Research Article

Circulating Estrogen Levels and Self-Reported Health and Mobility Limitation in Community-Dwelling Men of the Framingham Heart Study

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Abstract

Background: Self-rated health is a commonly used global indicator of health status. Few studies have examined the association of self-rated health and mobility with estrone and estradiol in men. Accordingly, we determined the cross-sectional, incident, and mediating relations between circulating estrone and estradiol levels with self-rated health, mobility limitation, and physical performance in community-dwelling men.

Methods: The cross-sectional sample included 1,148 men, who attended Framingham Offspring Study Examinations 7 and 8. Estrone and estradiol levels were measured using liquid chromatography tandem mass spectrometry at Examination 7. Self-reported mobility limitation and self-rated health were assessed at Examinations 7 and 8. Additionally, short physical performance battery, usual walking speed, and grip strength were assessed at Examination 7.

Results: In incident analysis, estradiol levels at Examination 7 were associated with increased odds of fair or poor self-rated health at Examination 8, after adjusting for age, body mass index, comorbidities, and testosterone levels; in an individual with 50% greater estradiol than other, the odds of reporting "fair or poor" self-rated health increased by 1.78 (95% confidence interval: 1.25–2.55; $p = .001$). Neither estrone nor estradiol levels were associated with any physical performance measure at baseline.

Conclusions: Higher circulating levels of estradiol are associated with increased risk of incident fair/poor self-rated health in community-dwelling men. The mechanisms by which circulating levels of estradiol are related to self-rated health in men need further investigation.

Keywords: Estrone—Estradiol—Self-rated health—Physical function

Self-rated health—a person's cognitively and socially influenced appraisal of one's own health—is an important indicator of health status and is a powerful predictor of health outcomes, including mortality (1). This is important for the epidemiology of aging, as declines in self-rated health (2) and function (3) are increasingly common among older adults.

A number of studies have reported that age-related declines in muscle mass, physical performance, and self-rated health are associated with age-related alterations in circulating endogenous testosterone levels (4–12). However, relatively few studies have examined the relation of estrogens with physical function, mobility,

and self-reported health in men, and the data are conflicting (5–7,9,11,12). Recently, the Concord Health and Ageing in Men Project (CHAMP) group reported that low serum estrone was associated with poor self-rated health and was predictive of subsequent deterioration in self-rated health; however, the CHAMP study included only men aged 70 years or older (9). While some studies have found little or no significant association between estradiol and muscle strength and physical performance in men (5–7), others have reported low grip strength and impaired mobility both with low (4,11) and high (12) estradiol levels. The estrogen levels in many studies were measured using immunoassays, which lack the accuracy and precision in the low range prevalent in men. Few studies have examined prospectively the relation of estradiol and estrone levels, measured using a sensitive and specific liquid chromatography tandem mass spectrometry (LC-MS/MS) assay, with self-rated health.

Accordingly, we examined whether estrone and estradiol levels are related to self-rated health, mobility limitations, and performance-based measures of physical function in community-dwelling older men. Additionally, we evaluated whether baseline levels of these hormones are associated with incident self-rated health and mobility limitation. We hypothesized that estrogen levels would be related to self-rated health either because of direct effects of estrogens on health or through their indirect effects on physical function and mobility, which could then affect self-rated health, as has been suggested previously (13). It is also possible that estrogen levels are a marker of health; those with a higher burden of comorbid conditions may have higher estrogen levels and are more likely to report poor self-rated health. We measured circulating estrone and estradiol levels by LC-MS/MS, widely considered the reference method for the measurement of estradiol and estrone levels (14). We adjusted the analyses for potential confounders, such as age, body mass index (BMI), comorbidities, and testosterone levels, which are known to independently affect estrogen levels.

Methods

The Institutional Review Boards of Boston University and Brigham and Women's Hospital approved the study. The participants provided informed consent.

