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Reproductive Factors and Postmenopausal FSH Levels

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REPRODUCTIVE FACTORS AND POSTMENOPAUSAL FOLLICLE STIMULATING HORMONES LEVELS

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ABSTRACT

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Recent studies have shown that postmenopausal follicle stimulating hormone (FSH) levels may be predictive of future cardiovascular disease risk. However, little is known about postmenopausal FSH levels, including the level of variation between women and factors associated with this variation. We assessed the relationship of multiple reproductive factors with FSH levels among 588 postmenopausal women in the Kuopio Ischemic Heart Disease Risk Factor Study. Participants were aged 53 to 73 years and not using hormone therapy at baseline (1998-2001). Reproductive factors were assessed at baseline, along with FSH levels. After adjustment for sex steroids, adiposity measures, plasma lipids, blood pressure, and behavioral factors, we observed that women with 3 or more births and an age at first birth of 25 or later had mean FSH levels that were significantly 7.6 IU/L lower than those of women with a 1 to 2 births and an age at first birth of 24 or less. Number of miscarriages was inversely correlated with FSH levels. Women reporting a 7 or more years of OC use and 4-6 or 7 or more years of HT use each had significantly higher mean FSH levels than women who had never used OCs or HT. In summary, multiple reproductive factors were associated with postmenopausal FSH levels, independent of estradiol, adiposity, and other factors. These findings warrant replication and further exploration of potential underlying mechanism.

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CHAPTER 1

INTRODUCTION

Recent studies have shown that postmenopausal follicle-stimulating hormone (FSH) levels may be inversely associated with prevalence of diabetes and atherosclerosis in postmenopausal women.[1,2] Findings from these studies suggest that postmenopausal FSH levels may be predictive of future cardiovascular disease risk. However, little is known about postmenopausal FSH levels, including the level of variation between women and the factors associated with this variation. Given the important role of FSH in follicle development and ovulation in premenopausal women, we hypothesized that reproductive history may be associated with postmenopausal FSH levels.[3]

Follicle-stimulating hormone is involved in menstrual cycle regulation and fluctuates cyclically during the premenopausal years via feedback with estradiol.[3] The release of FSH by the anterior pituitary stimulates the production of estradiol in the ovarian follicles. As the follicles mature, estrogen levels rise, creating a negative feedback effect with the anterior pituitary and causing FSH level to decline. After estrogen levels decline at the end of the cycle, this negative feedback is broken, and the cycle repeats.

As menopause approaches and follicular estradiol production declines, FSH levels increase in order to maintain estrogen levels, although the level of increase in FSH around the time of the final menstrual period varies among women.[4] Previous studies have shown that that there are three distinct trajectories of FSH change during the menopausal transition, including low, medium, and high rising. At the conclusion of the menopausal transition, FSH levels are believed to plateau and gradually decline.[1,4] Very

little is known concerning FSH function in the years after the menopause transition is complete, though FSH secretion continues and levels between women vary substantially.

Few studies have assessed whether reproductive factors including parity, pregnancy loss, age at first birth, exogenous hormone use, and gynecologic surgeries may be associated with postmenopausal FSH levels. One study of 173 sedentary, overweight postmenopausal women found that nulliparous women had higher FSH levels than parous women,[5] while a study of 270 healthy postmenopausal women found a positive association between pregnancy termination and FSH.[6] The association of other reproductive factors with FSH, and likelihood of potential confounding by estrogens and other hormones, have not been investigated. Thus, we evaluated the relation of multiple reproductive factors and postmenopausal FSH while accounting for other factors including adiposity, hormones, and behavioral factors among a population of Finnish women.

CHAPTER 2

METHODS

2.1 Study Population

The KIHD study is an ongoing population-based cohort study of risk factors for cardiovascular and metabolic conditions in men and women living in eastern Finland. Whereas male participants were enrolled in 1984 to 1989, female participants were first enrolled between March 1998 and February 2001. Women eligible for enrollment were a random sample of 1173 postmenopausal women living in Kuopio and surrounding rural communities. Women from four specific age groups were selected: 53-56 years, 59-62 years, 64-68 years, and 71-73 years. Of eligible women, 920 (78.4%) completed baseline clinical assessments and joined the cohort. Among the nonparticipants, 168 refused participation, 51 could not be contacted, and 34 were not included for other reasons. The study protocol was approved by the Research Ethics Committee of the University of Kuopio. All participants provided written informed consent.

2.2 Questionnaire Assessments

Participants reported data on demographic, behavior, reproductive, and health-related factors on questionnaires, which were then reviewed by a trained interviewer for completeness and clarity. Reproductive factors included age at menarche, history and duration of oral contraceptive use, number of full-term pregnancies, age at last menses, and history of hysterectomy and oophorectomy; use of hormone therapy (HT; ever use, current use and total duration) was also assessed. Postmenopausal status and age at menopause were defined by the absence of menses for at least 12 months, or at the time of oophorectomy for women who reported having undergone surgery prior to menopause.

Physical activity was assessed with the KIHD 12-Month Leisure Time Physical Activity History questionnaire and was used to estimate amount of physical activity (metabolic equivalent of task hours) per day. Each participant also completed a detailed alcohol use questionnaire which was used to estimate alcohol intake.

