Plasma Insulinlike Growth Factor 1 and Binding-Protein 3 and Risk of Myocardial Infarction in Women: A Prospective Study

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BACKGROUND: The aim of this study was to prospectively evaluate relationships between plasma concentrations of insulinlike growth factor 1 (IGF1) and insulinlike growth factor binding protein 3 (IGFBP3) and subsequent myocardial infarction (MI) in women.

METHODS: We used case-control sampling to select study participants from women who had already been selected for inclusion in the prospective Nurses' Health Study cohort. Blood samples were collected from 32 826 women in 1989–1990. During the follow-up period from sample collection through June 1998, MI (fatal and nonfatal) was diagnosed in 245 women. Cases were matched to controls 1:2 by age, cigarette-smoking status, and month and fasting status at the time of blood collection. Conditional logistic regression was used to adjust for potential confounders (menopausal status, parental history of MI, postmenopausal hormone use, diabetes mellitus, hypertension, hypercholesterolemia, aspirin use, alcohol use, body mass index, and physical activity).

RESULTS: Multivariable adjusted analyses did not reveal a statistically significant linear relationship between IGF1 or IGFBP3 concentrations or their molar ratio and risk of MI. Women in the highest IGF1 quartile had a multivariable-adjusted rate ratio of 1.46 (95% CI 0.79, 2.72; *P* for trend = 0.46) for MI, compared with those in the lowest. The corresponding rate ratios (95% CI) for IGFBP3 and the IGF1:IGFBP3 mol/L ratio were 1.24 (0.71, 2.17) and 1.29 (0.70, 2.37), respectively.

CONCLUSIONS: We did not observe a monotonic relationship between IGF1 or IGFBP3 and MI among predominantly postmenopausal women. Future studies are warranted to evaluate these relationships in other demographic groups including younger women.

Although the incidence of cardiovascular disease in the US and Western Europe is decreasing, cardiovascular disease remains a leading cause of mortality, especially among postmenopausal women *(1–4)*. Insulinlike growth factor 1 (IGF1),[5] an abundant naturally occurring peptide that has important effects on growth and development of many tissues, may play a role in several cancers *(5–7)*. Animal *(8, 9)* and pathophysiologic *(10, 11)* studies have suggested that IGF1 may be directly or indirectly involved in the pathogenesis of atherosclerosis. IGF1 stimulates the synthesis of plasminogen activator inhibitor 1 *(10)* and has antiapoptotic effects on vascular smooth muscle *(11)*. Increased IGF1 immunostaining is observed in human atherosclerotic plaque *(12)*, and IGF1 expression is increased in injured arteries *(8, 13)*. Furthermore, female mice with 1 inactivated copy of an IGF1-receptor gene lived 33% longer than wild-type females and were more resistant to oxidative stress *(14)*. In contrast, IGF1 increases nitric-oxide–induced vasodilation *(15, 16)*, increases insulin sensitivity *(17–19)*, and appears to improve lipid profiles *(19)*.

Epidemiologic data on IGF1 are limited. In retrospective analyses, individuals with hypopituitarism who were on replacement therapy were shown to have premature and accelerated atherosclerosis *(20, 21)*. A prospective study among adult men and women showed that low plasma IGF1 concentrations were associated with an increased risk of ischemic heart disease *(22)*, and another showed a similar inverse rela-

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tionship of IGF1 concentrations with ischemic heart disease mortality (23). A more recent prospective epidemiological study found no relationship between plasma IGF1 and subsequent myocardial infarction (MI) (24). Among patients with type 2 diabetes mellitus, a premature, age-related reduction of IGF1 (25) and low IGF1 are associated with poor glycemic control (26). Therefore, IGF1 might be of special significance in diabetic patients, although this association has not been thoroughly investigated in prospective studies.

