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Childbirth close to natural menopause: does age at menopause matter?**M.S. Gottschalk^{1,2}, A. Eskild^{1,2}, T.G. Tanbo^{2,3}, and E.K. Bjelland^{1*}**

¹Department of Obstetrics and Gynecology, Akershus University Hospital, P.O. Box 1000, N-1478 Lørenskog, Norway

²Institute of Clinical Medicine, University of Oslo, P.O. Box 1171 Blindern, N-0318 Oslo, Norway

³Department of Reproductive Medicine, Oslo University Hospital Rikshospitalet, P.O. Box 4950 Nydalen, N-0424 Oslo, Norway

***Corresponding author.** Elisabeth K. Bjelland, Department of Obstetrics and Gynecology, Akershus University Hospital, P.O. Box 1000, N-1478 Lørenskog, Norway. Tel: +47 92238389

E-mail: Elisabeth.Krefting.Bjelland@ahus.no

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Key message

More than fifty percent of the women with menopause before the age of 45 had a successful pregnancy within 10 years prior to natural menopause. Among women with menopause in their mid-fifties, less than one percent had a successful pregnancy within 10 years prior to natural menopause.

Abstract

Research question: Does a successful spontaneous pregnancy in the years close to natural menopause depend on age at menopause?

Design: A retrospective population based study of 4,157 parous postmenopausal women in Norway, born during the years 1925–1940. Data were obtained by two self-administered questionnaires in the HUNT2 Survey (1995–1997). We calculated the proportions of women who gave birth within 5 years and within 10 years prior to menopause among all women, and according to categories of age at menopause.

Results: Overall, 2.7% (114/4,157) of all women gave birth within 5 years, and 11.7% gave birth (487/4,157) within 10 years prior to menopause. Among women with menopause before the age of 45, 23.5% (81/344) gave birth within 5 years, and 55.5% (191/344) gave birth within 10 years prior to menopause. Among the women with menopause at the age of 55 or older, no women (0/474) gave birth within 5 years, and 0.2% (1/474) gave birth within 10 years prior to menopause.

Conclusions: More than half of the women with menopause before the age of 45 gave birth within 10 years prior to natural menopause, whereas that was true for virtually no women with menopause at the age of 55 or older. Thus, the length of the sterile interval prior to natural menopause may vary by age at menopause.

Key words: childbirth, fertility, menopause, parity, reproduction.

Introduction

In many countries women's mean age at first childbirth has increased (Mathews, 2016). Mean age at menopause, however, has remained relatively stable over time (Dratva et al, 2009; Schoenaker et al., 2014). Thus, the number of years for reproduction has declined.

It is well known that women's fecundity decreases in the years close to menopause (Broekmans et al., 2007), and that women's age at menopause varies largely (Schoenaker et al., 2014). It is assumed that a successful spontaneous pregnancy is rarely achieved within a 10-year interval prior to menopause (te Velde and Pearson, 2002; Towner et al., 2016), and that such interval is independent of age at menopause (Faddy and Gosden, 1996; Nikolaou and Templeton, 2003). Postponing pregnancy to the age of 35–40 may therefore reduce a woman's chance of giving birth, particularly if she will experience early menopause.

The assumption of a fixed sterile interval prior to natural menopause independent of age at menopause is poorly documented. The assumption is mainly based on retrospective data with comparison of the age distribution at last childbirth in one population with the age distribution of menopause in another population (Desjardins et al., 1994; te Velde and Pearson, 2002; Tietze, 1957). In these studies the difference between mean age at menopause and mean age at last childbirth was 10 years. Also the poor success rate of assisted reproduction treatment in women older than 40 years (Bopp et al., 1995; United States, National Summary Report, 2014) supports the assumption that women cannot give birth within 10 years prior to menopause, since women's mean age at menopause is approximately 50 years (Schoenaker et al., 2014). However, none of these studies accounts for the large individual variation in age at menopause. We are aware of no studies of childbirth in the years close to natural menopause using individual data of age at last childbirth and also of age at menopause.