2.3 Blood Collection and Biochemical Measurements

At the clinical interview, fasting blood samples were collected between 8:00 AM and 10:00 AM, after participants had abstained from eating or smoking cigarettes for 12 hours and consuming alcohol for 3 days.[2] Plasma was separated from other blood components within 60 minutes and stored at −20°C or−80°C until assay. Samples were assayed for FSH between June 2001 and February 2002. Serum FSH concentration was determined with a sandwich technique applying an immunoradiometric assay manufactured by Diagnostic Products Corporation (Coat-A-Count FSH IRMA; Diagnostic Products Corporation, Los Angeles, California). Serum 17-B-estradiol was assayed between 1999 and 2001 with a radioimmunoassay manufactured by DiaSorin (DiaSorin S.p.A., Stillwater, Minnesota). Serum testosterone (17B-hydroxy-4-androsten-3-one) was determined with the Spectria Testosterone radioimmunoassay kit (Orion Diagnostic, Espoo, Finland). I label measurements for FSH, E_2, and testosterone were carried out by gamma counter Wallac 1261 MultiGamma using a RiaCalc LM Evaluation Program. Coefficients of variation (CVs) were 5% for FSH, 7.6% to 12.0% for E_2, and 7.9% to 12.2% for testosterone.

Samples from all participants were assayed for high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides using laboratory

methods described in detail previously. CVs were 5.2% for LDL, 9.2% for HDL, and 1.9% for triglycerides.

2.4 Clinical Measures

At baseline, resting systolic and diastolic blood pressure were calculated as the average of six measurements, including three made supine after 5 minutes resting; one made standing; and two made sitting, with 5 minutes between measures. Height and weight were directly measured and used to calculate BMI (weight in kg/square of height in m). Waist and hip circumferences were measured with a standard measuring tape and used to calculate waist-to-hip ratio. All measurements were then repeated at the follow-up visit.

2.5 Statistical Analysis

The present analysis was limited to women not using HT at baseline (n=593). Additionally, five participants did not have FSH measurements and were excluded, leaving 588 women as the analytic population.

FSH was normally distributed and did not require transformation. We divided the participants by age based on the categories used for participant recruitment (53-56, 59-62, 64-68, 71-73) and compared mean FSH levels between the four categories using analysis of variance (ANOVA).

To determine if participant characteristics were related to FSH levels, we evaluated these associations using linear regression. We then used linear regression to assess how reproductive factors, including number of full-term births, history of

spontaneous abortion, timing of first pregnancy, age at menarche, age at menopause, number of reproductive years, OC use and duration, past HT use and duration, and gynecologic surgical history (i.e., oophorectomy and hysterectomy), were associated with FSH. Indictor variables were created for fixed categories. To account for confounding by demographic, hormonal and behavioral factors, we built two multivariate models. In the first, we adjusted for year of study entry, age, enrollment age category ,estradiol, testosterone, and SHBG. Model 3 included model 2 variables plus current smoking, pack-years of smoking, physical activity, alcohol use (g/week), waist:hip ratio, BMI, systolic and diastolic blood pressure, triglycerides, and LDL and HDL cholesterol. Information on variable categorizations are included in table footnotes.

We then conducted stratified analyses to evaluate whether associations between reproductive factors and FSH levels varied by age (53-62 versus 64-73 years) and BMI (normal weight, overweight, obese).

CHAPTER 3

RESULTS

The distribution of FSH by participant age group is presented in Table 1. Younger postmenopausal women (ages 53-56 years) had modestly higher mean FSH levels than older women (ages 71-73 years), although the means were not significantly lower among older women. Within each each group, there was a large variation in FSH levels. As shown in table 2, FSH levels were inversely associated with age, BMI, and waist-to-hip ratio, but were not associated with physical activity, alcohol intake, and smoking. FSH was significantly inversely associated with systolic blood pressure, estradiol, and testosterone, and significantly positively associated with plasma lipids and SHBG.

Association of pregnancy-related reproductive factors with FSH levels are presented in Table 3. In unadjusted analyses, mean age at first birth was inversely associated with FSH level. Women with a higher parity had lower FSH levels than women of a lower parity (model 1; *P* for trend 0.006). In the evaluation of age at first birth and parity simultaneously, both factors appeared to be independently inversely associated with FSH. Adjustment for sex steroids and SHBG attenuated results (model 2), but mean FSH levels remained significantly lower in women with three or more pregnancies and a later age at first birth than the reference groups (women with 1-2 births and first birth at <25 years). After additional adjustment for adiposity, behavioral, and clinical factors (model 3), a significant inverse trend for remained for parity and was suggestive for age at first birth. In the analysis of both factors simultaneously, mean FSH levels were significantly 7.6 IU/L lower among women with 3 or more births and first birth at age 25 or later. The reported number of miscarriages among participants ranged

from 0 to 5, with n=104 women reporting 1 and n=30 reporting 2 or more miscarriages. Number of miscarriages was inversely associated with FSH level in each set of models.