We conducted a nested case-control study within the Nurses' Health Study cohort to evaluate the relationship of circulating plasma concentrations of IGF1 and insulinlike growth-factor–binding protein 3 (IGFBP3) and the molar ratio of IGF1 and IGFBP3 to risk of subsequent MI in older women. Given the likely role of IGF1 in diabetes mellitus, we examined the possibility that diabetes mellitus modifies the association between IGF1 concentrations and MI risk. Given that estrogen administration has been found to be associated with decreased IGF1 concentrations (27), we also examined whether estrogen therapy modifies the effect of IGF1. Finally, we also explored whether the association varied by body mass index (BMI) and age at blood sampling.

Materials and Methods

STUDY POPULATION

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses, 30–55 years old, began completing and returning mailed questionnaires, thus providing data regarding the relationship between diet and lifestyle and subsequent disease. The cohort continues to be followed every 2 years by questionnaire to update exposure status and to identify cases of newly diagnosed disease. Data have been collected on many coronary artery disease risk factors, including height, weight, cigarette smoking, alcohol use, physical activity, age at menopause, postmenopausal hormone (PMH) use, diagnoses of hypertension and diabetes mellitus, history of aspirin use, and parental family history of MI. BMI was calculated by dividing the most recent weight before blood collection by the square of height reported in 1976.

From 1989 through 1990, blood samples were collected from 32 826 cohort members (27% of the original cohort), who were 43–69 years old when blood was collected. Details regarding the blood collection methods have been published previously (28). Briefly, each woman arranged to have her blood drawn and then shipped with an ice pack via overnight courier to our laboratory, where it was processed and separated into plasma, erythrocyte, and leukocyte components. Within 24 h of being drawn, 97% of the samples were received in our laboratory. The stability of IGF1 and IGFBP3 in whole blood for 24–48 h has been documented previously (7). Since collection, samples have been archived at −130 °C or colder in continuously monitored liquid nitrogen freezers. As of 1998, follow-up of the blood study subcohort was 99.8%.

Case women were those who had reported no MI diagnosis before blood collection and who were diagnosed with MI after blood collection but before June 1, 1998. Overall, 245 cases of MI (28 of which were fatal) were reported from among the 32 826 women eligible at baseline. For all cases of MI, hospital records were obtained and reviewed [with 19 exceptions, 13 of which were verbally confirmed by a nurse as hospitalized for MI and 6 by death certificate information (All cases were retained in the analysis)]. MI was classified as confirmed if symptoms met the criteria of the WHO (typical symptoms and either diagnostic electrocardiographic changes or increased cardiac enzymes). The median (10th to 90th percentiles) time from blood collection to diagnosis was 54 months (15, 91). Two controls were matched per case patient by age (±2 years), cigarette smoking status (current, past, and never smoker), month of blood collection, and fasting status at the time of blood collection (≥10 h since a meal vs <10 h or unknown). Of control matches, 81% were exact; the most relaxed age match was within ±3 years, and the most relaxed blood collection match was within ±6 months. The study was performed in compliance with the Declaration of Helsinki, and was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital. All study participants gave their informed consent to participate.

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LABORATORY ANALYSES

IGF1 was measured by an enzymatically amplified 1-step sandwich-type immunoassay, and IGFBP3 was measured by an enzymatically amplified 2-step sandwich-type immunoassay, both with reagents from Diagnostic Systems Laboratory. These assays were performed in 3 batches in 1994, 1996, and 1998. Matched case and control samples were measured within the same batch. Based on masked quality control samples (10% of the total number of samples) inserted among the case and control blood samples, the intraassay CV for IGF1 was 7.1%. The corresponding intraassay CV for IGFBP3 was 12.6%.

Total cholesterol was measured enzymatically (29) with an intraassay CV of 1.7%. HDL cholesterol was measured with a Roche Hitachi 911 analyzer (30), with an intraassay CV of 2.5%. C-reactive protein was determined with a high-sensitivity immunoturbidimetric assay on a Hitachi 911 analyzer, with an intraassay CV of 1.4%.

