ORIGINAL RESEARCH

Association Between Prolactin and Incidence of Cardiovascular Risk Factors in the Framingham Heart Study

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***Background*—**Prolactin is an anterior pituitary hormone that may modulate the adverse effects of obesity. Prolactin has been associated with cardiovascular disease mortality, but less is known about whether prolactin predicts incidence of cardiovascular disease risk factors.

***Methods and Results*—**Our sample (n=3232, mean age 40.4 years, 52.1% women) was drawn from Framingham Heart Study participants who attended 2 examinations an average of 6.1 years apart. After excluding those with elevated prolactin (>30 mg/dL for women, >20 mg/dL for men), multivariable-adjusted regressions modeled the associations between baseline prolactin and changes in cardiovascular disease risk factors. Models were adjusted for age, sex, baseline value of the risk factor, smoking status, hormone replacement therapy, and menopausal status and additionally for body mass index. Mean prolactin levels were 11.9 mg/dL (SD 5.2) in women and 8.0 mg/dL (SD 2.9) in men. No associations were observed for change in weight, body composition, total cholesterol, triglycerides, or fasting glucose. In women, for example, for each 5-mg/dL increment in prolactin, odds of incident hypercholesterolemia were 1.06, which was not significant (95% CI 0.91–1.23, *P*=0.46). Some exceptions were of note. In women, for each 5-mg/dL increment in prolactin, we observed increased odds of low high-density lipoprotein cholesterol at follow-up (odds ratio 1.50, 95% CI 1.18–1.91, *P*=0.001) that persisted after adjustment for body mass index (*P*=0.001). In men, a 5-mg/dL increment in prolactin was associated with increased odds of incident hypertension (odds ratio 1.61, 95% CI 1.18–2.20 *P*=0.002) and incident diabetes (odds ratio 1.70, 95% CI 1.04–2.78, *P*=0.03).

***Conclusions*—**Prolactin is not associated with a comprehensive panel of incident cardiovascular disease risk factors. Measurement of circulating prolactin levels in the community likely does not provide substantial insight into cardiometabolic risk. **(*J Am Heart Assoc*. 2016;5:e002640 doi: 10.1161/JAHA.115.002640)**

Key Words: epidemiology • hormones • obesity • population

Prolactin is an anterior pituitary hormone, and its receptor is expressed in most peripheral organs. Its most well-known physiological role is to support lactation, but it has broad functions in metabolic, osmoregulatory, and immunoregulatory pathways.[1] More recently, it has been discovered that prolactin is produced in adipose tissue and that the prolactin receptor is expressed in adipose tissue.[2]

Several observations from animal studies and clinical experience suggest that prolactin may act as an adipocytokine that modulates the effects of obesity. In rats, elevation of prolactin is associated with increased food intake and body weight.[3] In humans with prolactinomas, weight gain is often a prominent feature and is reversible with prolactin-lowering therapy.[4] Other metabolic abnormalities seen in prolactinomas include insulin resistance and dyslipidemia.[5] In animal models, prolactin promotes accrual of visceral adipose tissue (VAT).[6] Prolactin receptor knockout mice have reduced overall and abdominal adipose tissue.[7] In obese women, prolactin release is enhanced in proportion to body mass index (BMI) and VAT.[8]

Whether variability in prolactin within the physiological range is associated with cardiovascular disease (CVD) risk factors is unclear. A prior community-based study found no cross-sectional association between prolactin and BMI in either

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men or women.[9] A subsequent study from the same cohort later found that prolactin was associated with higher cardiovascular and all-cause mortality over a period of 10 years.[10]

We sought to examine the associations between prolactin and changes in body composition and CVD risk factors over time.

Research Methods

Study Participants

The Framingham Heart Study is a longitudinal study of CVD risk factors that began in 1948 with the enrollment of the original cohort.[11,12] Participants for the current study were drawn from the third-generation cohort. A total of 4053 participants attended the first examination cycle (2002–2005). Subsequently, 3411 participants attended a second examination (2008–2011). After excluding women with prolactin >30 mg/dL and men with prolactin >20 mg/dL and participants with missing covariates, the sample size was 3232 participants who attended both the baseline and follow-up examinations an average of 6.1 years apart (interquartile range 5.9–6.4 years). Participants with elevated prolactin were excluded because the goal of this study was to examine the associations of prolactin and CVD risk factors within the normal prolactin range.

