Burden illness of moderate & severe **menopause**-related vasomotor symptoms in **Denmark** – a back-of-the-envelope estimation

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Executive summary

- First attempt in estimating the burden of illness of moderate/severe menopause-related vasomotor symptoms (VMS) in Denmark.
- Many assumptions taken from the literature in lack of robust epidemiological data.
- The estimated prevalence of women with moderate/severe VMS ranges from 72-85,000
- With an average productivity loss of 12.2% per person, the production loss amounts to 3.6 to 4.3 billion DKK/year, depending on the amount of symptom relief already used.
- The quality-of-life implications are substantial and in parity with some severe conditions.
- There is a great lack in research on menopause and their effect on the society.

Introduction

All women that live beyond their 50ies will experience the menopausal transition, physiologically characterized by hormonal fluctuations followed by a drop in oestrogen production and final cessation of menstruation. In Denmark, the mean age of menopause is ~51, with some entering this phase as early as in their start 40s and others mid 50s. The transition phase, where changes in the hormonal regulation becomes irregular, can range from few years to almost a decade. For some, this phase in life is experienced as positive, empowering and freeing; whereas others experience severe menopause-related symptoms, year in, year out. These symptoms come in all forms, ranging from sleep disturbances, hot flushes (vasomotor symptoms), dry eye or vaginal mucus membranes, to joint pain, brain fog or depressive thoughts. Some have few symptoms for shorter periods, others many symptoms for longer periods. Despite this, there are limited research into what can be done to prevent or alleviate the symptoms and at the societal level, it has not been studied how big an impact menopause has.

Given the prevalence of vasomotor symptoms (VMS) due to menopause, this is one of the symptoms that have been best described in the literature while other symptoms, even those with high prevalence and obvious impact on wellbeing, are less studied. Moreover, there is a paucity in the estimation of societal burden of menopause related symptoms in a Danish context. While the impact of many experienced symptoms is clearly significant for the individual women, the societal level is less well appreciated. To give an estimation on the impact of menopause on the societal level, and to highlight that more research in Denmark is clearly needed, we calculated the cost of menopause-related VMS in a Danish context.

Although this technical report does not claim to be comprehensive review of the literature, the rather few studies identified which attempted to quantify the productivity impact, had some methodological limitations. The main limitation was that studies included women who were treated with hormonal therapy, and therefore would experience fewer symptoms than non-treated women with symptoms. Including untreated women on the other hand would create a problem in that not all women experience VMS and therefore should, correctly, not be treated. The root cause to this limitation in study designs is the lack of use of a diagnosis code to identify the patients.

This technical report describes a simple “back of the envelope” calculation of productivity loss in Denmark due to VMS. The calculations do not claim to be exact nor validated but should be seen as a first attempt in estimating the scope of the burden with the aim to increase awareness of the importance of menopause. A more elaborate and methodologically reviewed study may come to different results and with more granularity. Nevertheless, more research is warranted to understand

the implications of VMS on a societal level – both in terms of productivity loss, women's quality of life loss and implications for the labour force.

The work presented is the fruit of a collaboration between health economist, Ola Ghatnekar, PhD, Astellas Pharma a/s and Associate professor, Lasse Gliemann, PhD, Department of Nutrition, Exercise and Sports, University of Copenhagen.

Methods

As no reliable data is available on the prevalence of menopausal symptoms in Denmark, nor VMS in particular, the number of women who experience moderate to severe VMS has to be estimated based on references relevant for the Nordic countries [1-3]. The main reason for using studies including patients from the Nordics is to minimise the impact from structural and cultural differences in terms labour force participation and perceptions of moderate and severe VMS. However, even within the Nordics, there are variations that must be recognized.

Prevalence estimation

Three different sources for estimating the prevalent population of women experiencing moderate to severe VMS was used. The basis for all these calculations was the annual age-cohorts of Danish women, using the same age span as in the reported studies. Population data was taken from Statistics Denmark.

