social withdrawal and isolation. Although botulinum toxin is an effective and available treatment, relatively few persons with primary hyperhidrosis seek medical healthcare and a minority of those are men.

We investigated the prevalence of primary hyperhidrosis in Sweden and how the disease impairs quality of life, changes in daily activities, signs of depression and anxiety and alcohol consumption before and after treatment with botulinum toxin. The severity of hyperhidrosis according to the affected body sites was also investigated. Further on we explored mens experiences living with primary hyperhidrosis by interviews and content analysis.

Our results showed that primary hyperhidrosis occurs in 5.5% of the Swedish population. The disease reduces quality of life and affects mainly the psychological health of the individuals. Persons with palmar and axillary hyperhidrosis rated their symptoms as more severe and with much higher impact on their quality of life compared to persons suffering from hyperhidrosis elsewhere on the body. Individuals with axillary hyperhidrosis more often reported a later debut and signs of peripheral vasoconstrictions were more common in this group compared to individuals with palmar hyperhidrosis. This made us believe that factors other than genetics seem to play a role in triggering axillary hyperhidrosis. Treatment with botulinum toxin A had a significant effect in reducing the symptoms and their interferences on daily life while increasing the overall quality of life. This treatment was safe and no serious side-effects were noted. Signs of depression, stress and anxiety were also significantly reduced by treatment. Qualitative content analysis of interviews with 15 men suffering from primary hyperhidrosis resulted in the theme: To be captured in a filthy body. The experiences of men with excessive sweating were thus interpreted as stigmatising. Stigma has a negative effect on mental health which reinforces our findings in quantitative studies when investigating quality of life. It is our assumption that the symptoms act as a vicious circle reducing quality of life, stigmatising the individual and limiting daily interactions. Addressing hyperhidrosis with information when the disease debuts in young
people could reduce the stigma and enable early intervention via healthcare which may have a significant effect on the life of those affected.
Abbreviations

UmU Umeå University
TOC Table of Contents
Na/K-ATPase Sodium/ Potassium Adenosine Triphosphatase
SNARE Soluble NSF-attachment Receptor
NSF N-ethylmaleimide Sensitive Fusion Protein
PH Primary Hyperhidrosis
SH Secondary Hyperhidrosis
SAD Social Anxiety Disorder
DLQI Dermatology Life Quality Index
SF-36 Short Form Health Survey 36-items
VAS Visual Analogue Scale
HDSS Hyperhidrosis Disease Severity Scale
SPAR Statens personadressregister
HADS Hospital Anxiety and Depression Scale
AUDIT Alcohol Use Disorders Identification Test
WHO World Health Organisation
AS Alexander Shayesteh Afshar
CB Christine Brulin
EN Elisabet Nylander
χ² test Chi square test
t-test Student’s t-test
Sammanfattning på svenska


Vårt syfte var att undersöka förekomsten av primär hyperhidros i Sverige och ta reda på sjukdomens påverkan på livskvaliteten. Vi undersökte även hur dagliga aktiviteter, tecken på depression och ångest och alkoholkonsumtion förändrades hos personer med primär hyperhidros efter behandling med botulinumtoxin injektioner. Med tanke på att primär hyperhidros även kan drabba andra kroppsdelar än armhålorna undersökte vi svårighetsgraden och påverkan på livskvaliteten beroende på var på kroppen man svettades. Eftersom få drabbade söker sjukvård och män oftast är i minoritet bland dem som söker hjälp genomförde vi intervjuer med 15 män i syfte att undersöka deras erfarenheter av att leva med sjukdomen. Intervjuerna analyserades med kvalitativ innehållsanalys för att beskriva variationerna i deras berättelser.

Våra resultat visar att primär hyperhidros förkommer hos 5,5 % av den svenska befolkningen. Sjukdomen minskar livskvaliteten hos de drabbade med negativa effekter huvudsakligen på den psykiska hälsan. Individer med svettningar i händer och armhålpor uppskattar sina besvär som svårare och med mer negativ påverkan på livskvaliteten jämfört med dem som svettas på andra kroppsdelar. Genom att intervjuar män med primär hyperhidros kunde vi visa att sjukdomen är stigmatiserande. Symptomen orsakar en ond cirkel av nedsatt livskvalitet och tillbakadragande vilka förstärker känslan av stigma. Patienter med svettningar i armhålorna har en senare debut av sjukdomen och beskriver oftare tecken på perifer kärlsammandragning jämfört med dem som har svettningar i händerna. Enbart ärförlighet förklarar inte denna sena debut utan det måste finnas ytterligare orsaker som samverkar vid svettningar i armhålorna. Behandling av primär hyperhidros med botulinumtoxin A höjer livskvaliteten hos de drabbade och minskar symtomen på nedstämdhet, ångest och stress. Genom att informera om sjukdomen i tidig ålder skulle man kunna minska stigman associerade med överdrivna svettningar. På så sätt kan sjukvården möta och hjälpa de drabbade vilket kan göra en stor skillnad i deras liv.
List of papers

The thesis is based on the following papers which are referred to in the text using the Roman numerals I-IV:

Paper I


Paper II


Paper III


Paper IV


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Introduction

Sweat

Sweating is a physiological process vital for the body to maintain thermoregulation (1). Other functions of sweat are enhancing the grip for hands or feet during physical activities, moisturising the skin, controlling the desquamation of stratum corneum and releasing molecules that are pro- or anti-inflammatory (2,3). Human sweat consists of approximately 99% water and has a pH of 5.0-7.0 depending on the rate of production (1). Substances such as sodium, potassium, chloride, lactate, urea, ammonia, proteolytic enzymes, human epithelial growth factor and glucose can also be found in human sweat (1,2). There are two major types of sweat glands, eccrine and apocrine glands.

Sweat glands

Eccrine glands

A total of 1.6-4 million eccrine sweat glands are dispersed throughout the skin with the exception of lips, labia minora and glans penis (4). The density of the eccrine glands on the palms and soles are 600-700/cm² whereby only 64/cm² on the back (4). An eccrine gland is a merocrine, coiled, tubular structure consisting of a duct and a secretory portion. The secretory part is situated in the dermis and is 2-5 mm long (5). It consists of clear cells, dark cells and myoepithelial cells. While clear cells produce the isotonic fluid that becomes sweat, the role of dark cells is unclear (2). Dark cells have less mitochondria compared to clear cells and are rich with cytoplasmic granules (2,6). Myoepithelial cells surround the secretory tubules and discharge the fluid into the tubular secretory portion (6). Their function is regulating sweat production by acting as valves, allowing some cells to use the surrounding metabolites for sweat production while sealing others (7). The ductal portion of the gland is 2-5 mm long and is located both in the epidermis, acrosyringium, and the dermis (2). Acrosyringium consists of epithelial cells without borders to the epidermis while the dermal ducts consist of two or three layers of cells with a central lumen (5). The duct is responsible both for the transport of the fluid and for transforming the isotonic sodium chloride solution into a hypotonic solution via chloride and Na/K-ATPase channels (2). This process occurs on daily bases but also influenced by aldosterone that hastens the process (8). Eccrine glands are innervated by sympathetic cholinergic sudomotor axons (1,2). Nerve impulses are transmitted via synapses to the gland. This transmission is facilitated by acetylcholine vesicles docking on the pre-synaptic membrane and discharging
their content (2,9). A group of docking proteins called SNAREs (Soluble NSF-attachment receptors) are essential for the exocytosis of the acetylcholine vesicle (10). SNAREs such as synaptobrevin, syntaxin and snap-25 are important for this process and can be targeted by bacterial neurotoxins responsible for botulism and tetanus (11) (figure 1).

![Presynaptic membrane](image)

**Figure 1. Illustration of the sudomotor pre-synaptic membrane and the docking SNARE proteins of an acetylcholine vesicle.**

**Apocrine glands**

Apocrine glands are located within the deeper part of the reticular dermis down to the subcutaneous tissue. Apocrine glands are mostly found in the perianal, genital, mammilary and axillary regions with a density at most of 54 glands/cm² (12). The secretory portion of the gland consists of secretory and myoepithelial cells (13). Secretory cells are columnar shaped and their secretion can be influenced by emotion or stress (1). It has been described that apocrine glands do not possess neurofilament innervation and are rather influenced by catecholamines through a purinergic signalling system (12,14). Apocrine secretion contains of lipids, proteins, carbohydrates, ammonium and odour binding proteins (15). The secretion of the gland is emptied into a hair follicle (12). The disease bromhidrosis, develops when the apocrine secreted odour binding proteins interact with bacterias on the skin producing the distinct odour molecules (15).
Hyperhidrosis

Normal sweating is a physiological mechanism for regulating body temperature while in hyperhidrosis the sweating is excessive and tormenting in affected individuals (16). There is a distinction between primary (PH) and secondary hyperhidrosis (SH). PH is usually restricted to certain areas while SH is mostly general and rarely focal. Other types of hyperhidrosis such as gustatory, emotional, compensational and thermal types are usually termed due to the provoking stimuli.

Primary Hyperhidrosis

Epidemiology

Primary hyperhidrosis (PH) is idiopathic and occurs as focal or multifocal (16). It has been described that multifocal PH is more common than the focal form (17). The disease affects women and men in equal proportions (18). Onset of palmar hyperhidrosis is already in childhood while axillary hyperhidrosis occurs in adolescence or later (18,19). Axillary hyperhidrosis is the most common type of PH in ~50% of the cases (18) followed by palmar, plantar, groins, facial and other areas of the body affected (19). Self-reported family history for PH is described in 30-50% (20). A genetic background with an autosomal dominant transmission and a variable penetrance has been suggested as a possible cause (21,22). In some familial cases the source and loci for PH have been mapped to chromosome 2q31.1 and 14q11/2-q13 raising the question of whether unknown genes are involved due to the diversity of phenotypes (23,24). Some authors have not found any pathological changes in the sweat glands (25,26), while others have described an increased number of cells and a larger myelin sheath in the sympathetic ganglion in those with PH (9). An overstimulation of the sympathetic nerve fibres innervating the sweat glands has been suggested as a mechanism for the excessive sweat production (27).
Primary hyperhidrosis is a common disease with varying prevalence across the world (table 1).