A subset of this sample was used to investigate the association between prolactin levels and adiposity. From the previous sample of 3232 participants, 1132 participants also had multidetector computed tomography (MDCT) scans coupled with their baseline and follow-up examinations. Women were aged ≥40 years and men were aged ≥35 years for the first MDCT scan. Participants weighing >160 kg were excluded from MDCT scanning because of machine weight restrictions. Participants who met any of the following criteria were excluded nonhierarchically: (1) missing covariates, fat volume, fat quality, or weight at either examination (n=9); (2) BMI (in kg/m^2) <17 (n=2); (3) history of gastric bypass surgery (n=3); (4) history of a prevalent cancer (not including nonmelanotic skin cancer, n=64); (5) cardiovascular event on or before the follow-up examination and second MDCT scan (n=17); (6) death within 1 year after follow-up examination (n=2); (7) >7 months between either examination and the MDCT scan (n=244). The final analysis population for this subset had 832 participants (335 women, 497 men).

The study was approved by an institutional review committee, and all participants provided informed consent.

Assessment of Prolactin

Prolactin was measured on a morning fasting blood draw as part of the baseline examination. Prolactin was determined using a Roche cobas e411 analyzer in an electrochemiluminescence immunoassay. Intra-assay coefficient of variability was 2.2%, and interassay coefficient of variability was 3.6%.

CVD Risk Factor Assessment

CVD risk factors were assessed at baseline and follow-up examinations. Seated systolic and diastolic blood pressures were measured twice to the nearest 2 mm Hg, with results averaged as part of the physician examinations. Plasma glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured in fasting blood samples.

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or blood pressure–lowering treatment. Hypercholesterolemia was defined as total cholesterol ≥200 mg/dL or lipid-lowering treatment. Hypertriglyceridemia was defined as triglycerides ≥150 mg/dL or lipid-lowering treatment. Low HDL was defined as <50 mg/dL in women and <40 mg/dL in men. Type 2 diabetes was defined as fasting glucose ≥126 mg/dL or diabetes treatment. Overall, >95% of diabetes in this sample was type 2 diabetes. Metabolic syndrome was defined using modified Adult Treatment Panel III criteria.[13]

Assessment of Covariates

Height, weight (assessed using a Detecto scale), and waist circumference at the level of the umbilicus were measured onsite as part of each examination cycle. The scale undergoes professional calibration annually and calibration with a 22.5-kg weight monthly. Participants wore only a gown and socks for weight measurement, and weight was calculated to the nearest pound. BMI was calculated as the weight in kilograms divided by the square of the height in meters. A technician-administered physical activity questionnaire yielded a physical activity index based on average number of hours of daily sleep and level of reported activity (sedentary, slight, moderate, or high). Alcohol intake was assessed at the physician interview; moderate to heavy alcohol intake was defined as >14 drinks per week for men and >7 drinks per week for women. Participants were considered current smokers if they had smoked at least 1 cigarette per day for the previous year. Women were classified as being menopausal if they had no menstrual bleeding for at least 1 year. Use of hormone replacement therapy was assessed at the physician interview.

Measurements of VAT and Subcutaneous Adipose Tissue

VAT and subcutaneous adipose tissue (SAT) volumes were calculated by manually tracing the abdominal muscular wall on 5-mm contiguous MDCT scan slices. With the fat window set at −195 to −45 Hounsfield units with a center of

−120 Hounsfield units, VAT volume was measured as volume of fat within the abdominal wall, and SAT volume was fat outside the abdominal wall.[14] Interreader correlation for this method is >0.99.[15]

The same MDCT scans were used to measure VAT and SAT attenuation, using a method that has been described previously.[16] Within the fat window, the average Hounsfield unit was generated for the VAT and SAT areas. VAT and SAT average SD of attenuation was found to be 5.5 and 7.6 Hounsfield units, respectively.[16]

Statistical Analysis

Overall and sex-specific Pearson correlation coefficients were calculated between baseline prolactin and changes in CVD risk factors.