Specifically, Todorova et al. reports that 11.6% (739) of the surveyed Nordic women aged 40 to 65 years (6383) experienced moderate to severe VMS (11.4%, 224/1968, for Denmark alone, presentation by Professor Lindén Hirschberg at NFOG in Trondheim, 27-30 August 2023). However, as the age span is very wide, the density of post-menopausal women was 65.8% in the age of 51 to 60 years. In order not to overestimate the prevalence, an adjustment of 75% was applied. This assumption can be challenged in both directions.

To validate this assumption, we also included a Finnish longitudinal study which examined changes menopausal symptoms in women who had never used hormone therapy [2]. Here, it was reported that some 29% and 28% in a cohort aged 52-56 experienced moderate or severe sweating, respectively, among those reporting menopausal symptoms. However, as not all women experience menopausal symptoms, we adjusted the number by 75% in order not to overestimate the prevalence. This assumption was taken from a Swedish survey among 2009 women aged 51-54, see Figure 2 [3; Table 6, p.66].

Finally, from the same Swedish survey 62% reported moderate or severe hot flushes, Figure 3 [3]. The same adjustment by 75% was applied to avoid overestimation of the prevalence.

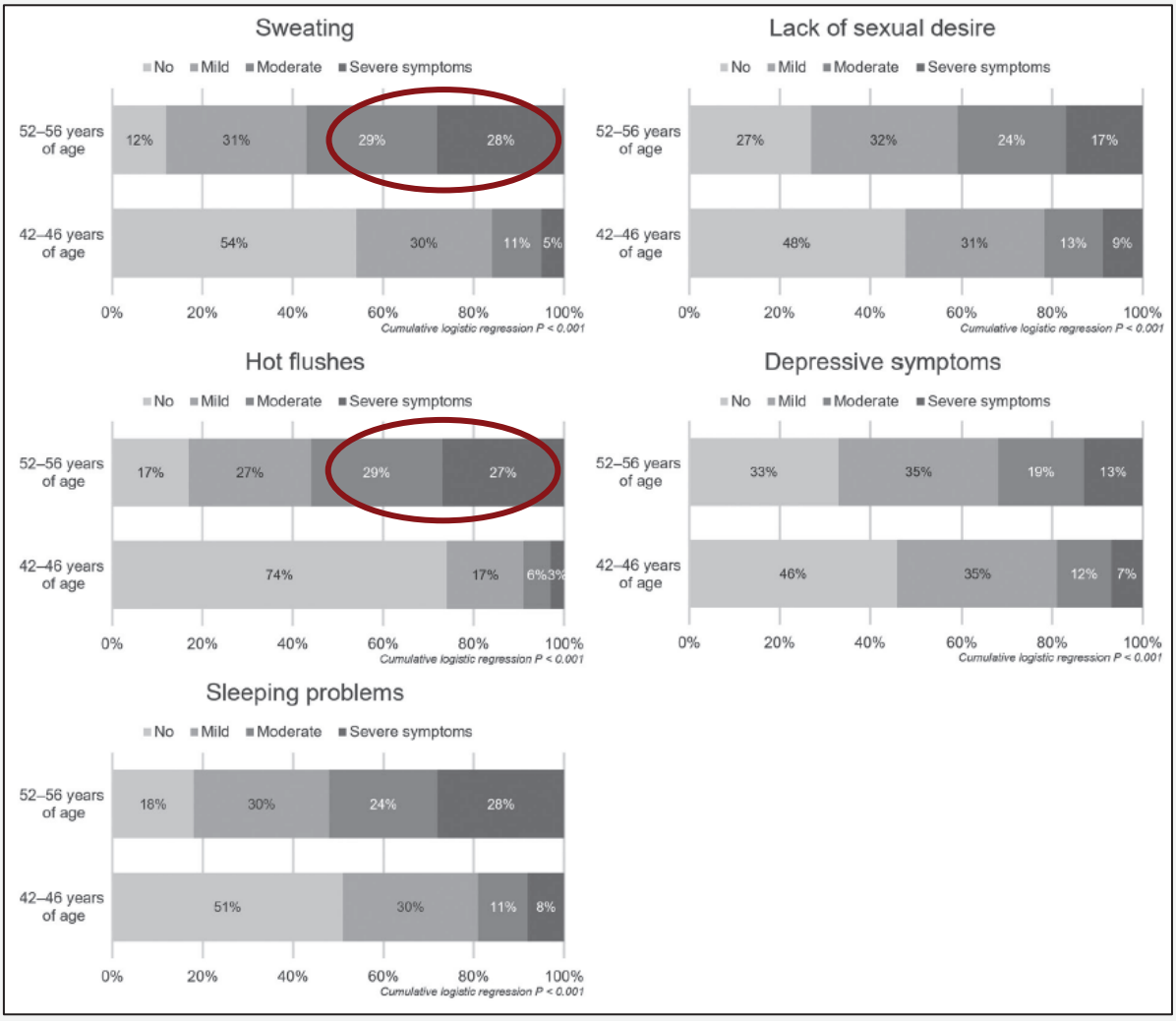

Figure 1. Prevalence (%) of the five most common climacteric symptoms (sweating, hot flushes, sleeping problems, lack of sexual desire and depressive symptoms) among women who have never used MHT (menopausal hormone therapy) at the age of 42–46 years and the age of 52–56 years. Lipasti et al. 2023 [1].

4. Är du i klimakteriet?	Antal	Procent
