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# Association of Follicle-Stimulating Hormone and Depression and Depressive Symptoms in Older Postmenopausal Women

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ASSOCIATION OF FOLLICLE-STIMULATING HORMONE AND DEPRESSION  
AND DEPRESSIVE SYMPTOMS IN OLDER POSTMENOPAUSAL WOMEN

A Thesis Presented

By

DANA L. FRITZ

Submitted to the Graduate School of the  
University of Massachusetts, Amherst in the partial fulfillment  
of the requirements for the degree of

MASTER OF SCIENCE

May 2018

Public Health  
Epidemiology and Biostatistics

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## DEDICATION

To Silke. Thank you for laying the foundation for the person I am now. I hope I made you proud.

## ACKNOWLEDGEMENTS

I would like to thank Elizabeth Bertone-Johnson for guiding me through this process. Her direction and support were unparalleled. I would also like to thank the member of my committee, Katherine Reeves, for contributing feedback throughout this process. Finally, thank you to the University of Eastern Finland whose data made this research possible.

## ABSTRACT

### ASSOCIATION OF FOLLICLE-STIMULATING HORMONE AND DEPRESSION AND DEPRESSIVE SYMPTOMS IN OLDER POSTMENOPAUSAL WOMEN

MAY 2018

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Worldwide, between 5 and 18% of postmenopausal women experience depression.<sup>1-3</sup> While the associations of estrogens with depression have been researched extensively, relations with other postmenopausal hormones remain unclear. We evaluated the association of follicle stimulating hormone (FSH) levels with prevalent depression the Kuopio Ischaemic Heart Disease Risk Factor Study (n = 588). Study participants were postmenopausal women aged 53 to 73 years and not using hormone therapy at enrollment (1998-2001). FSH was measured by radioimmuno-assays. Depression symptoms were measured using a scale based on DSM-III criteria (score range = 0-12), with a score  $\geq 5$  indicative of probable depression. We assessed the relation of FSH levels with depression in multivariable linear and logistic models adjusting for age, body mass index, estradiol, antidepressant use, and other factors, and evaluated effect modification by age. In adjusted analyses of all participants, higher FSH levels were associated with lower prevalence of depression (OR comparing  $\geq 50$  vs  $< 50$  IU/L = 0.50, P = 0.02). Each 10-unit increase in FSH was associated with a 17% lower prevalence of depression (95% CI 0.70-0.99). Regression coefficients for Quartiles (Q) 2-4 vs. Q1 of FSH were 0.208, -

0.170, -0.472, respectively ( $P = 0.14$ ). Associations were mainly observed in older women (aged 64-73 years). In this group, the OR of prevalent depression was 0.47 ( $P = 0.05$ ) compared to an OR of 0.57 ( $P = 0.25$ ) in the younger group (aged 53-63). Additionally, in this group, each 10-unit increase in FSH was associated with a 26% lower prevalence of depression (95% confidence interval: 0.57-0.95). Furthermore, FSH levels were inversely associated with symptom score in older women (regression coefficients for Q2-4 vs. Q1: -0.35, -0.95, -1.37, respectively;  $P = 0.02$ ). Higher FSH levels in older postmenopausal women were associated with lower prevalence of depression and depressive symptoms, independent of estradiol, adiposity measures, and other factors. Further research is warranted to evaluate mechanisms underlying these associations, including effects of FSH on immune function.

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## CHAPTER I

### INTRODUCTION

Depression is often not recognized and undertreated in developed and developing countries worldwide. Depression contributes to disease burden often leading to or exacerbating conditions such as cardiovascular disease, type 2 diabetes, arthritis, and cancer.<sup>4,5</sup> Depression also affects economic well-being, costing the United States \$210.5 billion per year in direct and indirect costs.<sup>6</sup> Of these costs, approximately \$99 million are directly attributable to depression. Established risk factors for depression include history of depression (self or familial), major life changes, certain illnesses, and the use of certain medications (e.g., isotretinoin, rimonabant, and corticosteroids).<sup>7,8</sup> The prevalence of depression is higher in women than men across all stages of life. In 2010, the global prevalence of depression was 5.5% in women and 3.2% in men.<sup>9</sup> This trend is visible throughout populations worldwide independent of race, education, diet, and other potential confounding factors suggesting that there may be biological differences due to sex.

The prevalence of depression in postmenopausal women is estimated to be between 5 and 18%.<sup>1-3</sup> While various external factors contribute to the onset of depression, internal factors should not be ignored. Hormonal changes that occur during the menopausal transition may also contribute to depression in postmenopausal women. When women go through the menopausal transition, they experience a rise in follicle-stimulating hormone levels and a drop in estradiol levels.<sup>10-12</sup> This fluctuation in hormonal levels is associated with an increased incidence of depression in perimenopausal women compared to premenopausal women.<sup>13</sup> After menopause, the

rate of change in hormone levels decreases substantially (FSH and estrogen levels slowly decline), but prevalence of depression still remains a major health concern.

## CHAPTER II

### PHYSIOLOGY OF FOLLICLE STIMULATING HORMONE AND DEPRESSION

Follicle stimulating hormone, or FSH, is one of two gonadotropic hormones, the other being luteinizing hormone (LH). Prior to menopause, FSH is primarily responsible for recruiting immature follicles to reach maturation so that an egg is released during ovulation.<sup>14</sup> Gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus, stimulates the production of FSH and LH in the pituitary gland.<sup>15,16</sup> FSH and LH travel to the ovary via the bloodstream stimulating follicular growth and ovulation, as well as estrogen production. Estrogen then travels back to the brain to slow the release of GnRH and, therefore, FSH through a process called negative feedback. Activins A, B, and AB stimulate the secretion of FSH, while inhibins A and B suppress its secretion.<sup>10</sup> Another protein, follistatin, also acts to suppress FSH by binding to activins depressing their secretion of the hormone. The menopausal transition introduces changes in the regulation and levels of these proteins and hormones. A deficiency in inhibin B first, followed by inhibin A, stimulates the initial (monotropic) rise in FSH levels.<sup>12,17</sup> A decrease in estradiol levels from the ovaries also contributes to the increased levels of FSH in postmenopausal women.<sup>11,12</sup> Estrogens continue to be produced by extragonadal tissues, such as adipose tissue, however not in a comparable amount to that produced prior to menopause.

While the main role of FSH relates to reproductive function, recent research has shown that FSH receptor (FSHR) activity also occurs in extragonadal tissues.<sup>18-22</sup> FSHR has been expressed in the pancreas,<sup>18</sup> osteoclasts,<sup>19</sup> and the liver.<sup>20</sup> These alternate locations of FSH and FSHR suggest that the role of the hormone may not be strictly

reproductive. Higher levels of FSH in postmenopausal women have been associated with reduced risk of cardiovascular disease,<sup>23</sup> obesity,<sup>24-27</sup> and type 2 diabetes.<sup>28</sup>

### Pathophysiology of Depression

There are a variety of factors that can lead to depression. Genetic influences may contribute to the onset of depression. This likely involves the combination of genetic and environmental factors, although many genes have been identified as potential mechanisms of depressive symptoms.<sup>29</sup> The main biochemical pathway that has been determined in the etiology of depression involves monoamine neurotransmitters.<sup>29,30</sup> Neurotransmitters are chemicals that are responsible for carrying signals from one neuron to another across a synapse. This process begins with amino acids traveling to the brain through the bloodstream, which trigger the conversion of precursor elements to become neurotransmitters. Neurotransmitters are then stored in vesicles and released into the synaptic cleft.

