The Association Between IGF-I and IGFBP-3 and Incident Diabetes in an Older Population of Men and Women in the Cardiovascular Health Study

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Context: Insulin-like growth factor-I (IGF-I) has structural and functional similarities to insulin and may play a role in glucose homeostasis, along with insulin-like growth factor binding protein-3 (IGFBP-3), which binds the majority of circulating IGF-I.

Objective: To assess whether IGF-I and IGFBP-3 are associated with a higher risk of incident diabetes in older adults.

Design: Participants in the Cardiovascular Health Study (n = 3133), a cohort of adults aged ≥65 years, were observed for 16 years (n = 3133) for the development of incident diabetes. Statistical models were fit separately for men and women because of interactions with sex (P interaction: IGF-I, 0.02; IGFBP-3, 0.009) and were adjusted for relevant covariates.

Setting: General community.

Participants: Older adults who were nondiabetic at baseline and who did not develop diabetes within the first year of follow-up.

Interventions: Not applicable.

Main Outcome Measure: Incident diabetes as measured by fasting plasma glucose (FPG) ≥126 mg/dL, non-FPG ≥200 mg/dL, use of pharmacological treatment of diabetes, or existence of two or more inpatient or three or more outpatient or (at least one inpatient and at least one outpatient) Centers for Medicare & Medicaid Services claims with the diagnostic International Classification of Diseases, Ninth Revision, Clinical Modification code of 250.xx.

Results: In women, higher IGFBP-3 (hazard ratio tertile 3 vs tertile 1 = 2.30; 95% confidence interval, 1.55 to 3.40; P trend < 0.0001) was significantly associated with incident diabetes. Total IGF-I was not significantly associated with incident diabetes. In men, neither IGF-I nor IGFBP-3 was significantly associated with incident diabetes.

Conclusions: We confirmed a previously reported association between circulating IGFBP-3 and diabetes risk in the older adult population, establishing that this association is present among women but could not be shown to be associated in men.

The growth hormone (GH)–insulin-like growth factor (IGF) axis is an evolutionarily conserved axis thought to regulate carbohydrate metabolism (1). Insulin-like growth factor-I (IGF-I), the primary mediator of the glucose regulatory function of this axis, circulates in a ternary complex along with an acid labile subunit and one of six IGF binding proteins (2, 3). Studies suggest that some of these binding proteins, particularly insulin-like growth factor binding protein-3 (IGFBP-3), may independently regulate glucose homeostasis as well (4, 5).

Although IGF-I and its binding proteins may plausibly be involved in normal carbohydrate metabolism, the relationship between IGF proteins and incident diabetes is not completely understood. GH stimulates the hepatic release of IGF-I, a protein that is structurally similar to insulin and promotes glucose uptake in peripheral tissues (6–8). Interactions of IGF-I with its binding proteins may modulate its biological activity (9). IGFBP-3 bound IGF-I accounts for 90% to 95% of the IGF-I in the blood (10).

Previous epidemiological studies on the relationship between IGF proteins and incident diabetes report conflicting findings (11–19). In the Nurses' Health Study and in the European Prospective Investigation Into Cancer and Nutrition Potsdam Study, total IGF-I levels were not associated with incident diabetes, whereas in an analysis including data from the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment study and the Study of Health in Pomerania, total IGF-I had a *U*-shaped relationship with incident diabetes (14, 18, 19). These studies did not adequately control for all known confounders, did not evaluate interactions with sex, and did not adjust for IGFBP-3 in models of IGF-I and incident diabetes.

This study examines the relationship between total IGF-I and IGFBP-3 in the risk of diabetes by using data from the Cardiovascular Health Study (CHS), a cohort of community-dwelling older adults aged ≥65 years.

Materials and Methods

Setting and participants

The CHS is a population-based, prospective longitudinal study of 5201 community-dwelling adults aged ≥65 years who were recruited in 1989 and 1990. An additional 687 people, most of whom were African Americans, were recruited in 1992 and 1993 (20). Participants were identified from Medicare eligibility lists at four US locations (Forsyth County, North Carolina; Sacramento County, California; Washington County,

Maryland; and Pittsburgh, Pennsylvania). Participants were recruited into the CHS if they were not receiving active treatment of cancer, were expected to remain in the study area for 3 years after recruitment, and were able to give informed consent without a proxy. Standardized examinations, blood draws, and questionnaires were administered annually through 1999, after which information on health status and key disease risk factors was updated through semiannual phone interviews. In 2006, the surviving participants were invited for another study clinic examination.