Among 4,157 postmenopausal women in Norway, born during the years 1925–1940, we calculated the proportions of women who had a successful pregnancy within 5 years and within 10 years prior to natural menopause, and we studied whether the proportions with successful pregnancy differed by age at menopause.

Methods

Study design and recruitment

We performed a retrospective study, using data from a population-based survey in Norway (the HUNT2 Survey). This survey aimed to include all inhabitants aged 20 or older in the Nord-Trøndelag county in Norway during the years 1995–1997. Details about the HUNT2 Survey are described elsewhere (Holmen et al., 2003; Krokstad et al., 2013).

Data were collected by using two self-administered questionnaires, and only postmenopausal women who had given birth and had answered both questionnaires were eligible for our study. Of all women aged 20 or older in the county of North-Trøndelag, 71% participated in the HUNT2 Survey and answered the first questionnaire. Of these, 87% also completed the second questionnaire that was answered by women aged 20–69 years. Thus, approximately 60% of women in this age group in the North-Trøndelag county answered both questionnaires (24,865 women). Women aged 60–69 years had the highest response rate.

We excluded women who had not given birth ($n = 3,554$), lacked information about number of childbirths ($n = 740$), and women who had not reached menopause ($n = 12,722$) (Supplemental Figure A.1). We also excluded women with missing or implausible values about age at last childbirth or age at menopause ($n = 460$). Additionally, we excluded women who had had both ovaries and/or the uterus surgically removed before natural menopause, or had missing information about age at such surgery ($n = 1,111$). To avoid overrepresentation of

women with early menopause, we excluded menopausal women born after 1940 ($n = 2,122$). Thus, 4,157 women, born during the years 1925–1940, could be included in our data analyses.

Study factors

The first questionnaire included questions about socio-demographic factors and health. The second questionnaire included questions about menstruation, childbirth, and surgery on the ovaries or uterus. Information about the number of childbirths and age at last childbirth was based on the following questions: “How many times have you given birth?”, “List the year of each childbirth”, and “How old were you at your last childbirth?”

Information about age at natural menopause was obtained by the following questions: “Do you still have menstrual periods? (yes/no)”. “If no, at what age did you have your last menstrual period?” In the analyses, age at menopause was categorized as: <45 (early menopause), 45–49, 50–54 and ≥ 55 years old.

The time interval between last childbirth and menopause was calculated by subtracting age at last childbirth from age at menopause and categorized as: childbirth within 5 years (yes/no) and childbirth within 10 years prior to menopause (yes/no). Number of previous childbirths was categorized as follows: 0–1, 2–3 and >3 previous childbirths.

Statistical methods

We used kernel density estimation to illustrate the age distributions at last childbirth and at menopause. Within the above defined categories of age at menopause, we calculated mean number of childbirths, mean age at last childbirth, mean age at menopause and the mean time interval between last childbirth and menopause with standard deviations (SD). Differences in means between categories were assessed by analysis of variance (ANOVA).

Thereafter, we calculated the proportions of women who gave birth within 5 years and within 10 years prior to menopause among all women, and within the categories of age at menopause. We repeated these data analyses after exclusion of women who had used oral contraceptives or had undergone sterilization. We also performed separate analyses among women born in 1930 or earlier, since these women had particularly limited access to oral contraceptives or intrauterine devices during their reproductive period.

In supplemental analyses, we calculated the proportions of women with childbirth within 5 years and within 10 years prior to menopause according to number of previous childbirths, and we repeated these analyses within the categories of age at menopause. All the data analyses were performed using Stata/SE version 14.2 (StataCorp, College Station, TX, USA).

Details of ethics approval

The HUNT2 Survey was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Data Protection Authority. All participants signed an informed consent form. The present study was approved by the Regional Committee for Medical and Health Research Ethics (reference no. 2017/105 REK South-East D) and the HUNT Research Centre Review Board (reference no. 2017/11178/TRS).