Table 4 presents results on the relation of gynecologic surgeries and benign gynecologic conditions with FSH levels. History of hysterectomy, but not oophorectomy, was significantly inversely associated with FSH level in our unadjusted analysis. Women with a history uterine myoma had lower FSH levels than women who did not, while a history of endometriosis was not associated with FSH levels. Results for all of these relations were attenuated and no longer significant after adjustment for sex steroids and SHBG (model 2) and in our fully adjusted model (model 3).

Associations of FSH levels with age at menarche and menopause, along with exogenous hormone use, are presented in Table 5. Age at last menses and age at menarche were not significantly associated with FSH level. Women with a history of HT use had higher FSH levels than women without HT use, with evidence of a dose-response relationship with duration of use. Women with the longest duration of OC use had higher FSH levels than women who never used OC, although no dose-response relationship was evident. Adjustment for sex steroids and SHBG (model 2) attenuated results, but mean FSH levels remained significantly higher for a long duration of HT use, and non-significantly higher with a longer duration of OC use. In our fully adjusted model (model 3), women reporting OC use for 7 or more years had significantly higher mean FSH levels than women who had never used OCs. Women who used HT for 4-6 years or 7+ years both had a significantly higher mean FSH levels than women who had never used HT. Age at menarche and last menses remained unassociated with FSH levels.

To determine if associations between the main reproductive factors and FSH differed between younger and older postmenopausal women, we stratified women by age group (ages 53-62 years vs. 64-73 years) and reran our fully adjusted model (Table 6). In the evaluation of age at first birth and parity simultaneously, associations for higher parity and higher age at first birth were strong and significant among younger postmenopausal women, but not among older postmenopausal women. Long duration of OC use was similarly associated with higher FSH levels in both young and older women. Similarly, longer duration of HT use was positively associated with FSH levels in younger and older women, though a dose-response relation was not observed, likely due to low power for these comparisons.

Because associations of reproductive factors with FSH levels could potentially be modified by adiposity, we then stratified our population according to World Health Organization BMI category (<25.0 (normal weight), 25.0-29.0 (overweight) or ≥ 30.0 (obese). We did not observe evidence of effect modification by BMI for any of the factors evaluated.

CHAPTER 4

DISCUSSION

In this study of older postmenopausal women, we observed significant associations between several reproductive factors and FSH levels. Women with both a high parity (3 or more births) and a later age at first birth (25 or later) had mean FSH levels that were significantly 7.6 IU/L lower than those of women with a lower parity (1 to 2 births) and a younger age at first birth (24 or less). Number of miscarriages was also inversely correlated with FSH levels. Women reporting a long durations of OC and HT use each had significantly higher mean FSH levels than women who had never used OCs or HT. Importantly, these associations existed after adjustment for sex steroids, adiposity measures, plasma lipids, blood pressure, and behavioral factors.

We found that parity was associated with lower FSH levels, while a long duration of OCs and HT was associated with higher FSH levels. Given that both pregnancy and HT are associated with estrogen exposure and suppression of FSH, it is surprising that these associations are not similar. To our knowledge, an association between reproductive factors and FSH, accounting for other factors including adiposity, hormones, and behavioral factors, has not been observed before. While two previous studies of reproductive factors and FSH levels suggested potential associations of pregnancy history, both studies did not account for potential confounding by biochemical and clinical factors. Consistent with our results showing lower mean FSH levels among parous women, Chubak and et[5] found that among 173 postmenopausal, sedentary, overweight or obese women, nulliparous women had 19% higher FSH concentrations than parous women ($p=0.02$), even after adjustment for age, body fat, alcohol consumption, marital status, race, and number of ovaries remaining. Ness et al[6] reported

that among 270 postmenopausal women, pregnancy termination was significantly related to a rise in FSH one year after menopause (p=0.03), after adjustment for BMI, education, oral contraceptive use, smoking, and alcohol consumption. However, this study focused on younger, as opposed to older, postmenopausal women. Consistent with our results, both of these studies found no association between age at menarche or age at last menses and FSH levels.

Postmenopausal FSH levels may an important indicator of future disease risk. Inverse associations of postmenopausal FSH levels with risk of T2D had been observed in prior studies.[1,7,8] In the KIHD population, women with FSH levels above the median (50 IU/L) had approximately half the risk of developing T2D over 7 to 9 years of follow-up than women with lower levels.[1] Furthermore, each 1 IU/L increase in FSH was associated with a 1.9% lower prevalence of diabetes. Wang et al[8] found that participants with FSH levels of 50.2 IU/L or less had three times the risk of prevalent diabetes than women with FSH levels of at least 82.5 IU/. Bjørnerem et al[7] found that women with diabetes had geometric mean postmenopausal FSH levels than were 7.4 IU/L lower than levels healthy postmenopausal women (*P*=0.03).

When combined with results from previous studies, our results of lower FSH levels among women with a high parity suggest that women with higher parity have a higher risk of T2D. Based on the approximately 7 IU/L difference in FSH levels between higher and lower parity women in our population, we would hypothesize that this magnitude of difference would translate into a 13% lower diabetes risk (e.g., 7 IU/L* 1.9% decreased risk per unit). This is consistent with findings from multiple studies that show that a high parity is associated with an increased risk of T2D.[9–15] Most recently,

Luo et al[9] observed than women with five or more live births had 1.13 times the risk of incident T2D compared to nulliparous women.

