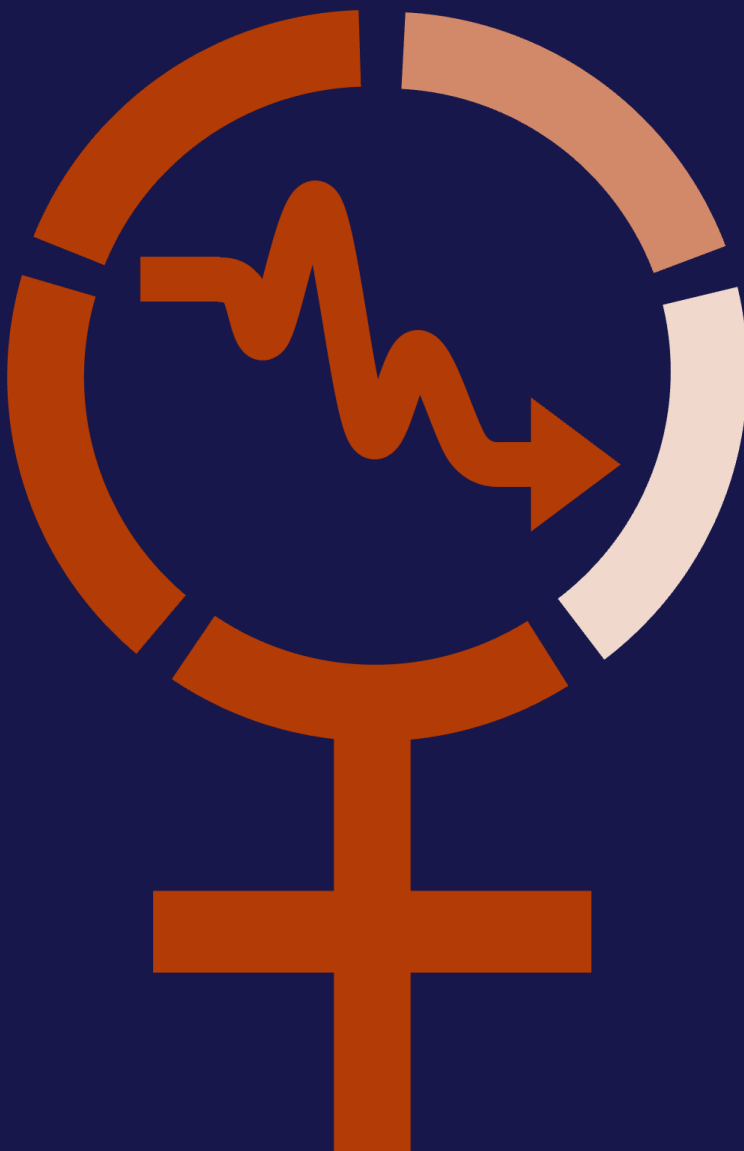



Productivity loss related to vasomotor symptoms (VMS) during menopausal transition among women in the Nordics

Chiara Malmberg, Rikard Althin
Sara Olofsson





PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

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Foreword

Vasomotor symptoms (VMS) occur in the majority of women during menopause and are the primary symptoms women seek treatment for during this time. The most common symptom are hot flushes and night sweats which vary in frequency and severity. Moderate to severe VMS have been shown in the literature to have a significant impact on productivity as they are experienced by women during their most productive years.

This report intends to raise awareness of the size of the burden of moderate to severe VMS in form of lost productivity. This includes both reduced productivity while at work (presenteeism) and absence from work (absenteeism). There is little information published in this area, and even less so specific for the Nordic countries.

The analysis in this report builds on a pragmatic literature review on productivity loss and prevalence of moderate to severe VMS, as well as employment and labour cost statistics from public European statistics.

Results are presented for each of the Nordic countries. Neither direct costs for health care visits and medication, nor the reduction in quality of life, were included for a complete burden of illness. The report also identifies a large knowledge gap around the menopausal transition on women, especially for the Nordics.

The report was funded by Astellas. Responsibility for the analysis, interpretations, and conclusions, as well as errors or omissions lies solely with the authors.

Lund, June 2024

Peter Lindgren
Managing Director, IHE

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Summary

Menopause, or the cessation of menstruation, is a biological process which occurs in all women. It marks the end of a woman's reproductive years and natural menopause usually occurs between the ages of 45 to 55 years, with a mean age of 52 years. Menopause is recognised to have occurred when menstruation has ceased for 12 consecutive months.

Menopause is associated with a number of symptoms which all can significantly impair women's quality of life. The most common symptoms are vasomotor symptoms (VMS) such as hot flushes and night sweats. Affecting women in their productive years, these symptoms lead to a significant burden in the form of productivity loss due to absence from work (absenteeism) and impairment while at work (presenteeism). Up until now, there is a lack of studies examining this burden in the Nordic countries.

The objective of this study was to estimate the productivity loss of women with moderate to severe VMS during menopausal transition in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden).

Costs that were calculated include those occurring due to absence from or impairment at work. Estimates on missed days from work, impaired time while at work and prevalence of moderate to severe VMS were derived from a study of VMS including Nordic countries (Todorova et al.). Information on work time, employment and labour costs were derived from public European statistics.

- The estimated annual number of hours of productivity loss, including absenteeism and presenteeism due to moderate to severe VMS, varied from approximately 95 hours in Denmark to 165 hours in Norway.
- Impairment while at work accounted for the larger share of hours, with 65% in Denmark and 80% to 90% in the other countries.
- Annual per person costs for this productivity loss varied from approximately €4,600 in Denmark to €8,700 in Norway.
- Annual population costs varied from approximately €13 million in Iceland to €290 million in Norway.
- For all the Nordic countries together, the annual population costs amount to approximately €865 million.

This study has shown that moderate to severe VMS in menopausal women leads to an economic burden related to productivity loss in the Nordic countries, resulting in a loss of on average 2.5-4 weeks per postmenopausal woman per year. This translates to 1-2% of the annual work time spent absent from work, and 4-10% of annual work spent impaired at work due to VMS. There is a potential for reducing the burden associated with moderate to severe VMS to the benefit both to the society and to the individual woman.

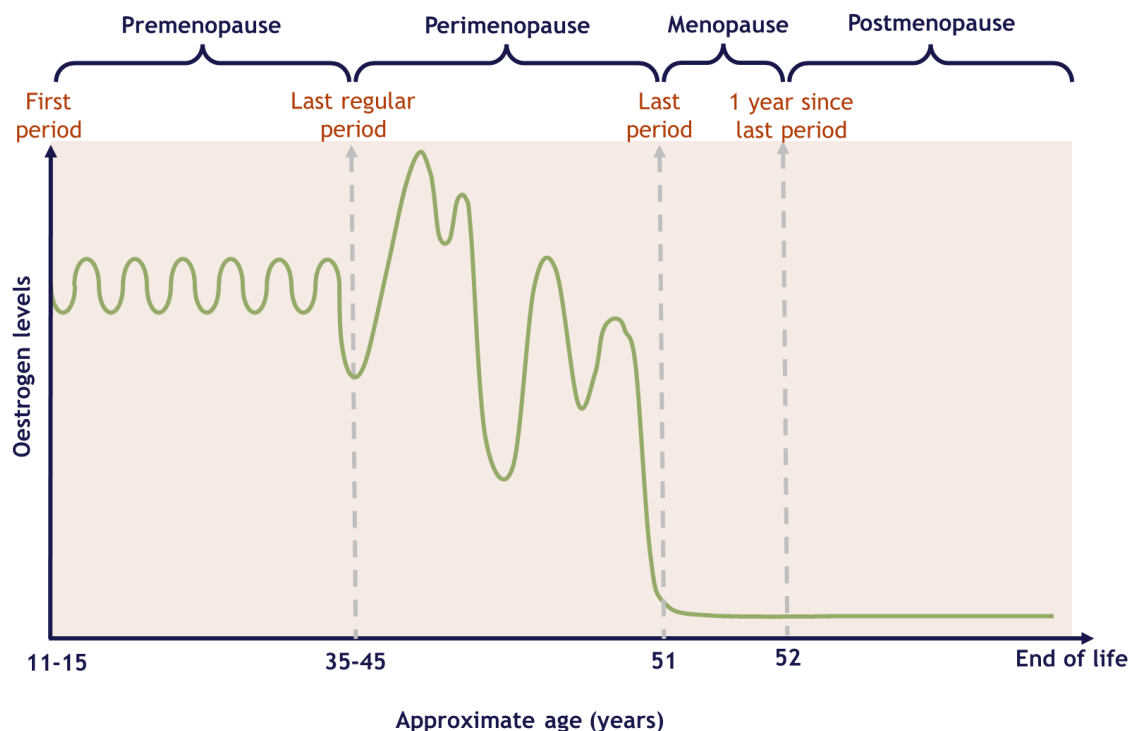
1. Background

1.1 Menopause

Menopause, or the cessation of menstruation, is a biological process which occurs in all women (1). It marks the end of a woman's reproductive years and is caused by the loss of ovarian follicular function as well as a decline in circulating blood oestrogen levels (2). It is associated with a number of symptoms, including hot flushes, night sweats, mood changes, sleep disturbances, and vaginal dryness, which all can significantly impair women's quality of life (2).

Natural menopause usually occurs between the ages of 45 to 55 years (2), with a mean age of 52 years (3). It is recognised to have occurred when menstruation has ceased for 12 consecutive months (1). Menopause can also be caused by surgical or medical procedures (1, 2).

Menopause can be divided into several stages. According to the European Menopause and Andropause Society (EMAS), premenopause is referred to as the reproductive period before the menopause. Perimenopause is the time of onset of clinical, biological and endocrinological symptoms indicating the approach of menopause. It includes vasomotor symptoms (VMS) and menstrual irregularity and ends 12 months after the final menstrual period (FMP). Perimenopause only occurs in natural menopause. Finally, postmenopause encompasses the time from the FMP (1). Menopausal transition includes perimenopause, menopause, and postmenopause (see Figure 1).