Results

The mean age of the women at data collection was 62.5 years (SD 4.2 years) (Table 1), and the mean number of childbirths was 3.2 (SD 1.3 childbirths). In total, 93.0% of the women had given birth to two children or more. Mean age at last childbirth was 31.7 years (SD 5.0

years), and mean age at menopause was 50.0 years (SD 4.1 years) (Table 1). Of all women, 12.7% had used oral contraceptives and 10% had undergone sterilization (in total 20.7%).

Figure 1A illustrates the distributions of age at last childbirth and age at menopause. In total, 6.3% (262/4,157) of the women gave birth at the age of 40 or older, and very few women gave birth at age of 45 or older (0.3%, 12/4,157). Most childbirths at the age of 40 or older were among women who reached menopause at the age of 50 or older (66.8%, 175/262). Nonetheless, the distribution of age at last childbirth was similar across categories of age at menopause (Figure 1B, Supplemental Table A.1). Thus, the proportion of women who had their last childbirth at the age of 40 or older was 4.1% (14/344) among women with menopause before the age of 45, and 6.6% (175/2,670) among women with menopause at the age of 50 or older. The mean time interval between last childbirth and menopause was 18.3 years (SD 6.3 years), and this time interval increased with increasing age at menopause (ANOVA, $P < 0.001$) (Supplemental Table A.1).

Among all women, 2.7% (114/4,157) gave birth within 5 years prior to menopause, and 11.7% (487/4,157) gave birth within 10 years prior to menopause. These proportions increased with decreasing age at menopause (Table 2). Among the 8.3% (344/4,157) who reached menopause before the age of 45, 23.5% gave birth within 5 years, and 55.5% gave birth within 10 years prior to menopause. Among the women who reached menopause at the age of 55 or older, no women gave birth within 5 years, and one woman gave birth within 10 years prior to menopause. We found similar pattern among the women who had not used oral contraceptives or undergone sterilization (Table 2). Among the women who were born in 1930 or earlier and had reached menopause at the age of 55 or older (114/1,199), no women gave birth within 5 years, and one woman gave birth within 10 years prior to menopause (Table 2).

The proportion of women with childbirth within 10 years prior to menopause, decreased with each remaining year to menopause (Figure 2), and only 1.0% (42/4,157) of all women gave birth within two years prior to menopause. However, among the women with menopause before the age of 45, 10% (34/344) gave birth within two years prior to menopause.

Also, the number of previous childbirths was related to childbirth in the years close to menopause. The higher the number of previous childbirths, the higher was the proportion of women with childbirth within 5 years and within 10 years prior to menopause (Supplemental Table A.2). This pattern was most prominent among women with menopause before the age of 45. In fact, 82.1% of the women with menopause before the age of 45 and with more than three previous childbirths gave birth within 10 years prior to menopause.

Discussion

In this retrospective population based study of 4,157 parous women, born during the years 1925–1940, more than half of the women with menopause before the age of 45 gave birth within 10 years prior to menopause, whereas that was true for less than one percent of the women with menopause at the age of 55 or older.

We performed a study of women in a population with many children, and with limited access to modern contraceptive methods during most of their reproductive period. Age at last childbirth and age at menopause may have been erroneously reported by some women in our study. However, studies report that recall for pregnancies and childbirths and also for age at menopause, is fairly accurate (Catov et al., 2006; Rodstrom et al., 2005; Tomeo et al., 1999). Particularly women with early menopause seem to report age at menopause accurately (den Tonkelaar, 1997). We have little reason to believe that possible erroneous reporting of age at menopause is related to age at last childbirth, and unsystematic errors in reporting may

underestimate rather than overestimate associations (Althubaiti, 2016). The prevalence of early natural menopause in our study was similar to reports from other studies (Cooper et al., 1998; Luoto et al., 1994). Nevertheless, some women may have been misclassified. We excluded women who stopped having menstrual bleedings due to surgical removal of both ovaries and/or the uterus. Also, some women may have had medical conditions or treatments which could have caused early menopause (Byrne et al., 1992; Sklar, 2005; Talsania and Scofield, 2017). In additional analyses, we identified 55 women who had been diagnosed with cancer prior to menopause, and 844 women with an autoimmune disease (rheumatoid arthritis, ankylosing spondylitis, hypothyroidism, and/or asthma). After exclusion of these women, we found virtually no changes in our results (data not shown).