Nej, jag är inte i klimakteriet ännu	131	7
Ja, men mensen har inte slutat ännu	258	13
Ja, har inte haft mens på minst 6 månader	821	41
Nej, jag har passerat klimakteriet	426	21
Jag vet inte pga hormonspiral/opererat bort livmoder	265	13
Vet inte	108	5
Totalt	2009	100

Figure 2. Women reporting on their menopause status: 1505 were in peri- or post menopause. Socialstyrelsen Rapport 2021 SWE [3].

6. Har du i samband med klimakteriet haft besvär med något av följande? Och i så fall var det milda, måttliga eller svåra besvär?
Bas: Är/har varit i klimakteriet. (Alternativ 2-4 i fråga 4).

	Nej		Ja, milda		Ja, måttliga		Ja, svåra		Vet inte		Totalt	
	Antal	%	Antal	%	Antal	%	Antal	%	Antal	%	Antal	%
Värmevallningar/nattliga svettningar	207	14	358	24	571	38	358	24	11	1	1505	100
Sömnproblem	404	27	391	26	382	25	298	20	30	2	1505	100
Psykisk och/eller fysisk trötthet	531	35	407	27	317	21	317	21	58	4	1505	100
Torra eller sköra slemhinnor i underlivet	554	37	352	23	368	24	191	13	40	3	1505	100
Oregelbundna blödningar	568	38	495	33	245	16	167	11	30	2	1505	100
Humör-svängningar	603	40	442	29	294	20	121	8	45	3	1505	100
Sexuella besvär	618	41	351	23	249	17	205	14	82	5	1505	100
Led-, muskel- eller ryggbesvär	659	44	322	21	281	19	169	11	74	5	1505	100
Nedstämdhet/depression	682	45	393	26	264	18	116	8	50	3	1505	100
Inkontinens, urinläckage	768	51	424	28	210	14	89	6	14	1	1505	100
Oro/ångest	836	56	299	20	220	15	107	7	43	3	1505	100
Hjärtproblem/hjärtklappning	900	60	335	22	157	10	50	3	63	4	1505	100
Urinvägsbesvär	955	63	293	19	171	11	68	5	18	1	1505	100

Figure 3. Women reporting on their menopause symptoms. Socialstyrelsen Rapport 2021 SWE [3].