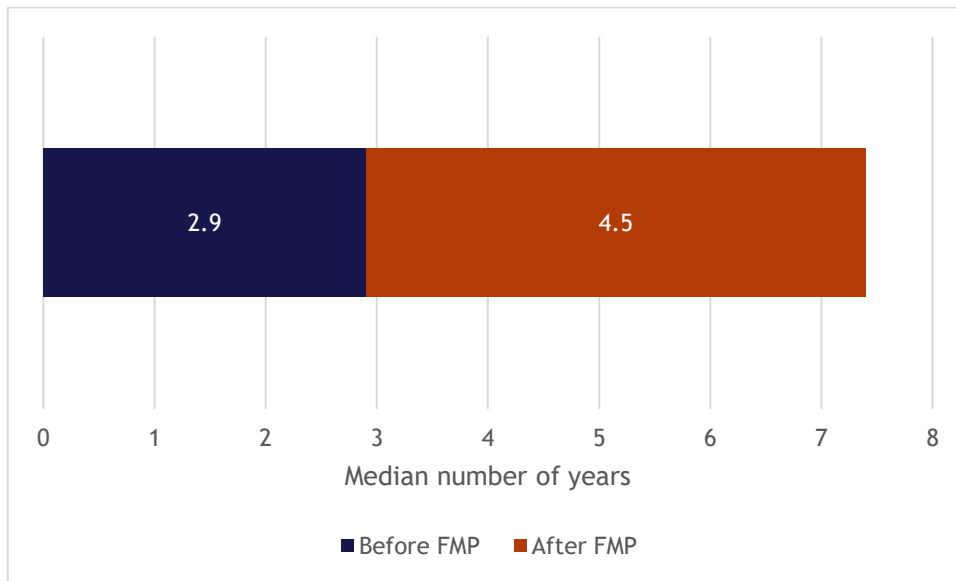


Adapted from My Menopause Center (4)

Figure 1 Menopause transition

1.2 Vasomotor symptoms (VMS)

Vasomotor symptoms, characterised by hot flushes and night sweats, are the most common menopausal symptoms (1). Hot flushes refer to a sudden feeling of heat in the face, neck and chest which are often accompanied by the flushing of the skin, sweating, palpitations as well as sudden feelings of physical discomfort. These symptoms can last for about half an hour per episode and a woman may experience several episodes a day (2). Presence of VMS has been reported to last 7-10 years (5, 6), with a median persistence of 7.4 years and a median of 4.5 years after FMP (6). Duration of VMS is also impacted by the time of occurrence of first symptoms: the longest duration, a median of 11.8 years, was observed in women who reported their first frequent symptoms during pre- or early perimenopause (6).



Based on Avis et al. (6)

Figure 2 Median number of years with vasomotor symptoms before and after final menstrual period (FMP)

1.2.1 Treatment

Treatment recommendations for the treatment of menopause-associated VMS have been published by the Endocrine Society (7) and EMAS (1).

Menopausal hormone therapy is considered an effective treatment for VMS associated with menopause (1, 7). It aims at replacing oestrogen, and its main components are oestrogen and progestogens (1). Women who have had a hysterectomy are usually offered hormonal therapy based on oestrogen-only therapy. For women who have not had a hysterectomy, progestogens are added to reduce the increased risk of endometrial hyperplasia and cancer (1). Treatment duration is usually approximately five years. However, it is difficult to predict for each individual woman whether they will be symptom-free when stopping treatment or not (1).

The benefits of menopausal hormonal therapy are, apart from the management of VMS symptoms and the improvement in quality of life, the improvement in cardiovascular and bone health. Particularly when initiated before the age of 60 years or during 10 years since the onset of menopause, hormonal therapy is considered to outweigh the risks (7-9).

Hormonal therapy is associated with an increased risk of breast cancer (1, 10). However, the risk attributable to hormone therapy is small and decreases once treatment is ended (1). Nevertheless, the individual risk for each woman should be considered prior to commencing therapy (7). There is inconsistent evidence with regard to the risk of dementia (1, 11).

Non-hormonal pharmacological therapy of VMS is recommended for women with moderate to severe VMS for whom hormonal therapy is contraindicated or who do not want to take hormonal therapy. Recommended agents include clonidine, paroxetine, citalopram, venlafaxine, desvenlafaxine, gabapentin and pregabalin, although these treatments tend to be less effective than hormonal therapy (1, 12). Recently, fezolinetant has been approved for the treatment of moderate to severe VMS (1, 13).

In women with less bothersome symptoms, non-pharmacological measures such as lifestyle changes, turning down the thermostat, avoiding alcohol or dressing in layers can be considered (7). Cognitive behavioural therapy may also be an effective treatment for VMS (1, 12).

1.2.2 Burden of VMS

Vasomotor symptoms occur throughout the day and have a significant impact on the quality of life and ability to work of women in menopausal transition. Due to the unpredictable nature of the occurrence, particularly women in employment are negatively impacted.

1.2.2.1 Quality of life impact

There are multiple studies which have reported on the negative impact of VMS on the quality of life of women in menopause. In a Latin American cohort, VMS of any degree were associated with a higher impairment in quality of life and the effect was even higher in women presenting with severe VMS (14).

Two studies reported quality of life impact as measured by the generic and preference-based instrument for measuring health-related quality-of-life (HRQoL), the EQ-5D. One was a large US survey in women reporting menopausal symptoms. Participants reported significantly lower levels of HRQoL, compared to women with no symptoms (no symptoms: 0.86, severe symptoms: 0.77, $p < 0.0001$) (15). This is aligned with another multinational cross-sectional survey investigating the burden of VMS. In a pooled analysis of five European countries (France, Germany, Italy, Spain and the UK) it was shown that women with VMS had significantly worse health utility scores compared to women without VMS. This relation increased with increasing severity of the symptoms (16).

Quality of life as measured with the Menopause-Specific QOL (MENQOL) instrument was presented in two additional studies (17, 18). The first study was conducted in a European cohort of postmenopausal women with moderate to severe VMS. The most common symptom reported in this study was 'Feeling tired or worn out'. Other frequently reported symptoms included hot flushes, sweating and night sweats. Women experienced a mean of 4.6 hot flushes and/or night sweats of any severity per day. Women more frequently experienced moderate (2.9) or severe (2.6) hot flushes and/or night sweats (17). The second study was also conducted as a survey in European (the UK, France, Germany, Italy and Spain) as well as US women. The overall mean MENQOL score (rated from 1=not experienced in the past month to 8=extremely bothered) reported was 2.5, with the highest mean score reported in the vasomotor domain (3.5). Moreover, overall and domain scores were higher in women with moderate/severe VMS (overall: 2.7-3.1; vasomotor domain: 3.9-4.7; physical domain: 2.5-2.9; psychosocial domain: 2.6-3.0;

sexual domain: 3.0-3.3) compared to women with mild VMS (overall: 2.1; vasomotor domain: 2.6; physical domain: 2.0; psychosocial domain: 1.9; sexual domain: 2.2) (18).

Additionally, there were two willingness-to-pay (WTP) studies conducted in women with menopause-related VMS. In a discrete choice experiment (DCE) based on an online survey, it was found that the WTP for substantially improved sleep, 80% reduction in VMS frequency and reduction in VMS severity from severe to mild was 35-46 \$/month (19). Another willingness-to-pay study conducted in Germany found that women currently receiving treatment for symptoms were willing to pay 24€ to 42€ per month for a new non-hormonal treatment. For the overall study population, the willingness-to-pay was 17€ to 35€ per month (20).

In summary, the literature is indicative of the burden on quality of life that VMS have for women in menopause. This burden appears to increase even further when specifically considering women with VMS of higher severity.

1.2.2.2 Work and economic impact

A review of the literature found that the majority of studies examining the relationship between menopausal symptoms and performance at work find a negative relationship. Moreover, this relationship was found to be more pronounced, the more severe the symptoms were reported to be (21).

Regarding work impairment, there are multiple studies reporting a negative impact of VMS. One study found the number of menopause symptoms faced by women at the age of 50 years to be associated with lower employment rates. Moreover, it was found that the more bothersome symptoms women experienced, the higher was the impact on their employment (22). A community-based cohort study in the UK reported that one-third of women had moderate or severe difficulties coping at work due to menopausal symptoms. The most prevalent of the reported symptoms were VMS (reported by 92% of the women) (23). A cross-sectional study conducted in women with moderate to severe VMS in the US, the UK and France found that VMS also impacted sleep due to interruption by sweating or overheating. Study participants experienced this to be the most bothersome aspect of VMS. Furthermore, as a consequence of sleep disturbance due to VMS, functioning the following day was impacted, including work productivity (24). Lastly, a cross-sectional study conducted in Irish hospital workers identified a significant association between severity of VMS at work and reduced work performance, career development decisions and attendance (25).

Vasomotor symptoms are also related to an increase in economic burden, both due to additional health care visits to treat menopause-related symptoms as well as productivity loss due to impaired work. A systematic literature review conducted to identify studies reporting evidence of work impairment in women with VMS identified three relevant studies (26). Firstly, in a large American survey, women with menopausal symptoms reported higher work impairment as measured by the Work Productivity and Activity Impairment (WPAI) questionnaire (Box 1) compared to women who did not report any symptoms. Presenteeism for women with mild, moderate and severe VMS was reported to be 4.04%, 14.46% and 24.28%, respectively (on a scale from 0% representing no impact to 100%, totally impaired). Healthcare utilization in the form of menopause symptom-related physician visits was also significantly greater among women with mild, moderate and severe symptoms compared to women without any symptoms (15). A similar observation was reported in another multinational cross-sectional survey investigating the burden of VMS, a pooled analysis of five European countries (France, Germany, Italy, Spain and the UK) showed that women with VMS, regardless of their symptom severity,

reported significantly more menopause-related physician visits compared to women without VMS (16). Secondly, a retrospective matched-cohort study conducted in the US and evaluating the direct and indirect economic burden of VMS found that women with untreated VMS had significantly higher health care resource utilization compared to women without VMS. The study found that mean direct costs (including pharmacy dispensing as well as outpatient, inpatient, emergency and other visits) per person per year were \$1,346 higher for women with VMS. The annual incremental indirect cost (including disability and medically related absenteeism) per person were \$770 higher in women with untreated VMS (27). Thirdly, a retrospective claims database analysis conducted in the US found that women with diagnosed menopause symptoms had significantly higher medical (\$4315 vs \$2972, $P < 0.001$), pharmacy (\$1366 vs \$908, $P < 0.001$) and sick leave costs (\$647 vs \$599, $P < 0.001$), compared to their controls (28).

Box 1.

The WPAI (Work and Productivity Impairment Questionnaire) is a questionnaire encompassing six questions related to current employment, missed hours from work in the past seven days as well as hours worked in the past seven days. Levels of impairment are reported on a scale from 0 to 10, with 0 indicating no effect on work activities/impairment and 10 completed prevention of activities/work. This scale is then converted to proportions between 0% and 100%. Results of the WPAI are reported as percentages of work hours missed (absenteeism) and impaired while working (presenteeism) during the past week as well as overall work and daily activity impairment (29, 30).

In summary, there is a significant impact on work productivity and related costs due to moderate to severe VMS, as they are experienced by females in their most productive years (15, 17, 31). The primary impact is in terms of reduced productivity while at work (presenteeism) but also includes time taken off from work (absenteeism). This has consequences for the individual in terms of stress, reduced income, and career prospects but also for the wider society in terms of lost productivity resulting in reduced output. Although the impact on work productivity has been shown in several studies (15, 17, 22-25, 31), few studies estimating the monetary burden associated with this consequence are available. In the available literature, there is also a lack of estimates for the Nordic countries. Results of the studies that are available may not be transferable to other country settings due to differences in prevalence and impact on work. Monetizing disease burden is a standard procedure to make a condition visible, interpretable, and comparable to other conditions. A monetary figure can help inform the debate, policy-making, and future health economic evaluations.

2. Objective

The objective of this study was to estimate the productivity loss of women with moderate to severe VMS during menopausal transition in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden).

Box 2.

Menopausal transition

Referred to all phases of menopause, i.e. perimenopause, menopause and postmenopause. However, due to a lack of data on the prevalence of VMS in perimenopause and menopause, this study only includes women in postmenopause.

Moderate to severe VMS

In line with US FDA definitions, moderate VMS were defined as having a sensation of heat with sweating and the ability to continue an activity. Severe VMS were defined as having a sensation of heat with sweating causing the cessation of an activity (32).