Study Sample

The Framingham Heart Study (FHS) began in 1948 as a prospective study to examine the risk factors for heart disease. In 1971, enrollment of offspring of the original participants and spouses of the offspring constituted the Framingham Offspring Study (15). The offspring cohort has completed nine examinations at 4- to 8-year intervals. Male members of the Offspring cohort who attended Examination 7 (1998–2001) were eligible for the present study. To determine whether estrone and estradiol are associated with incident mobility limitation and fair/poor self-rated health, men who attended Examination 8 (2005–2008) were examined on average 6.6 years later. For both cross-sectional analyses, we excluded men who had missing estrogen data ($n = 159$), had prostate cancer and were receiving androgen deprivation therapy ($n = 5$), were missing at Examination 8 ($n = 261$), had missing mobility limitation data at Examination 7 or 8 ($n = 28$), or had missing self-rated health data at Examination 7 or 8 ($n = 24$) resulting in an analytic sample of 1,148. Further, for the incident analyses, we excluded men with mobility limitation ($n = 52$) and fair/poor self-rated health ($n = 70$) at Examination 7 resulting in a final sample of 1,096 and 1,078

respectively, for the analyses of prevalent and incident mobility limitation and self-rated health.

Hormone Assays

The samples were obtained between 7.30 and 9.30 am after an overnight fast and stored at -80°C until the time of assay. The stability of these samples in storage has been evaluated by measuring the concentrations of cholesterol, HDL cholesterol, and triglycerides in 1991 prior to storage at -80°C and then repeating the measurement in 2007 (16).

Serum estradiol and estrone were measured using a highly sensitive LC-MS/MS assay, described previously (17). Twenty microliters of estrone-d4 and estradiol-d5 were added to 200- μL serum, extracted using methyl *t*-butyl ether (17,18), derivatized using dansyl chloride (3.7 mmol/L) in sodium carbonate (10 mmol/L, pH 10.5) at 60°C for 10 minutes, diluted in acetonitrile and water, and loaded onto API 4000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS Sciex) with turbo ion spray and a 1200 Agilent HPLC pump. The limit of quantitation for both hormones was 2 pg/mL. Interassay coefficients of variation for estrone were 4.5%, 7.7%, and 6.9% at 8, 77, and 209 pg/mL, respectively, and for estradiol 6.9%, 7.0%, and 4.8% at 8, 77, and 206 pg/mL, respectively.

We measured total testosterone using a CDC-certified LC-MS/MS assay (19). The limit of quantitation was 2 ng/dL. Interassay coefficients of variation were 15.8% at 12.0 ng/dL, 7.7% at 241 ng/dL, and 4.4% at 532 ng/dL, respectively.

Self-Rated Health

A standard self-rated health measure was used, which asked: "In general, how is your health now: excellent, good, fair, poor?" At Examination 8, there was an additional response option of "very good" ("In general, would you say your health is: excellent, very good, good, fair, poor?"). To be consistent across Examinations 7 and 8, the responses were reduced to a three-category variable: "excellent" health, "good" health (responses of good and very good), and "fair or poor" health (responses of poor and fair health).

Mobility Limitation

At Examinations 7 and 8, participants were queried about mobility limitations using a modified Rosow-Breslau questionnaire (20), which has shown high test-retest reliability (21). Participants were asked if they were able to (i) do heavy work around the house, like shovel snow or wash windows, walls, or floors without help, (ii) walk half a mile without help, and (iii) walk up and down one flight of stairs (22). At Examination 7, the last item was asked as part of the Katz Activities of Daily Living scale with the following directive: "During the course of a normal day, can you walk up and down one flight of stairs independently or do you need human assistance or the use of a device?" Response choices included (i) no help needed, independent; (ii) uses device, independent; (iii) human assistance needed, minimally dependent; (iv) dependent; and (v) do not do during a normal day. If the participant reported independence, he was considered able to perform the mobility task. A participant was considered to have mobility limitation if he reported inability to do one or more of the three items. Additionally, response option "do not do during a normal day" was coded as having a mobility limitation.

Additional physical performance measures were available on subsets of the men considered in analyses reported here (Table 1). The methods for assessing physical performance measures, including the short physical performance battery (SPPB), and hand grip strength, are described in Supplementary Appendix 1.