We are aware of no previous population based studies of childbirth in the years close to menopause, using individual data. Previous studies have compared the distribution of age at last childbirth in one population with the distribution of age at menopause in another population (Desjardins et al., 1994; Eijkemans et al., 2014; te Velde and Pearson, 2002). One of these studies compared the distribution of age at last childbirth in a 19th century Canadian natural fertility population with the distribution of age at menopause in a Dutch population of women born during the years 1911–1925 (te Velde and Pearson, 2002). The shapes of the distribution of age at last childbirth and age at menopause were almost identical, and the mean difference between the age distributions was approximately 10 years. A study from recent time of women who had undergone ovarian stimulation treatment, found that women who responded poorly, had higher risk of reaching menopause within 10 years after treatment compared to women who responded well, independent of age at treatment (Lawson et al., 2003). Based on these above studies, it has been suggested that there is a fixed interval between the onset of subfertility and menopause, independent of age at menopause (Faddy and Gosden, 1996; Nikolaou and Templeton, 2003). Few women reach menopause before the

age of 45. Thus, a possible shorter subfertile interval prior to menopause among women with early menopause than among women with late menopause will not easily be detected unless these groups of women are studied separately.

The number of oocytes that a woman is born with makes up her stock throughout life. Atresia of ovarian follicles starts already prior to birth and continues throughout the reproductive lifespan. Menopause is assumed to occur when less than 1,000 follicles remain (Faddy et al., 1992). Early menopause may therefore be a result of low initial number of ovarian follicles and high rate of ovarian follicle atresia (Depmann et al., 2015). The rate of follicle atresia may vary between women (Coxworth and Hawkes, 2010). The rate may also differ throughout the reproductive lifespan and accelerate after the age of 37, in particular (Faddy and Gosden, 1996). However, a later model suggests that there is a gradual increase in follicle atresia with increasing age (Hansen et al., 2008; Knowlton et al., 2014). We found that many women, who reached menopause before the age of 45, gave birth close to menopause. Hence, they were fecund and had functional oocytes close to menopause. This observation could suggest they had a high rate of follicle atresia from the time of last pregnancy until menopause. In fact, among women with menopause before the age of 45, the proportion of women with childbirth close to menopause was highest among the women with many previous childbirths. Such observation suggests high rate of ovarian follicle atresia prior to early menopause. Rapid ovarian follicle atresia prior to early menopause is also supported by a recent Dutch study of 111 women diagnosed with premature ovarian insufficiency (Daan et al., 2016). In that study the median time interval from the last conception to the final menstrual period was 4 years.

Among women with menopause in their fifties, very few gave birth within 10 years prior to menopause. This finding could be explained by inability to give birth, by no or infrequent sexual intercourse, or by use of methods to prevent pregnancy and childbirth. We

studied women who had not used oral contraceptives or undergone sterilization, separately. Also in these analyses, very few women with menopause in their fifties gave birth within 10 years prior to menopause. Unfortunately, we had no information about the use of other birth control methods. Some women may have had an induced abortion at advanced reproductive age, despite restricted legal access to pregnancy termination in Norway before 1979. However, the pregnancy termination rates (Vlietman et al., 2010) and the birth rates (Martin et al., 2017; Statistics Norway, 2017) in women older than 45 years have been very low. These observations suggest that women with menopause in their mid-fifties may have a long sterile interval prior to menopause.