Table 1. Prevalence of primary hyperhidrosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Population (n)</th>
<th>P (%)</th>
<th>Age (y)</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doolittle et al 2016 (28)</td>
<td>USA</td>
<td>8160</td>
<td>4.8</td>
<td>18-65+</td>
<td>Cross-sectional Online survey</td>
</tr>
<tr>
<td>Shayesteh et al 2016 (29)</td>
<td>Sweden</td>
<td>5000</td>
<td>5.5</td>
<td>18-60</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Augustin et al 2013 (30)</td>
<td>Germany</td>
<td>14336</td>
<td>4.6</td>
<td>16-60+</td>
<td>Screening for skin cancer, interviews, Survey</td>
</tr>
<tr>
<td>Fujimoto et al 2013 (31)</td>
<td>Japan</td>
<td>8250</td>
<td>12.76</td>
<td>5-64</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Westphal et al 2011 (32)</td>
<td>Brazil</td>
<td>293</td>
<td>5.5</td>
<td>16-46</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Li et al 2007 (33)</td>
<td>China</td>
<td>30 000</td>
<td>3.36</td>
<td>15-22</td>
<td>Cross-sectional survey</td>
</tr>
<tr>
<td>Strutton et al 2003 (18)</td>
<td>USA</td>
<td>150 000 households</td>
<td>2.8</td>
<td>0-65+</td>
<td>Cross-sectional survey</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of participants; P, prevalence; y, years.

Data indicates that the disease is more common in young adults while it becomes more rare with increasing age. The opposite is valid for SH which is more common with increasing age (18, 28-30). There are still unknown areas of knowledge, e.g. regarding the natural course of the disease, if PH changes into SH with increased age or whether it ebbs.

Co-morbidities

Co-morbidities in PH are rare but those described are Reynaud’s Disease, rheumatoid arthritis, erythromelalgia, nail-patella syndrome, keratosis palmaris et plantaris, pachyonychia congenita and epidermolysis bullosa of Weber
Cockayne type (34,35). Symptoms described as cardiovascular dysautonomia have also been linked to PH (36,37). Anxiety and stress is often reported by patients with PH however other psychological disorders involving temperament and character traits are not more frequent in PH compared with others (38-40). Anxiety due to sweating problems in those with severe hyperhidrosis may cause social anxiety disorder (SAD) but it is also very difficult to separate PH from focal sweating secondary to SAD (41). Cutaneous infections caused by bacterial, fungal and viral agents are also more common in PH clinically manifesting themselves as pitted keratolysis, dermatophytosis or verruca vulgaris (42).

Influencing factors

Exacerbating factors in PH have been described as stress, anxiety, heat, humidity and exercise (36). Food such as spices, coffee and alcohol can also worsen the problems. While some patients report an amelioration of symptoms with hard exercise others report the opposite (43). Alcohol affects the body’s thermoregulation in complex pathways not fully understood and few studies have investigated its effect in hyperhidrosis. While alcohol is described to increase sweating in persons with or without hyperhidrosis (44) consumption among those with PH is in parity with that of the Swedish population (45).

Anecdotes about tattoos and their effects on sweating have also been investigated in a small study and it was found that the capacity of sweating in a tattooed skin is less than in a non-tattooed skin (46).

Consequences of having primary hyperhidrosis

Primary hyperhidrosis has negative impacts on the psychosocial health of the individuals. The disease reduces the overall quality of life and interferes with the daily activities of those affected (29, 47-51). Individuals express stress and anxiety in conjunction with their sweating but also prior to private or social interactions. The impacts of PH can be different depending on the site of the body affected (51). In palmar hyperhidrosis sweating on papers or instruments, shaking or holding hands and avoiding certain social activities create a disability in daily interactions (47). While in axillary hyperhidrosis the stain and smell on clothes, limitations in type of clothes that can be worn and anxiety of sweating in social or private situations have a negative effect on health (52). Decisions such as choosing career path or occupation can be difficult and coping with hyperhidrosis is often stressful (50). In the society excessive sweating is associated with being nervous or unhygienic (53). Feedbacks from social interactions in childhood or in adult age create an uncertainty and reduce mental health resulting in a sense of unhappiness and feeling depressed (38). It has been described that the impairments in quality of life for axillary and
palmar hyperhidrosis according to Dermatology Life Quality Index (DLQI) is comparable to other diseases such as psoriasis, rosacea, acne, contact dermatitis, Hailey Hailey's disease and pruritus (50). Investigating quality of life in PH by Short Form Health Survey 36-items (SF-36) shows significant reductions mainly on mental health of those suffering from the disease compared to controls and the general population in Sweden (29,45).

Comparing the quality of life impairments depending on the localisation of PH has not been fully investigated. It is described that those with axillary hyperhidrosis spend more time and energy regarding their personal hygiene and have a greater impairment in daily life compared to persons with palmar hyperhidrosis (50). However in palmar hyperhidrosis the emotional impact from the sweating is more extensive compared to axillary hyperhidrosis (50). Our clinical impression is that individuals with axillary and palmar hyperhidrosis report greater disease interferences in their daily life compared with those suffering from excessive sweating on other body locations.

Gender specific impacts on quality of life in hyperhidrosis have not been investigated as well. While a majority (70-80%) of those seeking healthcare for sweating problems are women (54,45), the reason for this discrepancy is unknown. Women respond different than men to a dermatological disease and report a greater interference in their relation, sex-life and psychosocial health (55,56). Standard scales investigating the quality of life might not always reveal any difference between the genders. While men tend to get most of their support regarding health concerns from female partners, the pattern for seeking this support is not straightforward (57). Data regarding the experiences of men and women living with hyperhidrosis and what motivates them to seek healthcare is scarce. In general, it has been described that men rather seek healthcare with specific problems than concerns on general health and deal with barriers that can be systematic; time and access to healthcare or personal issues; traditional social roles, low interest in prevention, sense of immunity, immortality and control (57). A remark is that comparing men and women regarding healthcare consumption could be problematic since ethnicity and cultural conceptions may also be an influence. This has been described among Asian versus European women in New Zealand where Asian women seek medical help at primary health care less often (58).

**Diagnosis**

Initial cognizance in PH is focused on the medical history of the patient. While objective methods to diagnose PH are few and time consuming, several authors have described criteria for the disease (19). A major criterion is focal, visible, and excessive sweating of at least 6 months duration without apparent cause
and at least another two minor criteria have to be fulfilled: bilateral and relatively symmetric sweating; impairs daily activities; at least one episode per week; age of onset <25 years; positive family history; cessation of focal sweating during sleep. Diagnosing PH via surveys and without physical examination have also proved to be effective (59). Another method aiding the clinician to test the sudomotor function is the Minor test (60). Iodine solution is applied on the skin and after 2-5 minutes when it has dried corn or potato starch is sprinkled over the area of interest. Almost immediately or after just a few minutes black dots and stains start appearing on the powder where the sweating occurs.

Quantifying the sweat production can be done by gravimetry (61). In the axilla a production of 100 mg sweat in men and 50 mg sweat in women within 5 minutes has been suggested as being pathological (62). Gravimetry is mainly used in research and is not suitable for daily use in clinical practise.

Diagnosis of hyperhidrosis may also be aided by using scales such as Visual Analogue Scale (VAS) and Hyperhidrosis Disease Severity Scale (HDSS). VAS is a multi-point scale which ranges from no symptoms to the worst symptoms at a determined point. HDSS measures severity of hyperhidrosis with regard to the patient’s daily activities (63) and it has been validated against DLQI and gravimetric measurements (64). Larger and more extensive instruments such as DLQI and SF-36 are mostly used in research for either describing or comparing the quality of life or reporting gains after a certain treatment. DLQI investigates the impacts from a dermatological disease on an individual’s life within the previous week (65). The wide use of DLQI in dermatology makes it possible to compare quality of life across dermatological diseases. SF-36 assesses the overall health of an individual mainly over a period of four weeks (66) which can be compared to other diseases or to the general population.

**Treatments**

**Topical**

Topical treatments are the first line therapy in PH (67). Appropriate use and knowledge is important since many patients and clinicians consider them ineffective and side-effects as problematic. Topical remedies consist of ointments or solutions containing mostly aluminium salts together with alcohol which has proven to be an effective combination in hyperhidrosis (68). Aluminium complexes such as aluminium chlorohydrate (Al₂Cl(OH)₅) block the eccrine ductal system as a filter causing atrophy of the eccrine glands secretory portion (69). Alcohol promotes the penetration of aluminium salts but acts also against bacterias on the skin producing the unwanted odour (70). Antiperspirants should be applied at night to increase efficacy, limit skin
irritation and minimise destruction of clothes (67,68). Repeated applications are required, and clinical effect is usually noted after 1-2 weeks (67). Antiperspirant salts such as vanadium and indium work in a similar way however aluminium is less expensive and with less toxicity (71). Side-effects of aluminium chlorohydrate consist of irritation, dermatitis and destruction of the clothes adjacent to the skin which is mainly caused by the hydrochloric acid production (68). Applying hydrocortisone cream on the treated skin in the morning may control and reduce some of the side-effects (72).