Table 1. Baseline Characteristics of the Analytic Sample ($N = 1,148$) at the Framingham Offspring Examination 7 (1998–2001), Mean (SD) or n (%)

Characteristics	Mean (SD) or n (%)
Age, years	60 (9)
30–39	10 (0.9%)
40–49	132 (12%)
50–59	454 (40%)
60–69	366 (32%)
70–79	181 (16%)
80–89	5 (0.4%)
Body mass index, kg/m ²	28.8 (4.5)
Total estrone, pg/mL ^a	49 (39–60)
Total estradiol, pg/mL ^a	25 (20–31)
Mobility limitation	52 (5%)
Self-rated health	
Excellent	572 (50%)
Good	503 (44%)
Poor	70 (6%)
Physical activity index	38.7 (7.2)
Short Physical Performance Battery ($n = 659$)	11.0 (1.2)
Usual walking speed, m/s ($n = 662$)	1.3 (0.3)
Grip strength, kg ($n = 590$)	43 (12)

Note: ^aMedian and interquartile interval shown.

Statistical Analyses

Since exploratory analyses revealed modest right-skewing of the distributions of estrone and estradiol levels, log-transformed values were used. Estimates were scaled such that odds ratios (ORs) reported here may be interpreted in terms of the apparent effect of a (between-person) 50% increase of estrone or estradiol; that is, ORs compared a hypothetical man of any estrone or estradiol level to a man of similar age and covariates, but with 50% lesser estrone or estradiol level.

Cross-Sectional Analyses of Prevalent Illness

Baseline descriptive statistics (means $\pm$ SD) for continuous variables and percent for dichotomous variables were generated. Cross-sectional associations at Examination 7 among hormones, and self-reported mobility limitation and self-rated health were assessed using multiple logistic regression and multinomial (polytomous) logistic regression, respectively. Multiple linear regression was used for analyses of continuous outcomes (usual walking speed, handgrip strength, and SPPB score).

Analyses of Incident Illness

The primary analyses employed multiple logistic regression and multinomial logistic regression models to examine the relation between total estrone and estradiol levels at Examination 7 and incident mobility limitation and self-rated health at Examination 8 in men, respectively. Men with mobility limitation ($n = 52$) at Examination 7 were excluded resulting in a sample of 1,096 for the incident limitation analyses. Further, for self-rated health, we excluded men with fair/poor self-rated health ($n = 70$) at Examination 7 yielding an at-risk sample of 1,078. As in the cross-sectional analyses, self-rated health was modeled as a categorical variable with response options of “excellent” health, “good” health, and “fair/poor” health.

Both models of prevalent and incident endpoints were adjusted for age, BMI, smoking, comorbidity index (cardiovascular disease and/or cancer), and (in the case of estradiol only) total testosterone

obtained at Examination 7. We also assessed physical activity at baseline (Examination 7) as a covariate in the analyses. However, because the inclusion of physical activity did not alter the results significantly, we excluded physical activity as a covariate in the final models.

Robustness of Association Between Hormones and Self-Rated Health

In addition, we sought to address the degree to which prospective associations between hormones and self-rated health would be accounted for by control for mobility limitation. To do this, we considered logistic regression models of association between hormones and Examination 8 self-rated health, controlling for mobility limitation at Examination 8.

All data analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic Data

Baseline characteristics of men in our study sample are shown in Table 1. The men were on average 60 years of age with a mean (SD) BMI 28.8 (4.5) kg/m². At baseline, 52 (4.5%) men reported mobility limitation, and 70 (6.1%) reported fair or poor self-rated health. A majority of men were physically active with a mean (SD) Framingham physical activity index 38.7 (7.2); persons with scores of less than 30 in the Framingham physical activity index are considered inactive (23).

Cross-Sectional Relation Between Estrogens, Self-Rated Health, and Mobility Limitation

The cross-sectional associations between circulating levels of estradiol and estrone and mobility limitations and self-rated health at Examination 7 are presented in Table 2. Estrone was not significantly associated with self-rated health, but was positively associated with mobility limitation, after adjusting for all covariates. A cross-sectional positive difference of 50% in estrone was associated with a multiplicative increase in the odds of reporting mobility limitation increased of approximately 40% (multivariable-adjusted OR = 1.42, 95% CI: 1.01–1.99). Results were similar for estradiol. By contrast, neither estrone nor estradiol was significantly associated with mobility limitation or self-rated health after adjustment for age, BMI, smoking, comorbidities, and total testosterone. In supporting analyses, neither of the estrogens was associated with the other physical function measures (SPPB, walking speed, or handgrip strength).