Cholesterol is essential for synaptic transmission as it is found in plasma membranes and is used in the formation of various components of the neurotransmitter pathway. Lower cholesterol levels can lead to decreased firing of neurotransmitters.<sup>31,32</sup> Medical conditions and drugs can modify the rate of release into the synaptic cleft. Serotonin (5-HT), norepinephrine, or dopamine are monoamine neurotransmitters that influence a wide range of brain functions including mood, sleep, appetite, and cognition. Deficiencies of these neurotransmitters in the central nervous system (CNS) have been linked to increased rates of depression (the monoamine-deficiency theory). This mechanism of depression is further supported by the efficacy of many antidepressants which target the monoamine system.<sup>33</sup>

Serotonin is the most extensively researched of the monoamines in the depression pathway. Relationships between estradiol and serotonin have been established in prior literature.<sup>34,35</sup> One mechanism by which estradiol increases serotonin is through increased production of tryptophan hydroxylase (TPH), which is the limiting factor in converting tryptophan to serotonin.<sup>36</sup> Estradiol inhibits the serotonin reuptake transporter (SERT) which allows serotonin to remain in the body for longer amounts of time. Estradiol also enhances the binding capabilities of serotonin receptors 5HT<sub>1A</sub> and 5HT<sub>2A</sub>.<sup>36,37</sup> Decreased estrogen during the menopausal transition may contribute to both vasomotor and depressive symptoms as a result of decreased serotonin in the body.<sup>37</sup> However, this mechanism may be different in postmenopausal women. One study conducted by Haliloglu et al. found an inverse relationship between estrogens and serotonin in a postmenopausal population.<sup>38</sup> It is suggested that an increase in serotonin is a compensatory mechanism in response to cessation of estrogen production during the menopausal transition, however research on this pathway is lacking. Because FSH increases in postmenopausal women, in part, due to discontinued negative feedback from estradiol, the mechanism that relates estrogens to serotonin may also influence FSH levels.

Stress can also contribute to depression. When exposed to psychological stress, the hypothalamus produces corticotropin-releasing hormone (CRH), which ultimately releases cortisol into the body.<sup>30</sup> Altered CRH pathways have been associated with major depressive disorder (MDD). Stressors tend to influence people differently based on gender, and women tend to have a higher sensitivity to overall stress.<sup>29,30</sup> Structural modification of components of the brain may contribute to stress sensitivity. Untreated

depression has been associated with decreased volume of the hippocampus.<sup>39</sup> This may contribute to decreased ability to handle stress and the recurrence of depression.<sup>40</sup> Exposure to stressful situations can also stimulate an inflammatory response in the body by increased plasma cytokine levels. Experiments that administered interleukin-1 (IL-1), IL-2, and interferon- $\alpha$  have resulted in stress-like response and depressive symptoms.<sup>29,41</sup> Certain cytokines directly influence the body's serotonin response; for example, IL-1 is a regulator of the 5-HT transporter gene.<sup>30,41</sup> Activins and follistatin (both regulators of FSH) have been connected to inflammatory mechanisms.<sup>42</sup> Furthermore, FSH has been inversely associated with cytokine activity as well as intima-media thickness (IMT).<sup>43-45</sup>

Body composition, such as increased adiposity, may influence hormone regulation contributing to depressive symptoms in postmenopausal women. Estrogens are primarily produced by the ovaries prior to menopause; however, after menopause, estrogens are produced by extragonadal tissue including adipose tissue. Higher estrogen levels have been found in obese postmenopausal women compared to normal weight postmenopausal women.<sup>46</sup> These increased estrogen levels trigger the negative feedback loop lowering FSH levels in the body. In a randomized study conducted by Kim et al., overweight, postmenopausal women were randomly assigned to one of three intervention groups for one year with the goal of losing weight. Decreases in weight and BMI resulted in increased levels of FSH after adjusting for estradiol.<sup>25</sup> Observational studies have found the same association.<sup>24,26</sup> Furthermore, direct associations between obesity and depression have been reported in postmenopausal women.<sup>46-48</sup> A study conducted by Chedraui et al. found that abdominal obesity (waist circumference >88 cm) was associated with a 60% increased risk of depression (OR 1.6, 95% CI 1.0, 2.6).<sup>46</sup> In a study

conducted by Pan et al. showed that, compared to normal weight women, obese women were 11% more likely to experience depression (OR 1.11, 95% CI 1.03, 1.18) after full adjustment.<sup>48</sup>

Lipid profiles also change in the menopausal transition. Compared to premenopausal women, postmenopausal women tend to have higher total cholesterol, triglycerides, low density lipoprotein (LDL) levels, and very low density lipoprotein (VLDL) levels, while high density lipoprotein (HDL) levels are lower.<sup>49-51</sup> One study, conducted by Persons et al., found an association between LDL-c levels below 100 mg/dL and depressive symptoms in postmenopausal women.<sup>52</sup> These findings are consistent with other studies that have found an inverse relationship between cholesterol and depression.<sup>49,50</sup> In a study of 400 postmenopausal women, Song et al. reported decreased levels of FSH after administering estradiol treatment.<sup>20</sup> This further resulted in decreased levels of total cholesterol and LDL-c, independent of BMI. Additional analyses in this study found evidence that FSH levels may inhibit LDL receptor expression. A study conducted by Bertone-Johnson et al. found that total cholesterol and HDL levels were higher in women of higher FSH levels, while triglycerides tended to be lower.<sup>43</sup> Cholesterol profiles are important in the regulation of neurotransmitter function. Decreased cholesterol levels limit the ability of neurotransmitter (e.g. serotonin) firing contributing to depressive symptoms.<sup>29,30</sup>

FSH may be associated with these mechanisms of depression primarily through its relationship with estrogens. Because the aforementioned depression pathways are influenced by estrogen levels and FSH is regulated by an estrogen-mediated negative feedback loop, FSH levels may also be associated with depression.

## CHAPTER III

### EPIDEMIOLOGY OF FOLLICLE STIMULATING HORMONE AND DEPRESSION

Four cohort studies have explored the association between FSH and depression in postmenopausal women.<sup>55-58</sup> Bromberger et al. assessed the change in reproductive hormones and depressive symptoms in 3,296 women aged 42 to 52 years enrolled in the Study of Women's Health Across the Nation (SWAN) Study.<sup>55</sup> Data for this study were collected annually from baseline (December 1995) to January 2008. Depressive symptoms were assessed using the Center for Epidemiological Studies Depression (CES-D) Scale (scores of 16 or higher identified depression). Fasting blood samples were used to assess hormone levels (estradiol, FSH, testosterone, dehydroepiandrosterone sulfate (DHEA-S), free estradiol index, and free testosterone index). These samples were collected within 90 days of the anniversary of the baseline examination. Women were considered postmenopausal if bleeding had not occurred within the previous 12 months; four categories were determined: premenopausal, early perimenopausal, late perimenopausal, postmenopausal. Covariates assessed were age, race/ethnicity, education level, BMI, smoking status (current vs. not), medication for nerves or depression, vasomotor symptoms, social support (score ranged from 0 to 16), and upsetting life events (categorized as 0, 1 or  $\geq 2$  very upsetting events). No association was found between FSH levels and depressive symptoms in women regardless of menopause status ( $\log_{10}$ FSH OR = 1.05, 95% CI 0.97, 1.13).