We estimated adjusted Spearman correlation coefficients of IGF1, IGFBP3, and their molar ratio to the other covariates among controls by estimating the coefficients between respective residuals after doing linear regression with $\log_e$(IGF1), IGFBP3, $\log_e$(IGF1: IGFBP3 molar ratio), $\log_e$(HDL-to-total cholesterol ratio), $\log_e$(C-reactive protein), $\log_e$(BMI), $\log_e$(physical activity), and alcohol as outcome variables and age (modeled as natural cubic splines with 4 degrees of freedom), current PMH use, and batch as covariates.

Conditional logistic regression was used to estimate odds ratios, which were taken as direct estimates (31) of rate ratios (RRs) and 95% CIs (32). Mean IGF1 and IGFBP3 concentrations varied by batch: among controls, there were statistically significant differences in age-adjusted IGF1 between batches. As a result, we used batch-specific cut-points in the regression analyses. We also controlled for potential confounders that were not part of the matching scheme. To control more appropriately for confounding and other covariation by continuous variables, natural cubic splines (33, 34) with 4 degrees of freedom were used to smooth the relationships with the log-odds of MI. We estimated the following models: (a) a model that controls for matching factors only; (b) a model that adjusts for matching factors and plasma high-sensitivity C-reactive protein only (because this latter variable is a strong correlate of plasma IGF1), (c) a model that controls for matching factors and conventional nonbiomarker risk factors for MI (considered the definitive model); (d) a model that in addition to those in the foregoing, controls for the ratio of plasma total:HDL cholesterol and for plasma high-sensitivity C-reactive protein. Because matching for age was not perfect, we also adjusted for a linear function of age. The nonbiomarker risk factors of MI that we adjusted for were menopausal status (premenopausal, postmenopausal, or unknown menopausal status); parental history of MI (having a parent who had a history of MI before age 65); current use of PMH, duration of PMH use for more than 5 years; history of diabetes mellitus; history of hypertension; history of hypercholesterolemia; history of aspirin use (1–14 days per month and >14 days per month vs no use); mean daily alcohol intake in 1980, 1984, and 1986; BMI; and physical activity measured in metabolic equivalent–hours per week in 1988. Categorical variables were modeled with indicator functions. Physical activity was modeled as a linear variable because fitting problems occurred when we attempted to fit these data with natural cubic splines. Because body shape may influence IGF1 and MI risk, we adjusted for waist-hip circumference in the subset (165 matched sets) of study participants for which these data were available.

There were very few missing values in the covariates physical activity, C-reactive protein, and total:HDL cholesterol ratio (all <4%), and thus medians were used for imputation. In model (c) (the definitive model, which controls for matching factors and conventional nonbiomarker risk factors for MI), tests for interaction were done by including product terms between indicator functions of halves of the respective variable [age at blood draw (<60 vs ≥60 years), current PMH use (yes vs no), BMI (<25 vs ≥25 kg/m^2), and history of type 2 diabetes mellitus] and indicator functions of quartiles of IGF-1, IGFBP-3, and their molar ratio.

We conducted tests for trend by modeling the hormone concentration as a linear continuous covariate and calculating a Wald statistic (31). All P values were 2-sided. The statistical software programs used for analysis were SAS release 9 (32) and S Plus version 6 (33).

Results

At the time of blood sampling, the women in this study had a median age of 62 (10th and 90th percentiles, 50 and 68). The distribution of risk factors for MI at the time of blood sampling among case women and matched controls is shown in Table 1. Median IGF1 and IGFBP3 concentrations were very similar in case and control women. As expected, the medians of BMI, total cholesterol, and C-reactive protein and proportions of case women with histories of chronic aspirin use, diabetes mellitus, hypertension, or having had a parent with early MI were all higher in women who later developed MI than in control women. Similarly, the levels of physical activity and plasma HDL cholesterol concentrations were lower in the case women.

