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ORIGINAL STUDY

Is it possible to investigate menopausal age? A comparative cross-sectional study of five cohorts between 1968 and 2017 from the Population Study of Women in Gothenburg, Sweden

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Abstract

Objective: The aim of this study was to examine if the previously found trend of increasing menopausal age is continuing, taking into consideration hormonal use and surgical menopause in both 38- and 50-year-old women of today.

Methods: Cohort comparisons of five generations of population-based samples of 38- and 50-year-old women from the Prospective Population Study of Women in Gothenburg with start in 1968/1969, and with follow-ups in 1980/1981, 1992/1993, 2004/2005, and 2016/2017. Across the time periods newly recruited women as well as earlier participants were included. Use of hormonal contraceptives, estrogen plus progestogen therapy (EPT), and time for menopause was registered. Changes between different generations of 38- and 50-year-old women from 1968/1969 until today were studied. The overall sample size across the time periods was 1,873 individuals.

Results: The prevalence of oral contraceptives in 38-year-old women was about 10% in 1968/1969, increasing from 16% in 2004/2005 to almost 22% in 2016/2017. From 2004/2005 the use of hormonal intrauterine contraceptive method (the Levonorgestrel-releasing intrauterine system [LNG-IUS]) increased from about 11% to 14% in 2016/2017. The same pattern was found in 50-year-old women using LNG-IUS, increasing from 6% to 15.5% between 2004/2005 and 2016/2017. The total hormonal use, including LNG-IUS, oral contraceptives, and EPT, was 28% in 50-year-old women in 2016/2017. The total proportion of hormone use in 50-year-old women increased over the years and together with surgical menopause it reached over 37% in the 2016/2017 survey.

Conclusions: This study has shown an increase in the hormonal use, in both 38- and 50-year-old women, making it difficult to determine when the actual menopause occurs. Thus, the previously found increasing secular trend in menopausal age will be more complicated to assess in female generations of today and tomorrow.

Key Words: Epidemiology – Hormonal use – Menopausal age – Menstruation status – Population study.

There has been evidence for a secular upward trend in menopausal age (MPA), as well as observations of a secular downward trend for menarche, which implies a longer fertile period for women in more developed countries as in Europe and North America.[1-8]

Much knowledge about menopause is, however, based on clinic-based and cross-sectional studies rather than on longitudinal and population-based studies. Also, to be able to study the ''natural menopause,'' that is, nonsurgical and in the absence of treatment with exogenous hormones, these confounders must be taken into consideration. Thus, there are considerable difficulties associated with investigating whether a trend for later natural MPA still exists or not. Interesting ongoing research in defining the time of MPA could provide a solution in the future, but the technique still lacks standardization and there are still important gaps in scientific knowledge.[9]

Why is it important to study the timing of MPA?

The age of natural MPA is of intrinsic public health interest because MPA may be a marker of ageing and health.[10,11] It is also of great interest at what time fertility comes to an end because the maternal age has been advancing in developed countries.[12-14] Late menopause has been associated with longer survival, reduced rate of all-cause-mortality, less osteoporosis, but increased rates of breast cancer, endometrial cancer, and ovarian cancer.[15-21] A 37-year follow-up of almost 20,000 Norwegian women showed that age at natural menopause is inversely related to all-cause mortality.[20] It is also shown that early menopause before an age of around 45

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increases the risk for cardiovascular disease[22] and an increased risk of cardiovascular mortality linked to early menopause has also been suggested.[23,24] Furthermore, early onset of natural menopause has shown to be associated with a higher risk of type 2 diabetes.[25]

What different factors are influencing MPA?

The age of menopause has been shown to be influenced by several factors, ranging from genetic, ethnic, and developmental factors to the effects of hormonal, environmental, and lifestyle exposures.[26,27] Smoking is one of the most consistently shown environmental influences,[27-29] showing earlier menopause of around 1.5 years for women who smoke.[5] Even lower educational level is associated with an earlier menopause,[29,30] as well as nulliparity.[26] A link between age at menarche and the age at the final menstrual period has also been suggested. Although the findings in this area are mixed with observations suggesting that there is no relationship between menarche and menopause after adjusting for parity and cycle length,[27] other studies have shown that women with earlier menarche have an earlier age at menopause.[5,26]

MPA and the use of hormones

The use of hormonal treatment such as oral contraceptives often masks the natural cessation of menses,[27] and all types of hormonal contraceptives (HCs) can cause amenorrhea,[31] including a Levonorgestrel-releasing intrauterine system (LNG-IUS), which besides being a contraception also can be used for other indications.[32,33] Also, estrogen plus progestogen therapy (EPT) can affect the bleeding pattern. The extent of the use of hormonal treatments as well as which specific hormones are used can vary over time, thus influencing the possibilities to investigate the natural MPA.