Laboratory measurements

In accordance with standard procedures, fasting blood samples and a second blood sample obtained 2 hours after ingestion of a 75-g glucose load were collected, frozen on site, and deposited at −70°C (21). Levels of IGF-I and IGFBP-3 were measured in stored fasting blood samples from the 1993 to 1994 CHS clinic visit. IGF-I levels were measured with enzyme-linked immunosorbent assay methods, and IGFBP-3 levels were measured with chemiluminescence assays (Immunodiagnostic Systems Ltd, Boldon Business Park, Boldon, Tyne & Wear, England). A randomly selected sample of 501 patients at the 1993 to 1994 CHS examination underwent previous measurements of IGF-I performed with enzyme-linked immunosorbent assay methods (Diagnostics Systems Laboratory, Webster, TX). We found a high correlation (Pearson's $r = 0.93$) between the Immunodiagnostic Systems Ltd and Diagnostics Systems Laboratory measurements in a study involving split-sample measurements among 1158 samples. Thus, these additional observations were incorporated in the analysis after proper calibration. Details of this calibration procedure are reported elsewhere (22). The assay coefficient of variation was 3% to 14% for IGF-I and IGFBP-3. Standard methods were used to measure glucose, insulin, total cholesterol, and C-reactive protein (CRP) at the CHS Central Laboratory (21).

Clinical variables

Diabetes status was determined from data collected during CHS study contacts and clinical encounter data from the Centers for Medicare & Medicaid Services (CMS). Of all CHS participants, 77% had available data from CMS during the 1993 to 1994 baseline. The other 23% either were not enrolled in Medicare Part B coverage or did not have any clinic visits during the baseline year. In CHS, fasting plasma glucose (FPG) was measured approximately every 2 years from enrollment until 1999 and then again in 2006. Use of diabetes medications was ascertained annually *via* a medication inventory (20, 21). Diabetes was defined in our analyses as having an FPG ≥126 mg/dL, nonfasting plasma glucose ≥200 mg/dL, use of pharmacological treatment of diabetes, or existence of two or more inpatient or three or more outpatient (at least 1 inpatient and at least 1 outpatient) CMS claims during a 2-year time period that included a diagnostic International Classification of Diseases, Ninth Revision, Clinical Modification code of 250.xx at any position in the medical claim.

Other covariates were obtained from CHS study examinations including body mass index (BMI), total cholesterol (mg/dL), smoking status (never vs ever vs current), hypertension (normal vs prehypertensive vs hypertensive), alcohol consumption (number of drinks per week), leisure time physical activity (kcal/wk) (23), CRP (mg/dL), fasting insulin (IU/mL), and adiponectin (mg/L).

Statistical analysis

The 1993 to 1994 study visit was established as the baseline for analysis, and follow-up of study participants continued until 2009 to 2010. Participants were included in the current analyses if they had either IGF-I or IGFBP-3 measure available and had diabetes status follow-up either through CHS data alone or through CHS data supplemented by CMS data. Participants were excluded if they had prevalent diabetes at baseline or developed diabetes within the first year after the baseline year. A total of 5055 patients attended the 1993 to 1994 visit; 567 of them had unknown diabetes status, 856 had prevalent diabetes, and 21 lacked diabetes follow-up data and were all excluded. An additional 133 people who developed diabetes in the first year were excluded from the primary analysis but were included for sensitivity analysis. Of the 3479 people remaining, 230 did not have IGF measures available and 116 were missing at least one of the confounding variables included in the study. After all exclusions, 3133 people remained for analysis.

The population at risk for diabetes was defined as FPG <126 mg/dL during the 1992 to 1993 clinic visit and no reported use of diabetes medication or record of diabetes diagnosis in CMS data during the 1993 to 1994 study visit. Characteristics of study participants in the baseline years were summarized *via* descriptive statistics. In addition, Pearson correlations were used to assess bivariate relationships between each biomarker and covariates that were continuous variables.