Topical glycopyrrolate has shown to be effective in reducing sweat production and with few side-effects when used in patients with Frey’s syndrome and craniofacial hyperhidrosis (73,74). A commercial product is not available but can be compounded. Denaturing agents plugging the sweat ducts such as tannic acid, formaldehyde and glutaraldehyde are seldom used due to the risk of contact allergy and discoloration of the skin (70,71).

New generation antiperspirants such as aluminium zirconium tetrachlorohydrex glycine offer less irritation on the skin by reducing the hydrochloric acid production (75).

**Iontophoresis**

Tap water iontophoresis is used in the treatment of palmar or plantar hyperhidrosis (76). The mechanism of iontophoresis is not fully known, but it has been described that the anodal current leads to an accumulation of hydrogen molecules inside the sweat ducts, which in turn blocks the acrosyringium (77). Iontophoresis has been studied in several clinical trials with a positive outcome among the participants (77-80). It should be administered three times a week until satisfactory sweat reduction is achieved and then once a week as maintenance therapy (76). The effect can usually be noticed after 2-3 weeks and a significant reduction of hyperhidrosis is achieved after one month (78). Contraindications for iontophoresis treatment are pregnancy, electric implants such as pacemakers, medical history of cardiac arrhythmia and epilepsy (77,78). The side effects are few, local and described as erythema, blistering and burning pain (78).

Iontophoresis is also a method for transporting medications inside the skin and its entry portal is primarily the sweat glands (81). This mechanism has been used by adding anticholinergics in the tap water required for iontophoresis resulting in a more efficient reduction of sweat production compared to only water iontophoresis (82). Iontophoresis machines are commercially available and can be purchased for personal use at home.
**Botulinum toxin**

Botulinum toxin is an exotoxin produced by the anaerobic bacteria *Clostridium botulinum*. It consists of a neurotoxin which is approximately 150 kilodalton (kDa) (83). The toxin is stable at a pH of 5-7 and inhibits the release of acetylcholine from the synapses causing paralysis (84). This is achieved by a 3-step action by the toxin, first binding irreversibly to the pre-synaptic nerve surface. Then by receptor mediated endocytosis the neurotoxin enters the cytosol of the pre-synaptic end nerve terminal and finally cleaves the SNARE proteins preventing acetylcholine from exocytosis (10) (figure 1&2).

![Presynaptic membrane](image)

*Figure 1&2. Illustration of the pre-synaptic nerve end terminal for physiologic transmission of acetylcholine vesicle (left) and under the influence of botulinum toxin type A (right).*

There are seven immunological distinct botulinum neurotoxins, A to G (85) and each type exerts its effect on different sites within the SNARE complex (85). Botulinum toxin type A and type B are used commercially and for medical purposes. Data suggests that botulinum toxin type B compared to type A has a relatively lower effect on sudomotor nerve endings and α-motor neurons in muscles (86). The dosage of botulinum toxins is expressed in units and each unit corresponds to the median lethal intraperitoneal dose in mice within 72 hours (87). Commercial botulinum toxin products and their units are not comparable and differ in their potency (86).

In PH botulinum toxin is administered via intradermal injections. This treatment not only reduces sweat production but also increases quality of life for patients suffering from hyperhidrosis. The efficacy of botulinum toxin type A in axillary hyperhidrosis and its positive outcomes in terms of gains in quality of life have been described in several large randomised controlled trials (table 2).
Table 2. Large randomised double-blinded controlled trials investigating the effects of botulinum toxin in axillary hyperhidrosis*

<table>
<thead>
<tr>
<th></th>
<th><em>Lowe</em> et al 2007 USA (90)</th>
<th><em>Naumann</em> et al 2003 Germany, Belgium and Great Britain (89)</th>
<th><em>Naumann</em> et al 2002 Germany and Great Britain (88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration (m)</td>
<td>13</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Participants (start/end) (n)</td>
<td>322/252</td>
<td>256/223</td>
<td>320/307</td>
</tr>
<tr>
<td>Participants (age) (y)</td>
<td>18-69</td>
<td>18-75</td>
<td>17-74</td>
</tr>
<tr>
<td>Btx-A dosage (U)</td>
<td>Botox® 50 U and 75 U</td>
<td>Botox® 50 U</td>
<td>Botox® 50 U</td>
</tr>
<tr>
<td>Placebo</td>
<td>Saline</td>
<td>Saline</td>
<td>Saline</td>
</tr>
<tr>
<td>Duration of effect (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Btx-A</td>
<td>197</td>
<td>122</td>
<td>n/a</td>
</tr>
<tr>
<td>Control</td>
<td>96</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Btx-A vs Control</td>
<td>HDSS p&lt;0,001</td>
<td>SF-12 n/a</td>
<td>SF-12 p&lt;0,001</td>
</tr>
<tr>
<td></td>
<td>Gravimetry p&lt;0,001</td>
<td>HHIQ n/a</td>
<td>HHIQ p&lt;0,001</td>
</tr>
<tr>
<td></td>
<td>DLQI p&lt;0,001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side-effects</td>
<td>Pain and bleeding caused</td>
<td>Flu-like symptoms CH (4.3%) One case of death</td>
<td>Mild side effects CH (5%)</td>
</tr>
<tr>
<td></td>
<td>by injections CH (6-10%)</td>
<td>because of MI</td>
<td></td>
</tr>
<tr>
<td>Quality of the study</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Abbreviations: m, months; n, number of participants; y, years; U, units; d, days; Btx-A, botulinum toxin type A; n/a, not available; SF-12, Short Form Health Survey 12 items; HHIQ, Hyperhidrosis Impact Questionnaire; CH, Compensatory Sweating.

*Shayesteh et al. *Läkartidningen* 2011 (remade with permission from the publisher)

A dose of 50 units of Botox® Allergan (19) or 100 units of Dysport® Ipsen (91) per axilla have been suggested as effective with regards to costs and side-effects. The effect of botulinum toxin reaches a maximum after 2-4 weeks and may last for 4-16 months in axillary hyperhidrosis (89,90). Treatment with botulinum toxin has to be repeated to maintain effect. Common side-effects constitute of pain, subdermal bleeding and irritation on the injection site while major side-effects are muscle weakness, influenza like symptoms and compensatory sweating (45,88-90). Most side-effects are temporary and diminish with time. Contraindications for botulinum toxin type A are infections at the injection sites and hypersensitivity against albumin or other ingredients in the formulation (92). Caution is recommended in individuals with neurofunctional muscle disorders, co-administration with certain antibiotics (e.g. aminoglycosides), pregnancy and lactation (93).
Botulinum toxin A is also used off-label in the treatment of other body localisations with excessive sweating. In palmar hyperhidrosis a dose of 100-200 units Botox® is recommended per hand (94-96). The treatment can be painful because of the number of injections. Pain reduction is therefore necessary in most cases and ice-packs or nerve blocks can be used to achieve anaesthesia (19). A major side-effect of treating palms with botulinum toxin type A is weakness in the fingers or wrists impacting the grip ability (45). This side-effect can be reduced by using botulinum toxin B on the thenar eminences of the palms (97). Duration of effect from botulinum toxin injections may vary but usually lasts up to 9 months (45). Clinical experience suggests that Dysport® may diffuse more readily than Botox® and therefore may have more side-effects due to a higher diffusion rate (98). A head to head study in palmar hyperhidrosis using a conversion rate of 1:2.5 between Botox® and Dysport® described similar efficacy and safety in both products while the frequency of side-effects was higher in the group treated with Dysport® (99).

There is a considerable dearth of data regarding treatment of plantar and craniofacial regions, areas in the groins, back and other localisations of the body in PH. While some studies confirm the effect and gains in quality of life with botulinum toxin treatment on these areas (100-106), large randomised controlled trials are not available and further research is needed.

**Oral anticholinergics**

Systemic therapy of hyperhidrosis is mainly focused on anticholinergic drugs and their ability to reduce sweat production (107). A more widely used anticholinergic drug in PH is an antimuscarinic agent called oxybutynin. The effect of oxybutynin in reducing sweat production and its positive impacts on quality of life in axillary, palmar, plantar and facial hyperhidrosis have been described in several studies (108-112). Oxybutynin doses above 15 mg daily should be avoided because of side-effects (112). A remark however is that the majority of studies in hyperhidrosis regarding oxybutynin have been done by one research group. An expert opinion on oxybutynin was released by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) in 2016 establishing local and systemic use of anticholinergics beside botulinum toxin A as a possible therapy in PH (113). Contraindications for using oxybutynin are glaucoma, ulcerous colitis, myasthenia gravis and urinary tract obstructions (108). Side-effects consist of dry mouth, urinary retention, accommodation disorders, constipation and memory impairments (109). These side-effects are usually dose dependent and manageable. In recent years a link between anticholinergic usage and dementia in elderly has been described (114,115). While it is reasonable to be cautious when treating patients with oxybutynin it is also important to consider that the majority affected by PH
are young and the long-term usage of anticholinergics in this patient group has not been investigated.

**Surgery**

Surgical procedures in PH are uncommon and usually recommended as the last option when all other treatments fail (19). If surgery is indicated it is important to consider that even small surgical procedures have a recurrence rate of up to 26% (116). Subcutaneous curettage is preferred due to less scarring however there are still side-effects that can occur (117). Other invasive procedures such as endoscopic thoracic sympathectomy (ETS) are preferred compared to open thoracic sympathectomy due to lesser morbidities and faster recovery (118). Initial satisfaction has been described as high after sympathectomy but it declines with time and side-effects such as compensatory sweating, gustatory sweating and Horner’s syndrome may occur (119).