In addition to decreased number of ovarian follicles, also the oocyte quality decreases by age (Broekmans et al., 2007; Pellestor et al., 2006). The understanding of ovarian ageing is still insufficient (Cimadomo et al., 2018). It is possible that the recruitment of ovarian follicles and the selection of a high quality oocyte for ovulation is better in younger than in older women. Additionally, the meiotic divisions of the oocyte during ovulation or during the completion of the meiosis during the fertilization may fail more often in older than in younger women. Mitochondrial dysfunctions are assumed to play important roles (Jones, 2007; Bentov et al., 2015). Aneuploidy of the embryo is one of the most common causes of miscarriage (Tsutsumi et al., 2014). The low birth rates after the age of 45 in women who still have menstrual periods, may therefore suggest that the remaining oocytes are of insufficient quality for successful fertilization or for normal embryonic development.

Also, impaired fallopian tube motility and lower receptivity of the endometrium could reduce the chances of successful pregnancy at a high age (Klein and Sauer, 2001).

Furthermore, successful conception is not determined by the fecundity of the woman only. High age of the woman's male partner may reduce semen quality and thereby the couple's

chance of a successful spontaneous pregnancy (Hassan and Killick, 2003; Kidd et al., 2001; Sharma et al., 2015).

Conclusions

Among women with menopause before the age of 45, more than fifty percent had their last childbirth within 10 years prior to menopause. This was true for less than one percent of the women with menopause at the age of 55 or older. Thus, the length of the sterile interval prior to natural menopause may vary by age at menopause.

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Declarations of interest

None

Author's roles

A.E. had the original idea for this study. M.S.G., A.E. and E.K.B. discussed the design and planned the analyses. M.S.G. and E.K.B. performed the analyses and made the tables and figures. M.S.G., A.E. and E.K.B. interpreted the results and wrote the manuscript. T.G.T. contributed with interpretation of the results, critically revised the article, and agreed on the final version. E.K.B. is the guarantor of the study. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analyses. All authors have approved the submitted version of the manuscript.

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Marthe S. Gottschalk is currently PhD-student at the Department of Obstetrics and Gynecology, Akershus University Hospital, Norway. She obtained her MD degree at Pecs Medical School, Hungary and her International Master of Public Health at Hebrew University, Israel. Her research interests are in reproductive epidemiology, female fertility and menopause.