Hormone therapy use has been associated with lower diabetes risk in previous studies. Pentti et al[16] found that among 8483 postmenopausal women, past HT users had a 19% lower risk of T2D (95% CI 0.57-1.16) and women who continuously used HT during the follow-up period had a 69% lower risk of T2D (95% CI 0.16-0.60) compared to never-users. Randomized trials[17,18] have also shown that hormone therapy in postmenopausal women is associated with a significantly lower incidence of T2D compared to non-users, possibly mediated by a reduction in insulin resistance.[17] These findings are consistent with our results that a longer duration of HT is associated with increased FSH levels and with results from previous studies that higher FSH levels are associated with lower risk of T2D.[1] Previous studies have shown that OC use is not associated or is associated with an increased T2D risk. This association is opposite that of HT and is not consistent with our findings relating a long duration of OC use to higher FSH levels.

Inverse associations of FSH with insulin suggest that FSH may be related to TD2 through insulin resistance. Laboratory studies have observed FSH and/or FSH receptor activity in extragonadal tissues, suggesting that actions of FSH may extend beyond its functions in reproduction. Chu et al[19] identified FSH in the rat pancreas, reporting coexpression of FSH and FSH receptors in islet cells. FSH altered insulin and glucagon secretion by pancreatic cells in vitro in a U-shaped manner. It is unknown whether FSH may affect pancreatic insulin secretion in humans, and whether actions may vary by

menopausal status. Effects of pregnancy on insulin sensitivity suggest that parity may be related to T2D through the association of FSH and insulin.

The associations we observed between reproductive factors and FSH levels could plausibly be explained by confounding by adiposity, as higher adiposity is associated with higher endogenous estrogen production and consequently lower FSH levels. However, since we adjusted for both BMI and waist to hip ratio, confounding by adiposity and associations of adiposity with estrogens is unlikely to explain our findings. Results from our stratified analyses do not give any indication that associations are impacted by BMI or only observed among overweight and obese women.

Our study assessed FSH at a single time point and thus could not assess within-women variation in FSH. However, this limitation is unlikely to explain our findings, as we would expect misclassification relating to the use of a single FSH measure to attenuate association rather than exaggerate them. Because the KIHD study population is very homogenous with respect to race and ethnicity, additional evaluation of these relationships in diverse populations is needed. A strength of our study is the extensive data on biochemical, behavioral, and clinical factors, allowing us to adjust beta estimates for the effect of a large number of potential confounders. Associations persisted after adjustment, suggesting that associations for FSH are not explained by these factors or by other sex steroids. There may be residual confounding if some of the data on the confounders is misclassified. As the women are 53 and older, some of the historical data may be recalled incorrectly and some current data may be inaccurately reported. However, since the covariates that are most likely to be confounders, including estradiol,

testosterone, SHBG, and BMI were directly measured, confounding is unlikely to be an issue.

To our knowledge, this is the first study of multiple reproductive factors and postmenopausal FSH levels that accounted for other factors including adiposity, hormones, and behavioral factors. We observed evidence of significantly lower FSH levels among women with both a high parity and a later age at first birth, and significant higher FSH levels among with with a long duration of OC or HT use. Number of miscarriages was inversely associated with FSH levels. These associations were not explained by estradiol, adiposity, and other factors. Additional studies of reproductive factors and FSH in older postmenopausal women are needed to explore potential underlying physiological explanations, and whether FSH also underlies associations of reproductive factors with diabetes risk.

Table 1: Follicle-stimulating hormone levels among women who were not currently using hormone therapy, by age group, Kuopio Ischaemic Heart Disease Risk Factor Study, 1998-2001

	Follicle Simulating Hormone Level, IU/L							*P* value
	n	Mean	SD	Min	Median	Max	IQR	for mean
53-56	114	54.7	25.3	1.5	53.9	136.8	31.8	0.09
59-62	130	51.6	18.8	2.4	50.9	108.6	20.9	
64-68	163	51.3	16.0	4.8	49.4	102.8	17.0	
71-73	181	48.9	17.0	3.6	47.0	99.1	23.2	

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 2. Association of baseline characteristics with follicle-stimulating hormone levels among women aged 53-73 years who were not using hormone therapy, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