**Other treatments**

Using microwaves for the thermolysis of eccrine glands is a relatively new method in the treatment of hyperhidrosis (120). A device which is available for commercial use; MiraDry® is currently used in axillary hyperhidrosis. The microwaves are not selective for eccrine glands but also destroy apocrine glands and hair follicles (120). The procedure requires local anaesthetics, can be performed in an office or a clinic and does not create any down time for the patient. Side-effects such as transient median and ulnar nerve neuropathy (121) and one case of brachial plexus injury that did not recover (122) have been reported. MiraDry’s® long-term effects have not been investigated. Still microwave technology is promising and a complement in the treatment of PH.

Lasers have also been used in the treatment of PH with the aim of destroying the sweat gland thus permanently reducing the sweat production. Yttrium Aluminium Garnet (Nd: YAG) laser and Diode laser 924/975-nm have shown a promising effect in small studies (123,124). Diminishing side-effects are pain, redness, swelling, bruising, and itching (123,124).
Other types of hyperhidrosis

Secondary hyperhidrosis

Secondary hyperhidrosis can be caused by (125):

I. Endocrine diseases (hyperthyroidism, hyperpituitarism, diabetes, pheochromocytoma, carcinoid syndrome and acromegaly)
II. Infectious diseases
III. Malignancies
IV. Neurological diseases (Parkinson)
V. Intoxication
VI. Medications
VII. Ingested food and beverages

Secondary hyperhidrosis is usually general rather than focal and is more common than PH (45). Peripheral autonomic neuropathy in diabetes or complex regional pain syndrome could cause SH (126). In Harlequin syndrome and Frey’s syndrome an injury to the neuronal pathway could also cause SH (73,127). For example in Frey’s syndrome, damage to the facial nerve after parotid salivary gland surgery may result in an aberrant innervation of parasympathetic nerve fibres of the sweat glands causing hyperhidrosis (128). As a consequence when the patient eats or drinks the sweating termed gustatory hyperhidrosis becomes activated.

Anticholinergics have been used with some success in general excessive sweating (129). In managing SH the focus should be more on finding the responsible causes rather than treating the symptoms.

Compensatory hyperhidrosis

Compensatory sweating is a common complication after a surgical procedure such as sympathectomy (119) but could also occur after treatment with botulinum toxin injections (45, 89-91). The term compensatory sweating could create confusion and one must be aware that it can both relate to the thermoregulation of body heat when sweating is induced but also highlighting an increased sweating on a different body part for compensating an anhidrotic area due to a treatment. Compensatory sweating induced by botulinum toxin injections subsides in time and is seldom treated.
Aims

• To investigate the prevalence of hyperhidrosis in Sweden and how hyperhidrosis impairs the quality of life.

• To investigate quality of life, changes in daily activities, depression and anxiety and alcohol consumption among patients diagnosed with primary hyperhidrosis and the effect of botulinum toxin type A on these parameters.

• To investigate whether the impacts of primary hyperhidrosis on quality of life are different depending on the localisation of sweating on the body.

• To explore men’s experiences of living with primary hyperhidrosis.
Materials and Methods

Participants

Paper I

Addresses to 5000 individuals with an equal proportion of men and women were ordered from the Statens personadressregister (SPAR) in 2012. The addresses were randomly selected by a computer at SPAR for anyone between 18 and 60 years old living in Sweden. SPAR is connected to the Swedish Tax Agency and has information on all registered residents in Sweden. SPAR updates its data on daily basis from the Swedish Population Register. The purpose of SPAR is to update, supplement and verify personal information plus providing addresses for marketing, public service announcements and research.

Paper II

All hyperhidrosis patients referred to the Department of Dermatology and Venereology, Umeå University Hospital, Sweden during 2011-2013 were invited to participate in the study. Before referral patients were diagnosed by their general practitioner and had tried topical treatments with unsatisfying results. The Inclusion criteria were PH and HDSS ≥ 2 points. Exclusion criteria were HDSS ≤ 2 points, SH, pregnancy, lactation, neuromuscular disease and botulinum toxin treatment within a year prior to the visit. A total of 118 individuals, 11-62 years old were recruited. One hundred and fourteen individuals (27 men, 85 women and two with unspecified gender) were included after oral and written consent. Four patients were excluded: one due to pregnancy and three due to SH.

Paper III

A total of 188 cases with PH from our two earlier studies (Paper I & II) were evaluated post-hoc. Only those who had reported one site of their body as their most problematic area of sweating were included (n = 160/188) while individuals with multifocal PH without a most problematic area on the body were excluded (n = 28/188).
Paper IV

Fifteen men with PH were recruited in a non-probability sampling during 2016-2017 from the Department of Dermatology and Venereology University Hospital, Umeå. The inclusion criterion for the study was PH with HDSS >2 points. Exclusion criteria were 1. Individuals absent of a most affected sweating site 2. Multifocal (>2 sweating sites) hyperhidrosis, 3. Received treatment with botulinum toxin prior to the interview (one year minimum). The diagnosis of PH was confirmed by the general practitioner and verified by a dermatologist. To ensure credibility an adequate number of participants was selected and with purposing sampling those who had lived with hyperhidrosis the longest were prioritized. Dependability was addressed throughout the analysis between the authors by reflecting, discussing and moving back and forth between the text and its parts until consensus was achieved. Statements and quotes from participants were used to strengthen the results and for authenticity (130).

Scales, questionnaires and guides

Hyperhidrosis detecting questionnaire (Paper I)

To detect PH in the population a questionnaire was designed to separate PH from healthy individuals and SH. Constructing the questionnaire was done by studying research guidelines, manuals and literature. Face and content validity for the structure of the questionnaire were discussed within the research group and with experts in questionnaire design. The initial questionnaire was tested on 20 medical students and colleagues. After feedback the questionnaire was altered and re-tested for its reliability in detecting PH on 20 hyperhidrosis patients (Cronbach's alpha: 0.98). The final questionnaire consisted of 16 items investigating hyperhidrosis localisation, debut, co-morbidities, heredity, medications, aggravating factors, tobacco usage, health care contacts and severity of hyperhidrosis. The questionnaire was posted to the participants and they were asked to return it after one week (Appendix).

Hyperhidrosis specific questionnaire (Paper II)

A specific questionnaire was designed for collecting data from hyperhidrosis patients before and after treatment with botulinum toxin. The pre-treatment questionnaire concerned localisation, heredity, debut, co-morbidities, severity and impairments of the disease. Post-treatment questions investigated symptoms, severity, side-effects and improvements. The validation process included construction of questions by consulting relevant guidelines, manuals and literature. Some of the questions were open ended, some had a 10-point
VAS scale as answers and other questions had 4 answer alternatives: 1 = not at all; 2 = little; 3 = much; 4 = very much. The structure and content of the questions were discussed within the research group and altered after feedback from experts in questionnaire design. The modified questionnaire was distributed and tested both on hyperhidrosis patients and colleagues at the department of Dermatology and Venereology, University hospital, Umeå. After feedback the questionnaire was finally modified with more open-ended questions. The final questionnaire included 12 pre-treatment items and 11 post-treatment items. The pre-treatment questionnaire was tested for its reliability in 27 patients with PH at week 0 and week 2. Test re-tests correlation ranged between 0.98-0.80 except for one question investigating symptoms of hyperhidrosis in social life 0.69. The pre-treatment questionnaire was collected at the day of the visit and the post-treatment questionnaire was sent to us by post two weeks after the visit (Appendix).

**Hospital Anxiety and Depression Scale (Paper II)**

Hospital Anxiety and Depression Scale (HADS) measures signs and symptoms of anxiety (HADS-A) and depression (HADS-D) within the past 2 weeks. The scale consists of 14 questions, seven regarding anxiety and seven regarding depression. Each question has four answers giving a total score of 0-21 points respectively for anxiety and depression subscales (131). The internal consistency for HADS-A and HADS-D are above 0.80 and with a threshold of +8 points 70-90% of the cases with signs of anxiety or/and depression are detected (131).

**Alcohol Use Disorders Identification Test (Paper II)**

Alcohol use disorders identification test (AUDIT) is developed by the World Health Organisation (WHO) and identifies hazardous alcohol consumption in men and women. The scale consists of 10 questions with three or five alternative answers. It measures patterns of alcohol consumption, alcohol dependence and adverse consequences of heavy drinking within the last 12 months. In females a total score of 6 points or more and in males a total score of 8 points or more indicate symptoms of hazardous alcohol consumption (132). In the Swedish population the internal consistency for AUDIT was 0.82 for the total score and 0.69 for the hazardous use. Test-retest reliability was 0.93 for both the total score and hazardous use (132).
**Treatment with botulinum toxin (Paper II)**

Treatment consisted of botulinum toxin A injections with Dysport® Ipsen in axillary hyperhidrosis and Botox® Allergan used on the palms and soles. Both drugs were diluted with physiological, unpreserved saline. Botox® and Dysport® were diluted with a conversion factor of 1:2 giving the concentrations 100 U/ml and 200 U/ml respectively. The injections were performed using Braun Omnican 50 syringes 0.5 ml. Those with axillary hyperhidrosis received 60-100U Dysport® per axilla. In palmar hyperhidrosis 120-160U Botox® was administered on each hand; for plantar hyperhidrosis 160-200U Botox® was injected on each foot.

**Hyperhidrosis Disease Severity Scale (Paper I-III)**

Hyperhidrosis Disease Severity Scale is a quick scale with one question and four answers. Each answer corresponds to one point and for the whole test 1 to 4 points is achievable. One to two points is interpreted as a mild hyperhidrosis while a score of three or four points indicate moderate to severe hyperhidrosis. To achieve equivalence between the Swedish and English version the HDSS was translated from English to Swedish and then translated back from Swedish to English. Conceptual, item, semantic and operational equivalence for the Swedish version of HDSS was addressed by discussions within the research group and among patients with hyperhidrosis. Test re-test correlation for the reliability of the Swedish version of HDSS with 2 weeks apart was 0.98 in 27 patients with hyperhidrosis. The English version of HDSS is available for use in research and in clinical settings (Appendix).

