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A prospective study of low fasting glucose with cardiovascular disease events and all-cause mortality: The Women's Health Initiative

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ABSTRACT

Background. While there is increasing recognition of the risks associated with hypoglycemia in patients with diabetes, few studies have investigated incident cause-specific cardiovascular outcomes with regard to low fasting glucose in the general population.

Objective. We hypothesized that low fasting glucose would be associated with cardiovascular disease risk and all-cause mortality in postmenopausal women.

Methods. To test our hypothesis, we used both continuous incidence rates and Cox proportional hazards models in 17,287 participants from the Women's Health Initiative with fasting glucose measured at baseline. Participants were separated into groups based on fasting glucose level: low (<80 mg/dL), normal/reference (80–99 mg/dL), impaired (100–125 mg/dL), and diabetic (≥126 mg/dL).

Results. Participants were free of cardiovascular disease at enrollment, had mean age of 62 years, and were 52% Caucasian, 24% African American, 8% Asian, and 12% Hispanic. Median follow-up was 15 years. Graphs of continuous incidence rates compared to fasting glucose distribution exhibited evidence of a weak J-shaped association with heart failure and mortality that was predominantly due to participants with treated diabetes. Impaired and diabetic fasting glucose were positively associated with all outcomes. Associations for low fasting glucose differed, with coronary heart disease (HR = 0.64 (0.42, 0.98)) significantly inverse; stroke (0.73 (0.48, 1.13)), combined cardiovascular disease (0.91 (0.73, 1.14)), and all-cause mortality (0.97 (0.79, 1.20)) null or inverse and not significant; and heart failure (1.27 (0.80, 2.02)) positive and not significant.

Conclusions. Fasting glucose at the upper range, but not the lower range, was significantly associated with incident cardiovascular disease and all-cause mortality.

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1. Introduction

In spite of the wealth of literature on the health effects of glycemic levels and diabetes, little evidence exists for the health effects of low blood sugar outside of the context of clinical hypoglycemia. It is well-recognized that elevated fasting glucose both in the diabetic range (≥126 mg/dL), as well as in the impaired or "pre-diabetes" range (100–125 mg/dL) confers increased cardiometabolic risk [1]. At the other end of the spectrum, subclinical hypoglycemia (<80 mg/dL) could also be indicative of metabolic dysregulation. Individuals with fasting glucose below or in the lower range of normal might have difficulty maintaining stable glucose levels, either through dysfunctional counter-regulatory mechanisms or other co-morbidities that may increase their risk for cardiovascular diseases and early mortality.

There is increasing concern about the relationship between low fasting glucose and the combined outcomes of cardiovascular disease (CVD) or all-cause mortality [2–4]. This concern is further supported by studies showing a J-shaped relationship for hemoglobin A1c (HbA1c) with cardiovascular disease and mortality [5–7], as well as by evidence from the ACCORD Trial showing specifically that intensive therapy for glycemic control in patients with diabetes is associated with increased mortality [8]. Despite this concern, only a few studies have investigated incident cardiovascular disease or cause-specific cardiovascular outcomes with regard to low fasting glucose in the general population [2–4,9,10]. To our knowledge, there have also been no studies that determined if these more specific relationships differ by race.

We hypothesized that participants in the Women's Health Initiative (WHI) with low fasting glucose would be at increased risk of incident CVD and all-cause mortality compared to women with fasting glucose in the normal range. Based on prior work by Park et al., the meta-analysis by The Emerging Risk Factors Collaboration, and the results of the ACCORD Trial [3,4,11], we further hypothesized that these associations would be stronger in those younger than 70 years compared to older individuals. Similarly, we hypothesized a stronger relationship in those receiving treatment for type 2 diabetes, based on the known hypoglycemic risk of glucose lowering medications and the results of the ACCORD Trial [8]. Finally, to investigate these relationships in different racial groups, we hypothesized that there would be significant heterogeneity by race.

2. Methods

2.1. Study Population

The Women's Health Initiative cohort includes 161,808 postmenopausal women age 50–79 who enrolled in one or more of the WHI Clinical Trials or the Observational Study between 1993 and 1998 [12]. This study includes a stratified sample of participants from the WHI that had fasting glucose measured at baseline and were free of CVD at enrollment (n = 17,287). Fasting glucose measurements are available from a stratified random sample of WHI participants from the following WHI components: 8.6% of participants in the hormone trials, 1% of the observational study, and 4.5% of the Diet Modification Trial, as well as 1584 cases of treated type 2 diabetes and 2198 controls from an ancillary case–control study [13]. Minorities were specifically oversampled to approximate distributions in the general population [14]. The WHI protocol was approved by institutional review boards at all participating study sites and all participants provided written informed consent.