Cox proportional hazards regression models, analyzed separately for men and women, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationship between IGF and IGFBP-3 biomarkers and incident diabetes. Both biomarkers were analyzed in tertiles, with the lowest tertile as reference group. P values for trend were determined by modeling the median value in each tertile as a continuous variable to minimize the effects of extreme values. Covariates in the models were determined a priori based on previous studies and were added sequentially into the model to assess confounding effects (14). The final, fully adjusted models included covariates for age, sex, race, BMI, smoking status, alcohol consumption, cholesterol, hypertension, fasting insulin, adiponectin, CRP, and physical activity. Whereas most covariates were measured contemporaneous with the main risk factors of interest, others were from the previous annual visit if they were unavailable at the baseline study year.

Because of the strong correlation between IGF-I and IGFBP-3 levels, the Cox model for IGF-I was adjusted additionally for IGFBP-3 levels, and the model for IGFBP-3 was adjusted for IGF-I levels. Multivariable models for women also included adjustment for use of hormone replacement therapy (current vs none). In the final adjusted models, interactions were formally tested with binary interaction terms, defined as above or below sex-specific medians for age, BMI, and fasting insulin levels. The proportional hazards assumption implicit in Cox models was formally tested *via* Schoenfeld and scaled Schoenfeld residuals and graphically with log-log plots.

Sensitivity analyses were conducted to assess whether similar results were obtained if diabetes cases were identified using only CHS-measured glucose levels and medication use, without inclusion of CMS claim data. Analyses were repeated after inclusion of participants who developed diabetes within the first year after baseline and also after exclusion of those with FPG between 100 mg/dL and 125 mg/dL. All analyses were performed in Stata Version 12.1 (StataCorp LP, College Station, TX).

Results

Baseline characteristics

During the baseline year (1993 to 1994 clinic visits), characteristics were similar between the 1254 men and 1879 women included in the study. Mean age was 75 ± 4.9 years, 15% were black, and 16% of the women were currently using hormone replacement therapy (Table 1). Baseline IGFBP-3 levels were significantly higher in those who had prediabetes than in those who were normoglycemic, for both men ($P = 0.01$) and women ($P < 0.0001$) (Supplemental Table 1). Among the women, IGF-I levels were significantly higher in the prediabetic group than in normoglycemic groups ($P = 0.001$), whereas there was no difference in IGF-I levels in men ($P = 0.28$).

Bivariate relationships with IGF-I and IGFBP-3

IGF-I levels were inversely associated with age, more so in men than in women. IGF-I was positively associated with total cholesterol and FPG levels in women (Table 2). In both men and women, IGFBP-3 had a highly significant inverse association with age and adiponectin and a strong positive association with cholesterol levels. In women, IGF-I and IGFBP-3 were positively associated with fasting and 2-hour measures of glucose and insulin levels ($r = 0.08$ to 0.15), whereas men displayed weaker or absent associations of IGF-I and IGFBP-3 with glycemic traits.

Associations with diabetes risk

During a median 10.6 years of follow-up, 452 incident diabetes cases (men, n = 178; women, n = 274) occurred among 3133 patients studied from baseline.

Associations between IGF-I, IGFBP-3, and incident diabetes varied significantly by sex (P interaction: IGF-I, 0.02; IGFBP-3, 0.009). In women, total IGF-I was not significantly associated with risk of diabetes (Table 3). After adjustment for age, race, BMI, smoking, alcohol, cholesterol, hypertension, CRP, physical activity, fasting insulin, adiponectin, and total IGF-I levels, participants in the highest IGFBP-3 tertile (T3) had an approximate twofold increase in risk of diabetes when compared with those in the lowest tertile (T1) ($HR_{T3 \text{ vs } T1} = 2.30$; 95% CI, 1.55 to 3.40; P trend < 0.0001).