**Short Form Health Survey 36 (Paper I-III)**

Short Form Health Survey 36-items was used to measure the quality of life in individuals with hyperhidrosis. It consists of 36 questions yielding eight subscales of health functions; physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE) and mental health (MH). The subscales are summarised into physical (PCS) and mental (MCS) component summaries. A score of 0 indicates the lowest quality of health while the score of 100 indicates the highest (133). Norm-based score for the general population in SF-36 is set as mean 50 points and the standard deviation at 10 for all sub-scales (133). SF-36 has been tested in the Swedish population showing an internal consistency of 0.79-0.91 for its subscales (66).
Guide for the interviews (Paper IV)

The content of the interview guide was based on our experience of managing patients with hyperhidrosis. It included questions about the participants’ experiences and thoughts living with the disease at present, in childhood, adolescence and adult life. Examples of questions asked were “could you describe your experiences of having hyperhidrosis?” or “could you give an example from a situation when your sweating became a problem?” Areas such as private, social and professional life were also investigated with narrated examples. The participants were questioned about their definition of health in regard with suffering from hyperhidrosis and if the disease had affected their life-plan. The interview guide investigated also other parts of the daily life affected by PH and the results will be reported in future papers.

The interviews (Paper IV)

All interviews were performed by AS on mutual agreed time at Umeå University hospital, Department of Dermatology and Venereology in a large and a neutral room. After the first and the second interview the audio files were revised by CB and EN for feedback on the interview technique. The first interview was transcripted verbatim by AS. All other transcriptions were performed by secretaries at the Department of Dermatology and Venereology Umeå University Hospital implementing the same method as AS. Interviews lasted 30-50 minutes. The transcript of the third interview was revised at Umeå University, Department of Nursing among professionals in qualitative studies for feedback on questions and interview technique.

Ethical considerations

Paper I-III

Approval for the studies was given by the Ethical Review Board at Umeå University (dnr. 2010-199-31M). Voluntary participation and informed consent were ensured by a cover letter which included purpose, background, method, use and safe-keeping the data, funding and confidentiality. Persons who participated while visiting the Department of Dermatology and Venereology Umeå University Hospital were also asked for written consent before participation. Individuals participating via post gave their consent by answering the survey. All surveys were coded and only the research group had access to the survey material.
Paper IV

This study was approved by the Ethical Review Board at Umeå University (dnr. 2016-242-32M). The right to autonomy, dignity, informed consent, voluntariness and confidentiality for all participants was respected. Written consent for participation in the study was obtained on the day of the interview. Each individual was assigned an identification number to their interview only known by AS. In case the interview would become emotional and the person would need to talk to someone afterwards, the necessary information on whom to contact was provided.

Statistics

Paper I

Precision calculation showed a sample size of 753 responders necessary for our aim. Data regarding age, debut age, HDSS and SF-36 were normally distributed and reported with means and standard deviation. Descriptive statistics and tables were used for presenting the data. Mean scores were compared between controls and those with hyperhidrosis using Student’s t-test (t-test) while Chi square test ($\chi^2$-test) was used for analysis of comparison between the participants. The level of significance was set at $p<0.001$.

Paper II

Power calculation showed that 90 patients were needed to detect a 10% change in the mean values for HDSS, HADS and SF-36 before and after the treatment. Data was normally distributed and reported with means and standard deviation. Paired t-test was used comparing means before and after the treatment. The background data of post-treatment questionnaire for responders and non-responders was tested with $\chi^2$-test. Logistical regression was used for investigating association between the severity of hyperhidrosis and tobacco use, HADS, AUDIT and SF-36 results. The level of significance was set at $p<0.01$.

Paper III

Descriptive statistics was used for background characteristics. Continuous variables were expressed as means and standard deviation. Mean scores were tested by t-test and $\chi^2$-test was used for analysis of HDSS. The level of significance was set at $p<0.01$. 

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Results

Prevalence of hyperhidrosis (Paper I)

The responders (n=1353, mean age 43.1 ± 11.2 years) reported an increased frequency of SH with increasing age while PH was more frequent in young individuals. Severe hyperhidrosis (HDSS ≥ 3 points) was reported by 1 out of 4 in PH. There was no difference in gender for the prevalence of PH (p=0.72) while SH was more common in women (p<0.001) (table 3).

Table 3. Hyperhidrosis in Sweden

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Prevalence (%)</th>
<th>Mean debut (y) (SD)</th>
<th>Contact with healthcare (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PH</td>
<td>SH</td>
<td>PH</td>
</tr>
<tr>
<td>All</td>
<td>1353</td>
<td>5.5</td>
<td>14.8</td>
<td>15.3±3.4</td>
</tr>
<tr>
<td>Male</td>
<td>564</td>
<td>6.0</td>
<td>8.7</td>
<td>16.3±3.1</td>
</tr>
<tr>
<td>Female</td>
<td>747</td>
<td>5.4</td>
<td>20.1</td>
<td>14.4±3.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>PH</th>
<th>SH</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td>19.4</td>
<td>4.1</td>
</tr>
<tr>
<td>25-34</td>
<td>11.3</td>
<td>8.0</td>
</tr>
<tr>
<td>35-44</td>
<td>5.2</td>
<td>11.0</td>
</tr>
<tr>
<td>45-54</td>
<td>2.3</td>
<td>19.0</td>
</tr>
<tr>
<td>55-60</td>
<td>1.3</td>
<td>27.9</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of participants; y, years; SD, ± standard deviation; PH, primary hyperhidrosis; SH, Secondary hyperhidrosis. 112/1353 participants did not specify their age.

Characteristics of individuals with primary hyperhidrosis (Paper I-III)

The most common site for PH was the axilla (>50%). A positive heredity for PH was described in 40%. Mean debut age for individuals with palmar hyperhidrosis (11.58±6.44 years) was significantly lower than in axillary hyperhidrosis (14.93±3.24 years) (p<0.01). There was no significant difference in debut age between men and women within the groups. Signs of peripheral vasoconstriction were more common in axillary compared to palmar hyperhidrosis (p<0.01) regardless of gender. Co-morbidities (27%) often reported consisted of asthma (6%), endocrine diseases (3.6%), psychiatric diseases (3.6%) and dermatitis (3%). Trigger factors such as stress, heat and
food exacerbated the disease. Alcohol consumption (AUDIT mean score $6.29 \pm 3.16$ points in men and $4.91 \pm 3.51$ points in women), signs of depression and anxiety (HADS-D mean score $3.4 \pm 3.4$ points and HADS-A mean score $6.4 \pm 3.9$ points) and tobacco usage (25.7%) were not more common compared to the general population.

**Quality of life in hyperhidrosis measured by SF-36 (Paper I)**

Primary hyperhidrosis affected mainly the mental health of the individuals while SH affected both the physical and mental health measured by SF-36 Health Survey (figure 3).

![Figure 3. SF-36 mean scores in primary and secondary hyperhidrosis compared to controls. Showing means ± SD data in all SF-36 domains. PCS, physical component summary score and MCS, mental component summary mean scores are reduced when *** $p<0.001$ and N.S.; not significantly different.](image)

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Treatment with botulinum toxin (Paper II)

Response rate for the post-treatment questionnaire was 82%. Mean effect duration for treatment of axillary hyperhidrosis was 8.1 ± 3.7 months, palmar hyperhidrosis 9.1 ± 4.3 months and plantar hyperhidrosis 9.0 ± 4.2 months. Most common side-effects in axillary and palmar hyperhidrosis were weakness in fingers and wrists. All side-effects were reversible. Compensatory hyperhidrosis occurred in 18% of the patients. Binary logistic regression did not show any association in first-time visitors and re-visitors at base-line and after treatment regarding HDSS, HADS, AUDIT and SF-36 results The treatment with botulinum toxin A had a significant effect (p<0.01) in reducing the interferences of PH in daily life and in all scales except AUDIT (table 4&5).

Table 4. Reduction of hyperhidrosis problems two weeks after treatment with botulinum toxin type-A

<table>
<thead>
<tr>
<th>Hyperhidrosis problems*</th>
<th>n</th>
<th>Mean difference</th>
<th>SD</th>
<th>t</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holding hands</td>
<td>94</td>
<td>1.06</td>
<td>1.28</td>
<td>8.08</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Writing</td>
<td>94</td>
<td>0.59</td>
<td>1.00</td>
<td>5.68</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Using gloves</td>
<td>94</td>
<td>0.50</td>
<td>1.03</td>
<td>4.69</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Using socks</td>
<td>92</td>
<td>0.27</td>
<td>0.94</td>
<td>2.78</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Wearing clothes</td>
<td>94</td>
<td>1.45</td>
<td>1.31</td>
<td>10.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Daily life</td>
<td>93</td>
<td>1.66</td>
<td>1.25</td>
<td>12.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Social life</td>
<td>94</td>
<td>1.57</td>
<td>1.36</td>
<td>11.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Work</td>
<td>94</td>
<td>1.26</td>
<td>1.21</td>
<td>10.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Relation to partner</td>
<td>92</td>
<td>0.77</td>
<td>1.20</td>
<td>6.19</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Relation to family</td>
<td>94</td>
<td>0.52</td>
<td>0.90</td>
<td>5.61</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Refraining from certain activities</td>
<td>93</td>
<td>1.19</td>
<td>1.11</td>
<td>10.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Feeling stressed</td>
<td>94</td>
<td>1.41</td>
<td>1.30</td>
<td>10.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Feeling depressed</td>
<td>94</td>
<td>1.11</td>
<td>1.20</td>
<td>8.97</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of participants; SD, ± standard deviation; t, t-value which calculates the difference represented in units of standard error; p, significance (α = 0.01).