	Follicle-Stimulating Hormone Level, IU/L		
	n	β (SE)	*P* value
Year of enrollment			
1998	164	3.28 (1.95)	0.09
1999	220	0 (Referent)	
2000	186	5.49 (1.88)	0.004
2001	18	14.55 (4.63)	0.002
Age, years	588	-0.29 (0.12)	0.02
Age, years			
53-56	114	0 (Referent)	
59-62	130	-2.82 (2.44)	0.25
64-68	163	-3.34 (2.32)	0.15
71-73	181	-5.78 (2.27)	0.01
Body mass index[a]	588	-1.03 (0.14)	<0.0001
Body mass index			
Under/normal	147	0 (Referent)	
Overweight	225	-5.50 (1.95)	0.005
Obese	216	-13.09 (1.97)	<0.0001
Waist:hip ratio	587	-64.56 (12.23)	<0.0001
quartile 1	146	0 (Referent)	
quartile 2	147	-4.17 (2.17)	0.06
quartile 3	147	-7.72 (2.17)	0.0004
quartile 4	147	-10.32 (2.17)	<0.0001
Physical activity, MET h/d	588	0.20 (0.12)	0.09
Alcohol intake, g/week	585	-0.02 (0.02)	0.31
Pack-years of smoking[b]	581	-0.07 (0.12)	0.57
Current smoking			
no	537	0 (Referent)	
yes	49	-2.18 (2.85)	0.44
Systolic blood pressure, mm Hg	588	-0.13 (0.04)	0.004
Diastolic blood pressure, mm Hg	588	-0.09 (0.09)	0.30
Triglycerides, mmol/L	588	-3.72 (1.18)	0.002
HDL cholesterol, mmol/L	587	10.79 (2.47)	<0.0001
LDL cholesterol, mmol/L	586	1.86 (0.87)	0.03
Estradiol, pmol/L	588	-0.13 (0.02)	<0.0001
Testosterone, nmol/L	588	-2.01 (0.51)	<0.0001
Sex hormone-binding globulin, nmol/L	580	0.16 (0.03)	<0.0001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task.

[a]Weight (kg)/height $(m)^2$.

[b]Pack-years of cigarette smoking among ever smokers

Table 3. Association of reproductive factors with follicle-stimulating hormone levels (IU/L) among women aged 53-73 years who were not using hormone therapy, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

		Model					
		Model 1[a]		Model 2[b]		Model 3[c]	
	n	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
Parity, no. full-term pregnancies	587	-1.24 (0.47)	0.009	-0.92 (0.43)	0.04	-0.94 (0.44)	0.03
Parity, no. full-term pregnancies							
0	76	1.89 (2.61)	0.47	2.52 (2.44)	0.30	2.12 (2.44)	0.39
1	94	0.65 (2.43)	0.79	2.09 (2.23)	0.35	1.06 (2.24)	0.64
2	175	0 (Referent)		0 (Referent)		0 (Referent)	
3	128	-5.50 (2.21)	0.01	-4.01 (2.04)	0.05	-3.18 (2.05)	0.12
4+	114	-3.25 (2.28)	0.16	-0.81 (2.18)	0.71	-2.11 (2.24)	0.35
P for trend		0.006		0.02		0.02	
Age at first birth, years	507	-0.34 (0.19)	0.07	-0.23 (0.17)	0.18	-0.31 (0.17)	0.07
Age at first birth, years							
<20	50	0.53 (2.97)	0.86	-0.85 (2.69)	0.75	-0.63 (2.68)	0.81
20-24	253	0 (Referent)		0 (Referent)		0 (Referent)	
25-29	145	-2.49 (2.00)	0.21	-1.90 (1.80)	0.29	-2.52 (1.80)	0.16
30+	59	-4.92 (2.77)	0.08	-3.40 (2.49)	0.17	-4.33 (2.52)	0.09
P for trend		0.04		0.16		0.06	
Parity/age at first birth, years							
0 births	76	-1.24 (2.71)	0.65	-0.11 (2.52)	0.96	-0.45 (2.52)	0.86
1-2 births/<25	132	0 (Referent)		0 (Referent)		0 (Referent)	
3+ births/ <25	171	-6.35 (2.18)	0.004	-3.77 (2.03)	0.06	-3.99 (2.04)	0.05
1-2 births/ 25+	135	-5.42 (2.30)	0.02	-2.83 (2.10)	0.18	-3.72 (2.11)	0.08
3+ births/ 25+	69	-9.69 (2.79)	0.0006	-7.33 (2.61)	0.01	-7.65 (2.59)	0.003
Miscarriages, number	586	-2.74 (1.22)	0.03	-2.87 (1.11)	0.01	-2.92 (1.13)	0.01
Abortions, number	581	0.92 (1.89)	0.63	-0.70 (1.72)	0.68	-0.40 (1.73)	0.82

Abbreviations: SE, standard error.

[a]Model 1 unadjusted.

[b]Model 2 adjusted for year of enrollment, age (years), age (4 categories), estradiol (pmol/L), testosterone (nmol/L), and sex hormone binding-globulin (nmol/L).

[c]Model 3 further adjusted for body mass index (weight (kg)/height $(m)^2$), body mass index (WHO categories), waist:hip ratio (quartiles), physical activity (MET-hours/day), alcohol intake (g/week), pack-years of smoking (continuous), current smoking (yes,no), systolic and diastolic blood pressure (mm HG; continuous), triglycerides (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L).

Table 4. Association of reproductive factors with follicle-stimulating hormone levels among women aged 53-73 years who were not using hormone therapy, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

		Model					
		Model 1[a]		Model 2[b]		Model 3[c]	
	n	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
History of hysterectomy							
No	448	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	135	-4.51 (1.86)	0.02	-1.85 (1.72)	0.28	-1.09 (1.73)	0.53
History of oopherectomy							
No	486	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	85	-1.21 (2.25)	0.59	-1.22 (2.07)	0.56	-0.12 (2.07)	0.95
History of gynaceological surgery							
No	432	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	147	-3.21 (1.82)	0.08	-1.53 (1.67)	0.36	-0.79 (1.67)	0.64
Endometriosis							
No	525	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	38	3.73 (3.23)	0.25	0.70 (2.94)	0.81	0.39 (2.99)	0.90
Uterine myomas							
No	398	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	178	-3.25 (1.71)	0.06	-1.63 (1.57)	0.30	-0.94 (1.58)	0.55

Abbreviations: SE, standard error.