Productivity loss

Referred to the absence from work (absenteeism) as well as impairment while at work (presenteeism).

3. Methods

3.1 Data collection

Data collection was conducted in two steps. Firstly, epidemiological and productivity loss estimates were identified in a literature review. Secondly, statistical information on labour costs and work time in the Nordic countries were collected.

3.1.1 Literature review

A targeted literature review was conducted to identify two sets of inputs for the estimation of productivity loss: epidemiological estimates (i.e. prevalence and incidence estimates) as well as estimates of productivity loss of moderate to severe VMS in menopausal women.

Searches were conducted in March 2024 and included disease terms in English and local languages. Databases included PubMed and Google to identify both peer-reviewed and grey literature publications and no time restrictions on the publication of the studies were set.

Regarding the epidemiological inputs, studies were included if they were conducted in menopausal women in any of or all the Nordic countries who experienced moderate to severe VMS.

For studies concerning productivity loss, studies from any country were included, although studies from Nordic countries were preferred. However, due to the expectation that few such studies have been conducted in the Nordic countries, the geographic scope covered all countries. Furthermore, to be included, studies had to report estimates on productivity loss, specifically as numerical estimates for absenteeism or presenteeism.

3.1.2 Employment statistics

Statistical input data including information on salaries and social contributions, employment rate and working hours (part-time and full-time work) were collected for each of the Nordic countries specifically. Data was derived from relevant national or international statistical authorities.

3.2 Model for the calculation of productivity loss

This was a study to estimate the productivity loss of women with moderate to severe VMS associated with menopause. As opposed to direct costs which include resources that are required for the treatment and care due to an illness (both medical and non-medical), this study focused on indirect costs which occur due to decreased work ability caused by the illness. This study included both productivity loss due to absence from work (absenteeism) and impaired productivity while working causing a person to be unable to work at their full capacity (presenteeism).

This study took a prevalence approach (annual perspective), meaning costs were calculated for one year for all persons experiencing moderate to severe VMS regardless of if they had recently become postmenopausal or had been so for many years. The alternative would have been an incidence approach (lifetime perspective) for which costs are calculated from the time a cohort of persons starts experiencing moderate to severe VMS until the time the symptoms disappear. In general, the incidence approach presents results that can be used in a cost-effectiveness

analysis as it shows the total costs of a disease for one person over time. This would, however, be particularly relevant when a measure changes something today which has consequences for the person's remaining lifetime with the disease. Given the available data, an incidence approach was, however, not feasible. Additionally, the focus of this analysis was to estimate the size of the total annual indirect cost burden of moderate to severe VMS which may be better represented by a prevalence approach.

The productivity loss was calculated based on the human capital approach (33), including absenteeism and presenteeism. Absenteeism, or absence from work, was valued as gross hourly wage or salary and social contributions (corresponding to the cost to the employer which is assumed to represent the value of employee's work).

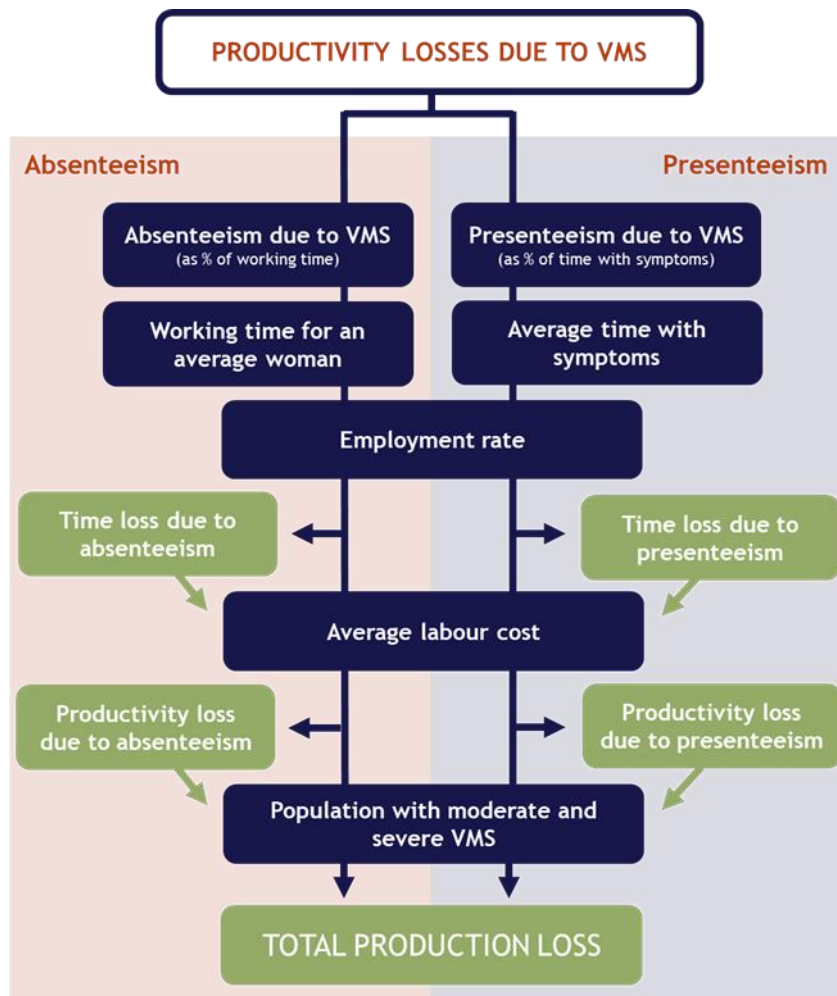
Presenteeism, or work impairment, was calculated similarly to absenteeism; however, as opposed to absenteeism, there were two possible alternatives to the determination of presenteeism which have both been previously used. This was due to two possible ways of interpreting the information on work impairment gathered by the WPAI (see Infobox in section 1.2.2.2). The first approach assumes that the percent work impairment represents the share of impaired working hours and valued with an hourly cost. Presenteeism is then calculated based on the following formula:

Equation 1 *presenteeism* = % *work impairment* × *working time* × *hourly labour cost*

For the second alternative, the percent work impairment is assumed to represent the percent of impairment while experiencing symptoms. For this second alternative, additional information on the impaired time is needed (e.g., frequency and duration of symptoms). Presenteeism is then calculated based on equation 2 below. For the analysis at hand, the second approach has been chosen as it was considered more conservative.

Equation 2 *presenteeism* = % *work impairment* × *time with VMS* × *hourly labour cost*

The price level of the costs represented the year 2023. An illustration of the calculations is presented in Figure 3.



Blue boxes refer to model parameters, green boxes refer to calculated results. The calculations follow a step-wise process, i.e. the boxes build on and feed into each other.

Figure 3 Productivity loss calculation flow

3.3 Model parameters

Productivity loss based on absenteeism and presenteeism was calculated as depicted in Figure 3. The parameters of the calculation are presented separately in the following sections.

3.3.1 Parameter: Average working time

Information on working time was derived from Eurostat. The number of part-time and full-time employees (34) and their actual hours worked (35), were used to adjust the weekly working time. For the number of part-time and full-time employees, data were derived for females specifically, in the age group 40 to 64 years. The number of part-time and full-time employees was converted to a proportion of the total working female population in order to calculate the average working time for female employees weighted by part-time and full-time employment. Regarding the average working hours, these were derived for the age group 20 to 64 years, as they were not available for the age group of 40- to 64-year-olds. However, upon comparing other available age groups (i.e. 35-49 years, 55-64 years, 50+ years), there were only slight differences in hours and thus the average working hours used for this calculation may be representative for the age group of 40-65 years as well.

The number of working days for each country was derived by subtracting weekends, bank holidays and legal vacation days from the number of days per year.

All inputs are depicted in Table 1 below.

Table 1 Work time

	Denmark	Finland	Iceland	Norway	Sweden	Reference
Proportion working full-time	82%	87%	83%	84%	82%	Eurostat (34)
Proportion working part-time	18%	13%	17%	16%	18%	Eurostat (34)
Actual working hours - part-time	21.7	21.1	22.7	20.8	25	Eurostat (35)
Actual working hours - full-time	36.5	35.7	37	35.9	37.5	Eurostat (35)
Actual working hours*	33.85	33.67	35.41	34.69	33.23	Weighted average of actual working hours of part-time and full-time employees
Workdays per year	222	218	224	226	223	

3.3.2 Parameter: Employment rate

The employment rate for each country was derived from Eurostat (36) to adjust work time to be applicable to an average women. The employment rate was derived specifically for females of the ages 20 to 64 years, Table 2.

Table 2 Employment rate

	Denmark	Finland	Iceland	Norway	Sweden
Employment rate	77.00%	78.10%	82.10%	77.80%	80.30%

Source: Eurostat (36)

3.3.3 Parameter: Absenteeism and presenteeism

In the literature review for productivity loss, nine publications were identified which reported estimates for absenteeism and presenteeism (15-18, 31, 37-40) (see Table A-2 in the appendix).

Except for one study which was a pooled analysis of two RCTs (37), all studies were conducted with a cross-sectional or survey design.

Regarding the geographic scope, only one study was conducted in the Nordic countries (31). The remaining studies were conducted in other European countries, the US, Canada and Japan.

Publications presented with variations in included populations with regard to age, with the widest age range covering the interval from 40 to 75 years (15, 16). Additionally, definitions of menopause varied between studies: One study applied the Stages of Reproductive Aging Workshop (STRAW) criteria (a nomenclature and staging system to define ovarian aging) (39) while all other specified phases relative to the cessation of menstrual bleeding (e.g., post-menopause was defined as the cessation of menstrual bleeding for at least 12 months). Except

for one study, which only included women in menopause (18), all studies included postmenopausal women or peri- and postmenopausal women.

The measurement instrument of productivity loss was the WPAI questionnaire in the majority of studies. Most of these studies used a modified version of the WPAI which specifically asked about the impact of VMS (WPAI-VMS) (15-18, 31, 37, 38, 40). Only one study used the Work Ability Index (WAI), an instrument for self-assessed work ability whose results are presented as low, moderate, good and very good work ability (39). As WAI does not contain any information on presenteeism and absenteeism, these results were irrelevant for the calculation of productivity loss. Four of the identified studies which applied the WPAI questionnaire presented productivity loss estimates. Two of these studies reported results for women experiencing moderate and severe symptoms separately (18, 38). One study reported results for presenteeism, but not absenteeism (15). Only one of the studies reported results for moderate to severe symptoms together (31). The results of the remaining publications were reported as change from baseline (37), regression coefficients (16) or only reported the impact scores of the WPAI (17, 40).

In summary, there is limited data available overall, and even fewer specifically for the Nordic countries. The majority of estimates of absenteeism and presenteeism identified were collected in studies from other European or American studies. Also, estimates were mostly reported for women with VMS in total, and not specifically for women with moderate to severe VMS. Among the identified studies, there was only one study which reported estimates from the WPAI-VMS specifically for the Nordic women with moderate to severe VMS. Thus, it was decided to base the intended analysis on this study, the WARM study, which was presented in the publication by Todorova et al. (31).