*Scoring system: 1 = not at all; 2 = little; 3 = much; 4 = very much.

**Paired sample t-test for equality of means.
Table 5. Improvements two weeks after treatment with botulinum toxin

<table>
<thead>
<tr>
<th>VAS, HDSS, AUDIT, SF-36 scales*</th>
<th>n</th>
<th>Mean difference</th>
<th>SD</th>
<th>t</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>92</td>
<td>5.45</td>
<td>2.83</td>
<td>18.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HDSS</td>
<td>101</td>
<td>1.86</td>
<td>0.88</td>
<td>21.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HADS</td>
<td>92</td>
<td>0.86</td>
<td>2.55</td>
<td>3.23</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HADS-D</td>
<td>92</td>
<td>1.01</td>
<td>2.99</td>
<td>3.24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HADS-A</td>
<td>92</td>
<td>-0.07</td>
<td>1.79</td>
<td>-0.35</td>
<td>0.73</td>
</tr>
<tr>
<td>AUDIT</td>
<td>92</td>
<td>-2.52</td>
<td>7.33</td>
<td>-3.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SF-36</td>
<td>92</td>
<td>-5.47</td>
<td>9.25</td>
<td>-5.68</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: VAS, visual analogue scale; HDSS, hyperhidrosis disease severity scale; HADS, hospital anxiety and depression scale (D: depression A: anxiety); AUDIT, alcohol use disorders identification test; SF-36, short form 36 health survey (PCS: physical component summary, MCS: mental component summary); n, number of participants; SD, ± standard deviation; t, t-value which calculates the difference represented in units of standard error; p, significance (α = 0.01).

*Scoring range (points): VAS = 1-10; HDSS = 1-4; HADS = 0-21; AUDIT = 0-40; SF-36 = 0-100.

** Paired sample t-test for equality of means.

Differences between sweating sites on the body (Paper III)

Severe to moderate hyperhidrosis (HDSS 3-4 points) were more often reported by individuals with axillary and palmar hyperhidrosis while SF-36 results for those without co-morbidities confirmed that axillary and palmar hyperhidrosis had the highest negative impacts on quality of life compared to other localisations of hyperhidrosis (table 6,7).

Table 6. HDSS results in individuals with primary hyperhidrosis

<table>
<thead>
<tr>
<th></th>
<th>AH</th>
<th>PH</th>
<th>Pl.H</th>
<th>FH</th>
<th>OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>105</td>
<td>34</td>
<td>10</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>HDSS score of 1-2 points*</td>
<td>39.4</td>
<td>48.5</td>
<td>60</td>
<td>83.3</td>
<td>85.7</td>
</tr>
<tr>
<td>HDSS score of 3-4 points*</td>
<td>60.6</td>
<td>51.5</td>
<td>40</td>
<td>16.7</td>
<td>14.3</td>
</tr>
<tr>
<td>p(HDSS 1-2 vs 2-3 points)</td>
<td>&lt;0.01 &lt;0.01</td>
<td>0.20</td>
<td>0.65</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>HDSS mean scoreb</td>
<td>2.75±0.95</td>
<td>2.67±0.78</td>
<td>2.10±1.1</td>
<td>1.67±0.82</td>
<td>2.01±0.38</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of participants; AH, axillary hyperhidrosis; PH, palmar hyperhidrosis; Pl.H, plantar hyperhidrosis; FH, Facial hyperhidrosis; OH, other hyperhidrosis; HDSS, hyperhidrosis disease severity scale (1-2 points= mild hyperhidrosis, 3-4 points= moderate to severe hyperhidrosis); p, significance (α = 0.01) tested by chi-2 test; vs, versus.

* Data as percentage (%)

b Data as mean ± standard deviation.
Table 7. Mean (±SD) scores for all dimensions of SF-36 health survey for individuals with PH and without co-morbidities

<table>
<thead>
<tr>
<th>SF-36 variables</th>
<th>AH</th>
<th>PH</th>
<th>OLH</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>n= 78</td>
<td>n= 24</td>
<td>n= 12</td>
<td>n=114</td>
</tr>
<tr>
<td>PFª</td>
<td>91.3±13.4</td>
<td>88.8±18.5</td>
<td>81.4±25.5</td>
<td>89.9±16.1</td>
</tr>
<tr>
<td>RPª</td>
<td>86.9±22.7</td>
<td>77.1±28.5</td>
<td>81.8±31.8</td>
<td>84.4±25.0</td>
</tr>
<tr>
<td>BPª</td>
<td>84.2±20.0</td>
<td>80.0±24.2</td>
<td>75.6±32.4</td>
<td>82.6±22.2</td>
</tr>
<tr>
<td>GHª</td>
<td>80.9±15.5</td>
<td>77.6±17.0</td>
<td>73.9±22.1</td>
<td>79.6±16.5</td>
</tr>
<tr>
<td>VTª</td>
<td>57.6±19.9</td>
<td>57.3±19.7</td>
<td>53.2±17.9</td>
<td>57.2±19.5</td>
</tr>
<tr>
<td>SFª</td>
<td>72.3±27.8</td>
<td>59.4±25.9</td>
<td>83.0±19.6</td>
<td>70.8±27.4</td>
</tr>
<tr>
<td>REª</td>
<td>79.5±31.9</td>
<td>75.0±35.8</td>
<td>87.9±16.8</td>
<td>79.5±31.5</td>
</tr>
<tr>
<td>MHª</td>
<td>68.3±19.1</td>
<td>68.2±15.2</td>
<td>74.2±20.3</td>
<td>68.9±18.4</td>
</tr>
<tr>
<td>PCS</td>
<td>54.7±6.44</td>
<td>52.5±5.90</td>
<td>48.8±10.1</td>
<td>53.7±6.91</td>
</tr>
<tr>
<td>MCS</td>
<td>41.6±11.6</td>
<td>40.0±12.6</td>
<td>47.0±9.05</td>
<td>41.9±11.0</td>
</tr>
</tbody>
</table>

Abbreviations: n, number of participants; AH, axillary hyperhidrosis; PH, palmar hyperhidrosis; OLH, other localised hyperhidrosis. SF-36 subscales: PF, physical functioning; RP, role functioning; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary.

ª 100 = highest score and 0 = lowest score
The general populations mean score is set at 50 and SD 10 in all subscales.

Experiences of living with hyperhidrosis (Paper IV)

Qualitative content analysis of the transcripts resulted in the theme: To be captured in a filthy body which is based on 5 categories and 12 sub-categories. The category Surrender to the condition reluctantly describes the captivity of the individuals by a disease that they could not address directly. Although it was possible to prepare for a sweat attack or withdraw from closed contacts thereby managing the symptoms indirectly, the disease was still present and withheld the sense of captivity. Also the continuity of the symptoms made the individuals worry about other people’s perception regarding excessive sweating. This was often associated with a feeling of embarrassment and being unclean which had an underlying meaning of being in a filthy body. For those who received support from their family and friends or were treated within healthcare there was a relief of the physical symptoms and they could reveal the condition securely enough to
those around them. Positive aspects of support and treatment would diminish the sense of being captured in a filthy body (Table 8).

**Table 8.** Subcategories, categories and theme from content analysis of interviews with men having hyperhidrosis

<table>
<thead>
<tr>
<th>Subcategories</th>
<th>Categories</th>
<th>Theme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness resignation</td>
<td>Surrender to the condition</td>
<td>To be captured in a filthy body</td>
</tr>
<tr>
<td></td>
<td>reluctantly</td>
<td></td>
</tr>
<tr>
<td>Stress and anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower self-esteem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being reminded of the disease</td>
<td>Prepare for a sweat attack</td>
<td></td>
</tr>
<tr>
<td>Customise the attire to hide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creating possible ways out</td>
<td>Withdraw from close contacts</td>
<td></td>
</tr>
<tr>
<td>Avoiding exacerbating situations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling odd or singled-out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worrying about the first</td>
<td>Worry about other’s perceptions</td>
<td></td>
</tr>
<tr>
<td>impression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noticing others ignorance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support by friends and family</td>
<td>Reveal the condition securely</td>
<td></td>
</tr>
<tr>
<td>Treatment helps</td>
<td>enough</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Living with primary hyperhidrosis

Primary hyperhidrosis is a disease stigmatising the individuals. The stigma from hyperhidrosis is constructed by patients and society through attributes given to hyperhidrosis such as being filthy, nervous or an odd individual. This stigma has an impact on mental health by creating shame, stress and anxiety in situations when there is a risk of being exposed. PH debuts in adolescence when the individual is unaware of the physiological changes that occur to the body. This uncertainty, while being discredited about the disease, leads to low self-esteem and withdrawal. The disease reminds of its presence in social situations when most unwanted thus creating a sense of captivity with difficulties to address the symptoms. While other people do not understand the problems of having excessive sweating, the individual struggles to adapt in social situations and take measures to conceal sweat marks and smell. These indirect measures to hide the disease are both time consuming and create barriers in social interactions. Later in adulthood the barriers that were created in childhood become more cemented. The individual gives up and resigns accepting to live with the disease while suffering quietly. In both men and women with PH there is a delay from the debut till the time of seeking medical help. Diseases affecting the mental health and causing stigma have been described to be responsible for this delay (134). Treatment usually breaks the social barriers created by hyperhidrosis thus removing anxiety and stress which restricts daily life. Stigma remains however until the individual reveals the disease for friends and family which often happens when symptoms are gone.