Mean IGF1 concentrations varied with current use of postmenopausal estrogens. Women who were taking postmenopausal estrogen at the time of blood sampling had significantly lower age- and batch-adjusted IGF1 and IGFBP3 concentrations relative to women who were not taking estrogen [26.5% (95% CI 21.5, 31.3) lower for IGF1 and 12.9 nmol/L (95% CI 5.5, 20.3) lower for IGFBP3]. IGF1 concentrations did not differ by diabetes status [0.5% (95% CI −14%,17%) for diabetic vs nondiabetic women], but women with diabetes mellitus had significantly higher IGFBP3 concentrations [19.6 mmol/L higher (95% CI 3.7, 35.5)]. The Spearman correlation coefficients between the age-, current PMH use–, and batch-adjusted residuals of the covariates and IGFBP3 and the natural logarithm of IGF1 and the IGF1: IGFBP3 mol/L ratio, respectively, among controls are shown in Table 2. Plasma IGF1 and IGF1:IGFBP3 mol/L ratio was negatively and statistically significantly correlated with plasma high-sensitivity C-reactive protein. The molar ratio was also negatively correlated with BMI, and

Table 1. Distribution of covariates in case and matched-control study participants.[a]		
Covariate and unit of measure	Cases (n = 245), median (10th to 90th percentiles)	Controls (n = 482), median (10th to 90th percentiles)
IGF1, nmol/L	18.9 (10.9, 32.3)	18.1 (11.1, 32.3)
IGFBP3, nmol/L	168.1 (114.6, 222.5)	168.5 (119.6, 22.4)
IGF1:IGFBP3 molar ratio	0.119 (0.079, 0.191)	0.121 (0.077, 0.193)
Age at blood draw, y[b]	62 (51, 68)	62 (51, 68)
Current smokers, n (%)[b]	79 (32.2)	162 (33.6)
BMI, kg/m^2	25.8 (20.4, 35.0)	24.5 (20.5, 31.3)
Waist to Hip Ratio	0.81 (0.72, 0.89)	0.78 (0.71, 0.88)
Average physical activity, MET[c]-h/week	7.9 (1.0, 34.7)	9.2 (0.9, 36.1)
Mean alcohol consumption, g/day	1.6 (0, 17)	3.4 (0, 21)
Parental history of myocardial infarction, n (%)	88 (36)	101 (21)
History of hypertension, n (%)	131 (53.5)	128 (26.6)
History of diabetes mellitus, n (%)	43 (17.6)	25 (5.2)
History of hypercholesterolemia, n (%)	26 (10.6)	49 (10.2)
Use of aspirin in 1988, n (%)		
None	80 (32.7)	156 (32.4)
1–14 d/month	91 (37.1)	215 (44.6)
>14 d/month	66 (26.9)	99 (20.5)
Postmenopausal, n (%)	210 (85.7)	405 (84.0)
PMH use in the 3 months prior to blood collection, n (%)	76 (31)	177 (37)
Estrogen only	40 (16.3)	86 (17.8)
Estrogen and progesterone	22 (9.0)	61 (12.7)
Transdermal/vaginal preparations	15 (6.1)	30 (6.2)
PMH duration ≥5 years, n (%)	55 (22.5)	97 (20.1)
Plasma total cholesterol, mmol/L	6.06 (4.71, 7.49)	5.75 (4.61, 7.07)
Plasma HDL cholesterol, mmol/L	1.29 (0.90, 1.83)	1.51 (1.04, 2.16)
Ratio of plasma total:HDL cholesterol	4.51 (3.13, 6.99)	3.82 (2.55, 5.79)
Plasma C-reactive protein, mg/L	3.1 (0.7, 14.9)	2.2 (0.5, 9.2)

[a] There were 23/211/12 cases and 57/406/22 controls of pre/post/uncertain menopausal status, respectively. Median age (range; 10th and 90th percentiles) at diagnosis was 65.8 years (44.9, 76.2; 54.3,73.6 years). Median time (range; 10th and 90th percentiles) from blood sample to diagnosis was 4.5 years (0.08,8.7; 1.25, 7.6 years). Waist-hip ratio was available for 168 cases and 339 controls. Information was available for the other covariates in more than 96% of study participants.
[b] Matching factors.
[c] MET, metabolic equivalents.