Sex-specific multivariable adjusted linear regression models (continuous outcomes) were constructed describing changes in CVD risk factors per 5-mg/dL increment, ≈1 SD, in prolactin. Sex-specific models were used because of the different prolactin distributions and reference limits in women and men. All multivariable models were adjusted for age, current smoking, hormone replacement therapy (women only), menopausal status (women only), and baseline levels of the outcome parameter. The systolic and diastolic blood pressure models excluded participants on antihypertensive medications at baseline and imputed 10 mm Hg to the systolic blood pressure and 5 mm Hg to the diastolic blood pressure if a participant was on antihypertensive medications at follow-up.[17] The glucose model excluded participants on diabetes medications at baseline. The triglyceride and HDL models excluded participants on lipid-lowering medications at baseline. Because of exclusions based on the baseline parameters, the sample sizes varied for each outcome. A second model adjusted the first model for BMI to test whether BMI, as an approximation of global adiposity, explained any significant observations. Sex-interaction *P*-values were calculated for each outcome.

We also constructed sex-specific multivariable adjusted logistic regression models (dichotomous outcomes). The model structures were similar to the linear regression models, and again, participants with the risk factor present at baseline were excluded.

To investigate the association between baseline prolactin and changes in weight, we used multivariable-adjusted linear regression models to calculate change in BMI, weight, VAT and SAT volume, and VAT and SAT attenuation per 5-mg/dL increment in prolactin. Age was the only covariate used for model 1 for these regressions. Model 2 included adjustments for age, smoking status, and menopausal status in women. Model 3 added adjustment for BMI.

Significant associations were defined as those with $P<0.05$. Analyses were hypothesis generating, and as such, no adjustments were made for multiple testing. Analysis was completed with SAS version 9.2 (SAS Institute).

Results

Study Sample Characteristics

Characteristics of the study sample are shown in Table 1. Of the 3232 participants, slightly more than half were women. Mean age was 40.2 years among women and 40.7 years among men. Mean BMI was in the overweight range for both women and men. Mean prolactin levels were 11.9 mg/dL (SD 5.2) in women and 8.0 mg/dL (SD 2.9) in men. Additional CVD risk factor data at baseline and follow-up are provided.

Correlation Between Baseline Prolactin and Changes in CVD Risk Factors

Age was negatively correlated with prolactin in women and men. In women only, baseline prolactin was positively associated with change in total cholesterol (correlation coefficient 0.05, $P<0.05$). There were other no significant age-adjusted Pearson correlation coefficients between baseline prolactin and changes in CVD risk factors from baseline to follow-up (Table 2).

Associations Between Baseline Prolactin and Changes in CVD Risk Factors

Prolactin was not associated with the odds of incident hypercholesterolemia, hypertriglyceridemia, or metabolic syndrome in women or men, and no significant sex interaction was observed for these outcomes (Table 3) ($P\geq0.10$). In multivariable-adjusted logistic regression models (Table 3), a 5-mg/dL increment in baseline prolactin was associated with higher odds of low HDL cholesterol in women (odds ratio 1.50, 95% CI 1.18–1.91, $P=0.001$), an association that persisted after adjustment for BMI ($P=0.001$). Similar but less significant results were seen in men. A 5-mg/dL increment in baseline prolactin in men was associated with higher odds of hypertension (odds ratio 1.36, 95% CI 1.08–1.71, $P<0.01$) at follow-up, which also persisted after adjustment for BMI ($P=0.004$). No association between baseline prolactin and incident hypertension was observed in women (odds ratio 0.99, 95% CI 0.65–1.49, $P=0.91$; sex interaction $P=0.02$). Higher baseline prolactin in men only was also associated with increased incident diabetes (odds ratio 1.70, 95% CI 1.04–2.78, $P=0.03$), but this association was attenuated on adjustment for BMI (odds ratio 1.51, $P=0.12$).