Freeman et al. looked at this association in 203 late-reproductive age women who were not using hormone therapy followed through the menopausal transition from the Penn Ovarian Aging Study (POAS).<sup>56</sup> During the 14-year follow-up of the study, all

participants reached natural menopause. Depression was assessed using the CES-D in which 16 or greater was determined as a high depressive symptom score. Follow-up assessments were conducted approximately 9 months apart for the first five years, then annually for the rest of the study. The timing of these visits was based on the early follicular phase of the menstrual cycle for cycling women. Two visits were scheduled for two consecutive menstrual cycles. For non-cycling women, these two visits occurred approximately one month apart. At these assessments, blood samples were obtained to assess hormone levels. Covariates assessed were history of depression, race, age, BMI, current smoking status at the final menstrual period. Postmenopausal women were identified as those who had not bled in the last 12 months. Current medication use (including antidepressants) was also assessed. This study did not report an association between absolute levels of FSH and risk of depression, but found that rates of change of FSH levels prior to the final menstrual period were predictors of depression in postmenopausal women. Specifically, higher rates of change of FSH levels over the span of 4 years were associated with decreased depressive symptoms postmenopause (OR = 0.65, 95% CI 0.46-0.91).

Ryan et al. assessed the relationship of endogenous hormones and depressive symptoms in 138 postmenopausal women from the Melbourne Women's Midlife Health Project (MWMHP).<sup>57</sup> This analysis utilized data from years 11 and 13 of the full MWMHP study. The average age of women at year 11 was 60.1 years (range 55.9-66.8 years). Women were determined postmenopausal if they had not bled in the last 12 months. Depressive symptoms were assessed using a shortened version of the CES-D (10 items) that contained questions concerning mood for the week prior. Scores were

summed for a maximum score of 30; a cutoff of 10 was used to identify clinical depression. Fasting morning blood samples were used to assess hormone levels. All hormones (sex hormone binding globulin (SHBG), free androgen, FSH, testosterone, and estradiol) were measured in year 11, but only FSH and estradiol were measured in year 13. Covariates assessed were age, BMI, level of education, living arrangement, and employment status, alcohol consumption (for the past week), and smoking status (current or past), and level of current physical activity. The following chronic health conditions were also assessed: high cholesterol (total cholesterol, HDL, LDL), diabetes, hypertension, chronic asthma, heart disease, stomach or bowel ulcers, arthritis, rheumatism, cancer, and migraine. Information for medications for these conditions was also obtained. The presence of 22 common symptoms (e.g. dizzy spells, headaches, lack of energy, etc.) in the two weeks prior were assessed using a shortened daily hassles scale. Women's attitudes towards menopause using an 8-item questionnaire were assessed. Absolute values of FSH and estradiol were not associated with depression in either year. Compared to women with FSH levels less than 70 IU/l, women with FSH levels at or above this threshold had an odds ratio of 0.78 (95% CI 0.33, 1.82) of depression (year 11). Compared to women with FSH levels less than 80 IU/l, women with FSH levels at or above this threshold had an odds ratio of 1.39 (95% CI 0.59, 3.26) of depression (year 13). This study, however, did find statistically significant results in the association between change in FSH over the 2-year period and risk of depression. A 9+ IU/l increase in FSH levels was associated with a 2.57 increased odds of developing depressive symptoms (95% CI 1.0-6.69,  $p=0.05$ ). Similarly, decreases in estradiol were associated with increased depression risk.

Woods et al. assessed this relationship in 302 women from the Seattle Midlife Women's Health Study (SMWHS).<sup>58</sup> Postmenopause was determined as 12 months without bleeding. Depression was measured using the CES-D for which 16 was determined to be the cutoff score for depression. A total of 87 postmenopausal women (obs = 319) provided data for this study. A first-voided morning urine sample was collected on a consistent date each month (for women with no bleeding) to measure hormone levels (estrone glucuronide, FSH, testosterone, cortisol, and creatinine). Covariates assessed through information obtained through questionnaires were history of sexual abuse and postpartum blues, live births, family history of depression, negative life event stress, hot flashes, BMI, and use of antidepressants. No association was found between FSH and depressed mood (numerical results were not included in the article).

In summary, two of these studies found no association between FSH levels and depressive symptoms or depression in postmenopausal women. One of the studies found a change in FSH levels over time is associated with depression. One study found rate of change of FSH prior to the final menstrual cycle was inversely related to depression outcome postmenopause. All four studies found no association between estradiol and depression. None of the studies included women who were using hormone therapy, similar to our study. These studies have provided a foundation for the research on FSH and depression in postmenopausal women. One gap in research that needs to be filled is the assessment of the relationship of FSH and depression in older postmenopausal women. The recruitment of pre- or perimenopausal women at baseline limits the generalizability of results to women who have been postmenopause for many years as hormone levels may vary as time since menopause increases.

While the studies with women of different menopausal status did attempt to look at FSH and depression in postmenopausal women as a component of their analyses, their results were difficult to interpret and may have suffered from misclassification. Two of the studies also had smaller sample sizes (n=203; n=138) which may limit the power of observed associations.<sup>56,57</sup> These two studies did not find associations between absolute hormone levels and depression, but rather associations between (rate of) change of hormone levels and depression. This may be a result of residual hormone fluctuations following menopause and may possibly only apply to postmenopausal women who have recently completed the transition. One study did not collect information on antidepressant use<sup>57</sup> which may have attenuated results. Findings that describe the relationship between FSH and depression in women of all menopausal stages (pre-, peri-, and postmenopausal), lack of data on older postmenopausal women, and small sample sizes leaves the relationship of FSH and depression in postmenopausal women not well understood.

## CHAPTER IV

### SUMMARY AND PROPOSED RESEARCH

The population we had data on represented a wide age range of postmenopausal women, some of which completed the transition many years prior to data collection. This is novel in that prior studies only evaluated women shortly after the menopausal transition. Because hormone levels may be different in women as a result of time since menopause, data on older postmenopausal women is pertinent. We also had access to a wide range of covariates for which we were able to adjust. The goals for our analysis were to examine the relationship between FSH and depression and depressive symptoms in an older postmenopausal population. We also stratified based on age and BMI to assess possible effect modification by these variables.

## CHAPTER V

### HYPOTHESES AND SPECIFIC AIM

#### Specific Aim:

Using data from the Kuopio Ischaemic Heart Disease Risk Factor Study, we evaluated the relationship between levels of follicle stimulating hormone (FSH) and depressive symptoms and depression in postmenopausal women.

#### Hypothesis 1:

There will be an inverse association between FSH levels and depressive symptoms.

#### Hypothesis 2:

There will be an inverse association between FSH levels and prevalence of depression.

## CHAPTER VI

### METHODS

#### Study Design and Population

We assessed the relationship between FSH levels and depressive symptoms and depression in postmenopausal women using data from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. The KIHD Study is an ongoing, population-based prospective cohort study that began in 1984, originally enrolling exclusively male participants to investigate risk factors for cardiovascular disease in Eastern Finland.<sup>59</sup> Female participants who had completed the menopausal transition were first enrolled in March 1998. Baseline examinations for women were conducted between March 1998 and February 2001 and included information on dietary intake, biochemical measures, neuropathological tests, and other risk factors. The proposed study will be cross-sectional using baseline data from 1998-2001.