2.2. Study Measures

Fasting serum glucose was measured using the hexokinase method on the Hitachi 747 [15]. For our primary analysis, we grouped participants according to fasting glucose level into four categories: low glucose (<80 mg/dL), normal glucose (80–99 mg/dL), impaired fasting glucose (100–125 mg/dL), and diabetes (≥126 mg/dL or diabetes diagnosis or diabetes medication use).

Participants were followed for incident coronary heart disease, stroke, heart failure, and all-cause mortality through September 30, 2014 and these events were adjudicated by local and central physician adjudicators [16]. For this study, specific CVD events were analyzed separately and as a combined CVD outcome. Some participants were censored because they did not consent to the extension studies [14].

Socioeconomic factors, smoking status, medical history, and physical activity were self-reported at baseline. Other covariates including BMI and blood pressure were measured at baseline using a standardized assessment protocol and cholesterol was assayed from fasting blood. Full documentation on data collection and variable definitions can be found on the WHI website: https://www.whi.org/researchers/data/Pages/Available%20Data.aspx.

2.3. Statistical Analysis

We calculated the means and standard deviations of baseline characteristics by glucose category and used non-parametric tests for trend to determine if there were significant differences across the levels of fasting glucose.

We investigated the continuous associations of fasting glucose with CVD events and all-cause mortality incidence rates using Poisson regression with linear spline terms and 3 knots at the cut-points for the fasting glucose categories. We calculated Kaplan–Meier survival curves and 95% confidence bands for CVD events and all-cause mortality by fasting glucose categories. We then used Cox proportional hazards models to determine hazard ratios and 95% confidence intervals for CVD events and all-cause mortality by fasting glucose categories using normal glucose as the reference. We included as confounders baseline demographic and socioeconomic factors of age, race, income, and education, as well as clinical CVD risk factors of total cholesterol, blood pressure, smoking, and body mass index (BMI). We also adjusted for diabetes treatment to account for confounding by indication.

Based on our a priori hypotheses that these associations would be stronger in those younger than 70 and that they would differ by race, we formally tested for differences by age and race. Finally, we performed a number of subgroup

analyses to determine whether our results were sensitive to cancer diagnosis, thyroid conditions, diabetes medication use, hormone replacement therapy, smoking status, family history of CVD, and reverse causality (by excluding the first 5 years of follow up). Subgroup analysis by diabetes medication use also accounted for any oversampling of participants with diabetes from the case–control study. All analyses were performed using STATA 11 [17].

3. Results

The study population of 17,287 participants had a mean age of 62 years at baseline (range 50 to 79 years) and was 52% Caucasian, 24% African American, 8% Asian, and 12% Hispanic. Participants with low fasting glucose at baseline were more likely to be younger, have income over $35,000 a year, have lower BMI, total cholesterol, and blood pressure, and have higher HDL cholesterol (Table 1). They were also more likely to have used hormone therapy (HT) and less likely to have liver disease. Participants with higher baseline fasting glucose had a higher incidence of combined CVD at follow-up, with the possible exception of low fasting glucose and heart failure, and had higher mortality. Participants who self-reported as African American, Hispanic, or Native American were more likely to be in the higher fasting glucose categories, while Caucasian participants were more likely to be in the low fasting glucose category. The mean follow-up was 13.6 years (range: <1 to 19.5 years).

Fig. 1 shows the continuous incidence rates of CVD events and mortality across the fasting glucose distribution. For coronary heart disease and stroke the relationships with fasting glucose appeared monotonic. For heart failure, combined CVD, and all-cause mortality a slight J-shape was visible, although the confidence intervals at the lower range of fasting glucose were very wide (Fig. 1A). This J-shape was no longer apparent and the curve in the upper range was attenuated when participants treated with diabetes medications were excluded (Fig. 1B). Supplemental Fig. 1 shows separation of the survival curves for fasting glucose in the normal, impaired, and diabetic ranges across all CVD events and mortality, but overlapping curves and confidence intervals for low and normal fasting glucose. For heart failure only, survival was consistently, but non-significantly, lower for fasting glucose in the low category compared to normal.