Table 1. Baseline Study Sample Characteristics

	Women (n=1685)	Men (n=1547)
Age, y	40.2 (8.7)	40.7 (8.6)
BMI, kg/m^2	25.8 (5.9)	27.9 (4.7)
Waist circumference, cm	87.9 (15.3)	98.3 (12.7)
Smoking status		
Current smoker, %	14.8 (249)	16.7 (259)
Former smoker, %	28.7 (484)	22.6 (350)
Never smoker, %	56.5 (952)	60.6 (938)
Moderate to heavy alcohol use*, %	13.8 (232)	16.1 (249)
Physical Activity, Physical Activity Index Score	36.5 (5.8)	38.6 (9.2)
Postmenopausal, %	13.9 (235)	NA
Hormone replacement, %	4.7 (79)	NA
Prolactin, mg/dL	11.9 (5.2)	8.2 (2.9)
Systolic blood pressure, mm Hg	113.2 (14.3)	120.7 (12.5)
Diastolic blood pressure, mm Hg	72.5 (9.1)	78.3 (9.2)
Fasting glucose, mg/dL	91.9 (17.1)	98.7 (19.1)
Total cholesterol, mg/dL	184.9 (32.9)	193.5 (37.7)
HDL cholesterol, mg/dL	61.5 (16.3)	46.8 (12.2)
Triglycerides, mg/dL	95.2 (56.6)	134.1 (107.8)
	80.0 (60.0–112.0)	107.0 (73.0–161.0)
Obesity (BMI >30, in kg/m^2), %	19.7 (332)	25.7 (397)
Hypertension, %	11.0 (185)	21.5 (332)
Hypertension treatment, %	6.4 (108)	9.8 (152)
Diabetes, %	2.1 (35)	3.5 (54)
Diabetes treatment, %	1.5 (25)	1.9 (30)
Hypercholesterolemia, %	32.6 (550)	49.6 (767)
Hypertriglyceridemia, %	14.4 (242)	35.8 (554)
Lipid treatment, %	3.7 (62)	11.4 (176)
Low HDL, %	23.3 (393)	28.7 (443)
Metabolic syndrome†, %	14.0 (234)	28.4 (439)
Change in systolic blood pressure, mm Hg	0.4 (12.0)	2.2 (11.5)
Change in diastolic blood pressure, mm Hg	−0.1 (8.6)	0.2 (8.6)
Change in fasting glucose, mg/dL	1.0 (14.0)	1.9 (19.6)
Change in total cholesterol, mg/dL	2.2 (30.0)	−6.8 (34.1)
Change in HDL cholesterol, mg/dL	5.8 (12.0)	4.0 (9.3)
Change in triglycerides, mg/dL	1.2 (52.3)	−2.5 (95.4)
Time between exams, y	6.1 (0.6)	6.1 (0.6)

Data are given as mean (SD) for continuous variables and percentage (number of participants) for categorical variables. For triglyceride data, median (25th–75th percentile) is also presented. BMI indicates body mass index; HDL, high-density lipoprotein.

*Moderate to heavy alcohol use is defined as >7 drinks per week for women and >14 drinks per week for men.

†Metabolic syndrome is defined as the combination of at least 3 of the following factors: (1) waist circumference ≥88 cm for women or ≥102 cm for men, (2) triglycerides ≥150 mg/dL, (3) HDL <50 in women or <40 in men, (4) blood pressure ≥130/85 mm Hg or use of a blood pressure–lowering agent, and (5) fasting plasma glucose ≥110 mg/dL.

In multivariable-adjusted linear regression models (Table 4), baseline prolactin was not associated with changes in most CVD risk factors at follow-up, and no significant sex interactions were observed (P≥0.13). An exception in men only was an association between baseline prolactin and change in systolic blood pressure: For a 5-mg/dL increment

Table 2. Age-Adjusted Pearson Correlation Coefficients Between Baseline Prolactin and Changes in Cardiovascular Disease Risk Factors

	Women	Men
Baseline age	−0.15†	−0.16†
Change in SBP	0.02	0.03
Change in DBP	0.03	0.03
Change in glucose	0.04	−0.01
Change in total cholesterol	0.06*	−0.01
Change in HDL cholesterol	−0.04	−0.01
Change in log triglycerides	0.03	−0.04

DBP indicates diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
*$P<0.05$.
†$P<0.0001$.

in prolactin, systolic blood pressure was 0.97 mm Hg higher (95% CI 0.05–1.90, $P=0.04$) at follow-up.

Associations Between Baseline Prolactin and Changes in Adiposity Measures

There were no significant associations between baseline prolactin and changes in BMI, fat volumes, or fat attenuation (all $P\geq0.10$) in women, in men, or overall (Tables 5 and 6). In addition, overall significant BMI interactions were not seen for associations between prolactin and incident CVD risk factors (data not shown).

Discussion

Principal Findings

Our principal findings are as follows. First, we generally observed very few associations between baseline prolactin and incident changes in CVD risk factors. Second, baseline prolactin was not associated with changes in adiposity. Taken together, these findings suggest that measuring serum prolactin levels in the community likely provides minimal benefit in predicting cardiometabolic risk.