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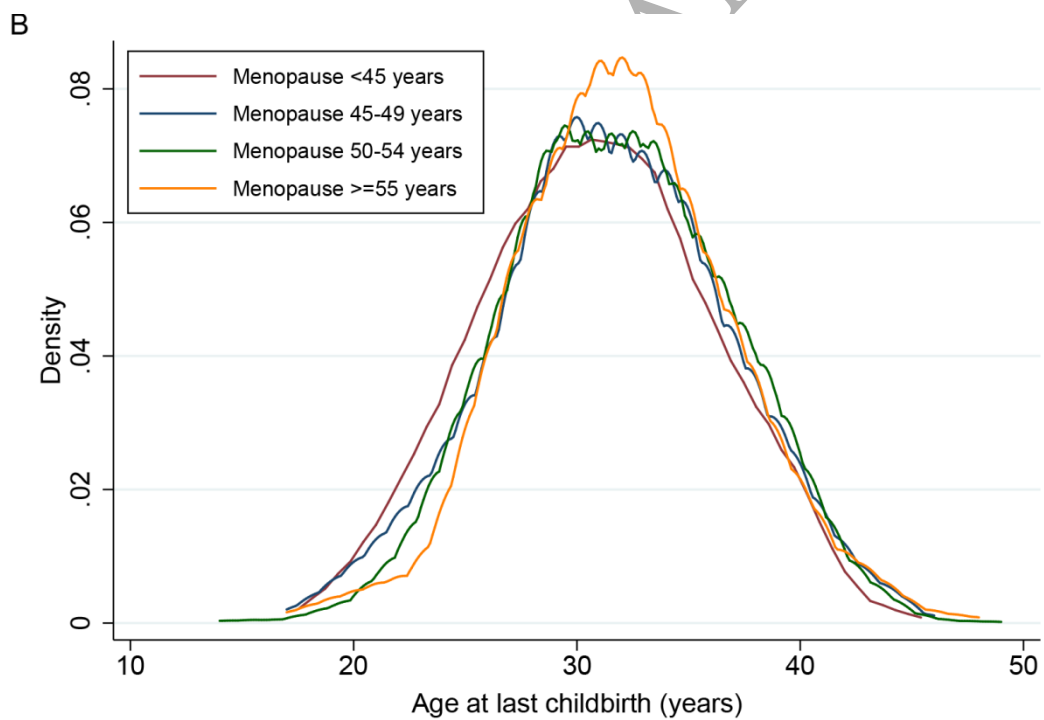
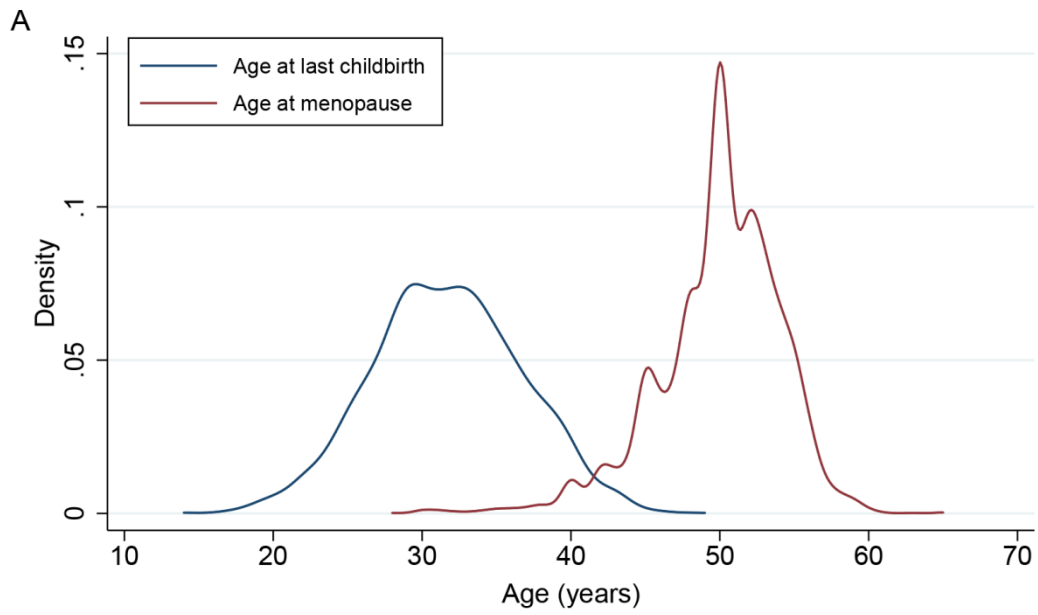
Figure legends**Figure 1.**