IGFBP3 positively correlated with the ratio of plasma total:HDL cholesterol.

After we controlled for matching factors and conventional nonbiomarker risk factors for MI, plasma IGF1 was not linearly related to the risk of MI (Table 3) [RR (95% CI) for top vs bottom quartile = 1.46 (0.79, 2.72); *P* value for linear trend = 0.46]. Similarly, plasma IGFBP3 and IGF1/BP3 mol/L ratios were not statistically significantly associated with risk of MI [For IGFBP3, RR (95% CI) for top vs bottom quartile 1.24 (0.71, 2.17), *P* value for linear trend = 0.61; and

for IGF1:IGFBP3 mol/L ratio, RR (95% CI) for top vs bottom quartile 1.29 (0.70,2.37), *P* value for linear trend = 0.74]. Additional adjustment for the biomarkers C-reactive protein and total:HDL cholesterol did not reveal an appreciable change in the nature of the relationships. A similar conclusion was reached after adjustment for waist-hip circumference in the subset of study participants for which these data were available.

The relationships between IGF1, IGFBP3, the molar ratio, and MI (See Supplemental Data file available with the online version of this manuscript at www.

Table 2. Spearman correlation coefficients (*P* value) between age-, current PMH use-, and batch-adjusted residuals of $\log_e$(insulinlike growth factor 1), insulinlike growth factor binding protein 3, and $\log_e$(their molar ratio), and residuals of continuous covariates among control study participants in the Nurses' Health Study.[a]

Covariate	IGF1	IGFBP3	IGF1:IGFBP3 ratio
BMI (kg/m^2)	−0.07 (0.12)	0.06 (0.23)	−0.13 (0.004)
Average physical activity (MET-h/week)	0.03 (0.55)	0.05 (0.28)	−0.01 (0.89)
Mean yearly alcohol consumption (g/day)	−0.01 (0.86)	0.09 (0.05)	−0.09 (0.06)
Plasma total:HDL cholesterol	0.04 (0.40)	0.11 (0.02)	−0.03 (0.50)
Plasma C-reactive protein (mg/L)	0.24 (<0.001)	0.01 (0.82)	−0.30 (<0.001)

[a] Residuals of log(variable) adjusted for analysis batch and age (modeled with natural cubic splines with 4 degrees of freedom)

clinchem.org) were not statistically significantly modified by PMH use or age ($\geq$60 or <60) (tests for interaction, $P > 0.05$). There was a modest statistically significant difference in the relationship between IGFBP3 and MI risk associated with BMI ($\geq$25 vs <25), but there was no significant linear trend in either subset. The association between IGF1 and risk of MI varied by type 2 diabetes mellitus status [χ^2 (3 degrees of freedom) for interactions = 35.7, $P < 0.001$]. Among women without diabetes (202 cases and 457 controls), IGF1 in the top quartile was associated with an RR (95% CI) of 1.69 (0.88, 3.26) for MI relative to the lowest quartile, whereas the corresponding RR (95% CI) among diabetic women (43 cases and 25 controls) was 0.39 (0.04, 3.49). The relationship between IGFBP3 and MI risk also varied significantly according to diabetes mellitus status [χ^2 (3 degrees of freedom) for interactions = 25.0, $P < 0.001$]. Among women without diabetes, IGFBP3 in the top quartile was associated with an RR (95% CI) for MI of 1.71 (0.93, 3.13) relative to the lowest quartile, whereas the corresponding RR (95% CI) among diabetic women was 0.17 (0.03, 1.11). There was no statistically significant variation in the association between IGF1:IGFBP3 mol/L ratio and MI by diabetes status ($P > 0.05$).