Comment: Again, the reason for using three different ways of estimating the prevalence of VMS symptoms is that no comprehensive registration of menopausal women, and VMS in particular, is available. Despite an ICD-10 code exist for these symptoms: N95 - *Menopausal and other perimenopausal disorders.*

Labour costs

Labour costs were taken from Statistics Denmark Table INDKP201 and includes 4 (wages and salaries), 5 (entrepreneurial income), and 32 (Income taxes and labour market contributions) [4]. Labour force participation rate was taken from Table RAS200 in the age-span 45 to 59 years of age (avg 81%) [4]. The weighted average annual labour cost was DKK417,307 weighted by the number of women in the age cohort and their labour force participation rate.

Comment: The first estimation (DKK396,533) was not weighted by the number of women in the age cohort and labour force participation rate. Furthermore, the labour force participation rate was assumed to be 80% and only line item 4 (Wages and salaries) was included, resulting in an underestimation.

Burden of illness

The burden of illness study describes the societal cost in terms of both monetary and humanistic values that are lost (also known as *tangible* and *in-tangible* values). The tangible resources captures both direct and indirect costs, where the direct costs are resources consumed due to a condition. This can be health care visits, travel to health care treatment, drugs and nursing. Indirect costs, on the other hand, are resources that are forgone due to the condition. This includes productivity losses which represents resources that were not generated due to the condition and should cover both the patient and in some cases when relevant, those of a caregiver if they have to e.g. stay home from work. The Work Productivity and Activity Impairment (WPAI) is the most widely used [5].

The intangible costs are those related to quality-of-life reductions for both the patient and the caregiver. Although there are many ways to measure this loss, the most widely used is EuroQol 5D which is a generic health profile [6]. Apart from being generic, i.e. disease independent, another advantage with this questionnaire is that it is grounded in welfare economics and is as such suitable for cost-effectiveness analyses and priority setting in the health care sector (used by e.g. NICE and Medicinrådet). In short, the questionnaire captures the reported health-related quality-of-life, and the responses can be converted into quality-adjusted life-years weights (called utility or QALY weight) based on a tariff elicited from the general population.

Productivity loss estimation

To estimate the productivity loss a study by DiBonaventura et al. in France, Germany, Italy, Spain, and the UK (EU5) was used [7], in the lack of Danish studies. This internet survey among 3801 women collected information on background health characteristics but also Menopause Rating Scale (MRS), WPAI and health related quality of life by EQ-5D-5L. Instead of trying to stratify the cohort of interest, DiBonaventura used multivariate regression models to analyse the subgroups.

While controlling for several covariates, the analysis showed that VMS-related overall work impairment for moderate and severe VMS, as measured by WPAI, were 8.71% and 19.69%, respectively (weighted average 12.2%), compared to women with “Mild VMS” [7]. Figure 4 shows that there were some variations between country of origin of the respondents.