Qualitative approach and our findings

Interviewing subjects on variations of their experiences living with a disease is useful when there is little known such as in PH. Applying content analysis to the text from our interviews is an obtrusive way of revealing interactions in thoughts and behaviours. Difficulties arise not only in the description but also in the interpretation of data. Data and its interpretation are both influenced by the investigated and the investigator. Purposing sampling is important for the richness of the interviews which is in contrast to quantitative studies where the sample size has to be calculated (135). It is also important to understand that in qualitative studies generalising logics of a phenomenon is the goal rather than generalising a probability to a population (136). Measures to increase the trustworthiness are important but it is finally the reader that determines the transferability of our descriptions and interpretations (137).
Our findings from exploring men’s experiences of living with PH are reinforced by our studies using quantitative methods (paper I-III). In these studies we showed that the disease reduces mental health in both men and women without any significant difference between sexes. We therefore assume that the main findings in our qualitative study may also be transferred to women. Our results from the quantitative studies do not however explain men’s reluctance to seek medical help. The reason for this may be that men and women in adolescence are treated differently when they reveal the disease for others. In some men at young age when they disclosed the disease they were met with ignorance rather than with actual help. If this is also the case in women is not known and we are unaware of any studies investigating the role of early social intervention affecting later contacts with healthcare. Our future study regarding women suffering from PH may shed some light on this matter.

**Measuring quality of life with SF-36**

Measuring quality of life and disease burdens with quantitative methods reveals a general concept on how the disease affects the individuals. By using SF-36 in paper I-III we were able to show that hyperhidrosis reduces quality of life compared to the general population. While other scales such as DLQI would have enabled us to compare PH with other dermatological diseases it must be considered that hyperhidrosis is a disease investigated by a range of specialities in medicine. It can therefore be argued that the disease is not restricted to the field of dermatology and a broad instrument such as SF-36 would be more suitable. At the same time certain items in the SF-36 are less relevant for investigating hyperhidrosis but in the absence of validated hyperhidrosis questionnaires on general health we believe that the SF-36 was the best option.

**Constructing questionnaires**

Validating and testing questionnaires can be challenging. Making items included in a questionnaire may be difficult as many aspects have to be considered. A question such as tobacco use could in theory sound relevant and interesting but issues such as the type of tobacco or what is considered as tobacco may result in unexpected responses. Therefore, seeing actual problems with specific questions before they arise is as important as testing the questions. While experience is a big advantage in constructing surveys, changes could occur in attitudes and views in a society that need different approaches.

Another issue once a survey is constructed and the data is collected can be the amount of data and the value attached to it produced by open-ended items. A question such as “If you could pay yourself free from the sweating problems, how much would it be worth?” resulted in more descriptive answers fitting for
content analysis than monetary units intended for quantitative analysis. Different ways to deal with these unexpected findings are either to exclude the questions from the results by highlighting the aim of the study or to abstract the results to a higher level such as describing those putting a value on being free from the symptoms and those who do not. This was a valuable experience and it is important to look beyond our roles as healthcare professionals since the truth can be different depending on how we perceive the world.

**Postal surveys and the matter of response**

Few investigations regarding the epidemiological data regarding hyperhidrosis have been done in Sweden. Until now no other study has published comparable results for the prevalence of hyperhidrosis from the Scandinavian countries. The response rate to our survey in paper I was not satisfactory. While accepted response rates for postal surveys have been described to be around 65% (138) it is also known that response rates to postal surveys in general are in decline and in some studies not more than 20% (139). There are several measures to increase the response rate from surveys. Random sampling, calculating precision, cover letter with informed consent, validating the survey, using an understandable language and reviewing the items format were all addressed in our study. Investigating unknown diseases associated with stigma is difficult since an absence of the disease might reduce willingness to participate while the opposite may be true for those suffering from the disease. This is a problem for most studies and very difficult or impossible to avoid. Using non-response analysis by considering the non-responders as healthy individuals is one way of addressing this problem. There are however strong ethical considerations on analysing data without consent. Mixed methods such as online and paper surveys have not been able to show an increased response to a survey (140). A reminder may have increased the response rate but not to a much higher level.

An important note is that studies investigating hyperhidrosis exclusively describe a low response but studies embedding hyperhidrosis with other health related questionnaires are able to achieve a much better response. Several attempts were made by us contacting Statistics Sweden and other local researchers for a joint investigation without success. In 2016 we were able to be included in SCAPIS (Swedish Cardio Pulmonary bio Image Study) which will investigate cardiovascular diseases and hyperhidrosis among 30 000 individuals in Sweden. The future results from SCAPIS will add further knowledge of how common hyperhidrosis is and describe possible co-morbidities related to the cardiovascular system (36,37).
There is more than genetics in primary hyperhidrosis

Primary hyperhidrosis debuts in adolescence and we found a significant difference (p<0.01) between the debut age in axillary (15 years of age) and palmar hyperhidrosis (11 years of age) (paper III). This finding has been described by others (18,19) but there has not been any investigation regarding this issue. Although a genetic predisposition for both axillary and palmar hyperhidrosis exists, individuals with axillary hyperhidrosis reported more often signs of peripheral vasoconstrictions (p<0.01) (Paper II). These signs are not the same as Reynaud’s phenomena and there was no significant difference between men and women in our material. It is known that hormonal fluctuations in women in adolescence around the same time as axillary hyperhidrosis debuts could induce peripheral angiospasm (141). This could indicate that in axillary hyperhidrosis there may be causes more than just genes involved for the disease to manifest itself.

Comparing hyperhidrosis according to body sites

Our data from paper III suggest that those with axillary and palmar hyperhidrosis rate the impacts of their symptoms worst. The number of individuals with hyperhidrosis on other body localisations was low in our material but it is also known that PH in the axilla and palms constitutes the majority of cases. Adding individuals with multifocal PH who suffered from sweating on several body sites could have increased the sample but would have made it difficult to interpret the results.

In recent years there has been a debate among colleagues and in general regarding the treatment of PH with botulinum toxin. Since botulinum toxin injections come with a cost it is important to discuss possibilities and limitations regarding this treatment within the state subsidised health care. In the light of our findings and as our data indicate we believe that the system should prioritise individuals with axillary and palmar hyperhidrosis since: 1. Data regarding the characteristics and co-morbidities associated with PH outside palms and axilla is scarce; 2. Axillary and palmar hyperhidrosis constitute the majority of the cases; 3. Those with axillary and palmar hyperhidrosis reported having the greatest impacts on daily life; 4. There are no randomised controlled trials supporting large gains in quality of life in the treatment of uncommon sites of the body with botulinum toxin; 5. There is no indication for botulinum toxin A or B from FDA (US Food and Drug Administration) or EMA (European Medicines Agency) for treatment outside the axillary region.
These arguments should however not automatically exclude individual cases when the law of “no rule without exceptions” will apply and each case has to be evaluated individually. Therefore, more research is needed until en masse recommendations are made regarding patients with PH on uncommon sites of the body.

**Treatment with botulinum toxin A and its (non) response**

Treatment of PH with botulinum toxin A is effective and the majority of the patients were satisfied with the duration of the effect. In palmar hyperhidrosis anaesthesia is necessary and peripheral nerve blocks were used to reduce the pain from the botulinum toxin injections. The nerve blocks contributed to weakness in fingers and wrists which was temporary but inconvenient. Other methods such as cooling, anaesthetic gels and oral medications have been used but none of them offer total pain removal from the injections. Some patients even choose treatment without any anaesthetics. It is therefore important to be humble regarding the patient’s wish in pain reduction and use a method with minimum side-effect.

Some patients may also experience no response (Primary non-responders) or a partial response (Secondary non-responders) to botulinum toxin A injections. In our clinical experience this happens seldom but when it occurs it causes difficulties for the care giver and the patient on how to proceed. While primary non-responders are extremely uncommon due to pre-existing neutralising antibodies against the botulinum toxin, it has been described that these antibodies have only been detected in roughly 50% of secondary non-responders (142). Factors (143) such as: handling the drug (safe-keeping, diluting), the particular drug used (manufacturing, amount of inactive toxins in the vial, accessory proteins and excipients), dose and treatment interval (cumulative dose, previous booster injections and treatment earlier than 2 months apart) and previous exposure (vaccination against botulinum toxin in US military personal or hypothetically tetanus vaccine with a similar structure to botulinum toxin) should be considered causing a secondary non-response. A test for serum antibodies is available only in research. We therefore suggest that these issues are taken into consideration before suspecting immunity to botulinum toxin. Other practical measures used by us in assessing non-response consist of sweat provocation test, re-treatment with the same product, treatment with another botulinum toxin type A, using botulinum toxin type B and testing muscle paralysis in the forehead.
Conclusions

This thesis contributes with new knowledge on primary hyperhidrosis and how the disease affects the individuals. Our results and conclusions could aid decision makers, those affected and the care-givers in approaching and managing PH. Our specific conclusions and recommendations are:

- The prevalence of PH is 5.5 % in Sweden and severe PH was reported in 25 % of the cases. In hyperhidrosis the primary form is more common in adolescence while the secondary form becomes more frequent with increasing age. The disease reduces quality of life and interferes with daily activities. The impacts on quality of life measured by SF—36 showed that PH mainly reduces the mental health while SH impacts on both mental and physical health.

- Axillary hyperhidrosis debuts later and we found that signs of peripheral vasoconstrictions were more often reported in axillary hyperhidrosis compared to persons with palmar hyperhidrosis. In PH anxiety, depression, tobacco and alcohol consumption were quite similar compared to the general population. Treatment with botulinum toxin A had a significant effect on reduction of the symptoms and the interferences of PH on daily life while increasing the overall quality of life. Signs of depression, stress and anxiety were also significantly reduced by this treatment.

- Persons with palmar and axillary hyperhidrosis without co-morbidities rate their symptoms as more severe and report a much higher impact on their quality of life compared to persons with hyperhidrosis elsewhere.