Eligible women were postmenopausal women who enrolled in the KIHD Study between March 1998 and February 2001. Postmenopausal status was defined by the absence of menses for at least 12 months, or at time of oophorectomy for women reporting surgery prior to menopause. Women eligible for enrollment in the KIHD Study were a random sample (n = 1173) living the city of Kuopio and surrounding rural communities during this time, and women in four specific age groups were targeted: 53-56, 59-62, 64-68, and 71-73 years. Of eligible women, 920 completed baseline clinical assessments and joined the cohort (78.4%). For the purpose of the proposed study, women who were missing data on FSH and/or depression were excluded (n = 7). Women

who were using hormone therapy at baseline were also excluded due to the influence hormone therapy has on FSH levels (n = 325).

#### Assessment of FSH

During the baseline examination, fasting blood samples were collected between 8 am and 10 am. Participants were asked to abstain from eating or smoking cigarettes for 12 hours prior to the examination and alcohol for three days prior. Plasma was separated from other blood components within 60 minutes of collection and stored at -20°C or -80°C until assay. Samples were assayed for FSH between June 2001 and February 2002. A sandwich technique was used which applied an immunoradiometric assay manufactured by Diagnostic Product Corporation (Coat-A-Count FSH IRMA; Los Angeles, CA). <sup>125</sup>I label measurements for FSH were carried out by gamma counter Wallac 1261 MultiGamma using a RiaCalc LM Evaluation Program. FSH levels in our data will be analyzed both categorically by quartiles and continuously. For quality control, triplicates of low, medium, and high Lyphocek controls were included in each run. Coefficients of variation were 5% for each set of controls.

#### Assessment of Depression

The DSM-12D was used to assess depressive symptoms in this study. This scale contained 12 questions for which participants answered yes or no to experiencing the presented symptoms nearly every day for the past two weeks. Symptoms assessed included sadness, feelings of worthlessness, difficulties in concentrating, variation of eating patterns (too much or too little), issues with sleeping (sleeping too much or trouble sleeping), and thoughts about death. This scale was developed using criteria similar to those from the DSM-IV. A cutoff score of 5 and greater identified depression for

analyses using a dichotomous outcome. This cutoff has been used in prior studies.<sup>60,61</sup>

Antidepressant use was also used as a proxy for depression in secondary analysis. In this analysis, we included antidepressant users as cases regardless of symptom score, as well as excluding them from our models to assess their possible influence on our results.

### Covariate Assessment

#### Clinical Measures

At a clinical interview, height and weight were directly measured and used to calculate body mass index (BMI; weight in kg/ht in m<sup>2</sup>). Waist and hip circumferences were measured with a standard measuring tape in order to calculate waist-to-hip ratios.

#### *Blood Collection and Biochemical Measurements*

In addition to FSH, estradiol, testosterone, and sex hormone binding globulin (SHBG) samples were also assayed using the blood samples mentioned prior. Serum 17- $\beta$ -estradiol was assayed between 1999 and 2001 with a radioimmunoassay manufactured by DiaSorin (Stillwater, MN). Four different types of controls were included in each run: Lyphocheck low and medium controls, in-house serum pool, and a control provided by the kit manufacturer. Concentrations of 17- $\beta$ -estradiol were in the physiologic range for the in-house pool, and higher for other control types. Coefficients of variation ranged from 7.6% (in-house pool) to 12.0% (manufacturer control). Serum testosterone (17 $\beta$ -hydroxy-4-androsten-3-one) was determined with Spectria Testosterone [<sup>125</sup>I] radioimmunoassay kit (Orion Diagnostica Espoo, Finland). In each assay were included three different controls: Lyphocheck low, medium, and high. Coefficients of variation ranged from 7.9% (high control) to 12.2% (low control). <sup>125</sup>I label measurements of estradiol and testosterone were carried out by gamma counter Wallac 1261 MultiGamma using a

RiaCalc LM Evaluation Program. Sex hormone binding globulin (SHBG) was evaluated using the 1235 AutoDELFIA automatic system based on a time-resolved fluoroimmunoassay (AutoDELFIA SHBG, Wallac, Turku, Finland).<sup>62</sup>

Samples from all participants were assayed for total, HDL and LDL cholesterol, and triglycerides using laboratory methods described in detail previously. Cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically; HDL fractions were separated from serum by combined ultracentrifugation and precipitation.<sup>63</sup> Coefficients of variation were 2.3% for total cholesterol, 5.2% for LDL, 9.2% for HDL, and 1.9% for triglycerides.

#### Questionnaire Assessments

Participants in the KIID Study completed questionnaires that included information on demographic, behavioral, reproductive, and health-related variables which were reviewed by trained interviewers for completeness and clarity. Covariates considered from the questionnaires included age, cigarette use (never, ever, current), antidepressant use, presence of other chronic diseases, education, marital status, and physical activity levels (MET hours/week). A detailed alcohol use questionnaire was used to determine alcohol intake (grams/week).<sup>64</sup> Physical activity was determined using the KIID 12-Month Leisure Time Physical Activity Questionnaire, which was used to estimate metabolic equivalent of task hours of activity per day.<sup>65</sup> Reproductive factors considered were age at menarche, age at menopause, number of full term pregnancies, prior use of hormone therapy (including duration), and use of oral contraceptives. Age at menopause was determined using the criteria for postmenopausal (mentioned prior).

Study physicians conducted interviews to obtain information on use of medications for hypertension, diabetes, heart disease, angina pectoralis, and high cholesterol.<sup>65</sup>

### Statistical Analysis

#### Specific Aim 1:

Using data from the Kuopio Ischaemic Heart Disease Risk Factor Study, we propose to evaluate the relationship between levels of follicle stimulating hormone (FSH) and depressive symptoms and depression in postmenopausal women.

#### Univariate Analysis

The study population size after accounting for exclusion criteria (missing data on FSH or depressive symptoms) who were not using hormone therapy was n=588.

#### Bivariate Analysis

Covariate relationships were compared across quartiles of FSH levels (Table 1). Continuous covariates were assessed using t-tests. Categorical covariates were assessed using chi-square tests. We assessed the association between FSH levels and depression (dichotomous) using logistic regression (Table 2) and the association between FSH levels and depressive symptom score (continuous) using linear regression (Table 3). P values from all tests were reported. Odds ratios and 95% CIs were reported.

#### Multivariable Analysis

Multivariable logistic regression was used to analyze the association between FSH and depression. FSH was assessed both continuously and dichotomously, dividing FSH levels at the median (50 IU/L, high vs. low). Model 1 adjusted for age. Model 2 used forward building to create the most parsimonious model representing the association

between FSH and depression. The covariates included in this model were age, BMI, waist-to-hip ratio, and estradiol. Other covariates tested for inclusion were identified from the existing literature<sup>2, 55-58, 66,67</sup> but not included were smoking status, alcohol consumption, past hormone therapy use and duration, oral contraceptive use, presence of other chronic diseases, physical activity levels, level of education, marital status, employment status, age at menarche, parity, age at menopause, and levels of testosterone and SHBG. Covariates were retained in the final model if they had a P value less than 0.10 using a likelihood ratio test or if their inclusion led to a change in the beta coefficient of the FSH-depression relationship greater than or equal to 10%.