Cox proportional survival models revealed a significantly increased risk for all CVD events and all-cause mortality in participants with impaired and high fasting glucose compared to those with fasting glucose in the normal range (Table 2).

Table 1 – Characteristics (mean (SD) of 17,287 adults aged 45–84 in WHI by fasting glucose category.

Characteristic	Low fasting glucose (<80 mg/dL)	Normal fasting glucose (80 to 99 mg/dL)	Impaired fasting glucose (100 to 125 mg/dL)	Diabetes (≥126 mg/dL or medication)	p-value for trend *
n	942	10,333	3901	2111	–
Fasting glucose (mg/dL)	75.4 (1.72)	90.2 (0.05)	107.7 (0.11)	158.8 (1.13)	–
Age (years)	61.8 (0.24)	62.3 (0.07)	62.8 (0.11)	62.9 (0.15)	<0.001
Race					<0.001
Caucasian	56.9 (1.61)	56.9 (0.49)	48.3 (0.80)	33.3 (1.03)	
African American	24.4 (1.40)	20.3 (0.40)	24.4 (0.69)	39.0 (1.06)	
Hispanic	10.9 (1.02)	11.5 (0.31)	13.4 (0.55)	15.3 (0.78)	
Asian	4.46 (0.67)	7.40 (0.26)	9.54 (0.47)	7.48 (0.57)	
Native American	1.59 (0.41)	2.07 (0.14)	2.33 (0.24)	3.41 (0.40)	
Education (% ≥ high school)	91.3 (0.92)	92.3 (0.26)	91.7 (0.44)	87.1 (0.73)	<0.001
Income (% ≥ $35,000)	60.2 (1.62)	56.5 (0.50)	51.6 (0.81)	43.2 (1.09)	<0.001
Current Smoking (%)	16.0 (1.77)	17.0 (0.55)	18.6 (0.92)	17.7 (1.22)	0.22
BMI (kg/m^2)	26.8 (0.18)	28.1 (0.06)	30.7 (0.10)	32.5 (0.14)	<0.001
Cholesterol (mg/dL)	212.9 (1.17)	218.1 (0.36)	218.2 (0.62)	212.4 (0.92)	<0.001
LDL (mg/dL)	123.4 (1.11)	128.2 (0.34)	130.9 (0.58)	124.9 (0.85)	0.28
HDL (mg/dL)	63.5 (0.50)	61.5 (0.15)	55.4 (0.23)	51.7 (0.28)	<0.001
Systolic BP (mmHg)	124.3 (0.55)	126.8 (0.17)	131.2 (0.28)	134.3 (0.39)	<0.001
Diastolic BP (mmHg)	75.4 (0.30)	75.7 (0.09)	77.4 (0.15)	76.7 (0.21)	<0.001
Liver disease (%)	1.80 (0.43)	2.11 (0.14)	2.31 (0.24)	3.32 (0.39)	0.005
HT use ever (%)	92.8 (2.93)	90.6 (0.85)	75.6 (1.28)	69.4 (1.69)	<0.001
Throughout follow-up					
CVD (%)	6.90 (0.83)	9.00 (0.28)	12.20 (0.52)	22.41 (0.91)	<0.001
CHD (%)	2.76 (0.53)	4.12 (0.20)	5.38 (0.36)	10.04 (0.65)	<0.001
Stroke (%)	2.34 (0.49)	3.48 (0.18)	4.28 (0.32)	6.87 (0.55)	<0.001
Heart failure (%)	2.12 (0.47)	1.71 (0.13)	3.02 (0.27)	6.87 (0.55)	<0.001
Mortality (%)	10.9 (0.31)	11.5 (0.31)	13.6 (0.55)	19.6 (0.86)	<0.001

Abbreviations: BMI (body mass index), BP (blood pressure), CVD (combined cardiovascular disease), CHD (coronary heart disease), HDL (high-density lipoprotein), HT (hormone therapy), LDL (low-density lipoprotein), SD (standard deviation).

* Cuzick non-parametric test for trend.