The WARM study was a cross-sectional survey conducted in women in Brazil, Canada, Mexico and Nordic Europe (Denmark, Finland, Norway and Sweden) with the primary objective to identify the prevalence of moderate to severe VMS in women in menopause. Secondary objectives included the evaluation of the impact of VMS on quality of life, work and daily activities, and sleep, as well as to assess treatment patterns and attitudes toward symptoms and available treatments (31). A questionnaire was sent to women between 40 and 65 years.

The WARM study had two objectives. The primary objective was to determine the prevalence of moderate to severe VMS in postmenopausal women. Secondary objectives, such as the impact on work, were determined in a population consisting of 90% women in postmenopause and 10% in perimenopause. Postmenopause was defined as no periods for at least 12 months, and perimenopause was defined as changes in periods, but not without period in 12 consecutive months (31). Women were included if they experienced at least one hot flush per day (over a 12 hour period) in the past month, experienced moderate to severe VMS, were not on breast cancer treatment and without anti-oestrogens and aromatase inhibitors and GnRH treatments in the last 12 months (31). Women were permitted to take part in the study if they received hormonal or non-hormonal prescription drugs and alternative medicine or other over the counter products.

For the primary objective, 12,268 women were included in the study. For the secondary objectives, 2,176 women were included in the study, of which 863 women were from the Nordic countries. This smaller subsample for the secondary objective was due to women not passing the screening criteria including moderate to severe VMS (n = 23,405), dropping out after starting the survey (n=6,201) or being perimenopausal and accessing the survey after the pre-specified

quota of 10% for perimenopause had been reached (n=5,242). The majority of women in this subsample were between the ages 51 and 60 years (66%).

For the total population of the WARM study, the absenteeism was reported to be 4.41% and presenteeism was reported to be 28.86% (31). After personal communication with study sponsor, WPAI data specific to each of the participating Nordic countries was made available. The estimates are however not presented here as a publication is currently in process. Iceland was assigned the value reported for the whole Nordic cohort in the WARM study, as it was not included in the WARM study.

3.3.4 Parameter: Frequency and duration of symptoms

As mentioned in section 3.1, for the calculation of presenteeism, the productivity loss was only calculated as a proportion of the time spent with symptoms. Therefore, in addition to the proportion of impaired work reported in the previous section, information on the frequency and duration of affected time is required. As this was not part of the questionnaire, an approximation was used for the analysis at hand. This approximation was based on the frequency of hot flushes and the duration of each hot flush episode which was part of the data collection of the WARM study and reported for each country specifically. For Iceland, the value of the Nordic cohort from the WARM study was used which was a mean number of hot flush episodes of 4.9 per day with a mean duration of 27 minutes (31). The country-specific values are not presented here as a publication for this data is currently in process.

Although information on night sweats was reported as well, it was not considered in this analysis as it was assumed that work occurred throughout daytime. Furthermore, it was assumed that all symptoms occurred during work time. Of note, the duration and frequency of symptoms concerned all VMS (including mild) as not each episode experienced was of moderate or severe severity. However, it was reported that the majority (60-70%) of symptoms were moderate to severe.

3.3.5 Parameter: Labour cost

To set monetary value on the hours missed or impaired at work, hourly labour costs for full-time equivalents were applied as reported by Eurostat (41). These consist of gross wages/earnings (including taxes, social contributions payable by the employee and net earnings), social contributions payable by the employee as well as other costs (such as taxes and training costs). Costs are presented in 2023 euros to facilitate a comparison between countries. Of note, hourly labour costs were only available from Eurostat as estimates for the whole population. Costs were not available by sex or age. Based on the Eurostat's information on gender pay gap (42), the pay gap in the age group 45 to 54 years and 55 to 64 years is 16% and 17% on average for the Nordic countries. This indicates that the hourly labour costs may be lower for female employees. At the same time, hourly labour cost may be higher for the age cohort 40-65 years than for the age cohort reported by Eurostat (20-64). Moreover, social contributions in Eurostat are only reflective of statutory contributions. Contracted contributions are not taken into account. This may underestimate labour costs, as for example in Sweden, the non-wage costs according to Eurostat amount to 30% of the labour costs (41), while taking all social contributions into account, these may amount up to 40% for Swedish employees (43). However, due to the common definition for all countries in the Eurostat data, this was the preferred source for the calculations at hand. Labour costs are presented in Table 3.

Table 3 Average hourly labour costs

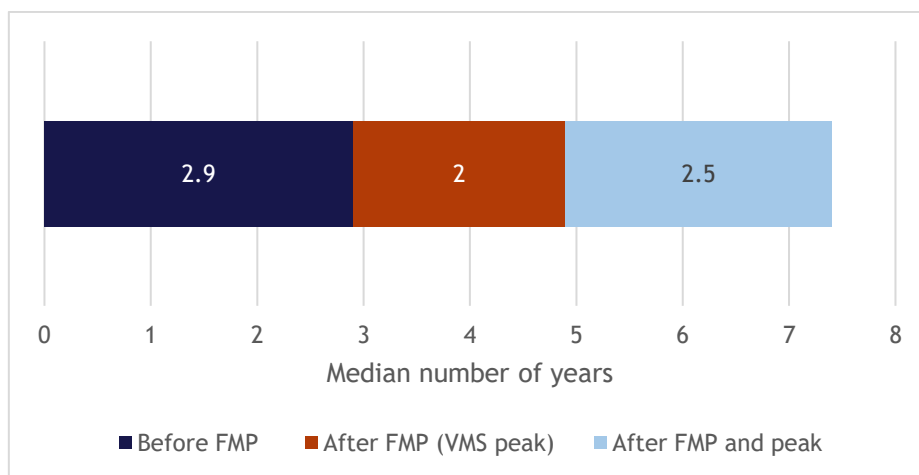
	Denmark	Finland	Iceland	Norway	Sweden
Hourly labour cost	€48.10	€37.10	€49.70	€51.90	€38.90

Source: Eurostat (41)

3.3.6 Parameter: Prevalence of moderate and severe VMS

Variations in the reporting of the VMS prevalence from epidemiological studies is subject to different definitions of severity used and the age range of the enrolled women. Some studies based the severity assessment on the US Food and Drug Administration (FDA) definition of severity. These include three levels, i.e. mild (sensation of heat without sweating), moderate (sensation of heat with sweating, able to continue activity) and severe (sensation of heat with sweating, causing cessation of activity). Other studies have based their assessment on the Menopause Rating Scale (44) or similar self-reported assessment instruments to rate the frequency of occurrence or impact of symptoms (22). The frequency of VMS is further associated with factors such as educational level, employment, smoking status, occurrence of premenstrual symptoms, feelings of depression or anxiety, age, weight, and level of physical activity (3). Also, ethnicity plays a role in the prevalence and persistence of symptoms, with African American women reporting highest rates and longest duration, while Asian women report lowest rates and shortest duration (3, 6).

Vasomotor symptoms are experienced by 60-80% of women at some point during their menopausal transition (3, 45). In a US cohort, the prevalence of moderate to severe hot flushes has been reported to be 80% of women, with a peak prevalence of 46% in the first two years after FMP. At ten years and at one year to FMP, the prevalence was 16% and 32%, respectively, and decreased again with time after the peak prevalence (5). A similar estimate of the prevalence of moderate to severe VMS was also found in a UK-based retrospective observational cohort study (46). This study also showed a variation in the prevalence and severity of symptoms depending on menopausal stage, with peak estimates in the first two years after FMP (5). Although prevalence may differ between publications depending on study design and included population, the literature indicates that a large proportion of women experience moderate to severe VMS at some point during their menopausal transition.



Based on Avis et al. (6) and Freeman et al. (5)

Figure 4 Median number of years with vasomotor symptoms (VMS) before and after final menstrual period (FMP) and VMS peak

In the literature review conducted for this study, twelve publications were identified in total in the epidemiological review (31, 47-57), see Table A-1 in the appendix. Of these, ten were peer-reviewed articles and two were reports identified from the grey literature (54, 55). With regard to geographic scope, the identified literature covered estimates for Denmark (one study (54)), Finland (three studies (49, 50, 53)), Norway (one study (48)) and Sweden (six studies (47, 51, 52, 55-57)). One study also presented estimates for the Nordics, including Denmark, Finland, Norway and Sweden (31). No studies reporting Icelandic estimates were identified. All studies were exclusively conducted either as cross-sectional surveys or surveys that were distributed to women who were part of larger cohort studies.

All publications reported prevalence estimates for VMS in their respective population (see Table A-1 in the appendix); however, five did not report the prevalence of moderate to severe symptoms specifically (47-50, 54). Studies reporting incidence estimates were not identified.

There were a number of aspects in which the included studies differed, including time period of data collection, population, treatments and definition of VMS.

Firstly, there was variation in the time periods for data collection of the included studies. The data collection period in seven of studies was fairly dated (1992-2010) (47, 48, 51-53, 56, 57); in the remaining five studies, data was collected more recently (2015-2023) (31, 49, 50, 54, 55).

Furthermore, there was variation with regard to study participants in terms of age and phase of menopause. All studies included participants based on pre-specified age ranges that differed between studies. The widest age range can be found in the study by Bardel et al. (47) with an age range of 36-64 years. The definition of the different phases of menopause (peri-menopause, menopause and post-menopause) as well as the proportion of women in each phase also differed between the included studies. The definition of these phases was most commonly determined by frequency of bleeding (e.g. seizing of periods in the last six or twelve months); only one study used the STRAW criteria (48) and one study determined phases based on S-FSH levels (50). Five studies even explicitly mentioned a pre-menopause phase (49-53), thus including also women who were not in menopausal transition.

Regarding treatments, these were reported in some, but not all studies. In particular, information on whether included women received hormonal treatments or not were not clearly stated in every study. There were three studies which included both women with and without hormonal therapy (31, 47, 52).

Lastly, the definition of VMS also differed between studies. Although all studies included hot flushes, only some of the studies included additional symptoms. If more than one symptom was reported to be included, the definition most commonly included sweating. This was either specified as daytime and/or nighttime sweating (31, 47, 48, 50, 54, 57) or generally referred to as sweating (49, 51, 55, 56).

In summary, the variations in definition of VMS, included populations and time periods of data collection render a comparison across studies difficult. Among the identified studies in the literature review, the publication by Todorova et al. reporting results from the WARM study (summarised in section 3.3.3) presented recent estimates for four of the Nordic countries. Moreover, it was considered advantageous to use this study as it was also the source of the estimations of absenteeism and presenteeism in this calculation.

Considering that the WARM study focused on postmenopausal women for the calculation of the prevalence of moderate to severe VMS, for the analysis at hand it was necessary to first determine the share of postmenopausal women between the ages of 40 to 65 years (which corresponds to the WARM study population). In a second step, the estimated prevalence of moderate to severe VMS could be applied to that population in order to determine the prevalent population in the respective countries included in this analysis.

Due to the lack of country-specific data from the WARM study, the share of postmenopausal women was approximated by calculating the share of postmenopausal women in the WARM study (12 268) among all women who accessed the survey regardless of whether they were in postmenopause (37 206), which results in a share of 33%. Although this share is associated with great uncertainty, it seems reasonable compared to previous reported shares of postmenopausal women among older cohorts of women in Sweden (~50% among women 45 to 55 years and 50-60 years (52, 53)). The prevalence of moderate to severe VMS reported in the WARM study was then applied to this population of postmenopausal women in each of the countries, respectively. Both population and prevalence estimates are presented in Table 4.