Multivariable linear regression was used to analyze the association between FSH and depressive symptom scores. FSH was assessed both continuously and by quartiles in linear models. Model 1 assessed the relationship between FSH and depressive symptoms adjusting for age, date of examination (year), and estradiol (quartiles). Model 2 included model 1 variables with further adjustment for BMI and waist to hip ratio. Model 3 included model 2 variables with further adjustment for employment status, marital status, education level, physical activity, past hormone use and duration, smoking status, alcohol consumption, parity, age at menopause, testosterone, and SHBG. Linear trends across quartiles of FSH were assessed by modeling the median value of each quartile as a continuous variable. Despite a non-normal distribution, we left depressive symptom score untransformed for purposes of interpretation. Trends were the same in transformed and untransformed models.

Models stratifying by BMI (normal/underweight, overweight, obese) and age were also created to assess possible effect modification. These models were assessed with

multiplicative interaction terms, and likelihood ratio test  $P < 0.05$  was considered significant. In secondary analysis, we assessed the relationship between FSH and depression while including women taking antidepressants as cases for depression regardless of symptom score (Table 8). We also assessed the relationship excluding antidepressant users (Table 9). Statistical analyses were completed with Stata/IC 15.1 for Mac (StataCorp LLC).

#### Sample Size and Power Calculations

The sample size for our study was  $n=588$ . High FSH and low FSH groups were created by dividing the sample size at the median of FSH (50.0 IU/L) resulting in a nearly 1:1 ratio. Post hoc power calculations using G Power indicate we had the ability to detect an odds ratio of 0.71 with 80% power for prevalent depression comparing women with high FSH levels to women of low FSH levels. Among quartiles of FSH, we are able to detect an effect size of 0.13 of FSH quartile on depressive symptom score with 80% power.

## CHAPTER VII

### RESULTS

Characteristics of participants by quartiles of FSH are presented in Table 1.

Women in the highest quartile of FSH were younger and had a lower BMI and waist-to-hip ratios than women in the lowest quartile of FSH. Estradiol was higher in quartile 1 of FSH than quartiles 2 to 4. FSH levels were inversely related to parity, but not related to age at menarche or age at menopause. Women with higher FSH were more likely to report the use of medication for hypertension, heart disease, diabetes, and angina pectoralis than women with lower FSH levels. The distribution of other factors did not differ significantly across quartiles of FSH. Most women had depressive symptom scores of 0 and 1 on the scale ( $n = 285$ ). Based on the cut off score of 5 for probable depression, 61 women were considered depressed.

As shown in Table 2, FSH was inversely related to the prevalence of depression when adjusting for age (OR = 0.45, 95% CI 0.25, 0.79; model 1). Additional adjustment for BMI, WHR, and estradiol (model 2) attenuated results slightly, but they remained statistically significant; women with FSH levels above the median had an OR for prevalent depression of 0.50 (95% CI 0.28, 0.89) compared to women with FSH levels below the median. Assessing the relationship between continuous FSH levels and depression showed that every 10-unit increase in FSH was associated with a 17% decrease in prevalence of depression (OR 0.83, 95% CI 0.70 – 0.99,  $P=0.04$ ).

Results from multivariable linear regression models assessing the association of quartiles of FSH and depressive symptom score are shown in Table 3. Mean depressive symptom scores of women in quartiles 1 through 4 of FSH were 2.2, 2.0, 1.8, and 1.4,

respectively ( $P = 0.01$ ). FSH was inversely associated with depressive symptom score in models adjusting for age, examination date, and levels of E2 (model 1;  $P$  for trend = 0.001) and adiposity measures (model 2;  $P$  for trend = 0.002). Full adjustment (model 3) resulted in beta coefficients of 0.186, -0.129, -0.478 for quartiles 2 through 4 of FSH, respectively, however this relationship was not statistically significant ( $P$  for trend = 0.15).

To determine if the association of FSH and depression varied by age, we stratified by age group (ages 53-62 years vs. 64-73 years; Tables 4 and 5). The association of higher vs. lower FSH and depression was similar in older and younger women ( $P$  for interaction = 0.87). In older women, each 10-unit increase in FSH was associated with a 26% lower prevalence of depression (OR = 0.74, 95% CI 0.57-0.95,  $P = 0.02$ ), though this linear relation was not observed in younger women (OR = 0.96, 95% CI 0.75-1.22;  $P$  for interaction = 0.20).

In analysis of depressive symptom score, similar results to assessing dichotomous outcome were obtained. In younger postmenopausal women, beta coefficients were 0.384, 0.646, and 0.664 across quartiles 2 through 4 of FSH, respectively ( $P$  for trend = 0.26). The beta coefficients for older postmenopausal women -0.345, -0.948, -1.374 ( $P$  for trend = 0.02;  $P$  for interaction = 0.44).

We also stratified according to WHO categories of BMI (<25.0, 25.0 - 29.9,  $\geq 30.0$  kg/m<sup>2</sup>; Tables 6 and 7). We observed a lower prevalence of depression with high FSH levels in normal weight and overweight women, but not in obese women ( $P$  for interaction = 0.11). In the normal weight group, an OR of 0.19 (95% CI 0.03-1.36) was observed; in the overweight group, an OR of 0.33 (95% CI 0.14-0.81); and in the obese

group, an OR of 0.90 (95% CI 0.38-2.15). In analyses of depressive symptom score, non-linear trends were observed across quartiles of FSH for normal and obese groups.

In secondary analysis, including antidepressant users as cases resulting in an attenuation of our results, however the observed trends persisted (Table 8). We observed a lower prevalence of depression in women with higher FSH levels (OR = 0.62, 95% CI 0.37, 1.04). When antidepressant users were excluded in linear models (Table 9), beta coefficients of 0.150, -0.236, -0.604 (P for trend = 0.09) were observed for quartiles 2 through 4 of FSH, respectively.

## CHAPTER VIII

### DISCUSSION

We observed significant inverse associations between FSH levels and depression and depressive symptoms among postmenopausal women. This trend was more pronounced in older postmenopausal women (ages 64-73 years). Effect modification by age and BMI was suggested by our results despite non-significant observed interaction. Prior studies have not assessed this relationship in older postmenopausal women, which is apparent by the enrollment of predominantly pre- or peri-menopausal women in studies. Of the four studies that have assessed this association in postmenopausal women, none found associations between absolute levels of FSH and depression. Two prior studies have found that rates of change in FSH levels are associated with depression, however, the application of this association may only be relevant to women going through the menopausal transition or early postmenopausal women as these are the time periods in which large hormone fluctuations typically occur. Furthermore, one of the studies evaluated rates of change in hormone levels prior to the onset of menopause which may not be applicable to older postmenopausal women.

Our study had a few limitations. Because our study is cross sectional, we cannot evaluate the temporality of the relationship between FSH and depression. The population enrolled in the KIID Study is very homogenous with respect to race and ethnicity limiting the generalizability to other races if pathways between FSH and depression are dependant on race or ethnicity. Nondifferential misclassification of the outcome could have occurred as depression is a cyclic disease, and women may not have been experiencing depressive symptoms at the time of the assessment. Had this occurred, it

would have attenuated our results. We had data on many variables for which we were able to control for, but potential confounders may have not been evaluated. Because research on this association is relatively novel, possible influential factors have not been established. Additionally, we did not have information on history of depression.