[a]Model 1 unadjusted.

[b]Model 2 adjusted for year of enrollment, age (years), age (4 categories), estradiol (pmol/L), testosterone (nmol/L), and sex hormone binding-globulin (nmol/L).

[c]Model 3 further adjusted for body mass index (weight (kg)/height (m)^2), body mass index (WHO categories), waist:hip ratio (quartiles), physical activity (MET-hours/day), alcohol intake (g/week), pack-years of smoking (continuous), current smoking (yes,no), systolic and diastolic blood pressure (mm HG; continuous), triglycerides (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L).

Table 5. Association of reproductive factors with follicle-stimulating hormone levels among women aged 53-73 years who were not using hormone therapy, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

		Model					
		Model 1[a]		Model 2[b]		Model 3[c]	
	n	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value
Age at menarche, years	580	0.25 (0.52)		0.07 (0.47)	0.89	-0.28 (0.47)	0.56
Age at menarche, years							
<12	105	-0.18 (2.47)	0.94	1.43 (2.25)	0.52	1.57 (2.27)	0.49
13	140	0 (Referent)		0 (Referent)		0 (Referent)	
14	128	-0.33 (2.34)	0.89	-0.08 (2.13)	0.97	-1.42 (2.13)	0.51
15	113	-1.19 (2.42)	0.62	-0.31 (2.20)	0.89	-1.21 (2.21)	0.58
16+	94	1.93 (2.55)	0.45	2.00 (2.31)	0.39	0.49 (2.31)	0.83
P for trend		0.66		0.89		0.51	
Age at last menses, years	569	-0.15 (0.18)	0.40	-0.06 (0.16)	0.73	-0.14 (0.16)	0.38
Age at last menses, years							
<50	257	2.58 (1.79)	0.15	1.52 (1.62)	0.35	2.48 (1.63)	0.13
50-52	204	0 (Referent)		0 (Referent)		0 (Referent)	
>52	127	-0.40 (2.16)	0.85	-0.31 (1.96)	0.87	0.08 (1.97)	0.97
P for trend		0.09		0.26		0.11	
History of OC use							
No	398	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	179	2.08 (1.72)	0.23	1.67 (1.70)	0.33	2.07 (1.73)	0.23
Duration OC use, years							
0	398	0 (Referent)		0 (Referent)		0 (Referent)	
<1	38	1.38 (3.24)	0.67	0.85 (3.10)	0.78	-0.10 (3.23)	0.97
1-3	65	0.94 (2.55)	0.71	2.39 (2.42)	0.32	3.14 (2.41)	0.19
4-6	41	-1.27 (3.13)	0.69	-1.93 (2.89)	0.50	-2.13 (2.89)	0.46
7+	35	8.90 (3.36)	0.01	5.41 (3.12)	0.08	6.79 (3.13)	0.03
P for trend		0.04		0.23		0.11	
Past HT use							
No	396	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	180	2.14 (1.68)	0.20	1.20 (1.53)	0.43	1.39 (1.54)	0.37
Duration HT use, years							
0	393	0 (Referent)		0 (Referent)		0 (Referent)	
<1	56	-0.86 (2.72)	0.75	-1.28 (2.45)	0.60	-0.98 (2.44)	0.69
1-3	59	1.04 (2.66)	0.70	-1.94 (2.44)	0.43	-1.12 (2.44)	0.65
4-6	31	8.16 (3.55)	0.02	8.12 (3.20)	0.01	8.65 (3.23)	0.01
7+	33	7.28 (3.45)	0.04	7.36 (3.17)	0.02	7.52 (3.21)	0.02
P for trend		0.005		0.003		0.003	

Abbreviations: SE, standard error; OC, oral contraceptive; HT, hormone therapy.

[a]Model 1 unadjusted.

[b]Model 2 adjusted for year of enrollment, age (years), age (4 categories), estradiol (pmol/L), testosterone (nmol/L), and sex hormone binding-globulin (nmol/L).

[c]Model 3 further adjusted for body mass index (weight (kg)/height $(m)^2$), body mass index (WHO categories), waist:hip ratio (quartiles), physical activity (MET-hours/day), alcohol intake (g/week), pack-years of smoking (continuous), current smoking (yes,no), systolic and diastolic blood pressure (mm HG; continuous), triglycerides (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L).