Aim

The aim of this study was to investigate the menstrual status in 50-year-old women by comparing different age-cohorts over time from 1968 to 2016 in a representative Swedish female population. A second aim was to investigate hormonal use and surgical menopause in both 38- and 50-year-old women because this can interfere with or mask the natural MPA. We wanted to examine whether there are indications in the 50-year-old women of a continuing trend of an increasing natural MPA or not. The Population Study of Women in Gothenburg is highly suitable for this purpose because of the longitudinal design and gynecological information available.[5,34]

MATERIALS AND METHODS

The population study of women in Gothenburg from 1968 to 1969 until 2004 to 2005

One of the aims in the Population Study of Women in Gothenburg (PSWG) was to compare different age-cohorts over time in pre-, post-, and perimenopausal women.[5,34] In 1968/1969, a representative sample of 1,622 women living in Gothenburg, Sweden, was invited to a free health examination. A total of 1,462 women, aged 38, 46, 50, 54, and 60 (90.1%), accepted and participated in the Prospective Population Study of Women in Gothenburg. Follow-up examinations of 38- and 50-year-old women were conducted in 1980 to 1981 (participation rate 78.9%), when two new age groups were included (born in 1942 and 1954—38 and 26 y old, respectively) in 1992/1993 (participation rate 70.1%) and in 2004 to 2005 (participation rate 60%), with the purpose of conducting cross-sectional comparisons over time (Table 1). During all follow-up examinations, women who had participated and moved from Gothenburg were invited as well.

The population study of women in Gothenburg examination 2016 to 2017

New samples of 38- and 50-year-old women were performed in 2016/2017, in which women born in 1978 were examined for the first time. A new group of women born in 1966 was recruited to reach representativeness, the remainder having participated in 2004/2005 (Table 1). Thus, a representative sample of 515 women aged 38 and 523 women aged 50 living in Gothenburg, reachable per telephone, were invited to a free health examination. The sample was obtained from the Revenue Office Register/Tax office and the sampling method was based on dates of birth to make it representative (same dates as previous examinations but in later examinations additional dates have been included to reach the desired number of women). The survey was performed over an 8-month period. Invitations were sent out by post and followed up with a phone call provided the phone number was

TABLE 1. *Participation rates among women 38- and 50-year-old, 1968 to 2016 (the Population Study of Women in Gothenburg)*

1968-1969			1980-1981			1992-1993			2004-2005			2016-2017		
Age	*n*	(%)	Age	*n*	(%)	Age	*n*	(%)	Age	*n*	(%)	Age	*n*	(%)
												38	263[a]	(63)
									38	207[b]	(60)	50	310[a]	(73)
						38	69[c]	(72)	50	393[b]	(58)			
			38	122[d]	(85)	50	99[c]	(76)						
38	372[e]	(91)	50	355[d]	(82)									
50	398[e]	(91)												

[a]38-year-olds: 263 newly recruited, 50-year-olds: 155 newly recruited and 155 follow-ups.
[b]38-year-olds: 207 newly recruited, 50-year-olds: 242 newly recruited and 51 follow-ups.
[c]38-year-olds: 69 newly recruited, 50-year-olds: 99 follow-ups.
[d]38-year-olds: 122 newly recruited, 50-year-olds: 45 newly recruited and 310 follow-ups.
[e]38- and 50-year-olds: newly recruited (372 and 398).

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available. Fourteen women were excluded because of difficulties in speaking and understanding Swedish. Fifty-year-olds who had previously participated in the PSWG were invited regardless of whether they lived in Gothenburg or not.

A total of 573 women (263: 38-y-olds and 310: 50-y-olds) accepted the invitation (63% and 73%, respectively) and participated in 2016/2017 (Fig. 1). As in previous investigations, physical examinations were performed according to the same protocol at all examinations.