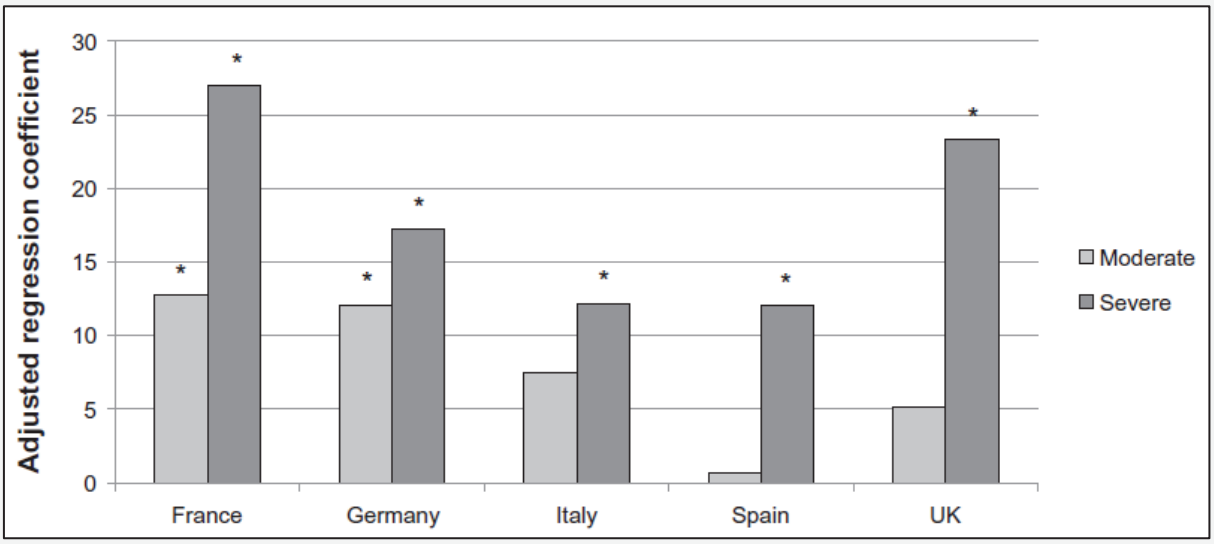

Figure 4. Adjusted regression coefficients of severity of vasomotor symptoms predicting the percentage of overall work impairment in the past seven days. [7: p267]
*Notes: *P < 0.05; Covariates included age, education, income, health insurance, BMI and the Charlson comorbidity index. DiBonaventura et al. 2013 [7].*

However, this estimation has not considered that many women are in fact receiving treatment either with prescription drugs, herbal medicine, cognitive behavioural therapy, or lifestyle changes. Although some treated women are not entirely free of symptoms or do not want any treatment, they may still experience VMS, but perhaps not with the intensity that that generates as many impairments. Nevertheless, not accounting for the current use of *VMS alleviation* in one form or another leads to an overestimation. According to a survey performed by Todorova et al. approximately 10% of Danish women with moderate to severe VMS were receiving menopausal hormone therapy (MHT) [16; Danish numbers presented by Professor Lindén Hirschberg at NFOG 2023]. Applying this fraction of MHT use, assuming that they then don't experience moderate to severe VMS, would result in productivity losses of approximately DKK3.8 billion. Increasing the share of MHT use to 15% would result in DKK3.6 billion.

Comment: In a study among 619 US women, the work productivity impact for moderate and severe VMS was estimated to 16% and 33%, respectively, compared to mild VMS [8]. As confirmed in other studies including WPAI, the majority of productivity loss stems from presenteeism (impairment while at work) and not absenteeism (missed work hours) [2,8,9].

Physician visits

Furthermore, the number of additional physician visits in the last 6 months due to moderate to severe VMS (reference 0.5 for "No VMS", which equals once per year) were estimated to 1.6 and 2.4, although a great variability between countries was seen, see Figure 5. The weighted average would be 3.73 *additional* visits per year. According to Medicinrådet's guidelines, the remuneration for a physician visit is DKK153.61 [10].