Table 6. Association of reproductive factors with follicle-stimulating hormone levels among women aged 53-73 years who were not using hormone therapy, stratified by age group, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

	Age Group					
	53-62 Years			64-73 Years		
	n	β (SE)[a]	*P* value	n	β (SE)[a]	*P* value
Parity, no. full-term pregnancies	244	-2.64 (1.00)	0.01	343	-0.44 (0.48)	0.35
Parity, no. full-term pregnancies						
0	22	6.79 (4.59)	0.14	54	1.08 (2.97)	0.72
1	37	0.25 (3.79)	0.95	57	1.90 (2.91)	0.51
2	107	0 (Referent)		68	0 (Referent)	
3	54	-8.51 (3.37)	0.01	74	1.36 (2.71)	0.62
4+	24	-5.76 (4.53)	0.20	90	-0.58 (2.73)	0.83
Age at first birth, years	221	-0.58 (0.32)	0.07	286	-0.15 (0.20)	0.46
Age at first birth, years						
<20	23	-6.16 (4.53)	0.18	27	3.89 (3.35)	0.25
20-24	119	0 (Referent)		134	0 (Referent)	
25-29	51	-7.46 (3.32)	0.03	94	0.39 (2.10)	0.85
30+	28	-7.31 (4.29)	0.09	31	-1.65 (3.14)	0.60
Parity/age at first birth, years						
0 births	22	2.92 (4.65)	0.53	54	0.95 (3.04)	0.75
1-2 births/<25	79	0 (Referent)		53	0 (Referent)	
3-4 births/ <25	63	-9.21 (3.30)	0.006	108	1.41 (2.70)	0.60
1-2 births/ 25+	64	-8.39 (3.32)	0.012	71	1.73 (2.84)	0.54
3-4 births/ 25+	15	-18.71 (5.44)	0.0007	54	-1.34 (3.05)	0.66
History of OC use						
No	120	0 (Referent)		278	0 (Referent)	
Yes	120	1.92 (2.70)	0.48	59	3.27 (2.41)	0.17
Duration OC use, years						
0	120	0 (Referent)		278	0 (Referent)	
< 1	29	1.63 (4.61)	0.72	9	0.52 (5.70)	0.93
1-3	40.000	1.86 (3.76)	0.62	25	5.17 (3.29)	0.12
4-6	27	-3.15 (4.27)	0.46	14	-1.33 (4.38)	0.76
7+	24	7.48 (4.46)	0.10	11	7.10 (5.23)	0.18
Past HT Use						
No	162	0 (Referent)		234	0 (Referent)	
Yes	80	-2.43 (2.68)	0.37	100	4.42 (1.89)	0.02
Duration HT use, years						
0	158	0 (Referent)		235	0 (Referent)	
<1	26	-5.70 (4.15)	0.17	30	3.79 (2.99)	0.21
1-3	21	-10.47 (4.80)	0.03	38	4.47 (2.78)	0.11
4-6	20	3.73 (4.68)	0.43	11	12.73 (4.88)	0.01
7+	15	10.83 (5.52)	0.05	18	4.15 (3.90)	0.29

Abbreviations: SE, standard error; OC, oral contraceptive; HT, hormone therapy.

[a]Results adjusted for year of enrollment, body mass index (weight (kg)/height (m)^2), body mass index (WHO categories), waist:hip ratio (quartiles), physical activity (MET-hours/day), alcohol intake (g/week), pack-years of smoking (continuous), current smoking (yes,no), systolic and diastolic blood pressure (mm HG; continuous), triglycerides (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), estradiol (pmol/L), testosterone (nmol/L), and sex hormone binding-globulin (nmol/L).

Table 7. Association of reproductive factors with follicle-stimulating hormone levels among women aged 53-73 years who were not using hormone therapy, stratified by Body Mass Index, Kuopio Ischemic Heart Disease Risk Factor Study, 1998-2001

	Body Mass Index[a]					
	<25.0 (Normal-Weight, n=147)		25.0-29.9 (Overweight, n=225)		≥ 30.0 (obese, n=216)	
	β (SE)[b]	*P* value	β (SE)[b]	*P* value	β (SE)[b]	*P* value
Parity, no. full-term pregnancies	-0.76 (1.26)	0.55	-1.37 (0.68)	0.04	-0.94 (0.68)	0.17
Parity, no. full-term pregnancies						
0	-4.82 (6.45)	0.46	2.84 (3.98)	0.48	6.55 (3.88)	0.09
1	-1.05 (4.97)	0.83	0.97 (3.97)	0.81	1.21 (3.65)	0.74
2	0 (Referent)		0 (Referent)		0 (Referent)	
3	-11.92 (5.68)	0.04	-2.63 (3.01)	0.43	-1.41 (3.11)	0.65
4+	-2.70 (5.54)	0.63	-5.27 (4.01)	0.19	0.22 (3.37)	0.95
Age at first birth, years	-0.30 (0.45)	0.51	-0.52 (0.27)	0.06	-0.20 (0.28)	0.47
Age at first birth, years						
<20	-14.19 (7.43)	0.06	1.39 (4.23)	0.74	3.23 (4.32)	0.46
20-24	0 (Referent)		0 (Referent)		0 (Referent)	
25-29	-10.79 (4.55)	0.02	0.89 (2.96)	0.76	-2.42 (2.86)	0.40
30+	-4.68 (6.09)	0.44	-8.12 (4.12)	0.050	-2.83 (3.90)	0.47
Parity/age at first birth, years						
0 births	-8.89 (6.38)	0.17	1.84 (4.21)	0.66	2.90 (3.96)	0.46
1-2 births/<25	0 (Referent)		0 (Referent)		0 (Referent)	
3-4 births/ <25	-8.23 (5.33)	0.13	-3.28 (3.55)	0.36	-4.16 (3.13)	0.18
1-2 births/ 25+	-7.77 (4.75)	0.10	-1.19 (3.75)	0.75	-6.12 (3.39)	0.07
3-4 births/ 25+	-16.87 (6.51)	0.01	-7.21 (4.35)	0.10	-4.81 (4.08)	0.24
Miscarriages, number	-2.38 (2.16)	0.27	-5.16 (2.15)	0.02	-2.48 (1.92)	0.20
Abortions, number	7.46 (4.34)	0.09	-1.61 (2.81)	0.57	-3.49 (2.75)	0.21
History of hysterectomy						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	-4.23 (5.02)	0.40	-1.38 (2.70)	0.61	2.29 (2.64)	0.39
History of oopherectomy						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	-3.39 (5.88)	0.57	-0.34 (3.22)	0.92	2.96 (3.23)	0.36