A total of 155 women born in 1966 who participated in the 2004/2005 examination as 38-year-olds also participated in 2016/2017 as 50-year-olds. In total, 1,889 women born in 1918, 1930, 1942, 1954, 1966, and 1978 (when 38- and 50-y-old) were included in this analysis.

The women were classified as ''still menstruating'' or ''stopped menstruating.'' If a woman stated that she had stopped menstruating less than a year ago, she was classified as ''still menstruating.''

Definition of menstrual status and hormonal treatments

Information about menstrual status, including surgical menopause and the use of EPT, was obtained from a questionnaire and checked by a standardized interview. Menopause was defined as more than 12 months without menstruation. Low-dose estrogen treatment for vaginal discomfort was not defined as hormonal treatment. Natural menopause was defined as nonsurgical and in the absence of treatment with exogenous hormones, that is, EPT, LNG-IUS, or other HC. Use of LNG-IUS was examined separately from the other types of HCs. The concept HC included not only oral contraceptives but also other HC methods such as patches and implants. EPT was defined as a combination of estrogen and progestogen.

The women also reported the occurrence of gynecological surgical operations, gynecological cancer, and treatment of gynecological cancer. Surgical menopause was defined if the woman had undergone bilateral oophorectomy and/or hysterectomy. All women who reported treatment for gynecological cancer also had undergone surgical menopause.

The reporting of menstrual status and hormonal treatment has been validated in previous studies of PSWG.[35-37]

Statistics

Standard methods were used for descriptive statistics. Frequencies were compared by using chi-square, two sided tests. Statistical significance was set at $P < 0.05$.

Ethical considerations

All women who participated in the Prospective Population Study of Women in Gothenburg were invited to a free health

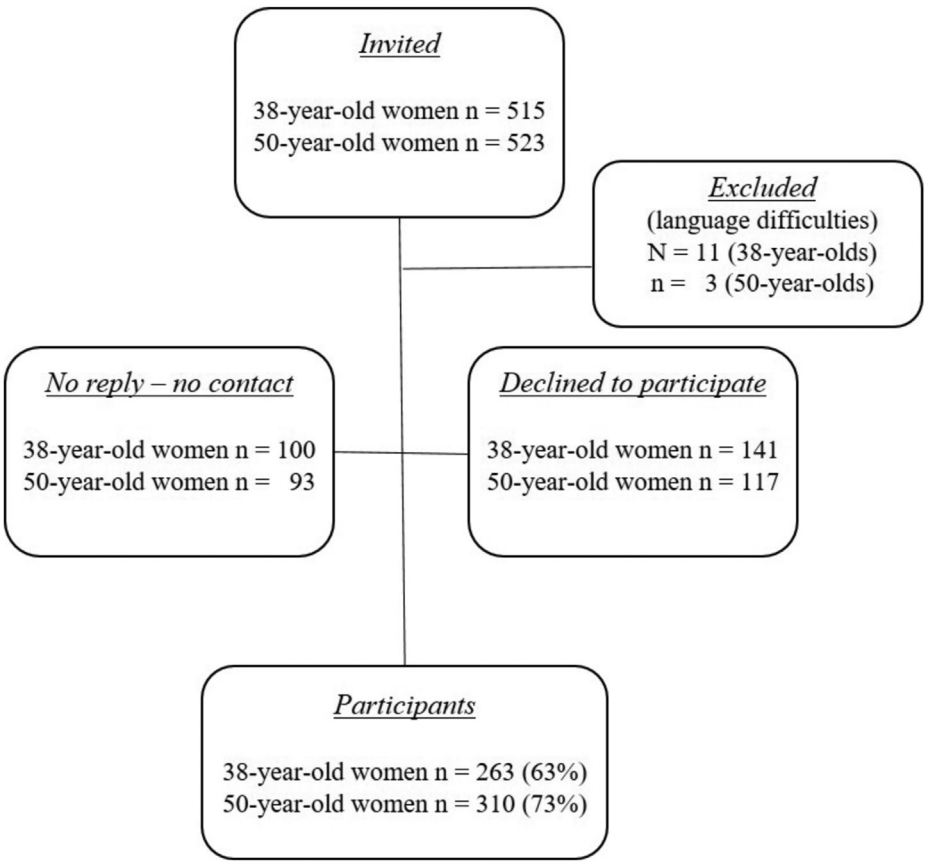

FIG. 1. Flow chart of the 2016 to 2017 examination in the Population Study of Women in Gothenburg.