The hazard ratios remained significant throughout adjustment. Compared to participants with normal glucose levels, low fasting glucose was associated with nonsignificant trends toward reduced risk of coronary heart disease and stroke, but higher heart failure risk. The only significant hazard ratios were for coronary heart disease and these associations were attenuated with adjustment for cholesterol, blood pressure, body mass index, smoking, and diabetes treatment. Relative to normal glucose, low fasting glucose was not associated with combined CVD or all-cause mortality. While estimates for heart failure were higher for low fasting glucose compared to the normal range, these estimates were not significant (Table 2). Inclusion of other CVD risk factors strengthened the estimate for the low fasting glucose group, but adjustment for diabetes treatment strongly attenuated all heart failure estimates, especially for the diabetic category. Failure to see such attenuation in the low or impaired fasting glucose categories may be explained by the higher level of diabetes treatment in the highest fasting glucose category (182 participants compared to 56 in the low category and 28 in the impaired category). Additional adjustment for physical activity produced similar results (data not shown).

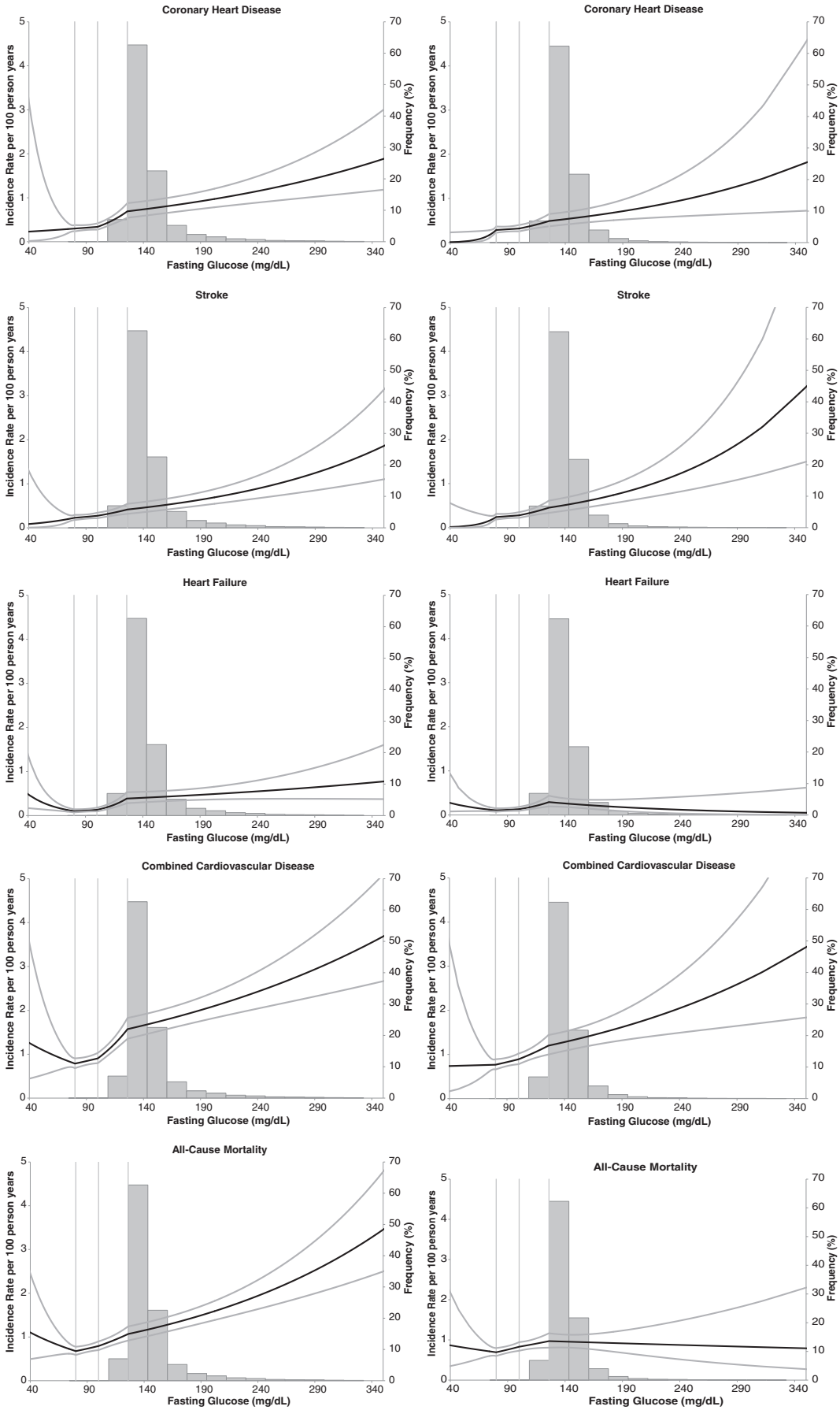
Statistically significant heterogeneity by age (<70 and ≥70 years) was observed for stroke and heart failure, but not coronary heart disease, all-cause CVD, or mortality (Table 3). For stroke, there was a significant inverse association for those <70 years of age, but a non-significant positive association for those ≥70. For heart failure, the subgroup results by age were the reverse of that for stroke. A significant overall difference by race was found only for all-cause mortality ($p = 0.044$), with higher risk associated with low glucose for those self-reporting as Hispanic/Latino compared to Caucasian. There were no overall differences by race for coronary heart disease, stroke, heart failure, and all CVD ($p = 0.44$, 0.25, 0.57, and 0.44 respectively). Event numbers in American Indian/Alaskan Native and other groups were too small for analysis. Other subgroup results were similar for all outcomes, except for several significantly different hazard ratios for heart failure (Table 3).