Table 1. Baseline Characteristics of CHS Participants

Characteristic	1993–1994	
	Women (n = 1879), Mean (SD)	Men (n = 1254), Mean (SD)
Demographics		
Age, y	75.3 (4.9)	75.9 (5.2)
Black race, n (%)	272 (14.5)	152 (12.1)
Anthropometrics		
BMI, kg/m²	26.6 (5.0)[a]	26.5 (3.6)[a]
Cardiovascular		
Systolic BP, mm Hg	134.6 (20.6)	132.3 (18.8)
Diastolic BP, mm Hg	70.0 (10.8)	71.4 (10.8)
Hypertension, n (%)	823 (43.8)	473 (37.7)
Cholesterol, mg/dL	209.0 (34.0)	188.0 (33.3)
Inflammation		
CRP, mg/L	5.2 (9.4)[a]	4.1 (7.1)[a]
Glucose metabolism		
FPG, mg/dL	96.9 (9.5)[a]	98.8 (9.5)[a]
2-H glucose, mg/dL	137.5 (44.8)[b]	127.9 (41.3)[b]
Fasting insulin, IU/mL	14.4 (6.3)[a]	14.4 (6.2)[a]
2-H insulin, IU/mL	85.2 (63.0)[b]	73.7 (52.7)[b]
Adiponectin, mg/L	16.2 (7.9)	11.5 (5.9)
Behaviors		
Physical act, kcal/wk	1321 (1603)[a]	1885 (1980)[a]
Smoking, n (%)	175 (9.3)	106 (8.5)
Alcohol, drinks/wk	1.6 (4.3)	3.5 (7.0)
Medication		
Hormone therapy, n (%)	299 (15.9)	n/a
IGF biomarkers		
Total IGF-I, µg/L	92.7 (30.7)	106.5 (34.2)
IGFBP-3, µg/L	3734 (843)	3398 (804)

Variables were log-transformed.

Abbreviations: BP, blood pressure; n/a, not applicable; SD, standard deviation.

[a]Values reported are extracted from data collected during the 1992 to 1993 visits. For BMI, height was measured during the 1992 to 1993 visits.

[b]Oral glucose tolerance tests were not performed at the 1993 to 1994 visits. Thus, values reported are means (SD) from 1996 to 1997 visits.

In men, levels of IGF-I and IGFBP-3 were not significantly associated with incident diabetes in fully adjusted models (Table 4).

Sensitivity analyses

In an analysis that limited ascertainment of diabetes to medications and glucose measurements, associations between IGF-I and IGFBP-3 with incident diabetes were generally consistent with the results reported. However, the power of this analysis was much lower because numerous diabetes cases were identified from CMS data. In addition, the strength of the association was lower. Inclusion of those who developed diabetes in the first year resulted in slightly weaker associations between IGF biomarkers and ghrelin with incident diabetes. Additional subgroup analysis in normoglycemic patients and those with prediabetes at baseline showed results with

similar direction of associations, although with wider CIs and larger P values, with the association between IGFBP-3 and incident diabetes reaching statistical significance in women (P = 0.03; Supplemental Tables 2–6). Among the women, exclusion of 299 participants who were receiving estrogen and progestin therapy did not alter the outcomes (IGF-I: $HR_{T3 \text{ vs } T1}$ = 0.85; CI, 0.56 to 1.30; P value for trend = 0.46; IGFBP-3: $HR_{T3 \text{ vs } T1}$ = 1.87; 95% CI, 1.22 to 2.87; P value for trend = 0.003) (Supplemental Table 7).

Discussion

In this study, we evaluated the association between circulating levels of IGF-I and IGFBP-3 and the risk of incident diabetes in a large prospective cohort of older men and women. Sexual dimorphism of the GH–IGF axis has been observed in animal models and human studies, which show different effects of IGF mutations and IGF protein levels between men and women with regard to associations with lifespan, body composition, and bone aging (24–29). Our results were consistent with these previously published data, which varied by sex. Among women, higher levels of IGFBP-3 were associated with a higher risk of incident diabetes. In men, IGF-I and IGFBP-3 had no statistically significant associations with diabetes risk. Our findings confirm and highlight long-known sex-related differences in animal models with respect to IGFs, glucose metabolism, and diabetes and support the hypothesis that IGF proteins may be biomarkers for diabetes risk (30).

High IGFBP-3 levels had a strong association with the higher risk of incident diabetes in women, even after additional adjustment for IGF-I levels and an array of potential confounders. Although IGFBP-3 binds 90% to 95% of circulating IGF-I and may modify diabetes risk by modifying IGF-I activity, IGF-I-independent effects of IGFBP-3 on glucose metabolism have also been reported. IGFBP-3 binds to nuclear receptors (retinoid X receptor-α, peroxisome proliferator-activated receptor-γ), which play a role in glucose and lipid metabolism (31, 32). In transgenic mouse models overexpressing IGFBP-3, circulating IGFBP-3 levels are five to eight times higher than in wild-type mice, and these mice have numerous metabolic derangements characteristic of type 2 diabetes (33). Evidence from *in vivo* animal models may not fully represent the biology of IGFBP-3 in humans. However, our findings are consistent not only with these mechanistic observations but also with previous epidemiological studies from the Nurses' Health Study (14). Unlike the previous study, which was limited to women, our report not only was able to confirm this previously reported association but also showed that the association was specific to women. Another study, the European