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examination, by post, followed by a telephone call. It was made clear that participation was voluntarily, could be terminated at any time, and that confidentiality was guaranteed. Participants were informed by a personal letter about results of all examinations, and if any results required further investigation (ethical approval Regional Ethical Committee Gothenburg 258-16 T853-16).

RESULTS

Hormone use in 38-year-old women

The assessments of the prevalence of hormone use in the cohort of 38-year-old women from 1968 until 2016 are described in Table 2. A considerable change was seen in the use of contraceptives with a tripled use of HC and an almost linear increase in the use of LNG-IUS from the beginning of the 1990s, when the use of HC and LNG-IUS was 7.2% and 0%, respectively, to the maximal prevalence of 21.7% and 14.1%, respectively, in 2016. Hence, in total, 35.8% of all 38-year-old women in the 2016 survey were using some kind of hormones.

Hormone use in 50-year-old women

The proportion of women using EPT reached a maximum level (28.3%) in 1992, but then decreased relatively sharply, and in 2016 the use of EPT was 3.9% (Table 3). None of the women in the 50-year-old cohort used any HC or LNG-IUS in 1992, but the proportion of users increased thereafter to 8.7% and 15.5%, respectively, in 2016. Noteworthy, the proportion of women using LNG-IUS more than doubled in the 12 years that had elapsed between 2004 and 2016, from 6.1% to 15.5%, and the use of HC more than tripled during the same time. When looking at HC, LNG-IUS, and EPT together, a total of 28.1% of the 50-year-old women in the 2016 survey were using hormone treatment, thus representing more than a quarter of the women in this age group.

Menstruation status in 50-year-old women

In 1968, the proportion of women still menstruating was 55.3%, increasing to 66.7% in 1992. A slight decrease to 64.2% was seen in women still menstruating in 2004, a proportion that remained unchanged in 2016 (Table 4). Since 1980 and until 2016, the proportion of women still menstruating remained rather unchanged. Consequently, the corresponding proportion of 50-year-old women who stopped menstruating reached a maximum in 1968 with 44.7% and decreased thereafter. Since 1980, the proportion of 50-year-old women who stopped menstruating has been relatively stable, remaining at approximately 35% (Table 4).

DISCUSSION

Principal findings

In the present study, no obvious trend in changed menstrual status in 50-year-old women after 1980 could be demonstrated. Between 1968 and 1980, a clear increase from 55.3% to 64.8% could, however, be seen in the proportion of 50-year-old women still menstruating, which is consistent with the increase in menopausal age shown in previous research.[5] In the following examinations, particularly in 1992 and in 2016, an increase was seen in the proportion of 50-year-old women who were either using hormonal treatment and/or who had surgical menopause. In 2016, the proportion of women in these categories reached just over 37% in total, thus making it difficult to obtain a valid assessment of the natural menopausal age of the population. Consequently, it is not possible to draw any certain conclusions about whether a time trend of later natural MPA still exists or not, even though no apparent trends in menstrual status can be seen after 1980. Another consequence of the increase seen in the use of HC and LNG-IUS, which can be used also before the first menopausal symptoms and mask the natural cessation of menses, is that it might be more difficult also for the women themselves to have knowledge about their own MPA.

The proportion of 38-year-old women with surgical menopause was low throughout the years, and in the two latest examinations none of the 38-year-old women had surgical menopause, possibly because of the increasing number of women using a LNG-IUS, which can in some cases be an alternative to surgical treatments for menorrhagia.[33] The total proportion of 38-year-old women using some kind of hormonal treatment has increased greatly since 1992. In 2016 almost 36% of the 38-year-old women were using either HCs or an LNG-IUS, an increase in use compared with any of the previous examinations, and since 1992 the use has more than quadrupled. This large increase seen in hormone use in 38-year-old women indicates that there might be further difficulties onward to investigate the natural menopausal age.