Table 7 Continued.

	Body Mass Index[a]					
	<25.0 (Normal-Weight, n=147)		25.0-29.9 (Overweight, n=225)		≥ 30.0 (obese, n=216)	
	β (SE)[b]	*P* value	β (SE)[b]	*P* value	β (SE)[b]	*P* value
History of gynaceological surgery						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	-2.91 (4.79)	0.54	-1.80 (2.58)	0.49	2.51 (2.64)	0.34
Endometriosis						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Age at menarche, years	-2.17 (1.13)	0.06	0.40 (0.83)	0.63	0.28 (0.77)	0.72
Age at menarche, years						
<12	-1.05 (6.04)	0.86	2.08 (3.99)	0.60	3.12 (3.31)	0.35
13	0 (Referent)		0 (Referent)		0 (Referent)	
14	-11.35 (5.41)	0.04	-0.72 (3.38)	0.83	0.37 (3.47)	0.91
15	-8.97 (5.37)	0.10	-4.47 (3.76)	0.24	4.76 (3.49)	0.17
16+	-12.56 (5.38)	0.02	5.85 (3.59)	0.10	2.93 (4.21)	0.49
Age at last menses, years	-0.02 (0.46)	0.97	0.08 (0.25)	0.74	-0.40 (0.26)	0.12
Age at last menses, years						
<50	-3.31 (3.97)	0.41	2.57 (2.68)	0.34	6.71 (2.53)	0.01
50-52	0 (Referent)		0 (Referent)		0 (Referent)	
>52	-3.00 (5.03)	0.55	1.48 (3.31)	0.66	1.54 (2.87)	0.59
History of OC use						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	6.50 (4.30)	0.13	-0.58 (2.86)	0.84	3.68 (2.77)	0.18
Duration OC use						
0	0 (Referent)		0 (Referent)		0 (Referent)	
< 1	8.67 (7.83)	0.27	-8.74 (5.22)	0.10	7.62 (5.24)	0.15
1-3	7.72 (6.61)	0.25	3.37 (3.89)	0.39	3.06 (3.77)	0.42
4-6	2.48 (6.19)	0.69	-5.24 (4.94)	0.29	-4.21 (5.12)	0.41
7+	10.13 (7.74)	0.19	4.47 (5.42)	0.41	8.82 (4.94)	0.08
Past HT Use						
No	0 (Referent)		0 (Referent)		0 (Referent)	
Yes	9.25 (3.71)	0.01	-2.22 (2.54)	0.38	1.77 (2.48)	0.48

Table 7 Continued.

	Body Mass Index[a]					
	<25.0 (Normal-Weight, n=147)		25.0-29.9 (Overweight, n=225)		≥ 30.0 (obese, n=216)	
	β (SE)[b]	*P* value	β (SE)[b]	*P* value	β (SE)[b]	*P* value
Duration HT use, years						
0	0 (Referent)		0 (Referent)		0 (Referent)	
<1	0.84 (6.34)	0.89	-5.33 (4.08)	0.19	2.17 (3.49)	0.53
1-3	13.59 (5.55)	0.02	-6.99 (3.98)	0.08	-3.92 (4.13)	0.34
4-6	30.70 (7.28)	<0.0001	0.23 (4.98)	0.96	3.72 (5.70)	0.51
7+	1.68 (7.42)	0.82	6.4 (4.25)	0.13	14.80 (8.36)	0.08

Abbreviations: SE, standard error; OC, oral contraceptive; HT, hormone therapy.

[a]Weight (kg)/height $(m)^2$.

[b]Results were adjusted for year of enrollment, age (years), age (4 categories), waist:hip ratio (quartiles), physical activity (MET-hours/day), alcohol intake (g/week), pack-years of smoking (continuous), current smoking (yes,no), systolic and diastolic blood pressure (mm HG; continuous), triglycerides (mmol/L), high-density lipoprotein cholesterol (mmol/L), low-density lipoprotein cholesterol (mmol/L), estradiol (pmol/L), testosterone (nmol/L), and sex hormone binding-globulin (nmol/L).

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