Table 2. Correlations Between IGF Variables and Covariates

	Total IGF-I		IGFBP-3	
	Women	**Men**	**Women**	**Men**
Age	−0.06[d]	−0.17[e]	−0.14[e]	−0.23[e]
BMI[a]	0.05[c]	0.05	0.04	0.09[e]
Systolic BP	−0.03	−0.01	−0.03	0.03
Diastolic BP	0.03	0.04	0.01	0.09[e]
Cholesterol	0.1[e]	0.06[c]	0.21[e]	0.22[e]
FPG[a]	0.11[e]	0.01	0.15[e]	0.06[e]
2-H glucose[b]	0.08[d]	0.04	0.14[e]	0.05
Fasting insulin[a]	0.13[e]	0.04	0.13[e]	0.04
2-H insulin[b]	0.13[e]	0.1[d]	0.15[e]	0.09[d]
Adiponectin	−0.05[c]	−0.13[e]	−0.11[e]	−0.15[e]
Physical activity, kcal/wk[a]	−0.02	0.02	0.01	0.05
Alcohol, drinks/wk	−0.03	−0.04	0.07[d]	0.08[e]
CRP[a]	−0.06[c]	−0.01	0.01	−0.03

Variables were log-transformed. Physical activity was measured in kilocalories per week, and alcohol was measured as number of alcoholic beverages per week.

Abbreviation: BP, blood pressure.

[a]Values reported are extracted from data collected during the 1992 to 1993 visits. For BMI, height was measured at the 1992 to 1993 visits.

[b]For correlations with total IGF-I and IGFBP-3, measures from 1996 to 1997 visits were used because oral glucose tolerance tests were not performed at the 1993 to 1994 visits.

[c]$P < 0.05$.

[d]$P < 0.01$.

[e]$P < 0.0001$.

Prospective Investigation Into Cancer and Nutrition Potsdam Study, did not demonstrate an interaction with sex; however, that a study of middle-aged adults, a fact that may yield different risk profiles given the age-related changes in IGFBP-3 levels (18). Thus, it remains plausible that high levels of IGFBP-3 may be useful to identify older women at increased risk for diabetes who may benefit from preventive measures.

Levels of IGF-I were not significantly associated with incident diabetes in either men or women. Recent studies

in the CHS have shown that IGFBP-1 and ghrelin levels both predict major health events such as stroke, heart failure, and myocardial infarction, as well as death in older adults (34). Given the established relationships between IGF axis proteins and adverse health outcomes, one would expect an association between total IGF-I and incident diabetes. However, total IGF-I may not reflect the biologically active subfraction, and thus variations in total IGF-I may not contain information about derangements in glucose metabolism. Data from animal studies suggest that overexpression of IGF-I is associated with moderate protection from diabetes (35). Findings from epidemiological studies have been conflicting. A functional polymorphism in the promoter region of the IGF-I gene is associated with lower IGF-I levels and a 70% higher risk of diabetes (17); however, a recent study failed to confirm this finding (11). Another study reported an association between low total IGF-I and diabetes risk but only in those with IGFBP-1 below median levels (15). Similarly, data from the Nurses' Health Study reported an association of high free IGF-I with diabetes risk in women with insulin levels below the median but low IGFBP-1 with diabetes risk in women with insulin levels above the median (14). Lewitt *et al.* (12) reported a positive association with incident diabetes in women, although these findings were not adjusted for confounders. One study reported a *U*-shaped relationship between IGF-I and risk of diabetes, but levels of IGFBP-3 were not assessed (19); thus, models were not adjusted for IGFBP-3 levels. Adjusting for IGFBPs, especially IGFBP-3, which sequesters the majority of IGF-I, is critical in the analysis of IGF-I and diabetes risk to identify independent effects of IGF-I. In the Nurses' Health Study, high total IGF-I was positively associated with diabetes risk in a multivariate regression model that excluded IGFBPs; however, addition of IGFBPs into the model showed that low IGF-I levels predicted diabetes, although the associations did not reach statistical significance (14). In our

Table 3. HR (95% CI) for Incident Diabetes by Tertile of IGF Proteins in Women (n = 1879)