TABLE 2. *38-year-old women and the use of hormones*

Examination year	Total	HC		LNG-IUS		EPT		Surgical menopause[a]	
	n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
1968	372	39	(10.0)	0	(0)	0	(0)	5	(1.0)
1980	122	9	(7.4)	0	(0)	0	(0)	2	(2.0)
1992	69	5	(7.2)	0	(0)	1	(1.4)	2	(2.9)
2004	207	33	(15.9)	22	(10.6)	0	(0)	0	(0)
2016	263	57	(21.7)[b]	37	(14.1)[c]	0	(0)	0	(0)

EPT, estrogen plus progestogen therapy; HC, hormonal contraceptives; LNG-IUS, Levonorgestrel-releasiing intrauterine system.
[a]Surgical menopause: bilateral oophorectomy and/or hysterectomy.
[b]$P < 0.001$ when comparing HC use in 2016 with 1968 to 2004.
[c]$P < 0.001$ when comparing LNG-IUS use in 2016 with 1968 to 2004.

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TABLE 3. *50-year-old women and the use of hormones*

Examination year	Total	HC		LNG-IUS		EPT		Surgical menopause[a]	
	n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
1968	398	0	(0)	0	(0)	6	(1.5)	25	(6.3)
1980	355	13	(3.7)	0	(0)	24	(6.8)	24	(6.8)
1992	99	0	(0)	0	(0)	28	(28.3)	10	(10.1)
2004	293	8	(2.7)	18	(6.1)	22	(7.5)	26	(8.9)
2016	310	27	(8.7)[b]	48	(15.5)[c]	12	(3.9)	28	(9.0)

EPT, estrogen plus progestogen therapy; HC, hormonal contraceptives; LNG-IUS, Levonorgestrel-releasiing intrauterine system.
[a]Surgical menopause: bilateral oophorectomy and/or hysterectomy.
[b]$P < 0.001$ when comparing HC use in 2016 with 1968 to 2004.
[c]$P < 0.001$ when comparing LNG-IUS use in 2016 with 1968 to 2004.

TABLE 4. *Menstruation status, hormonal use, and surgical menopause in 50-year-old women*

Examination year	Total	Still menstruating		Stopped menstruating		Any kind of hormonal treatment		Surgical menopause[a]	
	n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
1968	398	220	(55.3)	178	(44.7)	5	(1.3)	25	(6.3)
1980	355	230	(64.8)	125	(35.2)	37	(10.4)	24	(6.8)
1992	99	66	(66.7)	33	(33.3)	28	(28.3)	10	(10.1)
2004	293	188	(64.2)	104	(35.5)	48	(16.4)	26	(8.9)
2016	310	199	(64.2)	111	(35.8)	87	(28.1)[b]	28	(9.0)

[a]Surgical menopause: bilateral oophorectomy and/or hysterectomy.
[b]$P < 0.001$ when comparing any kind of hormonal treatment between the 2016 and 2004 examinations.

The most common type of hormone treatment among 50-year-old women in 2016 was found to be the LNG-IUS, a method that has increased largely since 1992. In 38-year-old women, HC was the most common hormonal treatment, but also in this group of women the LNG-IUS stands out with the large increase seen since 1992. Compared with, for example, oral contraceptives,[33] the LNG-IUS is a newer method, even though the first versions of this kind of intrauterine device were described several decades ago.[38] The locally administered levonorgestrel gives a suppression of the endometrium with atrophic glands, and the local effect often leads to amenorrhea. Besides contraception, the indications for the LNG-IUS[39-41] can also be menorrhagia as well as protection of the endometrium during estrogen treatment due to menopausal symptoms. Ovulation can be present both among amenorrheic women and women with regular menstruations using the LNG-IUS, thus all together further complicating investigations of possible changes in the natural MPA.

The total proportion of 50-year-old women using hormones in 2016 increased to 71.3% compared with 2004. The proportion in 2016 was, however, approximately as large as it was in 1992, but at that time EPT was the only hormone treatment used among 50-year-old women. EPT use then dropped dramatically from 28.3% in 1992 to 3.9% in 2016, when instead HC and LNG-IUS constituted the absolute majority of the hormone use.

The most likely explanations for the great decline in EPT use seen in this study are the negative attitudes and decreasing prevalence of EPT use in response to the findings of large randomized controlled trials such as the Women's Health Initiative trial (WHI) and the Heart and Estrogen/Progestin Replacement Study (HERS) in the beginning of the millennium.[42-46] These studies found an increased risk of breast cancer and venous thromboembolism in EPT users.[47,48] Although more recent studies have shown that the results from WHI might have been overestimating the risks in all-cause mortality since the women studied in the WHI were not quite representative[49], the risks versus benefits of EPT are still debated.