Discussion

In this nested case-control study of prospectively collected data from predominantly postmenopausal women, we observed no overall significant linear association between IGF1, IGFBP3, or their molar ratio and subsequent risk of MI. Our data suggest that diabetes mellitus is a modifier of the relationships between IGF1 and IGFBP3 concentrations and subsequent MI risk, in that risk appears to modestly increase with both IGF1 and IGFBP3 among nondiabetic women (although not in a linear fashion) but not among diabetic women. Our main finding of the lack of linear relationship between plasma IGF1 and MI risk is consistent with a recent report that evaluated the relationship among elderly men and women in the Cardiovascular Health Study *(24)*. Our findings differ, however, from those of a prospective evaluation done among a wider age range of Danish men and women, in whom low IGF1 and high IGFBP3 were associated with increased risk of ischemic heart disease *(22)*.

The protein IGF1 is morphologically similar to insulin *(34)*, and low IGF1 concentrations are associated with poor glycemic control *(26)*. Although in our study the number of patients with diabetes was low (43 cases and 25 controls), our observation that the nature of the relationship between IGF1 and MI in diabetic patients differs from that in individuals without diabetes is consistent with these prior findings. We did not, however, observe this effect modification with the IGF1:IGFBP3 mol/L ratio, and our observations may be due to chance or may reflect a premature age-related reduction of IGF1 among patients with type 2 diabetes mellitus *(25)*. If the latter is true, low IGF1 and low IGFBP3 may serve as markers of severity of diabetes mellitus.

This is the first large prospective study specifically aimed at women that has investigated the relationship between IGF1 and IGFBP3 and MI risk. Major strengths of this study are its prospective nature, its large study population, and its careful control of confounding factors, including age and cigarette smoking. Given the observational nature of the study, however, we cannot be sure that all unknown confounders have been adequately controlled. Furthermore, it is challenging to make causal inferences about biomarkers from a dynamic system that seeks equilibrium, particularly when using measurements of isolated hormones collected at one point in time. Single IGF1 measurements, however, have been found to reasonably reflect concentrations occurring during a 3-year period *(35)*. The fact that both IGF1 and IGFBP3 were analyzed in separate batches is another weakness of this study, and this feature likely contributed to some loss of power to detect true differences. This shortcoming was

Table 3. RR of myocardial infarction and 95% CI by quartile of IGF1 and IGFBP3 concentrations and their molar ratio among predominantly postmenopausal women in the Nurses' Health Study.

Factor	Quartile categories				*P* for linear trend
	1	2	3	4	
IGF1 (nmol/L)[a]					
Cases/controls, n	54/122	56/125	77/117	58/118	
Simple RR[b] (95% CI)	1.0 (referent)	1.05 (0.66, 1.67)	1.53 (0.98, 2.37)	1.16 (0.72, 1.87)	0.57
Adjusted RR[c] (95% CI)	1.0 (referent)	1.10 (0.68, 1.79)	1.88 (1.18, 2.98)	1.50 (0.90, 2.49)	0.13
Adjusted RR[d] (95% CI)	1.0 (referent)	1.31 (0.74, 2.33)	2.09 (1.17, 3.72)	1.46 (0.79, 2.72)	0.46
Adjusted RR[e] (95% CI)	1.0 (referent)	1.24 (0.67, 2.29)	2.06 (1.10, 3.87)	1.44 (0.73, 2.83)	0.55
IGFBP3, (nmol/L)[f]					
Cases/controls, n	56/121	57/121	68/122	64/118	
Simple RR[b] (95% CI)	1.0 (referent)	0.98 (0.62, 1.53)	1.21 (0.78, 1.88)	1.19 (0.76, 1.86)	0.72
Adjusted RR[c] (95% CI)	1.0 (referent)	0.99 (0.63, 1.57)	1.20 (0.77, 1.87)	1.15 (0.73, 1.82)	0.76
Adjusted RR[d] (95% CI)	1.0 (referent)	1.06 (0.63, 1.79)	1.49 (0.87, 2.53)	1.24 (0.71, 2.17)	0.61
Adjusted RR[e] (95% CI)	1.0 (referent)	1.02 (0.58, 1.81)	1.31 (0.74, 2.32)	0.89 (0.48, 1.64)	0.67
IGF1:IGFBP3 molar ratio[g]					
Cases/controls, n	63/122	62/119	57/123	63/118	
Simple RR[b] (95% CI)	1.0 (referent)	1.04 (0.67, 1.59)	0.92 (0.59, 1.43)	1.06 (0.67, 1.69)	0.91
Adjusted RR[c] (95% CI)	1.0 (referent)	1.11 (0.72, 1.72)	1.20 (0.75, 1.91)	1.46 (0.89, 2.42)	0.15
Adjusted RR[d] (95% CI)	1.0 (referent)	1.24 (0.73, 2.10)	1.03 (0.57, 1.84)	1.29 (0.70, 2.37)	0.74
Adjusted RR[e] (95% CI)	1.0 (referent)	1.45 (0.82, 2.57)	1.31 (0.68, 2.52)	1.68 (0.84, 3.34)	0.36