Table 4 Population and prevalence estimates

Country	Population (women 40-65 yrs)	Proportion of women in post-menopause	Prevalence of moderate to severe VMS	Post-menopause women w moderate to severe VMS	Reference
Denmark	949 645	33%	11.40%	35 697	(58), (31)
Finland	865 303	33%	11.60%	33 097	(59), (31)
Norway	866 945	33%	14.00%	40 020	(60), (31)
Sweden	1 591 123	33%	11.40%	59 809	(61), (31)
Iceland ^b	56 107	33%	11.60%	2 146	(62), (31)

^bAs Iceland was not included in the WARM study, it was assigned an average value based on estimates from the other Nordic countries

4. Estimated productivity loss

4.1 Estimated missed and impaired work time

Work time missed due to absenteeism and presenteeism in postmenopausal women, adjusted for employment rate, is presented in Table 5 below. It can be observed that for all countries, presenteeism had a larger impact on lost productivity than absenteeism. This was expected based on the available estimates of presenteeism and absenteeism. Expressed in proportions of work year, absenteeism accounts for 1-2% of the annual average work time, while presenteeism accounts for 4-10% of the annual average work time. On average in the Nordics, a woman's productivity is impacted on average for 2.5-4 weeks per year due to VMS.

Table 5 Estimated missed work time per person

Country	Missed time due to absenteeism		Missed time due to presenteeism	
	Number of hours missed per year	Proportion of work year	Number of hours impaired at work per year	Proportion of work year
Denmark	34.03	2%	62.48	4%
Finland	10.20	1%	93.06	6%
Norway	23.14	2%	144.70	10%
Sweden	12.43	1%	103.01	7%
Iceland*	21.69	1%	95.53	6%

*Based on input data from the Nordic cohort of the WARM study

4.2 Estimated annual costs

Based on the estimated missed and impaired work time per person presented in Table 5, the annual cost of productivity loss per person for postmenopausal women was calculated. Estimates for all countries are presented in Figure 5 (see Table A-3 in the appendix for details). Comparing across countries, it can be observed that with regard to absenteeism, the highest estimates are reported for Denmark. For presenteeism, the highest estimates were reported for Norway. The difference between absenteeism and presenteeism is smallest in Denmark, and the largest gap can be observed for Norway.

Differences between the countries may be due to structural differences in work but could also be based on differences in subjective experiences of VMS. Furthermore, particularly for Norway, the sample size may have had an impact on the estimates and thus the analysis at hand. This may contribute to the uncertainty in these calculations.

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
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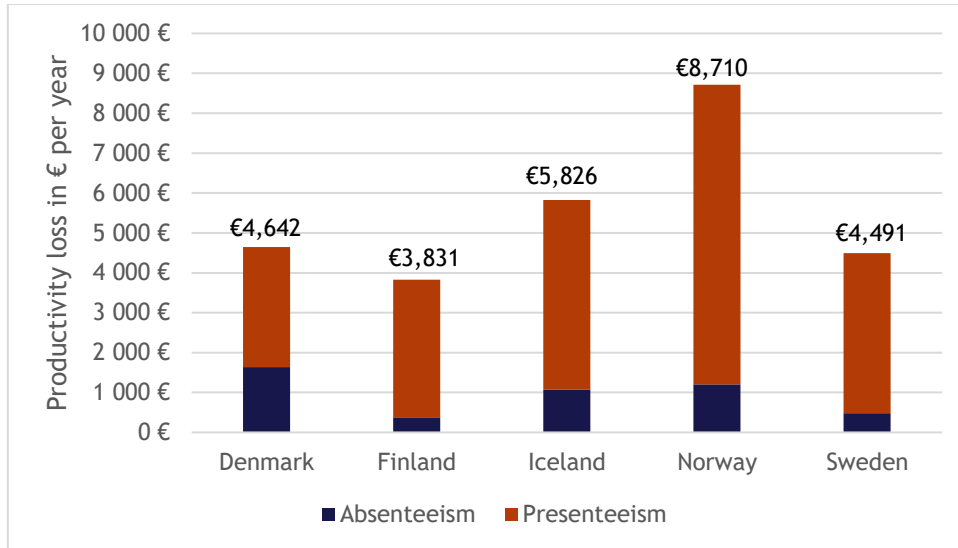


Figure 5 Annual costs of productivity loss per person with moderate to severe VMS

Results of the productivity loss extrapolated to the population level are presented in Figure 6. These costs represent the productivity loss of postmenopausal women with moderate to severe VMS per country. While productivity loss due to presenteeism still accounts for the larger share of total productivity loss, Norway presents with the highest impact on productivity loss due to presenteeism, despite a larger number of women experiencing VMS in Sweden (40,020 women in Norway vs 59,809 women in Sweden).

Detailed per person and population estimates are presented in Table A-3 in the appendix.

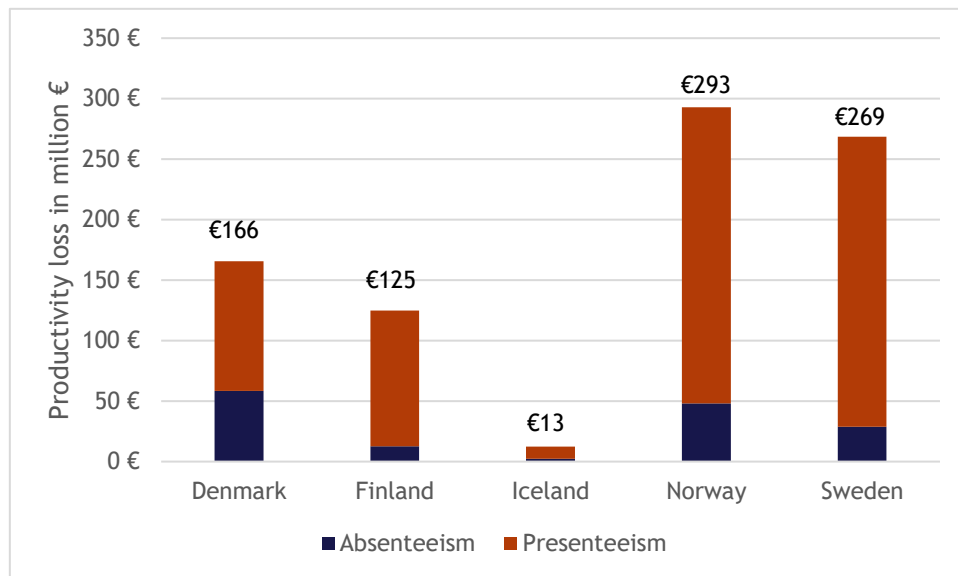
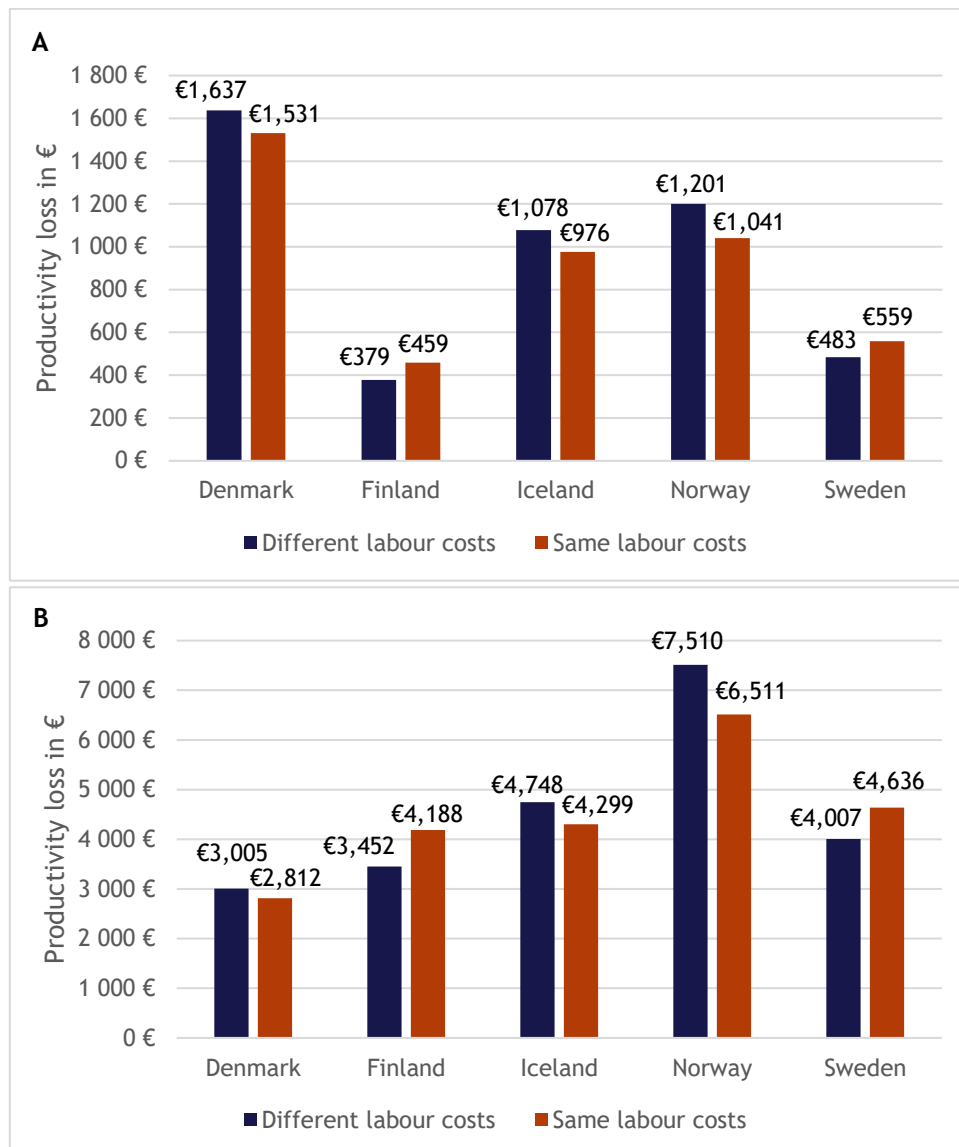


Figure 6 Annual population costs of productivity loss for postmenopausal women with moderate to severe VMS (in million Euros)

4.3 Scenario analysis

4.3.1 Labour costs

Some of the cost differences could be argued to occur due to different labour cost levels in the four countries. Therefore, a scenario analysis was conducted where the hourly labour costs were set to be the same in all countries (45 € per hour, equivalent to the average of the hourly labour costs across all countries). The results of this analysis are presented in Figure 7 in Panel A for absenteeism and in Panel B for presenteeism. There are slight differences across countries: In Denmark, Iceland and Norway, productivity loss estimates decrease when the same labour costs are applied, while they increased for Finland and Sweden. Although it can be noticed that the hourly labour costs do appear to have some impact on the results, they seem to be mainly driven by the productivity loss.



Panel A depicts estimates for absenteeism. Panel B depicts estimates for presenteeism.