Assessing the the relationship between FSH and depression based on prior depressive episodes may have provided alternate results. Evaluating the relationship of FSH and depression in studies including more diverse populations should be a goal of future research. Strengths of our study include access to extensive data on covariate measures to adequately assess potential confounding relationships and effect modification. We also had data on women of many ages allowing our results to be likely generalizable to all postmenopausal women not using hormone therapy.

To our knowledge, this is the first study to assess the association between FSH and depression and depressive symptoms in older postmenopausal women, for which hormone levels may be different compared to younger postmenopausal women. We observed evidence of lower prevalence of depression for women with higher FSH levels, which was not explained by confounding factors such as estradiol and adiposity measures. Future steps should focus on absolute hormone levels in postmenopausal women of all ages (rather than focusing primarily on early postmenopausal women) and how these measures relate to depressive symptoms. Understanding the biochemical and inflammatory mechanisms involved with this relationship and how they might change as postmenopausal women age is another important step for future research.

Table 1. Characteristics of Women not Using Hormone Therapy by Quartile of Follicle Stimulating Hormone, Kuopio Ischaemic Heart Disease Risk Factor Study, 1998-2001.

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
FSH Ranges (IU/L)	1-39.3	39.4-50.0	50.1-61.8	61.9-150	
n	147	149	145	147	
	M (SD)	M (SD)	M (SD)	M (SD)	P Value
Age, y	64.5 (6.8)	65.1 (5.9)	64.4 (6.1)	62.9 (6.9)	0.02
Body Mass Index (kg/m <sup>2</sup> )	31.1 (5.7)	29.0 (5.4)	28.8 (5.0)	26.8 (4.4)	<0.001
Waist:hip ratio	0.87 (0.07)	0.85 (0.06)	0.84 (0.06)	0.83 (0.06)	<0.001
Estradiol, pmol/L	55.8 (77.6)	35.1 (19.8)	32.5 (12.5)	34.1 (19.5)	<0.001
Testosterone, nmol/L	1.5 (2.9)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)	0.06
Sex-hormone binding globulin, nmol/L	45.5 (23.0)	49.5 (21.2)	55.0 (24.3)	58.2 (27.7)	<0.001
Alcohol consumption, g/wk	15.4 (32.2)	23.6 (53.2)	15.2 (29.4)	13.6 (26.0)	0.09
Exercise, MET h/d	45.2 (5.8)	46.0 (7.0)	46.3 (6.1)	47.3 (7.4)	0.05
Age at menarche, y	13.7 (1.6)	13.9 (1.4)	14.1 (1.5)	13.9 (1.6)	0.16
Age at menopause, y	49.8 (4.3)	49.5 (4.3)	48.9 (4.7)	49.3 (4.2)	0.44
Parity, full term pregnancies	2.5 (1.6)	2.4 (1.8)	2.5 (1.8)	2.0 (1.5)	0.02
Past hormone therapy duration, y	2.0 (1.2)	2.0 (1.3)	2.0 (1.0)	2.6 (1.4)	0.05
	N (%)	N (%)	N (%)	N (%)	P Value
Smoking status					0.37
Never	116 (78.9)	120 (80.5)	118 (81.4)	121 (82.3)	
Former	19 (12.9)	15 (10.1)	11 (7.6)	19 (12.9)	
Current	12 (8.2)	14 (9.4)	16 (11.0)	7 (4.8)	
Oral contraceptive use					0.17
Never	106 (72.1)	112 (75.2)	94 (64.8)	97 (66.0)	
Former	41 (27.9)	37 (24.8)	51 (35.2)	50 (34.0)	
Past hormone therapy use	38 (25.9)	45 (30.2)	48 (33.1)	49 (33.3)	0.47
Marital Status					0.65
Married/Living as couple	97 (66.0)	96 (64.4)	90 (62.1)	91 (61.9)	
Not married	8 (5.4)	14 (9.4)	13 (9.0)	18 (12.2)	
Separated/Divorced	12 (8.2)	13 (8.7)	14 (9.7)	17 (11.6)	
Widowed	30 (20.4)	26 (17.5)	28 (19.3)	21 (14.3)	
Employment status					0.02
Retired	109 (74.2)	121 (81.2)	114 (78.6)	90 (61.2)	
Employed full time	22 (15.0)	18 (12.1)	18 (12.4)	34 (23.1)	
Employed part time	7 (4.8)	2 (1.3)	3 (2.1)	6 (4.1)	
Unemployed	9 (6.1)	8 (5.4)	10 (6.9)	17 (11.6)	

	N (%)	N (%)	N (%)	N (%)	P Value
Current medication use <sup>a</sup>					
Antidepressants	7 (4.8)	4 (2.7)	7 (4.8)	5 (3.4)	0.73
Hypertension	83 (56.5)	77 (51.7)	63 (43.5)	51 (34.7)	0.001
Heart disease	27 (18.4)	20 (13.4)	13 (9.0)	11 (7.5)	0.02
High cholesterol	5 (3.4)	11 (7.4)	7 (4.8)	4 (2.7)	0.23
Diabetes	14 (9.5)	6 (4.0)	6 (4.1)	2 (1.4)	0.01
Angina	25 (17.0)	18 (12.1)	12 (8.3)	7 (4.8)	0.01
Education					
Low	19 (12.9)	13 (8.7)	10 (6.9)	13 (8.8)	0.6
Low moderate	48 (32.7)	50 (33.6)	58 (40.0)	44 (29.9)	
High moderate	64 (43.5)	71 (41.7)	64 (44.1)	77 (52.4)	
High	16 (10.9)	15 (10.1)	13 (9.0)	13 (8.8)	

<sup>a</sup> Not mutually exclusive

Table 2. Follicle Stimulating Hormone Levels and Prevalent Depression, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depression											
	Unadjusted			Model 1 <sup>a</sup>			Model 2 <sup>b</sup>					
	Cases	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P		
Low FSH (n = 296)	41	13.9	referent		0.45	0.25, 0.79	0.01	0.50	0.28, 0.89	0.02		
High FSH (n = 292)	20	6.9	0.45	0.25, 0.79	0.01	0.45	0.25, 0.79	0.01	0.50	0.28, 0.89	0.02	
FSH (per 10 IU/L)	61	10.4	0.82	0.71, 0.96	0.01	0.82	0.71, 0.96	0.01	0.83	0.70, 0.99	0.04	

<sup>a</sup> Model 1: Adjusted for age (years)

<sup>b</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>; continuous), waist-to-hip ratio (continuous), and estradiol (continuous)

Table 3. Follicle Stimulating Hormone Levels and Mean Depressive Symptom Score, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

Mean Depressive Symptom Score (SD) <sup>a</sup>	Depressive Symptom Score											
	Unadjusted			Model 1 <sup>b</sup>			Model 2 <sup>c</sup>			Model 3 <sup>d</sup>		
	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P
<b>Follicle Stimulating Hormone</b>												
Continuous FSH	1.9 (2.0)	-0.011 (0.005)	0.02	-0.010 (0.005)	0.03	-0.006 (0.005)	0.22	-0.005 (0.007)	0.48			
Quartile 1 (median = 32.1 IU/L)	2.2 (2.1)	Referent		Referent			Referent			Referent		
Quartile 2 (45.1)	2.0 (2.3)	-0.262 (0.247)	0.29	-0.204 (0.249)	0.41	-0.074 (0.244)	0.76	0.208 (0.385)	0.59			
Quartile 3 (55.4)	1.8 (1.9)	-0.424 (0.249)	0.09	-0.354 (0.254)	0.16	-0.234 (0.249)	0.35	-0.170 (0.411)	0.68			
Quartile 4 (72.8)	1.4 (1.6)	-0.798 (0.249)	0.001	-0.775 (0.254)	0.002	-0.506 (0.253)	0.05	-0.472 (0.404)	0.25			
<i>P for trend</i>	<i>0.013</i>	<i>0.001</i>		<i>0.002</i>		<i>0.03</i>		<i>0.14</i>				