In line with the reasoning above, a possible explanation for the increase seen in the use of HC in 50-year-old women might be that many women continue to use HC for a longer time because of an unwillingness to use EPT.

Implications in relation to other studies

A significant secular trend of increase in MPA has previously been shown in the Population Study of Women in Gothenburg, independent of variations in socioeconomic status, smoking status, oral contraceptive use, or use of EPT as well as other potential confounders, with 1 year later natural menopausal age found among women born 10 years later.[5] These women, born in 1908, 1914, 1918, 1922 and 1930, were followed over menopausal age. Thus, the women born in the latest of these cohorts turned 50 years in 1980. The mean menopausal age for women born in 1930 was shown to be 51.5 for never smokers and 50.0 for ever smokers. The increase in 50-year-old women still menstruating that was seen in our study between 1968 and 1980 is, as discussed above, consistent with the increase in menopausal age shown in this previous study, which is logical since the women in both these studies were part of the same population study.

The increase between 1968 and 1980 in women still menstruating can also be regarded as consistent with an increase in menopausal age shown by Nichols et al.[1] In this

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American study, a continuing increase in menopausal age was, however, also seen for women born in later years. In our study we also observed a continued increase, although not as large as during the previous years, in the 50-year-old women still menstruating between 1980 and 1992. However, since the total amount of confounders in terms of hormonal treatments and surgical menopause was considerable in 2016 it is not possible to draw any conclusions about whether this increase constitutes part of a continuing trend in menstrual status or not.

The studies of trends in menopausal age also differed from our study, not only by studying menopausal age rather than menstrual status, but also by excluding certain groups of women. In the Rödström study,[5] women who had ever taken EPT or HCs after the age of 45 or had undergone surgical menopause or both were excluded. Also, the comparisons in the study by Nichols concerned women who had never used EPT, with the possible consequence that the results may not be applicable for women having used hormone treatments.

In a study of secular trends in menopausal age in Finland, the median menopausal age was 50 years in 1997 and 51 years in 2007, with a larger difference in mean menopausal age between smokers and nonsmokers in 2007 than in 1997.[50] The authors of this study, however, reached the conclusion that a secular trend in menopausal age may not have taken place. EPT treatment was considered in the Finnish study, but not other hormonal treatments such as HCs or LNG-IUS. On the basis of results showing that EPT had decreased in Finland, among other factors, the conclusion was drawn that determination of menopausal age may become easier in the present decade. Thus, the conclusion of the Finnish study is completely different from the one in our study, where other hormonal treatments such as LNG-IUS and HCs were taken into account and were shown to increase, thus rather leading to the conclusion that determination of menopausal age might become more difficult going forward.

As stated in the introduction, the former observed trends in menopausal and menarcheal age might imply a longer fertile period for women in some parts of the world. If determination of menopausal age were, however, to become more difficult onward, a natural consequence of this is that it might also be more difficult to determine the total fertile period of women. To be able to determine potential trends in the upper limit of the reproductive life span as constituted by the menopausal age, this study indicates the need for more and larger studies, with the extensive use of hormones among women currently shown taken into account.

Strengths and limitations of the study

A strength of this study is that the comparisons made among different cohorts are based on women who have all been examined in the same longitudinal study—the Population Study of Women in Gothenburg. This ensures that the examinations have been performed in the same way and that the questionnaires were similar throughout.

Another strength is the consideration of both surgical menopause and different kinds of hormone use among the women in the comparisons among the different cohorts. It is, however, not possible to determine the exact menopausal age in this study since the women have not been followed after 50 years of age. Instead, it is the menstrual status in 50-year-old women that is studied, but any trend in this age is likely to be valid also for the menopausal age in women.

A possible weakness of the study is that 14 women were excluded because of language difficulties, which might have had some influence on the representativeness due to less participation among immigrants. The overall participation rate has declined during the years, but the 2016 to 2017 examination is comparable to 2004 to 2005 and must be regarded as acceptable for today's population studies.[51] The sample could thus be regarded as representative for Swedish women, but cannot be generalized across other populations. Furthermore, it cannot be excluded that the choice of contraceptive method might, to some degree, depend on the attitudes of the local gynecologists, a possibility that was noted in another study from the Gothenburg region.[52]

CONCLUSIONS

In this study, we do not claim to assess the MPA. Rather we consider the difficulties in estimating the MPA, as the increasing amount of hormone users make the confounding factors stronger and we can therefore not draw any conclusions about MPA.