Figure 7 Scenario analysis of hourly labour cost impact on annual productivity loss per person

4.3.2 Alternative calculation for presenteeism

In a second scenario analysis, the alternative option of calculating presenteeism was applied (see Equation 1 in section 3.2). This entailed applying the estimate for presenteeism to the full worktime instead of only to the time while women reported experiencing VMS. As anticipated and illustrated in Figure 8, this approach led to higher estimates of impacted work time for each of the countries. With this alternative approach (Equation 1), the annual per person productivity loss increased 4-fold for Denmark and 3-fold for the remaining countries, compared to the approach chosen for the analysis (Equation 2).

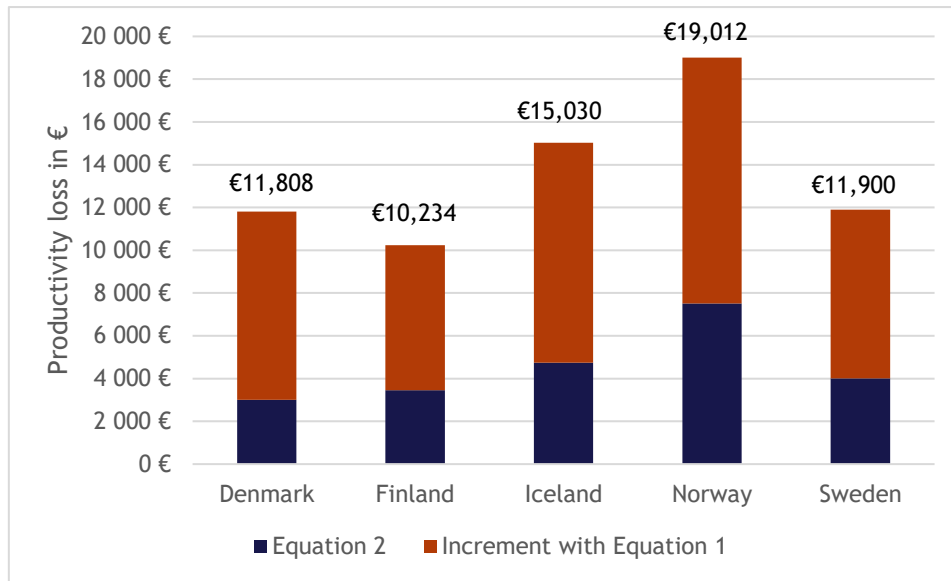


Figure 8 Scenario analysis of impact of presenteeism calculation approach on annual per person productivity loss

4.3.3 Inclusion of perimenopausal women

In the analysis at hand, only postmenopausal women were included as the WARM study only included these women in the calculation of the prevalence of moderate to severe VMS. However, restricting the analysis to postmenopausal women may underestimate the productivity loss of VMS in the population, as also women in perimenopause can experience VMS. Therefore, a scenario analysis was conducted to include perimenopausal women in the estimation of productivity loss. Due to the lack of data in the literature regarding the prevalence of perimenopause in the same age group as included in the WARM study (i.e. 40 to 65 years), this scenario analysis was based on the assumption that including perimenopausal women would increase the prevalence by 50%, from 33% to 49% of women.

The results of this scenario analysis are depicted in Figure 9. It can be observed that including perimenopausal women leads to an increase in the annual population productivity loss costs. For all countries, the productivity loss increased by approximately 1.5 times the amount compared to when perimenopausal women were not included.

Although a significant increase in productivity loss costs could be observed, it should be noted that the prevalence of moderate to severe VMS would likely also be impacted. However, as it is unclear whether the prevalence would decrease (due to a larger population being considered

in the analysis) or increase (as the prevalence in perimenopausal women may increase the prevalence), this was not considered for this scenario analysis.

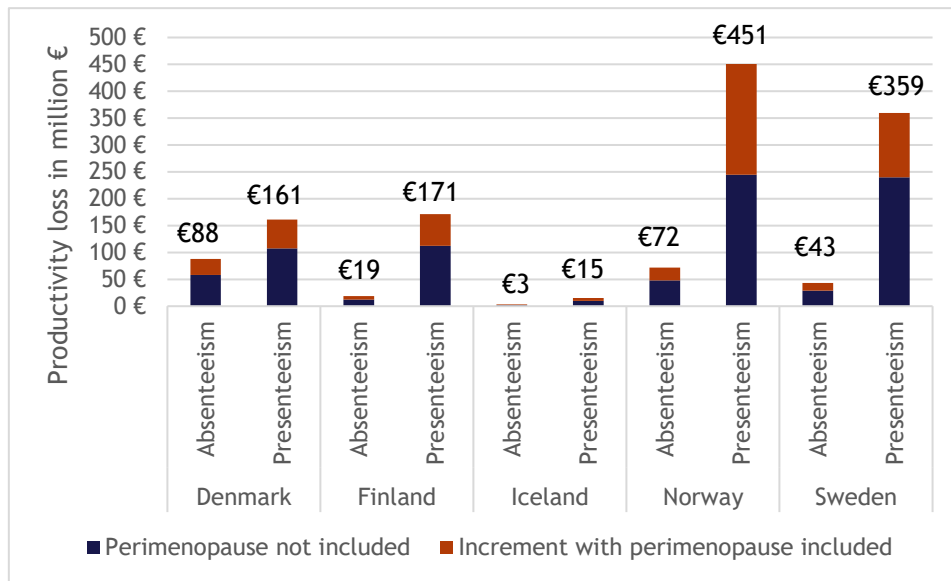


Figure 9 Scenario analysis of including perimenopausal women and its impact on the annual population productivity loss

4.3.4 Simulated cost per person over time

In this analysis, a prevalence approach was chosen for estimating the productivity loss of women with moderate to severe VMS. However, as mentioned previously in this report, the literature shows that women can be affected by their symptoms for several years (see sections 1.2 and 3.3.6). The median duration of symptoms has been reported to be 7.4 years (6) and this estimate has been applied in this scenario analysis. The results of the analysis are presented in Figure 10 below. As anticipated, a significant increase in productivity loss costs could be observed when considering the reported median duration of VMS. This estimation should, however, be treated with caution as the literature does not cover symptom development over time in detail.

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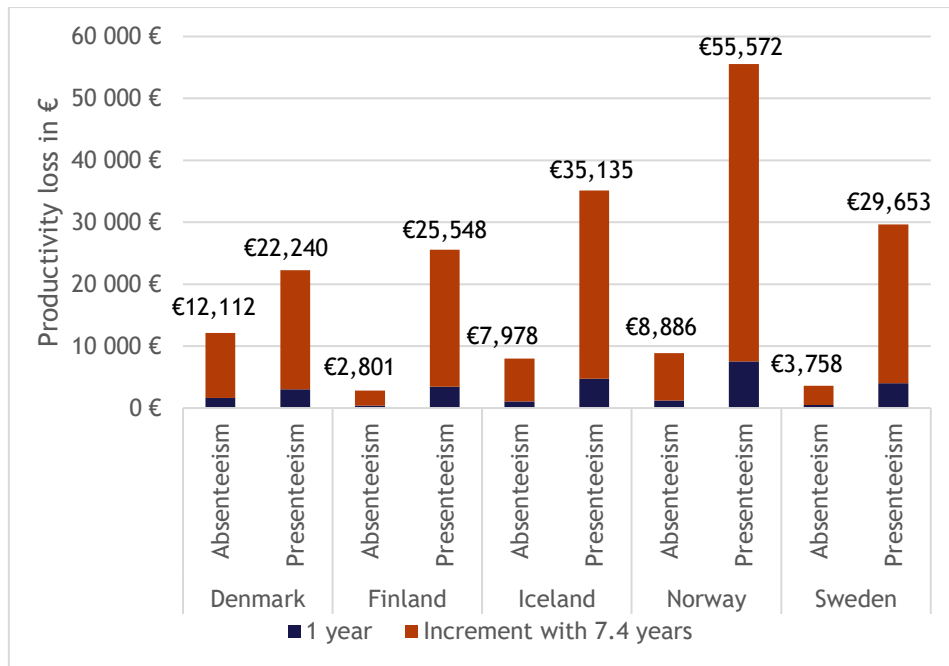


Figure 10 Scenario analysis of duration of VMS on annual per person productivity loss

4.4 Putting the result in perspective: Comparison to other studies

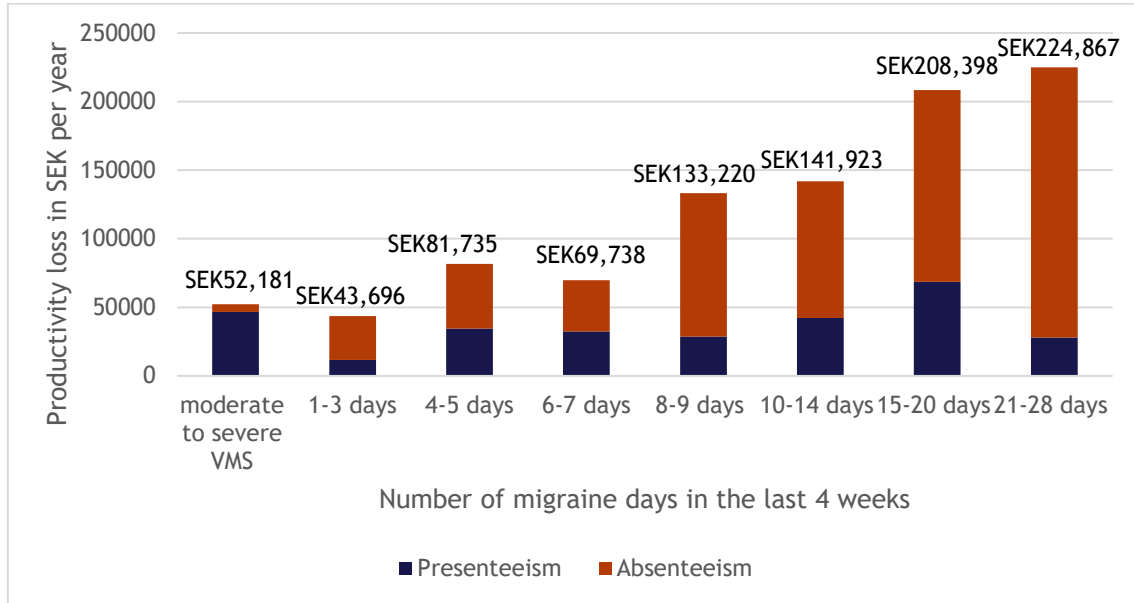
There were two US studies identified during the literature review which reported costs for absence from work due to menopause symptoms. Both studies used insurance data for their analysis (27, 28). The first study presented a mean annual cost of \$647 (2010 USD) for sick leave and 3.57 sick leave days (28). In comparison, the cost estimate is similar to the estimates for absenteeism in the analysis at hand for countries in the middle of the cost interval of this study (€364-1,546). However, considering that this US study included all diagnosed menopause symptoms (i.e., was not restricted to VMS), the estimates for VMS-related costs for absenteeism may in fact be lower than reported. The second study included only untreated women and examined their disability and medically related absenteeism due to VMS (27). It included an annual per person cost of \$1,401 (2011 USD). This is in the higher range of the reported absenteeism costs of this analysis; however, this may be due to the included population, women did not receive treatment for their symptoms, while in the analysis in this report, women did receive different forms of treatment (including hormonal treatment) which may have reduced the productivity loss.