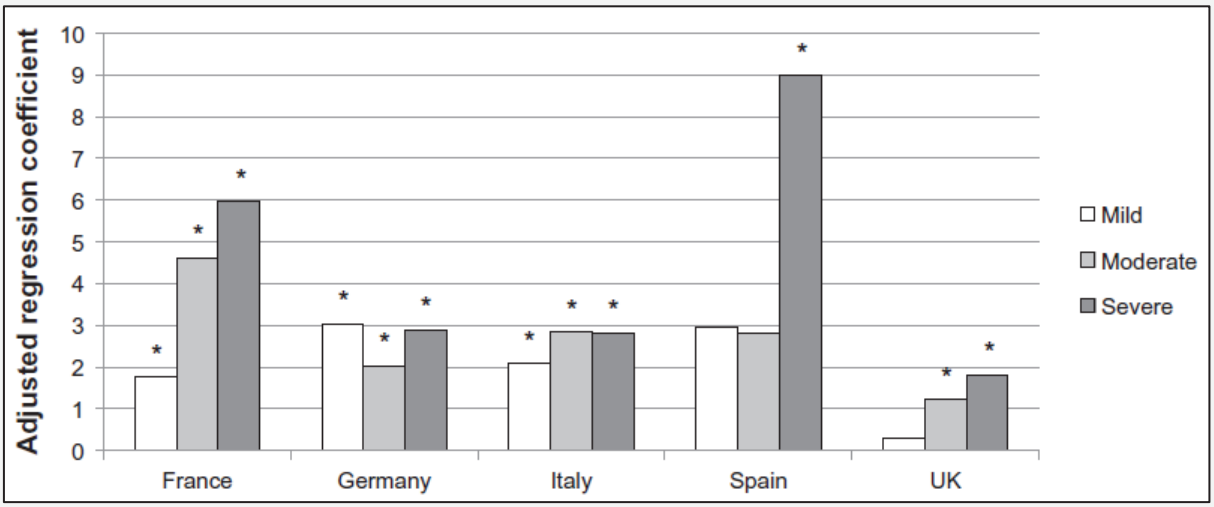

*Figure 5 Adjusted regression coefficients of severity of vasomotor symptoms predicting the number of physician visits in the past six months. [7: p266]. Notes: *P < 0.05; Covariates included age, education, income, health insurance, BMI and the Charlson comorbidity index. DiBonaventura et al. 2013 [7].*

Quality of life

Finally, the Di Bonaventura et al. study also report the quality-of-life implications from moderate and severe VMS [7]. Compared to "No VMS" the reported dis-utilities were 0.074 and 0.170, respectively, on a scale from 0.0 (dead) to 1.0 (perfect health). The dis-utility for "Mild VMS" was 0.03 which is a small but both clinically meaningful and statistically significant difference [11]. The average utility in the general female population aged 45- 59 is 0.86 [12,13]. This translates to QALY weights of 0.761 and 0.665 for moderate and severe VMS, respectively.

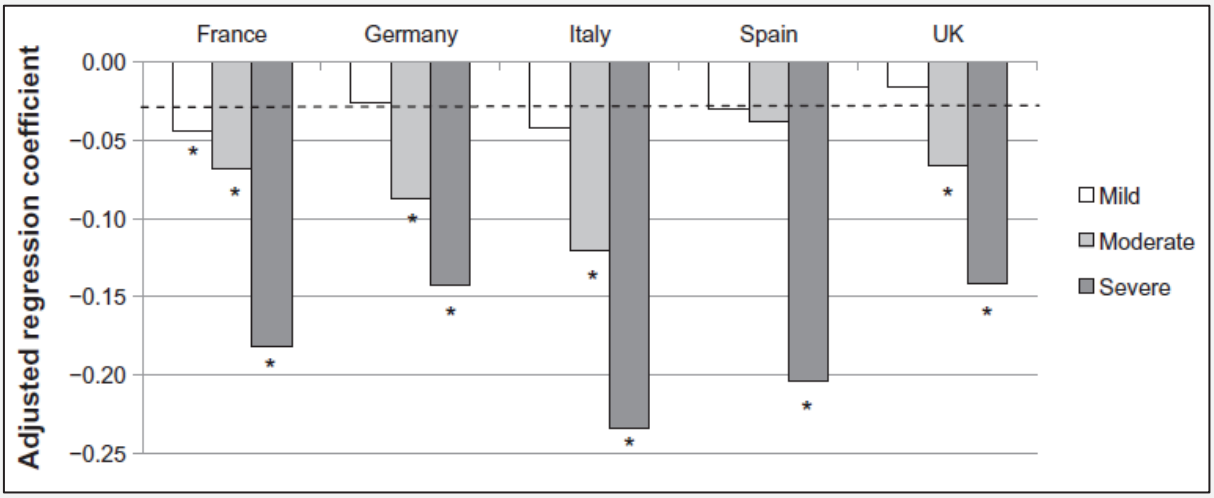

*Figure 6. Adjusted regression coefficients of severity of vasomotor symptoms predicting health status as measured by the EQ-5D. DiBonaventura et al. 2013 [7]. Notes: *P < 0.05; Covariates included age, education, income, health insurance, BMI and the Charlson comorbidity index. Dotted line represents clinically meaningful cut-off for the EQ-5D*

Comment: According to Di Bonaventura et al. "*… the health utilities observed among these [severe VMS] women (mean 0.63) are lower than those observed among patients with obesity, hypertension, hip/knee pain, and depression, and are similar to those observed among patients with asthma and diabetes.*" [7, p267; referencing 14]. As a reference, adjusted to the Danish population of women in the age group 45-54 cervical cancer survivors and advanced breast cancer patients have estimated their corresponding QALY weight to 0.67 and 0.69, which is in par with severe VMS [15].