	HR (95% CI)			
	Tertile 1 (n = 627)	**Tertile 2 (n = 626)**	**Tertile 3 (n = 626)**	**P (trend)**
Total IGF-I, μg/L	26.5–77.4	77.4–101.3	101.3–281	
Subjects, cases/total	79/627	87/626	102/626	
Adjusted for age, race, and BMI	Reference	1.04 (0.77–1.41)	1.28 (0.95–1.72)	0.09
Multivariate adjusted	Reference	0.80 (0.57–1.12)	0.74 (0.50–1.09)	0.171
IGFBP-3, μg/L	1425–3357	3358–4077	4078–6841	
Subjects, cases/total	64/627	82/626	122/626	
Adjusted for age, race, and BMI	Reference	1.30 (0.93–1.80)	1.94 (1.43–2.64)	0.0001
Multivariate adjusted	Reference	1.52 (1.07–2.16)	2.30 (1.55–3.40)	0.0001

Multivariate adjusted: age, race, BMI, smoking, alcohol, cholesterol, hypertension, CRP, physical activity, adiponectin, and fasting insulin. For IGF-I, multivariate-adjusted models adjusted additionally for IGFBP-3 levels; for IGFBP-3, multivariate-adjusted models adjusted additionally for IGF-I levels.

Table 4.   HR (95% CI) for Incident Diabetes by Tertile of IGF Proteins in Men (n = 1254)

| | HR (95% CI) | | | |
	Tertile 1 (n = 418)	Tertile 2 (n = 418)	Tertile 3 (n = 418)	P (trend)
Total IGF-I, μg/L	24.9–89.6	89.7–116.4	116.5–412.4	
Subjects, cases/total	62/418	55/418	60/418	
Adjusted for age, race, and BMI	Reference	0.81 (0.56–1.17)	0.85 (0.59–1.22)	0.418
Multivariate adjusted	Reference	0.78 (0.52–1.17)	0.78 (0.49–1.25)	0.348
IGFBP-3, μg/L	1235–3042	3043–3727	3730–7633	
Subjects, cases/total	54/418	62/420	61/416	
Adjusted for age, race, and BMI	Reference	1.06 (0.74–1.53)	0.95 (0.65–1.38)	0.763
Multivariate adjusted	Reference	1.14 (0.76–1.70)	1.06 (0.66–1.71)	0.821

Multivariate adjusted: age, race, BMI, smoking, alcohol, cholesterol, hypertension, CRP, physical activity, adiponectin, and fasting insulin. For IGF-I, multivariate-adjusted models adjusted additionally for IGFBP-3 levels; for IGFBP-3, multivariate-adjusted models adjusted additionally for IGF-I levels.

analyses, total IGF-I was not significantly associated with incident diabetes in either men and women; however, it should be noted that addition of IGFBP-3 into the model did change the direction of the association, even if the P values were not statistically significant. The reasons for the inconsistencies reported by IGF studies are unknown, and additional sex-stratified studies that control for confounders and IGFBPs are needed. Given the age-related differences in IGF protein levels, extrapolating results from middle-aged adults to older populations should be done cautiously.

Our analyses adjusted for several confounders of the relationship between IGF proteins and incident diabetes; however, we cannot eliminate the effects of residual confounders that have not been identified. In addition, subgroup analyses in only older adults who were normoglycemic and those with prediabetes at baseline showed that IGFBP-3 was directly associated with incident diabetes; however, this association reached statistical significance only in the prediabetes group. Possibly, our study was not powered to detect differences in risk in the normoglycemic subgroup. Our study overcomes limitations of many similar previous studies that lacked assessment of multiple confounders, used self-report without repeated glucose measurements to ascertain diabetic status, and lacked sex-specific analyses. Our study is one of the largest to date in older adults, but it is unknown whether results will be the same in younger adults. Although we showed that associations were sex-specific, women in CHS were uniformly postmenopausal, and it is unknown whether menopausal status or endogenous sex hormone levels may influence the associations. Another strength was the use of multiple sources to identify diabetes cases, including fasting and nonfasting glucose measures, use of diabetes medication, and administrative codes, which are particularly important for frail older adults least likely to attend study visits.

Conclusions

In conclusion, circulating levels of IGFBP-3 are associated with risk of diabetes in women but could not be shown to be associated in men. These findings may be informative for determining which patient populations will benefit from diabetes prevention programs.

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