4. Discussion

In the Women's Health Initiative, impaired fasting glucose and glucose in the diabetic range were associated with increased risk for cardiovascular disease and all-cause mortality. Despite some minor visual evidence of J-shaped relationships between fasting glucose levels and CVD events, there were no significant associations with low fasting glucose. Results for all outcomes except heart failure were robust to multiple subgroup and sensitivity conditions. With the exception of age for heart failure and stroke and race for all-cause mortality, there was little evidence to support our hypotheses about heterogeneity. The contrast of Hispanic participants being more likely to have fasting glucose in the impaired or diabetic ranges compared to Caucasian participants, yet having a higher mortality risk associated with low fasting glucose, requires further consideration.

While other risk factors that exhibit a J-shaped association for all-cause mortality, such as body mass index, exhibit a much more linear association with cardiovascular risk, the evidence for fasting glucose exhibits a different pattern. A large meta-analysis of prospective observational studies using individual participant data by The Emerging Risk Factors Collaboration found a J-shaped association between fasting glucose and coronary heart disease risk [4]. Although studies of incident cardiovascular events are rare, several smaller studies have found similar results. Wei et al. found significant associations for low fasting glucose (<80 mg/dL) with cardiovascular and all-cause mortality in adults aged 25–64 years from the combined Aerobics Center Longitudinal and San Antonio Heart Studies [2]. Similarly, Tanne et al. found increased risk for incident stroke at both ends of the fasting glucose range in older participants with stable coronary heart disease in Israel [9]. and Park et al. found similar results for both incident coronary heart disease and stroke in the Korean Cancer Prevention Study among participants without diagnosed diabetes at baseline [3]. The study by Preiss et al. is an exception in the field, finding no significant increase in cardiovascular risk for either low (by quintiles) or impaired fasting glucose in white men from the West of Scotland Coronary Prevention Study [10]. Park et al. and The Emerging Risk Factors Collaboration also found an interaction by age in the relationship between fasting glucose and incident CVD, suggesting a stronger association in younger individuals [3,4]. Specifically, Park et al. observed a significantly higher CVD risk in women under age 55 with low glucose (<70 mg/dL) compared to older women [3]. Having found no significantly increased risk associated with low fasting glucose, our results are not consistent with the prior literature. Variations in the source population or in analysis, including the adjustment for diabetes and diabetes medication use, may explain these differences. Specifically, the attenuation of the association in the lower glucose range when we excluded participants taking diabetes medication suggests that the increased risk associated with low fasting glucose may be a result of pharmacological treatment of diabetes, consistent with the results of the ACCORD Trial [8], and not a marker of risk in the general population. Evidence about the role that sex and age play in these relationships is also lacking.

Evidence about the health risks of low fasting glucose is sparse, but recent studies offer contradictory evidence on the association between HbA1c in the lower range (below 5.0% or 31 mmol/mol) and risk for all-cause mortality [5–7,18,19]. Selvin et al. not only provide evidence for a difference in shape in the all-cause mortality relationship for HbA1c compared to fasting glucose (J-shaped and more linear, respectively) in a non-diabetic population, but also strongly suggest that HbA1c is a better indicator of cardiovascular risk [5]. While fasting glucose and HbA1c share a similar clinical purpose, the measurements differ in several ways including potentially different determinants for low values [6,20], and different distributional association with risk for cardiovascular disease and mortality [5]. HbA1c is a much more stable indicator of average glucose levels than fasting glucose. As such, a single low fasting glucose measurement in an individual may be accompanied over time by greater variation in glucose levels [21,22]. While glucose variability is associated



A. All participants

B. Participants not taking medication for diabetes

Table 2 – Cox proportional hazard ratios and 95% confidence intervals (HR (CI)) for cardiovascular disease and all-cause mortality by fasting glucose category in WHI.