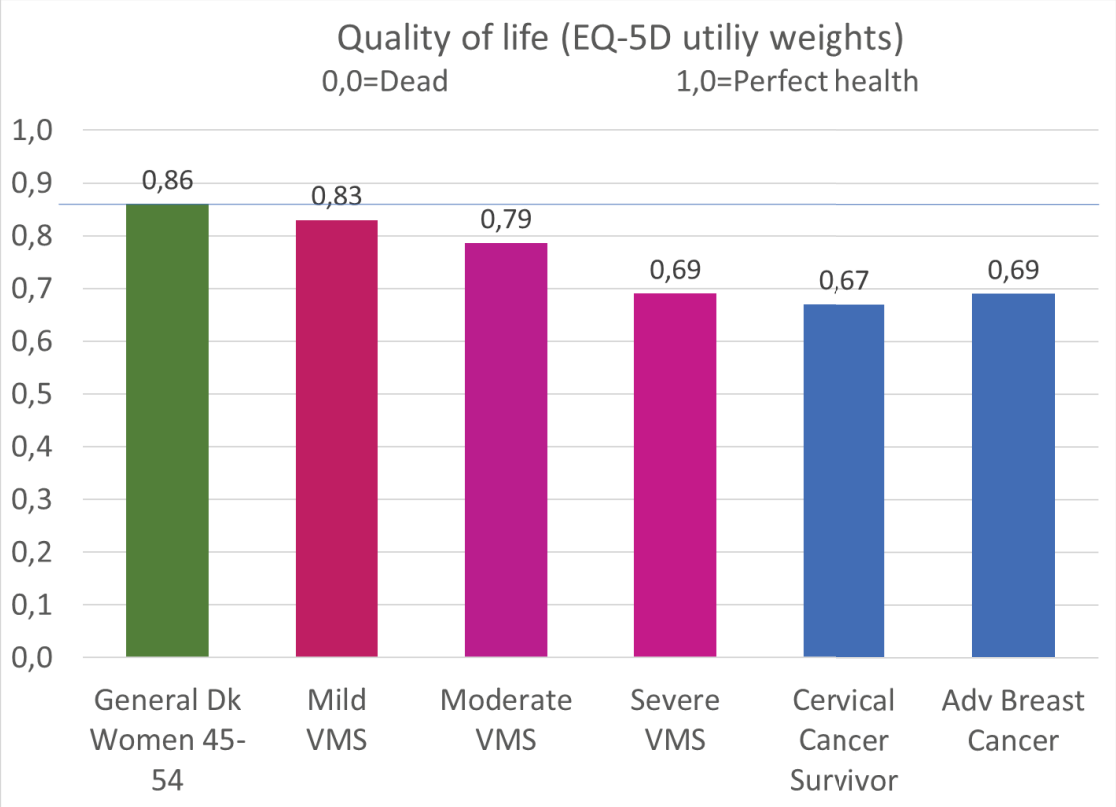

Figure 7. Estimated quality of life in the general Danish population (green bar), with mild, moderate and severe VMS (purple bars) and cancer patients (blue bars). Kaur et al. 2022 [15].

Results

The three different prevalence calculations produced rather consistent results despite substantial differences between the underlying survey designs. As seen in the top row of Table 1, the (untreated) prevalence of women with moderate or severe VMS ranges from 72,000 to 84,500 depending on the underlying source.

Combining the prevalence numbers, the annual labour cost (DKK 417,307) and productivity loss (12.2%) gives us the expected annual production loss. Using the information from the Todorova et al. publication as the base case generates production losses in the range of 3.6 to 4.3 billion Danish Kronor, depending on the assumption on the level of current VMS treatment.