In order to put the results of this analysis into perspective a comparison with an IHE study measuring the productivity loss of patients with migraine in Sweden was conducted (63). This study was designed as a web-based survey to members of the patient association for migraine in Sweden. The survey was conducted in adult patients in 2018. The productivity loss in this study was also based on absenteeism and presenteeism as measured with the WPAL. Furthermore, presenteeism was calculated analogous to this study, i.e., presenteeism was calculated only during the time that a patient experienced symptom.

The results of this comparison are presented in Figure 11. Swedish estimates from the analysis at hand were converted to local currency (SEK) to facilitate this comparison of per person costs due to productivity loss (1 EUR = 11.62 SEK). This resulted in SEK 5,618 for absenteeism and

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SEK 46,563 for presenteeism. With regard to absenteeism, women with moderate to severe VMS accrue lower costs due to absenteeism compared to migraine. However, when considering presenteeism, the impact on women with moderate to severe VMS is comparable to adults with moderate migraine. This indicates the relatively high burden on women with moderate to severe VMS on their work life.



Source: based on Hjalte et al. (63), current analysis

Figure 11 Productivity loss per patient in migraine patients and women with VMS

In a review of the economic burden of diseases in the Nordic countries (64), the mean annual cost per person varied from €1,668 for chronic obstructive pulmonary disease to €93,041 for multiple sclerosis. The costs for rheumatic diseases were reported to range from €17,224 to €28,115. The methodologies varied greatly across studies, but the result put the productivity loss for VMS (€5,760) into some perspective, even if this report does not include all components of the economic burden (e.g., not including any health care or medication costs).

5. Discussion

This study has shown that moderate to severe VMS cause substantial productivity losses in menopausal women in the Nordics, equivalent to 1-2% of the annual work time spent absent from work, and 4-10% of annual work time spent impaired while at work. It also shows that losses due to presenteeism account for the largest share of productivity losses compared to absenteeism. These losses occur despite some women receive treatment for the symptoms they experience, including hormonal treatment. Furthermore, some variation can be observed in the annual per person productivity loss in the Nordic countries. While the prevalence of moderate to severe VMS was fairly similar in the Nordic countries, differences could be observed in the reported presenteeism, particularly for Norway; however, this difference may also be due to the small sample in the underlying data. In summary, the results indicate that decreasing symptoms in women with moderate to severe VMS can potentially decrease the burden due to productivity loss in women in menopausal transition. Additionally, there is the potential for non-monetary gains in terms of quality-of-life improvements and non-paid work (caregiving, cooking, cleaning, gardening etc.). Differences between the countries were to some extent also driven by differences in the hourly wage.

This study presents the first analysis of costs due to productivity losses in the Nordic countries. It is based on data from the peer-reviewed literature. The WARM study is the first study to include Nordic countries and estimating both prevalence of moderate to severe VMS as well as absenteeism and presenteeism. It focused on postmenopausal women between the ages 40 and 65, an age interval reflective of women in their productive years experiencing menopause. Moreover, treatment was not a specific eligibility criterion, thus women were included regardless of whether they received hormonal treatment or not, rendering the sample representative of postmenopausal women who can receive different types of treatment modalities.

Furthermore, this analysis uses statistical data for all countries from the same source. Eurostat presents reliable data for all Nordic countries in a uniform manner, and thus all inputs are based on the same definitions of inputs and comparable across countries.

This analysis is, however, not without shortcomings. In short, the limitations include the following:

- Limitations related to the study design of the WARM study
- Uncertainties in the method of calculation of presenteeism
- Statistical input such as employment rates and hourly labour costs were not available for the specific population included in this analysis

Firstly, there is a lack of a control group (i.e., women without VMS) in the WARM study, increasing the risk of confounding factors in the estimates of productivity loss. Even though study participants were specifically asked about absenteeism and presenteeism related to VMS, the estimates could also be connected to other problems that are known to be prevalent in this population, e.g., stress, general mental health problems etc. Furthermore, as the study was conducted in the form of a survey, the estimates are also subject to the subjective memory (recall bias) of each woman regarding severity and prevalence of VMS.

The WARM study focused on postmenopausal women, and thus may not be representative of all women in menopausal transition. As also women in perimenopause can experience symptoms, the productivity loss among women aged 40 to 64 years may therefore be underestimated, as

shown in the scenario analyses. Moreover, the prevalence of VMS symptoms was primarily measured in postmenopausal women (90%) who are at least 12 months from FMP. The study did not include information about the time from FMP and may include a sample with several years from FMP, beyond the peak of VMS which takes place in the two years following FMP. Additionally, the response frequency and country-specific information regarding the number of postmenopausal women was not available in the publication. Therefore, a crude estimate of the proportion of women in postmenopause was calculated.

Secondly, there are uncertainties in the estimation of presenteeism. There is no clearly defined approach how this should be calculated based on the WPAI. As mentioned in section 3.1, are two alternative approaches identified in the literature of how the WPAI estimate for presenteeism could be used in calculations of productivity loss. For the analysis at hand, the approach that is considered more conservative is chosen. This approach, however, is dependent on additional data regarding both the frequency and the duration of symptoms. The strength with the WARM study is that both these variables are reported by the same women. Moreover, there was one additional study conducted by Nappi et al. which was identified during the literature review and which reported the duration and frequency of VMS (17). This study was conducted in France, Germany, Italy, Spain and the UK. The participants of this study reported symptoms occurring on average 4.3-5.5 times per day, lasting for 18-30 minutes per episode (17). These estimates are similar to the estimates from the WARM study for the Nordic countries. This indicates that although self-reported, these estimations may be representative of women with VMS, based on available reports from the literature.

Regarding the estimation of the proportion of presenteeism, there were three additional studies identified in the literature review which also reported percentages for absenteeism and presenteeism as measured by the WPAI-VMS (15, 18, 38). These studies were conducted in the US and Europe, included menopausal or postmenopausal women and included women of similar age ranges compared to the WARM study (40-65 years in two of the studies (18, 38) and 40-75 years in the third (15)). With regard to presenteeism, the estimates reported in the WARM study were within the same range as two of these studies which reported the percentage of presenteeism to be between approximately 15% to 32%, depending on symptom severity ((15, 18). The third study (38) reported estimates that were significantly higher than any of the other studies (50-65%). However, this may be due to the inclusion criterion of women having to have experienced at least 14 episodes of VMS per week. This study also reported estimates for the percentage of absenteeism that were higher compared to the other studies (12-15%) (38). Of the other two studies, one did not report any estimates for absenteeism (15), and the other reported similar estimates as were reported for the WARM study (2-3%) (18). This indicates that the estimates of the WARM study are plausible compared to other reports from the literature.

Thirdly, the productivity loss calculations are based on the traditional definition of employment. This means that non-paid work such as work in the home is not taken into account. In the population included in this report, non-paid work is likely to account for a large share of time spent.

Lastly, there are some limitations in the statistical inputs used. Inputs for average working hours, employment rate and labour costs were not available for the age group of 40 to 65 years specifically. Instead, inputs were derived for the age group 20 to 64 years. This may lead to an over- or underestimation of the costs. Furthermore, labour costs were not presented by sex, thus the hourly labour costs were derived from both male and female employees. Another aspect regarding labour costs is that these include only legal social contributions; negotiated social contributions from collective agreements are not taken into account.

The above limitations imply that the base case estimations in this report is on the conservative side; (i) only postmenopausal women were included (as opposed to perimenopausal and postmenopausal women), (ii) proportion of work impairment was only applied to time with symptoms (as opposed to all working time), (iii) some inputs for calculation were based on age group 20-64 years (as opposed to the age group 40-64 years who can be expected to have a higher employment rate and labour cost), and (iv) non-paid work was not included. Even though we can expect estimations to be somewhat underestimated, the burden on productivity is significant both on an individual and population level. It also deserves to be mentioned that although the purpose of this report was to estimate the burden related to VMS, menopausal transition includes additional symptoms that may add to this burden.

However, the burden is mostly invisible since a large share of the productivity loss is presenteeism and there is no reported sick leave for this time. Interestingly, the share of presenteeism varied across countries. Denmark reported the lowest share of presenteeism. A possible explanation is difference in insurance schemas across countries. For example, no payment is made for the first day of sick leave in Sweden (karensdag) while this is not the case for Denmark or Norway. Moreover, the level of compensation differs, where sick leave may be associated with larger income losses in some countries. This may discourage individuals from taking sick leave. There may also exist cultural or gender taboo of taking sick leave for symptoms associated with menopause. An interesting area for further research is to investigate reasons for not taking sick leave among women with VMS and if and how they may compensate for work impairment, e.g., taking work with them home and trying to compensate at evenings when feeling better (at expense of family life).

The literature review conducted for this project has indicated a need for additional and also more recent research regarding the impact of menopausal transition on women. The dearth of information pertains to, among other things, estimates on the incidence and prevalence of menopausal symptoms in different phases of the menopausal transition, but also from a population perspective. Another study of interest would be an estimation of the individual burden of VMS over time, an incidence approach. A rough calculation (included in scenario analyses) suggest that this may amount to a significant burden. A possibility is to perform a prospective, longitudinal study. A less costly and time consuming alternative would be a cross-sectional survey of women at different points of menopausal transition identified from internet panels or patient organizations. This type of survey could also ask for HRQoL, health care use, and other impacts such as compensatory work at home.

This study shows that the moderate to severe VMS presents an important burden for women in menopausal transition. There appears to be a need for improved support for these women to manage their symptoms to decrease the impact that moderate to severe VMS has on their life, including work life. Decreasing VMS for this group of women may also present a potential for cost savings for society as a whole if women are less impacted in their work.