- The outcome of interviews and content analysis in 15 men with PH was the theme: *To be captured in a filthy body.* Our interpretation from these experiences is that PH is stigmatising and stigma reduces the mental health reinforcing our earlier findings. Addressing hyperhidrosis early and specifically targeting young people with information could reduce the stigma and enable early intervention via healthcare.
Future perspectives

The number of patients with PH seeking healthcare will increase and it is important to discuss priorities and evolve new strategies in managing this patient group. The disease debuts early and there is a great delay until individuals become aware that help exists. Informing the public about the disease and the role of healthcare in managing hyperhidrosis should therefore be a priority. While botulinum toxin is the treatment of choice for most patients there is still a need for new treatments that are safe, cost-effective and increase quality of life. There are also many questions in hyperhidrosis which require further research. A question such as if PH is a symptom of other diseases debuting much later or if PH occurs prior to SH is interesting and relevant. One way to answer these questions is long-term access to individual data and a hyperhidrosis registry. We are already involved in the investigation of hyperhidrosis on several fronts from changes on cellular level to hyperhidrosis in elderly. Data obtained from these studies would make us understand the disease better and possibly alter the management of the patients.
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My mother, father, brother and sister
For your love and support.
Ladan, Gabriel and Isabell

For your love, care and letting me be a part of your life. Our best adventures are yet to come.
**References**


34. Leachman SA, Kaspar RL, Fleckman P, Florell SR, Smith FJ, McLean WH, Lunny DP, Milstone LM, van Steensel MA, Munro CS, O'Toole EA, Celebi JT,


45. Shayesteh A, Boman J, Janlert U, Brulin C, Nylander E. Primary hyperhidrosis: Implications on symptoms, daily life, health and alcohol


136. Popay J, Rogers A, Williams G. Rationale and standards for the systematic review of qualitative literature in health services research. *Qual Health Res.* 1998; **8**:341-351.


Appendix

Hyperhidrosis Detecting Questionnaire

Code nr._____________

Instructions

Mark an X where you think that the response option fits best with your answer. Some possible answers are marked with a blank line where you can fill in the answer.

Gender: □ Man □ Woman Age: __________ years

1. In what type of relation do you live?

□ Married/Partner □ Living apart together □ Single

□ Other____________________

2. What do you do?

□ Work □ Study □ Unemployed □ Sick leave

□ Other____________________

3. a) Do you use tobacco (snuff, smoke)?

□ Yes □ No

b) If yes:

□ I use tobacco daily

□ I use tobacco each week but not daily

□ I use tobacco sometimes but not each week

4. What do you consider as normal sweating? (Choose one or several alternatives)

□ Sweating during daily activities

□ Sweating during physical activities
□ Sweating at rest
□ Sweating during the night
□ Sweating in childhood (<18 yrs.)

5. Have you in the past week had problems with increased sweating?
□ Yes □ No

6. Have you in the past six months had problems with increased sweating?
□ Yes □ No

If you have answered No to question 5 and 6 please proceed to the health survey SF-36.

7. a) Did your sweating problems start after intake of medications?
□ Yes □ No □ Don’t know

b) What was the medication you took before the start of your sweating problems?
□ Heart/blood pressure medications □ Analgesics
□ Anxiety or depression medications □ Herpes or other antiviral medications
□ Antibiotics □ Antacids or stomach ulcer medications
□ Diabetes medications □ Thyroid gland hormones
□ Allergy medications □ Anti inflammation medication
□ Other________________________

8. Do you have any illnesses?
□ Yes (please describe what/which):________________________
□ No, I am healthy

9. Where on the body do you have most trouble with excessive sweating? (Choose one option)
□ Hands □ Armpits □ Feet □ Face □ Other________________________

10. Do you have excessive sweating on other parts of your body??
□ Yes (Choose one or several options)
□ Hands □ Armpits □ Feet □ Face □ Other________________________
□ No
11. Is there anyone in your family who also suffer from excessive sweating?

☐ Yes  ☐ No  ☐ Don’t know

12. How old were you when the sweating problems started?

______________ years

13. Do you sweat regularly at nights on specific parts of your body?

☐ Yes (Choose one or several options)

☐ Hands ☐ Armpits ☐ Feet ☐ Face ☐ Other______________

☐ No

14. What worsen your sweating problems?

☐ Heat  ☐ Alcohol  ☐ Tobacco  ☐ Food  ☐ Stress  ☐ Drugs

☐ Other_______________________

15. Have you been in contact with healthcare or received any treatment for your sweating problems?

☐ Never seeked help or healthcare.

☐ Seeked healthcare but never received any treatment.

☐ Seeked healthcare and received treatment.

16. How would you rate the severity of your hyperhidrosis?

☐ My sweating is never noticeable and never interferes with my daily activities

☐ My sweating is tolerable but sometimes interferes with my daily activities

☐ My sweating is barely tolerable and frequently interferes with my daily activities

☐ My sweating is intolerable and always interferes with my daily activities
Hyperhidrosis specific questionnaire

Pre-treatment questionnaire

Code nr: ________

□ Male           □ Female       Age: ________

1. Where are your worst symptoms of increased sweating located? (Mark 1 as the worst, 2 as next etc.)
   □ Feet           □ Hands         □ Axilla       □ Face         □ Other, where?

2. Does anyone else in your family suffer from increased sweating?
   □ No             □ Yes           □ Unknown

3. How old where you when your sweating problems started? ________ years

4. Do you suffer from any illness?
   □ No, I am healthy
   □ Yes, I have other illnesses which are: __________________________________________

5. Do you get white (and cold) fingertips and toes for example when temperature changes or you are emotionally affected?  □ No       □ Yes

6. What do you consider worst about your sweating problems?
   _______________________________________________________________________

7. Do you use any kind of tobacco? □ No             □ Yes________________________

8. The next questions are regarding your actual problems of sweating. Choose one alternative for each question in the table below

<table>
<thead>
<tr>
<th>My sweating(s) create problems with</th>
<th>Not at all</th>
<th>Little</th>
<th>Much</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touching/holding hands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writing on a paper</td>
<td></td>
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<td>Wearing/using gloves</td>
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<td></td>
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<tr>
<td>Wearing/ using clothes such as a thin shirt/light underwear</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>My sweating symptoms have disturbed/affected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work/studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9. Use the scales and mark the severity of your actual sweating symptoms.

<p>| | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

**Hands**

No symptoms  Intolerable symptoms

**Feet**

No symptoms  Intolerable symptoms

**Axilla**

No symptoms  Intolerable symptoms

**Other localisations**

No symptoms  Intolerable symptoms

**All localisations on my body**

No symptoms  Intolerable symptoms

10. How do you rate the severity of your hyperhidrosis?
☐ My sweating is never noticeable and never interferes with my daily activities
☐ My sweating is tolerable but sometimes interferes with my daily activities
☐ My sweating is barely tolerable and frequently interferes with my daily activities
☐ My sweating is intolerable and always interferes with my daily activities

11. If you could “buy yourself free” from the sweating problems, how much would it be worth?
☐ Less than a month’s salary
☐ A month’s salary
☐ Three month’s salary
☐ A year’s income
☐ Everything I own
☐ Other_______________________________________________________________

12. Do you have any additional comments?
____________________________________________________________________

Post-treatment questionnaire

Code nr: __________
☐ Male           ☐ Female           Age: __________

1. Where on your body have you been treated?
☐ Hands         ☐ Axillas          ☐ Feet           ☐ Face           ☐ Other, where?________________

2. Did the treatment reduce your sweating problems?
☐ Yes, completely ☐ Yes, partially ☐ No, not at all

3. Which of these symptoms were reduced?
☐ No symptoms at all ☐ Production of sweat ☐ Sweat odour
☐ Difficulties choosing clothes ☐ Stress ☐ Anxiety ☐ Freezing
☐ Other

____________________________________________________________________

4. How would you rate the severity of your hyperhidrosis?
☐ My sweating is never noticeable and never interferes with my daily activities
☐ My sweating is tolerable but sometimes interferes with my daily activities
☐ My sweating is barely tolerable and frequently interferes with my daily activities
My sweating is intolerable and always interferes with my daily activities

5. Did the treatment fulfil your expectations?

0 1 2 3 4 5 6 7 8 9 10

Not at all Absolutely

6. What was the best thing with your treatment?

____________________________________________________________________________

7. Did you have any side effects from the treatment?

□ No

□ Yes:

____________________________________________________________________________

8. Would you recommend the treatment you received to a friend?

□ No

□ Yes

□ Not sure

9. Choose an alternative answer in the table below. The questions regard your sweating for the moment:

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<tr>
<td>My social life</td>
</tr>
<tr>
<td>My work/studies</td>
</tr>
<tr>
<td>Relationship to my partner</td>
</tr>
<tr>
<td>Relationship to my family</td>
</tr>
</tbody>
</table>
Abstaining from activities I would have wanted to participate in

<table>
<thead>
<tr>
<th>My sweating symptoms have made me feel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stressed</td>
</tr>
<tr>
<td>Depressed</td>
</tr>
</tbody>
</table>

10. Use the scales and mark the severity of your sweating symptoms as they are for the moment.

<table>
<thead>
<tr>
<th>Hands</th>
<th>0 1 2 3 4 5 6 7 8 9 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Intolerable symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feet</th>
<th>0 1 2 3 4 5 6 7 8 9 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Intolerable symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Axilla</th>
<th>0 1 2 3 4 5 6 7 8 9 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Intolerable symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other localisations</th>
<th>0 1 2 3 4 5 6 7 8 9 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Intolerable symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All localisations on the body</th>
<th>0 1 2 3 4 5 6 7 8 9 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Intolerable symptoms</td>
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12. Do you have any additional comments?