To put the numbers into perspective it represents 8,700 to 10,200 employee equivalents (dividing the productivity loss by DKK 417,307).

Table 1. Prevalence of moderate/severe VMS and annual production loss by current use of VMS treatment

	Lipasti et al.	**Todorova et al.**	**Socialstyrelsen**
Overall prevalence, **number of women (0% VMS treatment)**	84 465	**83 792**	72 074
Current VMS treatment	Annual production loss (DKK)		
0%	4 289 890 256	**4 255 716 556**	3 660 583 440
10%	3 860 901 230	**3 830 144 901**	3 294 525 096
15%	3 646 406 718	**3 617 359 073**	3 111 495 924

Likewise, the additional visits due to moderate/severe VMS, i.e. in addition to the 0.52 done by the respondents in the last 6 months, would result in 268,000 (with 15% current VMS treatment) to 315,000 (with 0% current VMS treatment) *additional* physician visits per year. Applying the remuneration for a physician visit of DKK154 it totals around 45 million DKK. Apart from the financial resources, it also puts a lot of strain on the physical resources in the health care sector.

Finally, the implications on quality of life are substantial for women who experience moderate to severe VMS. Applying the disutility, i.e. the amount of reduced quality of life compared to the general population, to the estimated size of the population results in 8,700 quality-adjusted life-years lost.

Discussion

This back-of-the-envelope calculations estimate the productivity loss from moderate to severe vasomotor symptoms (VMS) due to menopause in Danish women. The results indicate that some DKK4.250 billion could be lost annually, or almost DKK51,000 per person. This would be equivalent to 10,200 female employees in the age span of 45-54 years. However, as there is a fraction of women who already today use some forms of symptom relief, the "untreated" productivity loss is probably closer to 3.6 to 3.8 billion DKK per annum, or 8,700 to 9,200 employments. To date, there does not seem to be any other attempt to estimate the burden of illness of all VMS (treated or untreated) in Denmark and while these calculations were based on the best available data, it is clear that there is a need for a larger scale study that is specific to the Danish society only and with wider representation of the population.

These are very large numbers and has some caveats. The main obstacle for estimating the burden with some precision is the fact that there is a paucity in reliable data that reports on the frequency in VMS among Danish women. There are some surveys performed in Sweden and Finland on this topic, but the size of the surveys was rather small in relation to the number of women in these age cohorts. It could raise some questions around the representativeness of the data to the rest of the female population. Furthermore, the transferability of the results between countries/cultures has not been considered in this report, although we can assume that no major differences exist between the Nordic countries. (Some additional caveats have been added in the concerned sections as well.) In addition, this report leans mainly on one publication for both productivity losses and quality of life implications. To get a more comprehensive perspective, a structured literature review is warranted, especially for the quality-of-life implications as Di Bonaventura et al. is the only source.

Furthermore, as women are overrepresented in many occupations that are important to society, like teachers, nurses and other social services, it is important to make sure that we can make best use of this resource - without wearing it out. Other implications of VMS on the labour force structure, such as gender representativeness, or wage differentials. There have been anecdotal testimonials that women have stood back from pursuing career-options due to VMS which may have an implication of future (higher) incomes and fewer representation of women in managerial positions. This is in contrast with the ambition that every person should have the ability to live according to her capability and full potential [Amartya Sen's capability theory]. These aspects are beyond the scope of this report, but nevertheless important policy topics that warrants further research.

Finally, it is also very important to remember, however, that menopause is not a disease – it is part of a natural process and for many persons the symptoms are bearable. Every person should have the right to decide if it creates a problem and if they need help. Menopause and VMS should not be seen as a labour force problem which can be solved by interventions but emphasise should instead be on the acceptance of individual decisions and to avoid stigmatising middle aged women. Nevertheless, it is the responsibility of the health authorities to secure sufficient evidence and provide the information that makes informed decisions possible.

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