Association Between Estrogen Levels, Self-Rated Health, and Incident Mobility Limitation

A total of 139 men with no mobility limitation at Examination 7 reported limitation at Examination 8. In unadjusted analyses, both total estrone and estradiol were significantly associated with good and fair or poor self-rated health at Examination 8 (Figure 1). However, as shown in Figure 1, after adjusting for age, BMI, smoking, comorbidity index, and total testosterone, estradiol level at Examination 7 was a significant predictor of fair or poor self-rated health at Examination 8. A baseline difference of 50% in total estradiol levels was associated with an increase in the odds of reporting “fair or poor” self-rated health, as compared with excellent health of 78% (OR = 1.78, 95% CI: 1.25–2.55).

Table 2. Cross-Sectional Associations Between Circulating Estradiol and Estrone Levels, Mobility Limitation, and Self-Rated Health ($N = 1,148$)

	Mobility Limitation ^a		Self-Rated Health ^b			
			Good vs. Excellent		Fair/Poor vs. Excellent	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Total estrone	1.42 (1.01–1.99)	.04	1.01 (0.88–1.67)	.87	1.05 (0.78–1.41)	.74
Total estradiol	1.42 (0.98–2.05)	.06	1.09 (0.93–1.27)	.29	1.13 (0.82–1.56)	.46

Notes: CI = confidence interval; OR = odds ratio.

^aAt baseline, 52 individuals reported mobility limitation. Estimated multiplicative increase in odds of mobility limitation attending a 50% positive cross-sectional difference in estrone or estradiol. Estimates derived from a logistic regression model adjusted for age, body mass index, smoking status, and comorbidities. Estimates of estradiol effects also adjusted for total testosterone.

^bAt baseline, 503 individuals reported “good” and 70 “fair or poor health”. Estimated multiplicative increase in odds of good or fair/poor self-rated health, relative to excellent self-rated health, attending a 50% positive cross-sectional difference in estrone or estradiol. Estimates derived from a polytomous logistic regression model adjusted for age, body mass index, smoking status, and comorbidities. Estimates of estradiol effects also adjusted for total testosterone.

Figure 1. Association between circulating total estrone and estradiol levels, and incident mobility limitation and self-rated health for male Framingham Offspring Study participants (age range: 30–80 years) over 6.6 years. Estimated odds ratios (point estimates and 95% confidence intervals are shown) quantify association between a 50% positive difference in estrone or estradiol and increase in the incidence of mobility limitation, “good,” and “fair or poor” self-rated health. Adjusted models control for age, smoking, body mass index, comorbidities (cancer and/or cardiovascular disease), and total testosterone (for estradiol only). “Excellent” self-reported health was the reference group in these models.

No significant associations were observed between estrone or estradiol and incident mobility limitation.

Robustness of Association With Self-Rated Health

To further explore the association between estradiol and incident fair/poor self-rated health, we considered the robustness of the association between estradiol and self-rated health to simultaneous consideration of mobility limitations. A multinomial logistic regression model controlling for mobility limitation produced similar results to those described earlier; odds of good health (as compared with excellent) demonstrated a multiplicative increase of 1.22 (95% CI: 1.03–1.45), whereas those of fair/poor health demonstrated a multiplicative increase of 1.97 (1.33–2.92). That these results demonstrate negligible attenuation of the strength of association with addition of mobility suggests that the association between estradiol levels and self-rated health is for the most part not due to the mobility limitations that attended increased estradiol, described earlier.

Discussion

In this community-based sample, consisting of generally overweight but well-functioning men (based on SPPB score and physical activity index), greater estradiol levels were significantly associated with higher odds of reporting incident “fair” or “poor” self-rated health.

The role of estrone and estradiol in predicting poor self-rated health has been examined previously in one other study (9). Contrary to our results, the CHAMP study found low levels of estrone, but not estradiol to be predictive of self-rated health. Further, low serum estrone significantly predicted deterioration in self-rated health. The CHAMP Study was limited to men 70 years of age or older, whereas the FHS includes men of a much wider age range. The disproportionate representation of the oldest old in the CHAMP study may introduce a survival bias toward inclusion of healthier men.