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Appendix Literature review summary

Table A-1 Epidemiological studies identified

Author (year) Country	Time period of data collection	Sample size	Source	Age (years)	Menopausal phase (n (%))	Definition of VMS	VMS, regardless of severity	Moderate to severe VMS
Bardel (2002) (47) Sweden	1995	2991	Cross-sectional postal questionnaire study in Uppsala-Örebro health care region	35-64	Menopause: 120 (4%) Postmenopause: 1207 (40.4%)	Flushing, sweating during daytime and sweating during nighttime	Menopausal women - any symptoms: 51% - flushing: 29.2% - sweating during day time: 40.8% - sweating at night: 40.8% Postmenopausal women - any symptoms: 40% - flushing: 15.9% - sweating during day time: 25.1% - sweating at night: 31.6%	-
Gjelsvik (2011) (48) Norway	- Baseline 1997-1999, then approximately every 2 years - in 2010, 7	2002	HWC study, a subset of the Hordaland County Health Survey	- 40-44 at date of inclusion - 53-57 in 2010	- daily hot flushes: Perimenopause: 174 (25)	Hot flushes and night sweats.	Hot flush, (almost) never/monthly/weekly/daily: - 41-42 years: 86/10/2/2% - 43-44 years: 85/10/3/2%	-

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

questionnaires
completed

Postmenopause: 533 (75)	- 45-46 years: 83/10/3/4%
-	- 47-48 years: 75/13/6/6%
weekly/monthly hot flushes:	- 49-50 years: 67/14/9/10%
Perimenopause: 273 (39)	- 51-52 years: 56/15/13/16%
Postmenopause: 429 (61)	- 53-54 years: 46/16/17/22%
- never/almost never hot flushes:	- 55-56 years: 46/15/19/20%
Perimenopause: 351 (60)	Sweats/nights sweats, (almost) never/monthly/we ekly/daily:
Postmenopause: 229 (40)	- 41-42 years: 80/13/4/2%
	- 43-44 years: 76/16/6/2%
	- 45-46 years: 73/16/7/3%
	- 47-48 years: 68/18/9/5%
	- 49-50 years: 61/21/11/8%
	- 51-52 years: 54/19/16/12%
	- 53-54 years: 51/17/17/15%
	- 55-56 years: 52/17/17/14%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

<p>Hyvärinen (2023) (49) Finland</p>	<p>- baseline measurement: 2015-2016 - follow-up: 2019-2020</p>	<p>-ERMA: 1393 - 4-year follow-up EsmiRs: 298</p>	<p>cross-sectional ERMA and longitudinal EsmiRs study</p>	<p>47-55</p>	<p>- baseline (cross-sectional): perimenopause: 474 (34) Postmenopause: 530 (38) - baseline (longitudinal): Perimenopause: 105 (35) Postmenopause: 93 (31) - follow-up (longitudinal): Perimenopause: 42 (14) Postmenopause: 241 (81)</p>	<p>Sweating and hot flushes</p>	<p>- baseline, no symptoms (cross-sectional): 41% - baseline, 2 symptoms (cross-sectional): 29% - baseline of follow-up period, no symptoms (longitudinal): 49% - baseline of follow-up period, 2 symptoms (longitudinal): 23%</p>	<p>-</p>
<p>Kalleinen (2021) (50) Finland</p>	<p>- baseline measurement: 2001-2007 - follow-up: 2013-2017</p>	<p>57</p>	<p>“Woman 46” study (recruited through newspaper announcements in the Turku city area)</p>	<p>46</p>	<p>Postmenopause: 100% at follow-up</p>	<p>Night sweats and hot flushes</p>	<p>Night sweat at follow-up: - almost daily: 12.5% - once a week: 23.2% - once a month: 7.1% - seldom or never: 57.1% Hot flashes at follow-up: - almost daily:</p>	<p>-</p>

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

							<ul style="list-style-type: none"> 13.8% - once a week: 15.5% - once a month: 10.3% - seldom or never: 60.3% 	
Li (2002) (51) Sweden	1996	4943	WHILA study	- women born between 1935 and 1945, living in Lund in 1995 were included - mean age post-menopause : 57	Postmenopause: 2591 (52%)	Hot flushes/sweats in women <u>not</u> on hormonal therapy	- total group: 44.4%	<ul style="list-style-type: none"> moderate: - total: 38% - year 1: 30% - year 2: 34.3% - year 3: 41.3% - year 4-5: 43.2% - year >=6-10: 38.4% severe: - total: 17.9% - year 1: 21.6% - year 2: 16% - year 3: 13.5% - year 4-5: 15% - year >=6-10: 19.3%
Lindh Astrand (2015) (52) Sweden	2010	- total, used for prevalence of symptoms: 1314 - used for menopause status: 1004	Survey sent to women living in Östergötland	47-56	Perimenopause: 182 (18.1%) Postmenopause: 537 (53.5%)	Hot flushes	<ul style="list-style-type: none"> not using HT - any hot flushes: 51% - on some occasions each week: 34% - daily: 17% postmenopausal women: - any hot flushes: 68.2% - less than daily: 63.7% - daily: 36.3% 	<ul style="list-style-type: none"> - not using HT, any hot flushes, moderate: 49% - not using HT, any hot flushes, severe: 18.7%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

Lipasti (2023) (53) Finland	in 2000 and 2010	1491	QoL Study, a subset the HeSSup Study	- 42-46 in 2000 - 52-56 in 2010	- at age 42-46 years: Perimenopause: 177 (12) Postmenopause: 46 (3) - at age 52-56 years: Perimenopause: 164 (11) Postmenopause: 733 (51)	Sweating and hot flushes	-	hot flushes, 42-46 years - moderate: 6% - severe: 3% hot flushes, 52-56 years - moderate: 29% - severe: 27% sweating, 42-46 years - moderate: 11% - severe: 5% sweating, 52-56 years - moderate: 29% - severe: 28%
Menokonsult (2023) (54) Denmark	2022-2023	362	Survey among women of Rigshospitalet, Kbh's Professionshøjskole and three Facebook groups	46.5	-	Hot flushes and night sweats	- hot flushes: 8% - night sweats: not legible	-
National Board of Health and Welfare (2021) (55) Sweden	November 2020	ca 2000 (1505 answered question about VMS)	Survey	50-59	Perimenopause: 13% Menopause: 41% Postmenopause: 21%	Hot flushes and sweating	86%	62%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

Stadberg (1997) (56) Sweden	1992	4528	Random sample from population register for birth cohorts 1946, 1942, 1938, 1934 and 1930 who are residents of the city of Gothenburg	- 42-46 - menopausal age (crude average): 48.7 - age after adjustment (for e.g. surgery): 51.5	-	Hot flushes and sweats	- total: 53% - 46 years of age: 40% - 50 years of age: 51% - 54 years of age: 69% - 58 years of age: 61% - 62 years of age: 49%	- total: - - 46 years of age: - - 50 years of age: 33% - 54 years of age: - - 58 years of age: 22% - 62 years of age: -
Thunell (2004) (57) Sweden	1992 and 1998	3750	- every second woman from the birth cohorts 1946, 1942, 1938, 1934 and 1930 (i.e. women aged 46, 50, 54, 58 and 62 years) resident in the city of Göteborg (n = 5990) was sent a postal questionnaire - randomly selected from population register	46-62	- in 1992: Perimenopause: 363 (10%) Postmenopause: 364 (10%) - in 1998: Perimenopause: 404 (11%) Postmenopause: 544 (15%)	Hot flushes and/or night sweats	1992 - total: 52% 1998 - total: 62% - women aged 52 years: 64% - women aged 56 years: 65%	1992 - NR 1998 - total: 50%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

Todorova (2023) (31) Nordics	Nov 2021 - Jan 2022	6383	Online survey, recruited through websites, social media and e- mail lists	40-65	Perimenopause: 124 (14.4) Postmenopause: 739 (85.6)	≥1 daily hot flush in the past month	100%	- Nordic: 11.6% - Denmark: 11.4% - Sweden: 11.4% - Finland: 11.6% - Norway: 14%
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Abbreviations: HeSSup Study: Health and Social Support Study; HWC: Hordaland Women's Cohort; ERMA: Estrogenic regulation of Muscle Apoptosis; EsmiRs: Estrogen MicroRNAs and the risk of Metabolic Dysfunction; QoL Study: Quality of Life among Middle-aged Women Study; WHLA: Women's Health in Lund Area

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

Table A-2 Productivity loss studies identified

Author (year) Country	Time period of data collection	Sample size	Source	Age (years)	Menopausal phase	Measurement instrument	Presenteeism (%)*	Absenteeism (%)*
Cano (2024) (37) US, Canada, Europe	2019-2021	-Total: 1022 - Placebo: 342 - Fezolinetant 45 mg: 341 - Fezolinetant 30 mg: 339	Pooled analysis of SKYLIGHT 1 and SKYLIGHT 2 clinical trials	≥40 to ≤65 years	Postmenopause: 100%	WPAI - VMS	-	-
DePree (2023) (38) US	Mar-Jun 2021	619	non-interventional, cross-sectional, online survey conducted	40-65 years	- overall: Perimenopause: 210 (33.9%) Postmenopause: 409 (66.1) - moderate: Perimenopause: 82 (30.8%) Postmenopause: 184 (69.2%) - severe: Perimenopause: 120 (45.3%) Postmenopause: 145 (54.7%)	WPAI (focus on VMS)	- moderate: 50.2% - severe: 64.3%	- moderate: 11.8% - severe: 15.0%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

DiBonaventura (2013) (16) France, Germany, Italy, Spain, UK	2010	3801	National Health and Wellness Survey	40-75	Postmenopause: 3801 (100%)	WPAI-VMS	-	-
Humeniuk (2019) (39) Poland	2016	287	Women with non-manual work from various institutions in the Lublin region	45-60	Early perimenopause: 98 Late perimenopause: 43 Postmenopause: 146	WAI	-	-
Nappi (2021) (40) Europe, US, Japan	Dec 2019 to Feb 2020	2035 (European sample)	cross-sectional online survey, random sample	40-65	Postmenopause: 100%	WPAI	-	-
Nappi (2023) (17) Europe	Dec 2019 to Feb 2020	2035	cross-sectional online survey	40-65	Postmenopause: 100%	WPAI	-	-
	Feb-Oct 2020	854	Adelphi VMS Disease Specific Programme (DSP), a point-in-time survey	40-65	Menopause: 100%	WPAI:SHP for VMS	- overall: 20.1% - moderate: 24.2% - severe: 31.7%	- overall: 1.3% - moderate 1.9% - severe: 3.0%

PRODUCTIVITY LOSS RELATED TO VASOMOTOR SYMPTOMS (VMS)
DURING MENOPAUSAL TRANSITION AMONG WOMEN IN THE NORDICS

Todorova (2023) (31) Nordics	Nov 2021 - Jan 2022	6383	Online survey	40-65	Perimenopause: 124 (14.4) Postmenopause: 739 (85.6)	WPAl and WPAl-VMS	Moderate to severe: 28.68**	Moderate to severe: 4.41**
Whiteley (2013) (15) US	2010	3267	Annual, cross- sectional, self- administered Internet survey (NHWS)	40-75	Postmenopause: 100%	WPAl (modified for VMS)	- mild: 4.04% - moderate: 14.46% - severe: 24.28%	-

Abbreviations: NHWS: National Health and Wellness Survey; VMS: Vasomotor symptoms; WAI: Work Ability Index; WPAl: Work Productivity and Ability Impairment questionnaire

*Refers to the percent absenteeism and presenteeism reported by the study participants

**Results represent measurements with WPAl-VMS

Appendix Productivity loss

Table A-3 Productivity loss estimates

	Denmark	Finland	Iceland	Norway	Sweden
Annual per person cost					
Costs due to absenteeism	€1,237	€379	€1,078	€1,201	€483
Absenteeism as percent of total	35%	10%	19%	11%	11%
Costs due to presenteeism	€3,005	€3,452	€4,748	€7,510	€4,007
Presenteeism as percent of total	65%	90%	81%	89%	89%
Total productivity loss	€4,642	€3,831	€5,826	€8,410	€4,491
Annual population cost					
Costs due to absenteeism	€58,426,395	€12,529,105	€2,313,596	€48,054,917	€28,917,156
Absenteeism as percent of total	34%	10%	18%	12%	10%
Costs due to presenteeism	€107,281,702	€112,293,731	€10,013,627	€244,725,616	€239,665,260
Presenteeism as percent of total	66%	90%	82%	88%	90%
Total productivity loss	€165,708,098	€124,822,837	€12,327,223	€292,780,533	€268,582,416

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