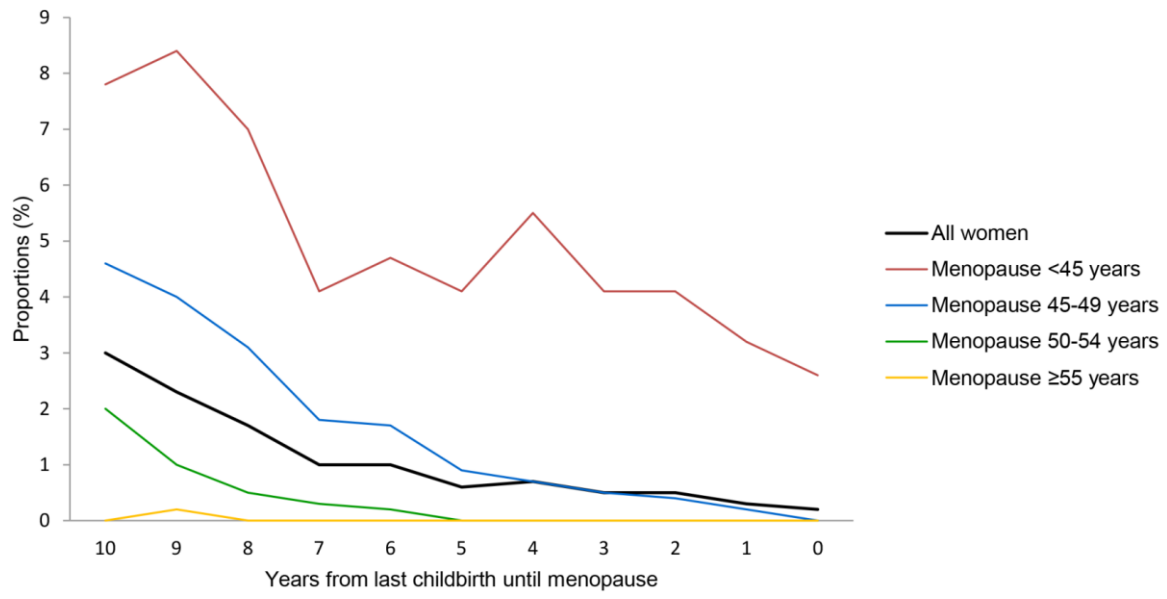
Distribution of age at last childbirth and age at menopause presented by using kernel density estimation ($n = 4,157$). A) Age at last childbirth and age at menopause. B) Age at last childbirth according to categories of age at menopause.

Figure 2.

Proportions of women who gave birth within each year during the 10 years prior to menopause among all women, and according to categories of age at menopause ($n = 4,157$).

Supplementary Figure A.1. Flow chart of the study sample; 4,157 women in the HUNT2 Survey in Norway, 1995–1997.





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Table 1. Descriptive characteristics of the study sample; parous women who had undergone natural menopause (n = 4,157).

	Mean	SD	Median	IQR
Age (years)	62.5	4.2	62.3	58.8– 66.1
Year of birth	1933	4.2	1934	1930– 1937
Number of childbirths	3.2	1.3	3	2–4
Age at menopause (years)	50.0	4.1	50	48–53
Age at last childbirth (years)	31.7	5.0	32	28–35
Interval ^a (years)	18.3	6.3	19	14–23

SD, standard deviation. IQR, interquartile range

^aInterval between last childbirth and menopause.

Table 2. Proportions of women with childbirth within 5 years and within 10 years prior to menopause among all women, and according to categories of age at menopause.

	Model 1			Model 2			Model 3		
	All women in the study sample, born 1925-1940 n = 4,157			Women with oral contraceptive use or sterilization are excluded n = 3,298			Women born after 1930 are excluded n = 1,199		
	5 years	10 years		5 years	10 years		5 years	10 years	
	Total	n (%)	n (%)	Total	n (%)	n (%)	Total	n (%)	n (%)
All women	4,157	114 (2.7)	487 (11.7)	3,298	93 (2.8)	388 (11.8)	1,199	49 (4.1)	220 (18.3)
Age at menopause (years)									
<45	344	81 (23.5)	191 (55.5)	261	64 (24.5)	142 (54.4)	112	33 (29.5)	68 (60.7)
45–49	1,143	31 (2.7)	206 (18.0)	898	28 (3.1)	170 (18.9)	343	16 (4.7)	99 (28.9)
50–54	2,196	2 (0.1)	89 (4.1)	1,763	1 (0.1)	76 (4.3)	630	0 (0.0)	52 (8.3)
≥55	474	0 (0.0)	1 (0.2)	376	0 (0.0)	0 (0.0)	114	0 (0.0)	1 (0.9)