<sup>a</sup> Unadjusted mean depressive symptom score

<sup>b</sup> Model 1: Adjusted for age (years), date of examination (years), and estradiol (quartiles)

<sup>c</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>) and waist to hip ratio (continuous)

<sup>d</sup> Model 3: Model 2 further adjusted for antidepressant use, employment status, marital status, education, physical activity (MET hours per day), past hormone therapy (HT) use (yes, no), duration of HT use (3 categories), smoking status (current, past, never), alcohol use (grams per week), parity (number of full-term pregnancies), age at menopause (continuous), testosterone (continuous), and sex hormone binding globulin (continuous)

Table 4. Follicle Stimulating Hormone Levels and Prevalent Depression Stratified by Age, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depression											
	Unadjusted			Model 1 <sup>a</sup>			Model 2 <sup>b</sup>					
	Cases N (%)	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P		
<b>Ages 53-62 years (n = 244)<sup>c</sup></b>												
Low FSH (n = 110)	16	14.6	referent		referent			referent				
High FSH (n = 134)	9	6.7	0.43	0.18, 1.01	0.05	0.43	0.18, 1.01	0.05	0.57	0.23, 1.46	0.25	
FSH (per 10 IU/L)	25	10.3	0.89	0.74, 1.08	0.26	0.89	0.74, 1.09	0.26	0.96	0.75, 1.22	0.72	
<b>Ages 64-73 years (n = 344)</b>												
Low FSH (n = 186)	25	13.4	referent		referent			referent				
High FSH (n = 292)	11	7.0	0.47	0.22, 0.99	0.05	0.45	0.21, 0.96	0.04	0.47	0.22, 1.00	0.05	
FSH (per 10 IU/L)	36	10.5	0.73	0.57, 0.93	0.01	0.71	0.55, 0.92	0.01	0.74	0.57, 0.95	0.02	

<sup>a</sup> Model 1: Adjusted for age (years)

<sup>b</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>, continuous), waist-to-hip ratio (continuous), and estradiol (continuous)

<sup>c</sup> P for interaction: FSH (high vs. low) \* age = 0.87; FSH (continuous) \* age = 0.20

Table 5. Follicle Stimulating Hormone Levels and Mean Depressive Symptom Score Stratified by Age, Kuopio Ischaemic Heart Disease Risk Factor Study, (1998-2001).

		Depressive Symptom Score															
		Unadjusted				Model 1 <sup>a</sup>				Model 2 <sup>c</sup>				Model 3 <sup>d</sup>			
Mean Depressive Symptom Score (SD) <sup>e</sup>		beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	
<b>Follicle Stimulating Hormone</b>																	
<b>Ages 53-62 years (n = 244)</b>																	
Quartile 1 (median = 32.1 IU/L)	2.0 (1.8)	Referent				Referent				Referent				Referent			
Quartile 2 (45.1)	2.0 (2.6)	-0.035	(0.377)	0.93	0.004	(0.395)	0.99	0.031	(0.383)	0.94	0.384	(0.623)	0.54				
Quartile 3 (55.4)	1.5 (1.4)	-0.509	(0.358)	0.16	-0.339	(0.384)	0.38	-0.215	(0.376)	0.57	0.646	(0.598)	0.28				
Quartile 4 (72.8)	1.5 (1.8)	-0.506	(0.343)	0.14	-0.443	(0.360)	0.22	-0.194	(0.355)	0.49	0.664	(0.604)	0.28				
	<i>P</i> for trend	0.29				0.16				0.51				0.26			
<b>Ages 64-73 years (n = 344)</b>																	
Quartile 1 (median = 32.1 IU/L)	2.4 (2.4)	Referent				Referent				Referent				Referent			
Quartile 2 (45.1)	2.0 (2.0)	-0.443	(0.330)	0.18	-0.512	(0.332)	0.12	-0.349	(0.330)	0.29	-0.345	(0.529)	0.52				
Quartile 3 (55.4)	2.0 (2.2)	-0.370	(0.345)	0.28	-0.440	(0.350)	0.21	-0.34	(0.344)	0.32	-0.948	(0.629)	0.14				
Quartile 4 (72.8)	1.3 (1.4)	-1.070	(0.361)	0.003	-1.239	(0.364)	0.001	-0.983	(0.369)	0.008	-1.374	(0.600)	0.02				
	<i>P</i> for trend	0.005				0.001				0.01				0.02			

<sup>a</sup> Unadjusted mean depressive symptom score (not transformed)

<sup>b</sup> Model 1: Adjusted for age (years), date of examination (years), and estradiol (quartiles)

<sup>c</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>) and waist to hip ratio (continuous)

<sup>d</sup> Model 3: Model 2 further adjusted for antidepressant use, employment status, marital status, education, physical activity (MET hours per day), past hormone therapy (HT) use (yes, no), duration of HT use (5 categories), smoking status (current, past, never), alcohol use (grams per week), parity (number of full-term pregnancies), age at menopause (continuous), testosterone (continuous), and sex hormone binding globulin (continuous)

<sup>e</sup> P for interaction: FSH \* age = 0.44

Table 6. Follicle Stimulating Hormone Levels and Prevalent Depression Stratified by BMI, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depression									
	Unadjusted			Model 1 <sup>a</sup>			Model 2 <sup>b</sup>			
	Cases N (%)	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
<b>Under/Normal Weight (n = 147)<sup>c</sup></b>										
Low FSH (n = 56)	4	7.1	referent		referent			referent		
High FSH (n = 91)	2	2.2	0.31, 1.77	0.19	0.28, 0.05, 1.61	0.15	0.19	0.03, 1.36	0.10	
FSH (per 10 IU/L)	6	4.1	0.74, 0.49, 1.13	0.16	0.74, 0.50, 1.12	0.14	0.62	0.37, 1.05	0.08	
<b>Overweight (n = 225)</b>										
Low FSH (n = 104)	19	18.3	referent		referent			referent		
High FSH (n = 121)	8	6.6	0.31, 0.13, 0.75	0.01	0.33, 0.13, 0.79	0.01	0.33	0.14, 0.81	0.02	
FSH (per 10 IU/L)	27	12.0	0.71, 0.56, 0.90	0.01	0.70, 0.54, 0.90	0.01	0.68	0.52, 0.90	0.01	
<b>Obese (n = 216)</b>										
Low FSH (n = 136)	18	13.2	referent		referent			referent		
High FSH (n = 80)	10	12.5	0.87, 0.38, 2.0	0.75	0.85, 0.37, 1.98	0.71	0.90	0.38, 2.15	0.82	
FSH (per 10 IU/L)	28	13.0	1.10, 0.86, 1.41	0.45	1.10, 0.86, 1.40	0.48	1.12	0.85, 1.46	0.42	