[a] Quartile categories vary by batch. Blood samples were assayed in 3 different batches: IGF-1 ranges for quartiles 1–4 were, respectively, <12.7, 12.7–16.2, 16.3–21.8, and ≥21.9 nmol/L for batch 1; <13.3, 13.3–16.8, 16.9–22.0, ≥22.1 nmol/L for batch 2; and <17.5, 17.5–23.0, 23.1–30.3, and ≥30.4 nmol/L for batch 3.

[b] Conditional logistic regression model controlling for matching factors only.

[c] Conditional logistic regression controlled for matching factors [including only age at blood draw (as a linear continuous variable)] and plasma C-reactive protein (modeled as continuous variable with natural cubic splines).

[d] Conditional logistic regression controlling for matching factors, age at blood draw (as a linear continuous variable), menopausal status (postmenopausal vs premenopausal vs uncertain), parents' history of myocardial infarction, current PMH use, duration of PMH use for more than 5 years, history of diabetes mellitus, history of hypertension, aspirin use (none, 1–14 d/month, >14 d/month), cigarette smoking, physical activity in metabolic equivalents (MET)–hours/week, mean daily alcohol intake, and BMI (the latter 2 variables modeled as continuous variables with natural cubic splines) (final model).

[e] Conditional logistic regression controlled for factors listed in the previous footnote and also for plasma C-reactive protein and total:HDL cholesterol ratio. (The latter 2 variables were modeled as continuous variables with natural cubic splines.)

[f] Quartile categories vary by batch. Blood samples were assayed in 3 different batches: IGFBP-3 ranges for quartiles 1–4 were, respectively, <131.6, 131.6–157.2, 157.3–188.4, and ≥188.5 nmol/L for batch 1; <151.3, 151.3–184.7, 184.8–212.9, ≥213.0 nmol/L for batch 2; and <146.8, 146.8–165.3, 165.4–194.9, and ≥195.0 nmol/L for batch 3.

[g] Quartile categories vary by batch. Blood samples were assayed in 3 different batches: IGF-1:IGFBP-3 ratio ranges for quartiles 1–4 were, respectively, <0.092, 0.092–0.114, 0.115–0.147, and ≥0.148 for batch 1; <0.082, 0.082–0.103, 0.104–0.128, and ≥0.129 for batch 2; and <0.120, 0.120–0.152, 0.153–0.187, and ≥0.188 for batch 3.

lessened, however, by the use of batch-specific cutoff points for biomarkers and the use of matched conditional logistic regression models to conduct all analyses. Blood samples were collected from only 27% of the original cohort, but the overall distribution of conventional risk factors, such as age, smoking status, and BMI, are comparable among women who provided blood samples vs those who did not. Moreover, this feature is unlikely a threat to the internal validity of our findings.

In summary, our investigation did not reveal a monotonic relationship between IGF1 and IGFBP3 concentrations and subsequent risk of MI among predominantly postmenopausal women. Similar studies are needed among younger women. This study should also be replicated among a larger group of patients with diabetes mellitus.

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