In the Context of the Current Literature

The present analysis is among the first large community-based studies to prospectively examine the association between prolactin and incident CVD risk factors. Our findings suggest few associations between prolactin and incident CVD risk. This is consistent with a previous study that found that prolactin variation within the normal range did not predict coronary artery disease.[18] Some specific findings in our study, however, warrant mention. Our findings of associations between prolactin and incident hypertension and diabetes (in men) and HDL cholesterol (in women) lend support to a prior study that found an association between prolactin and cardiovascular mortality over 10-year follow-up.[10] In that study, results were adjusted for hypertension but were not adjusted for BMI. Our hypertension findings were independent of BMI, suggesting that these risk factor associations were not fully explained by associations between prolactin and overall adiposity.

Prolactin has previously been associated with incident self-reported hypertension in a Nurses Health Study subset of 874 postmenopausal women.[19] Positive associations between prolactin within the normal range and arterial blood pressure and aortic stiffness were also seen in a small cross-sectional study of menopausal women.[20] Our cohort was large, with prolactin and risk factors measured onsite, and our findings differed in identifying this association only in men. Our findings in women may have differed because, compared with the Nurses Health Study, our sample was younger and included a mix of pre- and postmenopausal women. Out study could have been underpowered to see this association because our sample had only 8.3% incident hypertension over time compared with 20.9% in the Nurses Health Study.[19]

The association between prolactin and HDL cholesterol has not been as widely characterized in the existing literature. A small nonrandomized clinical study found that HDL cholesterol was not lower in 15 hyperprolactinemic patients compared with controls, and HDL cholesterol did not change significantly after treatment with cabergoline.[21] In contrast to our findings, a pediatric study reported a positive association between baseline prolactin and HDL cholesterol at 1-year follow-up.[22] Our longer study duration, different patient population, and evaluation of prolactin within the normal range may partially account for our findings. In addition, because a significant association was seen with low HDL incidence but not with low HDL as a continuous outcome, our findings may be related in part to the use of a threshold to define low HDL.

The association between elevated prolactin and incident diabetes in men is consistent with prior literature in which diurnal plasma prolactin has been found to be higher in obese diabetic patients than in lean healthy subjects.[23] Prolactin release is inhibited by dopamine. A current US Food and Drug Administration (FDA)–approved treatment for type 2 diabetes is bromocriptine mesylate, a dopamine receptor agonist.[24] By activating dopamine receptors, this drug inhibits prolactin release, and patients have seen an expected decrease in serum prolactin while taking the medication.[25] The mechanism through which this drug decreases blood glucose levels has not been completely characterized but may be related in part to the medication's prolactin-lowering effects.[26] We did

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Table 3. Incident Changes in Cardiovascular Disease Risk Factors From Baseline Prolactin (Dichotomous Outcomes)

	Women			Men			Overall		
	Event Rate*	OR† (95% CI)	*P* Value	Event Rate*	OR† (95% CI)	*P* Value	Event Rate*	OR† (95% CI)	*P* Value
Hypertension	8.2% (123/1494)			13.9% (169/1214)			10.8% (292/2708)		
MV‡		0.99 (0.80–1.21)	0.91		1.61 (1.18–2.20)	0.002		1.15 (0.97–1.36)	0.11
MV+BMI§		1.01 (0.82–1.24)	0.96		1.57 (1.15–2.15)	0.004		1.16 (0.98–1.37)	0.09
Diabetes	1.6% (27/1644)			3.4% (51/1489)			2.5% (78/3133)		
MV		0.99 (0.65–1.49)	0.94		1.70 (1.04–2.78)	0.03		1.22 (0.89–1.66)	0.22
MV+BMI		0.97 (0.64–1.48)	0.89		1.51 (0.90–2.53)	0.12		1.17 (0.85–1.62)	0.34
Hypercholestolemia‖	21.1% (239/1134)			22.7% (177/779)			21.7% (416/1913)		
MV		1.06 (0.91–1.23)	0.46		1.30 (0.97–1.76)	0.083		1.10 (0.96–1.25)	0.16
MV+BMI		1.06 (0.91–1.23)	0.46		1.29 (0.95–1.74)	0.10		1.10 (0.96–1.25)	0.16
Low HDL¶	4.4% (57/1290)			6.3% (69/1102)			5.3% (126/2392)		
MV		1.50 (1.18–1.91)	0.001		1.16 (0.77–1.74)	0.48		1.40 (1.14–1.72)	0.002
MV+BMI		1.50 (1.17–1.91)	0.001		1.12 (0.74–1.69)	0.60		1.39 (1.13–1.72)	0.002
Hypertriglyceridemia#	12.1% (174/1441)			22.3% (221/992)			16.2% (395/2433)		
MV		0.87 (0.73–1.04)	0.13		0.99 (0.75–1.30)	0.95		0.91 (0.78–1.05)	0.19
MV+BMI		0.87 (0.73–1.04)	0.13		0.97 (0.74–1.28)	0.84		0.90 (0.78–1.05)	0.18
Metabolic syndrome	9.0% (129/1438)			15.6% (172/1103)			11.8% (301/2541)		
MV		0.97 (0.81–1.17)	0.77		1.23 (0.93–1.63)	0.15		1.04 (0.89–1.21)	0.62
MV+BMI		0.96 (0.79–1.17)	0.72		1.14 (0.85–1.53)	0.38		1.01 (0.86–1.19)	0.86