<sup>a</sup> Model 1: Adjusted for age (years)

<sup>b</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>; continuous), waist-to-hip ratio (continuous), and estradiol (continuous)

<sup>c</sup> P for interaction: FSH (high vs. low) \* BMI = 0.11; FSH (continuous) \* BMI = 0.02

Table 7. Follicle Stimulating Hormone Levels and Mean Depressive Symptom Score Stratified by BMI, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depressive Symptom Score												
	Unadjusted			Model 1 <sup>a</sup>			Model 2 <sup>c</sup>			Model 3 <sup>d</sup>			
	Mean Depressive Symptom Score (SD) <sup>e</sup>	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	beta	SE	P
<b>Follicle Stimulating Hormone</b>													
<b>Normal/Underweight (n = 147)<sup>e</sup></b>													
Quartile 1 (median = 32.1 IU/L)	2.5 (2.4)	Referent			Referent			Referent			Referent		
Quartile 2 (45.1)	0.9 (1.6)	-1.594 (0.442)	<0.0001	-1.924 (0.465)	<0.0001	-1.893 (0.463)	<0.0001	-0.402 (0.937)	Referent		Referent		0.67
Quartile 3 (55.4)	0.9 (1.0)	-1.629 (0.444)	<0.0001	-1.982 (0.463)	<0.0001	-1.951 (0.460)	<0.0001	0.913 (1.061)	Referent		Referent		0.40
Quartile 4 (72.8)	1.1 (1.4)	-1.417 (0.412)	0.001	-1.677 (0.419)	<0.0001	-1.692 (0.416)	<0.0001	-0.758 (1.093)	Referent		Referent		0.49
<i>P for trend</i>	0.001			0.03		0.01		0.41					
<b>Overweight (n = 225)</b>													
Quartile 1 (median = 32.1 IU/L)	2.5 (2.4)	Referent			Referent			Referent			Referent		
Quartile 2 (45.1)	1.8 (2.1)	-0.635 (0.403)	0.12	-0.503 (0.404)	0.21	-0.475 (0.406)	0.24	-0.784 (0.653)	Referent		Referent		0.23
Quartile 3 (55.4)	1.8 (1.7)	-0.700 (0.400)	0.08	-0.497 (0.406)	0.22	-0.479 (0.410)	0.24	-1.353 (0.615)	Referent		Referent		0.03
Quartile 4 (72.8)	1.5 (1.5)	-0.903 (0.404)	0.03	-0.829 (0.408)	0.04	-0.806 (0.411)	0.05	-1.351 (0.618)	Referent		Referent		0.03
<i>P for trend</i>	0.15			0.04		0.06		0.07					
<b>Obese (n = 216)</b>													
Quartile 1 (median = 32.1 IU/L)	2.0 (1.9)	Referent			Referent			Referent			Referent		
Quartile 2 (45.1)	2.8 (2.5)	0.821 (0.408)	0.05	0.819 (0.411)	0.05	0.902 (0.405)	0.03	1.594 (0.625)	Referent		Referent		0.01
Quartile 3 (55.4)	2.6 (2.3)	0.543 (0.424)	0.20	0.602 (0.437)	0.17	0.667 (0.429)	0.12	1.184 (0.755)	Referent		Referent		0.12
Quartile 4 (72.8)	1.8 (2.0)	-0.194 (0.488)	0.69	-0.155 (0.496)	0.76	0.036 (0.492)	0.94	0.740 (0.735)	Referent		Referent		0.32
<i>P for trend</i>	0.11			0.95		0.97		0.68					0.30

<sup>a</sup> Unadjusted mean depressive symptom score (not transformed)

<sup>b</sup> Model 1: Adjusted for age (years), date of examination (years) and estradiol (quartiles)

<sup>c</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>) and waist to hip ratio (continuous)

<sup>d</sup> Model 3: Model 2 further adjusted for antidepressant use, employment status, marital status, education, physical activity (MET hours per day), past hormone therapy (HT) use (yes, no), duration of HT use (5 categories), smoking status (current, past, never), alcohol use (grams per week), parity (number of full-term pregnancies), age at menopause (continuous), testosterone (continuous), and sex hormone binding globulin (continuous)

<sup>e</sup> P for interaction: FSH \* BMI = .01

Table 8. Follicle Stimulating Hormone Levels and Prevalent Depression Including Antidepressant Users as Cases, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depression										
	Unadjusted			Model 1 <sup>a</sup>			Model 2 <sup>b</sup>				
	Cases N (%)	OR	95% CI referent	P	OR	95% CI referent	P	OR	95% CI referent	P	
Low FSH (n = 296)	49 16.6										
High FSH (n = 292)	28 9.6	0.53	0.33, 0.88	0.01	0.53	0.32, 0.87	0.01	0.62	0.37, 1.04	0.07	
FSH (per 10 IU/L)	77 13.1	0.82	0.72, 0.94	0.004	0.82	0.72, 0.94	0.004	0.84	0.72, 0.98	0.03	

<sup>a</sup> Model 1: Adjusted for age (years)

<sup>b</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>; continuous), waist-to-hip ratio (continuous), and estradiol (continuous)

Table 9. Follicle Stimulating Hormone Levels and Mean Depressive Symptom Score Excluding Antidepressant Users, Kuopio Ischaemic Heart Disease Risk Factor Study (1998-2001).

	Depressive Symptom Score											
	Mean Depressive Symptom Score (SD) <sup>a</sup>			Unadjusted		Model 1 <sup>b</sup>		Model 2 <sup>c</sup>		Model 3 <sup>d</sup>		
	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P	beta	(SE)	P
<b>Follicle Stimulating Hormone</b>												
Continuous FSH	1.8 (2.0)	-0.013 (0.005)	0.01	-0.013 (0.005)	0.01	-0.008 (0.005)	0.10	-0.008 (0.008)	0.30			
Quartile 1 (median = 32.1 IU/L)	2.2 (2.1)	Referent		Referent		Referent		Referent		Referent		
Quartile 2 (45.1)	1.9 (2.2)	-0.333 (0.245)	0.18	-0.297 (0.248)	0.23	-0.179 (0.243)	0.46	0.150 (0.395)	0.71			
Quartile 3 (55.4)	1.7 (1.8)	-0.575 (0.249)	0.02	-0.533 (0.255)	0.04	-0.422 (0.250)	0.09	-0.236 (0.427)	0.58			
Quartile 4 (72.8)	1.4 (1.5)	-0.882 (0.248)	<0.001	-0.874 (0.254)	0.001	-0.597 (0.253)	0.02	-0.604 (0.419)	0.15			
<i>P for trend</i>			0.013		<0.001		0.01		0.09			

<sup>a</sup> Unadjusted mean depressive symptom score (not transformed)

<sup>b</sup> Model 1: Adjusted for age (years), date of examination (years), and estradiol (quartiles)

<sup>c</sup> Model 2: Model 1 further adjusted for body mass index (kg/m<sup>2</sup>) and waist to hip ratio (continuous)

<sup>d</sup> Model 3: Model 2 further adjusted for employment status, marital status, education, physical activity (MET hours per day), past hormone therapy (HT) use (yes, no), duration of HT use (5 categories), smoking status (current, past, never), alcohol use (grams per week), parity (number of full-term pregnancies), age at menopause (continuous), testosterone (continuous), and sex hormone binding globulin (continuous)

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