Since 1980 the total proportion of hormone use in 50-year-old women has largely increased, thus making natural menopause, that is, nonsurgical and in the absence of treatment with exogenous hormones, more difficult to investigate. In the latest examination of the Population Study of Women in Gothenburg, the different categories of hormone use and surgical menopause in 50-year-old women reached just over 37% in total, a proportion that is high enough to clearly compromise the validity of any attempts to assess natural menopausal age. Therefore, it is not possible to determine in the present study if there are any indications of a continuing time trend in later natural MPA or not. Furthermore, the total proportion of 38-year-old women using some kind of hormonal treatment has also increased and might possibly still be increasing. This indicates that investigating natural menopausal age might also be difficult in the near future and onward.

REFERENCES

1. Nichols HB, Trentham-Dietz A, Hampton JM, et al. From menarche to menopause: trends among US Women born from 1912 to 1969. *Am J Epidemiol* 2006;164:1003-1011.
2. Flint M. Is there a secular trend in age of menopause? *Maturitas* 1978;1:133-139.
3. Dratva J, Gomez Real F, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. *Menopause* 2009;16:385-394.
4. Olesen AW, Jeune B, Boldsen JL. A continuous decline in menarcheal age in Denmark. *Ann Hum Biol* 2000;27:377-386.

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5. Rodstrom K, Bengtsson C, Milsom I, Lissner L, Sundh V, Bjourkelund C. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. *Menopause* 2003;10:538-543.
6. Harris MA, Prior JC, Koehoorn M. Age at menarche in the Canadian population: secular trends and relationship to adulthood BMI. *J Adolesc Health* 2008;43:548-554.
7. Helm P, Helm S. Decrease in menarcheal age from 1966 to 1983 in Denmark. *Acta Obstet Gynecol Scand* 1984;63:633-635.
8. Aksglaede L, Sorensen K, Petersen JH, Skakkebaek NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. *Pediatrics* 2009;123:e932-e939.
9. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97:1159-1168.
10. Snowdon DA, Kane RL, Beeson WL, et al. Is early natural menopause a biologic marker of health and aging? *Am J Public Health* 1989;79:709-714.
11. Cooper GS, Sandler DP. Age at natural menopause and mortality. *Ann Epidemiol* 1998;8:229-235.
12. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol* 2004;104:727-733.
13. Carter D, Watt AM, Braunack-Mayer A, et al. Should there be a female age limit on public funding for assisted reproductive technology? *J Bioeth Inq* 2013;10:79-91.
14. Breart G. Delayed childbearing. *Eur J Obstet Gynecol Reprod Biol* 1997;75:71-73.
15. de Graaff J, Stolte LA. Age at menarche and menopause of uterine cancer patients. *Eur J Obstet Gynecol Reprod Biol* 1978;8:187-193.
16. Kritz-Silverstein D, Barrett-Connor E. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women. *Am J Public Health* 1993;83:983-988.
17. Franceschi S, La Vecchia C, Booth M, et al. Pooled analysis of 3 European case-control studies of ovarian cancer: II. Age at menarche and at menopause. *Int J Cancer* 1991;49:57-60.
18. van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. *Osteoporos Int* 2003;14:525-530.
19. Monninkhof EM, van der Schouw YT, Peeters PH. Early age at menopause and breast cancer: are leaner women more protected? A prospective analysis of the Dutch DOM cohort. *Breast Cancer Res Treat* 1999;55:285-291.
20. Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. *Am J Epidemiol* 2003;157:923-929.
21. Ossewaarde ME, Bots ML, Verbeek AL, et al. Age at menopause, cause-specific mortality and total life expectancy. *Epidemiology* 2005;16:556-562.
22. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. *Maturitas* 2010;65:161-166.
23. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016;1:767-776.
24. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet* 1996;347:714-718.
25. Muka T, Asllanaj E, Avazverdi N, et al. Age at natural menopause and risk of type 2 diabetes: a prospective cohort study. *Diabetologia* 2017;60:1951-1960.
26. Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod* 2017;32:679-686.