All sex-interaction *P* values were ≥0.10 with the exception of the sex interaction for hypertension (*P*=0.02). BMI indicates body mass index; HDL, high-density lipoprotein; MV, multivariable.

*Event rate given as [incident cases]/[population at risk at baseline]=% incidence.

†Change in at follow-up examination per 5-mg/dL increment in prolactin.

‡Multivariable model: age, sex, baseline level of outcome parameter, current smoking, hormone replacement therapy, and menopausal status.

§MV+BMI: additionally adjusts MV model for baseline BMI.

‖Hypercholesterolemia was defined as total cholesterol ≥200 mg/dL or lipid-lowering treatment.

¶Low HDL was defined as <50 mg/dL in women and <40 mg/dL in men.

#Hypertriglyceridemia was defined as triglycerides ≥150 mg/dL or use of lipid-lowering treatment.

Table 4. Incident Changes in Cardiovascular Disease Risk Factors From Baseline Prolactin (Continuous Outcomes)

	Women		Men		Overall	
	Incident Change* (95% CI)	*P* Value	Incident Change* (95% CI)	*P* Value	Incident Change* (95% CI)	*P* Value
Change in SBP						
MV[†]	0.31 (−0.21 to 0.83)	0.25	0.97 (0.05–1.90)	0.04	0.45 (0.00–0.89)	0.052
MV+BMI[‡]	0.32 (−0.19 to 0.84)	0.21	0.88 (−0.05 to 1.80)	0.06	0.42 (−0.02 to 0.86)	0.06
Sex interaction						0.30
Change in DBP						
MV	0.11 (−0.25 to 0.47)	0.55	0.60 (−0.05 to 1.25)	0.07	0.20 (−0.12 to 0.51)	0.22
MV+BMI	0.10 (−0.26 to 0.46)	0.59	0.55 (−0.11 to 1.20)	0.10	0.17 (−0.14 to 0.49)	0.28
Sex interaction						0.13
Change in glucose						
MV	0.38 (−0.18 to 0.95)	0.19	0.07 (−1.44 to 1.58)	0.93	0.30 (−0.31 to 0.91)	0.33
MV+BMI	0.37 (−0.19 to 0.92)	0.20	−0.11 (1.61 to 1.39)	0.89	0.26 (−0.35 to 0.86)	0.40
Sex interaction						0.48
Change in cholesterol						
MV	1.06 (−0.20 to 2.33)	0.10	−0.87 (−3.42 to 1.68)	0.50	0.50 (−0.67 to 1.67)	0.40
MV+BMI	1.09 (−0.17 to 2.34)	0.09	−0.46 (−2.99 to 2.06)	0.72	0.59 (−0.57 to 1.75)	0.32
Sex interaction						0.76
Change in HDL						
MV	−0.36 (−0.90 to 0.17)	0.18	−0.49 (−1.28 to 0.30)	0.23	−0.42 (−0.84 to 0.01)	0.06
MV+BMI	−0.34 (−0.87 to 0.19)	0.21	−0.42 (−1.21 to 0.36)	0.29	−0.39 (−0.81 to 0.04)	0.07
Sex interaction						0.92
Change in log triglycerides						
MV	0.01 (−0.01 to 0.02)	0.38	0.00 (−0.04 to 0.03)	0.79	0.00 (−0.01 to 0.02)	0.58
MV+BMI	0.01 (−0.01 to 0.02)	0.41	−0.01 (−0.04 to 0.03)	0.75	0.00 (−0.01 to 0.02)	0.61
Sex interaction						0.97

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MV, multivariable; SBP, systolic blood pressure.
*Change in at follow-up examination per 5-mg/dL increment in prolactin.
[†]MV model: age, sex, baseline level of outcome parameter, current smoking, hormone replacement therapy, and menopausal status.
[‡]MV+BMI: additionally adjusts MV model for baseline BMI.

not observe an association between increments in prolactin and increases in fasting glucose levels in men despite seeing the association with increased diabetes risk; this result may have been related to a threshold effect.