Relatively few studies have examined the relation of estrone and estradiol with muscle performance, mobility limitation, and physical function in men. Most studies have shown inconsistent or no association of the estradiol level with muscle strength (5–7) or physical performance (5,7) in men. Contrary to findings from our study, Schaap and colleagues (4) reported that low levels of estradiol were associated with impaired mobility and low muscle strength. However, these studies were cross-sectional in design, used an immunoassay, whose accuracy and precision in the low range are suboptimal, and did not adjust for testosterone levels. Although both estrogen receptor subtypes, ER α and ER β , are expressed in the skeletal muscle (24), the effects of estrogens on muscle growth and function have also been inconsistent in preclinical models, varying substantially in different experimental models. Thus, estradiol has been reported to exert an anabolic effect on the muscle in sheep and cattle (25). However, estradiol administration to ovariectomized rats decreases muscle mass and isometric contractile force (26). Genetic disruption of CYP19aromatase gene is associated with reduced contractile force of the muscle (27). In contrast to the inconsistent association of estrogen levels with muscle performance and physical function, serum free testosterone levels have been more consistently associated with measures of muscle performance, physical function, and mobility limitation in men (5–7,10).

The robustness of the association between estradiol and self-rated health after controlling for mobility limitation suggests a potential mediating role for mobility limitation. Since self-rated health is a dynamic measure of health, individuals may rate their health as poor due to their current health status or recent changes in

health (28). Thus, poor self-rated health may be an effect of mobility limitation as has been suggested in our study. However, it is also possible that factors that contribute to poor self-rated health and mobility limitation, such as obesity and poor physical performance, may also be associated with elevated estradiol levels. Circulating estradiol is derived mostly from peripheral conversion of testosterone, and this conversion is increased in obesity and in illness, which would be expected to be associated with poor self-rated health (29). Among these, obesity is potentially a remediable factor.

The present study has several strengths, including its longitudinal design and inclusion of community-dwelling men over a wide age range. Additionally, this is one of the few studies of community-dwelling men to evaluate the relation of mobility and physical function with estrogen levels, in which the estrogen levels have been measured using LC-MS/MS, widely considered the reference method for the measurement of estradiol and estrone levels (14). Further, the estrogen levels of this population are in the broad range of the general population (5). Our study also has some limitations. First, our study population was predominantly White and not population based. Hence, our findings may not be generalizable to other race/ethnicities and to the wider general male population. Second, we did not have estrogens measured at Examination 8 to evaluate the correlation between the change in estrogen levels and incident mobility and self-rated health. Further, estrone and estradiol levels were measured in single morning samples and may not reflect hormone levels over time. Fourth, an additional response option of "very good" was added at Examination 8. This variation in assessment might have affected the participant's response. Further, our findings suggest a significant association of estrone with mobility limitation at Examination 7 while exhibiting no association with other physical performance measures in the cross-sectional analyses. It might be that impaired physical function is only one of many contributors to mobility limitation. It is also possible that comorbid conditions which may contribute to mobility limitation may also result in higher estrone levels.

The apparent lack of association of estrone with both mobility limitation and poor self-rated health in the incident analyses is in contrast to our previous findings of estrone as a novel health predictor of increased risk of incident diabetes in the FHS men (30). These observations are consistent with the considerable receptor subtype specificity in the target organ effects of estrogens.

The relative strength of the association between estradiol levels and self-rated health can be contextualized by contrasting the observed associations with those reported previously with circulating testosterone levels. The association observed here between estradiol levels and self-rated health is stronger than that observed (and widely recognized) between testosterone levels and measures of sexual desire and activity (31) and is similar to that which we have reported previously between circulating estrone levels and the risk of incident diabetes mellitus (30). With each 50% between-person difference in circulating estradiol level—comparable with the within-individual change that might attend aging from a 20-year old to a middle-aged man (17)—we observed that the odds of reporting "fair or poor" self-rated health would be increased by 1.78, indicating the potential for nontrivial implications for self-rated health of increases in male estrogen levels with aging.

These results suggest that high estradiol levels may be a marker of poor self-rated health in men, a scale widely used as an indicator of general health. It is possible that estradiol levels might be affected by comorbid conditions, which may influence self-rated health as

well as mobility. Because self-rated health is an excellent marker of general health and even mortality, an understanding of contributors to self-rated health is important. Given the complexity and multi-dimensional nature of the outcome of interest, it is unlikely that a single factor might be isolated. The underlying mechanisms by which circulating levels of estradiol predict self-rated health in men need further investigation.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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