Model	Fasting glucose categories			
	Low (<80 mg/dL)	Normal (80–99 mg/dL)	Impaired (100–125 mg/dL)	High/Diabetes (≥126 mg/dL)
CHD				
Model 1	0.70 (0.47, 1.04)	1.00 (REF)	**1.33 (1.13, 1.57)**	**2.83 (2.40, 3.34)**
Model 2	**0.64 (0.42, 0.98)**	1.00 (REF)	**1.38 (1.17, 1.63)**	**2.95 (2.49, 3.50)**
Model 3	0.66 (0.43, 1.02)	1.00 (REF)	**1.28 (1.07, 1.52)**	**2.63 (2.20, 3.15)**
Model 4	0.66 (0.43, 1.02)	1.00 (REF)	**1.28 (1.07, 2.58)**	**2.15 (1.53, 3.02)**
Stroke				
Model 1	0.69 (0.45, 1.06)	1.00 (REF)	**1.26 (1.05, 1.52)**	**2.33 (1.92, 2.83)**
Model 2	0.73 (0.48, 1.13)	1.00 (REF)	**1.22 (1.01, 1.47)**	**2.15 (1.76, 2.63)**
Model 3	0.71 (0.45, 1.10)	1.00 (REF)	1.14 (0.94, 1.39)	**2.03 (1.64, 2.50)**
Model 4	0.70 (0.45, 1.10)	1.00 (REF)	1.14 (0.94, 1.39)	**2.08 (1.58, 2.72)**
Heart failure				
Model 1	1.29 (0.81, 2.05)	1.00 (REF)	**1.75 (1.39, 2.21)**	**4.23 (3.39, 5.27)**
Model 2	1.27 (0.80, 2.02)	1.00 (REF)	**1.80 (1.42, 2.67)**	**4.14 (3.30, 5.21)**
Model 3	1.46 (0.91, 2.32)	1.00 (REF)	**1.47 (1.15, 1.88)**	**2.91 (2.28, 3.73)**
Model 4	1.45 (0.91, 2.31)	1.00 (REF)	**1.48 (1.16, 1.89)**	1.45 (0.95, 2.17)
All CVD				
Model 1	0.91 (0.73, 1.13)	1.00 (REF)	**1.29 (1.16, 1.43)**	**2.63 (2.36, 2.94)**
Model 2	0.91 (0.73, 1.14)	1.00 (REF)	**1.30 (1.17, 1.45)**	**2.53 (2.26, 2.83)**
Model 3	0.96 (0.77, 1.20)	1.00 (REF)	**1.18 (1.06, 1.32)**	**2.18 (1.94, 2.46)**
Model 4	0.96 (0.77, 1.20)	1.00 (REF)	**1.18 (1.06, 1.32)**	**1.57 (1.32, 1.87)**
All-cause mortality				
Model 1	1.01 (0.83, 1.23)	1.00 (REF)	**1.22 (1.10, 1.35)**	**2.01 (1.79, 2.24)**
Model 2	0.97 (0.79, 1.20)	1.00 (REF)	**1.24 (1.12, 1.37)**	**2.06 (1.83, 2.31)**
Model 3	1.01 (0.82, 1.24)	1.00 (REF)	**1.16 (1.04, 1.29)**	**1.84 (1.63, 2.08)**
Model 4	1.01 (0.81, 1.24)	1.00 (REF)	**1.16 (1.04, 1.29)**	**1.23 (1.02, 1.48)**

Model 1: Adjusted for age; model 2: model 1 + race, income, and education; model 3: model 2 + total cholesterol, blood pressure, body mass index, smoking.
Model 4: Model 3 + diabetes treatment (n = 56, 28, and 182 for treatment in low, normal, and impaired categories) **Bold indicates statistical significance at the $p < 0.05$ level.**

with chronic disease complications, including the development of CVD, in diabetic populations [23], the evidence is sparse and the association in non-diabetic groups and the general population is mostly unknown [5]. The cumulative nature of glucose exposure reflected by HbA1c compared to the immediate indication offered by fasting glucose may help explain the discrepancies between studies investigating these two glycemic markers.