Finally, the lack of associations observed between prolactin and changes in adiposity and body composition is not consistent with results published in primarily clinical studies. Prolactinomas producing high levels of prolactin are typically associated with weight gain.[4] In addition, a study in obese women found that increased BMI and VAT are associated with an increased prolactin secretion rate.[8] Similar to our findings, however, a previous cross-sectional community-based study did not find an association between BMI and prolactin in either men or women.[9] This study excluded participants with pituitary disease and, with this exclusion, likely removed most persons with prolactin levels outside of the physiological range. Our exclusion of participants with abnormally elevated prolactin may have similarly contributed to the lack of associations we observed, if these associations are better observed with very elevated prolactin.

Potential Mechanisms

Several mechanisms potentially explain the association between prolactin and hypertension. Studies in rats have demonstrated that high prolactin has chronotropic and vasoconstrictive effects.[27] A physiological study of 27 men with untreated hypertension and normal prolactin found that diurnal peaks in prolactin coincided with reduced endothelial function, which may play a role in elevating blood pressure.[28]

Higher baseline prolactin may also reflect perturbations in other hormonal axes known to affect blood pressure and

Table 5. Age-Adjusted Pearson Correlation Coefficients With Prolactin

Metabolic Parameters	Prolactin Level	
	Women	Men
BMI	−0.03	−0.04
Weight	−0.02	−0.02
Change in BMI	−0.07	−0.04
Change in VAT volume	−0.07	−0.02
Change in SAT volume	−0.05	−0.05
Change in VAT attenuation	0.05	0.07
Change in SAT attenuation	0	−0.05
Change in weight	−0.06	−0.04

All $P \geq 0.13$. BMI indicates body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

lipids, thus explaining both our hypertension and HDL cholesterol findings. Elevated prolactin may result from untreated hypothyroidism because hypothalamic thyrotropin-releasing hormone, which is commonly elevated in hypothyroidism, stimulates both prolactin synthesis and release from the pituitary.[29] Hypothyroidism is associated with hypertension and elevations in HDL cholesterol.[30,31] Nevertheless, this mechanism is speculative.

The association we observed between elevated prolactin and diabetes in men may be related to a possible mechanism of sex hormone–binding globulin, a glycoprotein that binds to androgens and estrogens and mediates their interaction with hormone receptors.[32,33] Prolactin has been found to inhibit production of sex hormone–binding globulin in vitro.[34] Low sex hormone–binding globulin has been prospectively associated with increased odds of incident diabetes.[33,35,36] Although the mechanism and causality of this association has not been fully characterized, it is possible that elevated prolactin may influence diabetes risk by inhibiting production of sex hormone–binding globulin.

Implications

The results of the present study suggest that prolactin levels are associated with incident hypertension, diabetes, and low HDL but generally are not associated with the development of comprehensive abnormal CVD risk factors over time.

An implication of our findings of increased incident diabetes and hypertension in men pertains to the action and side effects of the recently FDA-approved diabetes treatment bromocriptine mesylate, which lowers blood glucose and inhibits prolactin release.[24] A possible side effect of bromocriptine medications is hypotension.[26,37] Bromocriptine acts a dopamine-2 receptor agonist, through which it inhibits

Table 6. Changes in BMI, Weight, and VAT and SAT Measurements From Baseline Prolactin