27. Gold EB. The timing of the age at which natural menopause occurs. *Obstet Gynecol Clin North Am* 2011;38:425-440.
28. Midgette AS, Baron JA. Cigarette smokingv and the risk of natural menopause. *Epidemiology* 1990;1:474-480.
29. Santoro N, Brockwell S, Johnston J, et al. Helping midlife women predict the onset of the final menses: SWAN, the Study of Women's Health Across the Nation. *Menopause* 2007;14 (3 Pt 1):415-424.
30. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol* 2001;153:865-874.
31. Bixo M. Läkemedelsboken—Allmän Gynekologi. In Läkemedelsverket. Available at: https://lakemedelsboken.se/kapitel/gynekologi/allman_gynekologi.html#i3_3. Accessed March 28, 2018.
32. Suvanto-Luukkonen E, Kauppila A. The levonorgestrel intrauterine system in menopausal hormone replacement therapy: five-year experience. *Fertil Steril* 1999;72:161-163.
33. Luukkainen T, Toivonen J. Levonorgestrel-releasing IUD as a method of contraception with therapeutic properties. *Contraception* 1995;52:269-276.
34. Bengtsson C, Blohme G, Hallberg L, et al. The study of women in Gothenburg 1968-1969—a population study. General design, purpose and sampling results. *Acta Med Scand* 1973;193:311-318.
35. Bengtsson C, Hallberg L, Hällström T, et al. The population study of women in Göteborg 1974-1975—the second phase of a longitudinal study: general design, purpose and sampling results. *Scand J Soc Med* 1978;6:49-54.
36. Rödström K, Bengtsson C, Lissner L, Björkelund C. Pre-existing risk factor profiles in users and non-users of hormone replacement therapy: prospective cohort study in Gothenburg. *Sweden BMJ* 1999;319:890-893.
37. Rödström K, Bengtsson C, Lissner L, Björkelund C. Reproducibility of self-reported menopause age at the 24-year follow-up of a population study of women in Göteborg, Sweden. *Menopause* 2005;12:275-280.
38. Pharriss BB, Erickson R, Bashaw J, Hoff S, Place VA, Zaffaroni A. Progestasert: a uterine therapeutic system for long-term contraception: I. Philosophy and clinical efficacy. *Fertil Steril* 1974;25:915-921.
39. Nilsson CG, Allonen H, Diaz J, Luukkainen T. Two years' experience with two levonorgestrel-releasing intrauterine devices and one copper-releasing intrauterine device: a randomized comparative performance study. *Fertil Steril* 1983;39:187-192.
40. Nilsson CG, Lahteenmaki PL, Luukkainen T. Ovarian function in amenorrheic and menstruating users of a levonorgestrel-releasing intrauterine device. *Fertil Steril* 1984;41:52-55.
41. Nilsson CG, Luukkainen T, Arko H. Endometrial morphology of women using a d-norgestrel-releasing intrauterine device. *Fertil Steril* 1978;29:397-401.
42. Sievert LL, Saliba M, Reher D, et al. The medical management of menopause: a four-country comparison care in urban areas. *Maturitas* 2008;59:7-21.
43. Constantine GD, Graham S, Clerinx C, et al. Behaviours and attitudes influencing treatment decisions for menopausal symptoms in five European countries. *Post Reprod Health* 2016;22:112-122.
44. Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust* 2008;188:641-644.
45. Ekstrom H. Trends in middle-aged women's reports of symptoms, use of hormone therapy and attitudes towards it. *Maturitas* 2005;52:154-164.
46. Waaseth M, Bakken K, Lund E. Patterns of hormone therapy use in the Norwegian Women and Cancer study (NOWAC). *Maturitas* 2009;63:220-226.
47. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
48. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.
49. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women's health initiative randomized trials. *JAMA* 2017;318:927-938.
50. Pakarinen M, Raitanen J, Kaaja R, Luoto R. Secular trend in the menopausal age in Finland 2007 and correlation with socioeconomic, reproductive and lifestyle factors. *Maturitas* 2010;66:417-422.
51. Bjorkelund C, Andersson-Hange D, Andersson K, et al. Secular trends in cardiovascular risk factors with a 36-year perspective: observations from 38- and 50-year-olds in the Population Study of Women in Gothenburg. *Scand J Prim Health Care* 2008;26:140-146.
52. Hagstad A. Gynecology and sexuality in middle-aged women. *Women Health* 1988;13:57-80.

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