Outcome*	Model†	Women	*P* Value	Men	*P* Value	Overall	*P* Value
BMI change, kg/m^2	Model 1	−0.2 (−0.5 to 0.1)	0.20	−0.2 (−0.5 to 0.2)	0.34	−0.2 (−0.4 to 0.0)	0.10
	Model 2	−0.2 (−0.5 to 0.1)	0.17	−0.1 (−0.4 to 0.2)	0.60	−0.2 (−0.4 to 0.0)	0.12
Weight change, kg	Model 1	−0.4 (−1.1 to 0.3)	0.27	−0.4 (−1.4 to 0.6)	0.41	−0.4 (−1.0 to 0.2)	0.18
	Model 2	−0.5 (−1.2 to 0.3)	0.22	−0.2 (−1.2 to 0.8)	0.70	−0.4 (−0.9 to 0.2)	0.21
VAT volume change, cm^3	Model 1	−23.5 (−77.9 to 30.9)	0.40	−4.6 (−125.4 to 116.1)	0.94	−14.1 (−73.5 to −45.3)	0.64
	Model 2	−27.5 (−82.6 to 27.5)	0.33	7.8 (−114.4 to 130.1)	0.90	−15.2 (−75.5 to 45.0)	0.62
	Model 3	−27.0 (−81.9 to 27.9)	0.34	9.1 (−112.0 to 130.1)	0.88	−15.2 (−75.3 to 45)	0.62
SAT volume change, cm^3	Model 1	−41.1 (−133.8 to 51.5)	0.38	−57.9 (−158.0 to 42.2)	0.26	−47.8 (−112.5 to 16.9)	0.15
	Model 2	−50.8 (−143.8 to 42.2)	0.29	−36.2 (−137.0 to 64.5)	0.48	−42.2 (−107.5 to 23.0)	0.21
	Model 3	−49.8 (−143.0 to 43.3)	0.30	−36.4 (−137.2 to 64.5)	0.48	−42.2 (−107.5 to 23.1)	0.21
VAT attenuation change, HU	Model 1	0.19 (−0.34 to 0.72)	0.48	0.57 (−0.17 to 1.30)	0.13	0.34 (−0.08 to 0.76)	0.12
	Model 2	0.17 (−0.36 to 0.70)	0.53	0.45 (−0.30 to 1.19)	0.24	0.27 (−0.16 to 0.70)	0.21
	Model 3	0.19 (−0.32 to 0.70)	0.46	0.38 (−0.34 to 1.11)	0.30	0.26 (−0.15 to 0.67)	0.21
SAT attenuation change, HU	Model 1	0.01 (−0.35 to 0.37)	0.94	−0.03 (−0.52 to 0.46)	0.90	−0.01 (−0.30 to 0.27)	0.94
	Model 2	0.01 (−0.36 to 0.37)	0.97	−0.18 (−0.67 to 0.32)	0.49	−0.06 (−0.35 to 0.22)	0.66
	Model 3	0.00 (−0.36 to 0.37)	0.98	−0.18 (−0.67 to 0.32)	0.49	−0.07 (−0.35 to 0.22)	0.65

All sex-interaction $P > 0.54$. BMI indicates body mass index; HU, Hounsfield units; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
*Estimates given change in dependent variable associated with each additional 5-mg/dL increment in prolactin.
†Model 1 included age, sex, baseline value of the variable. Model 2 included model 1 plus smoking status and in women, menopausal status. Model 3 included model 2 plus BMI.

prolactin release, α2-adrenergic receptor agonist, and an α1-adrenergic receptor antagonist.[26] Together, these actions produce arteriolar and venous dilation and a decrease in blood pressure.[37] Prolactin participates in a short feedback loop with dopamine (ie, elevated prolactin decreases dopamine synthesis).[38,39] Consequently, elevated prolactin may decrease dopamine receptor activation by dopamine and thus increase sympathetic tone and blood pressure. Further research could explore this potential pathway.

Strengths and Limitations

The large sample size is a strength of our study. Our sample included a large proportion of men and thus expands the existing literature, which has focused mainly on women. The data are prospective and allowed us to assess CVD risk factor changes over time. Key covariates and CVD risk factors were robustly assessed or directly measured onsite, which is more reliable than self-report. Some limitations warrant mention. We could not adjust for either estrogen or insulin resistance. Because this study was observational, we cannot infer causality between prolactin and the measured outcomes and are unable to elucidate mechanisms. The Framingham cohort is primarily white, thus results may not be generalizable to other ethnicities. We did not account for multiple testing; therefore, results should be considered hypothesis generating.

Conclusion

Variations in prolactin within its normal range are not associated with comprehensive changes in CVD risk factors over time. These results suggest that, in general, measurements of circulating prolactin levels in the community likely would not provide substantial insight into cardiometabolic risk.

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Disclosures

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