Therefore, the primary limitation of this study is the inability to determine whether our findings would differ if we had been able to assess HbA1c in addition to fasting glucose. Unfortunately, HbA1c levels were not measured in the WHI cohort, so these studies will have to be conducted in other cohorts. Second, as in many other studies, fasting glucose was only measured at a single time point so we could not determine glucose variability and whether such variability was associated with incident CVD and mortality. Third, as the WHI consists only of women, we could not determine whether these relationships differ by sex. Fourth, the significant heterogeneity for heart failure, specifically by age and smoking status, may indicate that the association between low fasting glucose and this outcome varies by subgroup. The explanation for this heterogeneity is unclear. The sensitivity analysis indicates that the relationship may be weaker at older ages, suggesting that by using this postmenopausal population we are missing associations that might be significant in a younger population. Finally, this study shares the limitations common to observational studies, such as residual confounding.

This study has a number of strengths. The large number of participants with measured fasting glucose and the large number of events provided an opportunity to assess these associations separately for specific CVD event types and to determine whether these relationships were the same for CVD and for all-cause mortality. The WHI also has the benefit of racial diversity, which allows us to determine whether these relationships exhibit heterogeneity by race. The use of WHI also

Fig. 1 – Continuous incidence rates and 95% confidence bands for coronary heart disease, stroke, heart failure, combined cardiovascular disease, and all-cause mortality across the fasting glucose distribution in 17,287 WHI participants for A. All participants and B. Participants not taking medication for diabetes. Vertical gray lines indicate the cut-points for low (<80 mg/dL), normal (80–99 mg/dL), impaired (100–125 mg/dL), and diabetic (≥126 mg/dL) glucose levels.

Table 3 – Sensitivity analyses for low fasting glucose (<80 mg/dL) compare to normal glucose (80–99 mg/dL) and cardiovascular disease: hazard ratios and 95% confidence intervals.

Analytic approach	Coronary heart disease	Stroke	Heart failure	All cardiovascular disease	All-cause mortality
Primary analysis *					
# events	874	694	458	2133	2237
HR (95% CI)	**0.70 (0.47, 1.04)**	0.69 (0.45, 1.06)	1.29 (0.81, 2.05)	0.91 (0.73, 1.13)	1.01 (0.83, 1.23)
Excluding deaths in the first 5 years of follow up					
# events	816	671	416	2022	1935
HR (95% CI)	0.69 (0.46, 1.04)	0.72 (0.47, 1.11)	**1.38 (0.86, 2.19)**	0.92 (0.74, 1.15)	1.10 (0.90, 1.36)
Age < 70 years					
# events	564	506	279	1498	1416
HR (95% CI)	0.72 (0.44–1.18)	0.44 (0.23–0.83)	**1.69 (1.00–2.86)**	0.87 (0.66–1.13)	1.06 (0.83–1.36)
Age ≥ 70 years					
# events	310	188	179	635	821
HR (95% CI)	0.65 (0.33–1.28)	**1.36 (0.75–2.48)**	0.69 (0.25–1.88)	1.01 (0.68–1.48)	0.95 (0.67–1.34)
Caucasian					
# events	484	343	283	1122	1409
HR (95% CI)	0.57 (0.33–1.00)	0.96(0.59–1.56)	1.18 (0.67–2.09)	0.78 (0.57–1.05)	0.85 (0.65–1.10)
African American					
# events	236	212	122	619	471
HR (95% CI)	0.79 (0.40–1.57)	0.27 (0.07–1.09)	1.17 (0.46–2.98)	0.91 (0.60–1.38)	1.24 (0.81–1.89)
Asian/Pacific Islander					
# events	49	48	12	113	118
HR (95% CI)	1.23 (0.17–9.20)	0.90 (0.12–6.66)	6.25 (0.70–56.14)	1.93 (0.70–5.35)	1.06 (0.33–3.36)
Hispanic/Latino					
# events	73	71	34	194	165
HR (95% CI)	0.41 (0.06–3.06)	0.27 (0.04–1.97)	1.38 (0.17–11.02)	1.20 (0.62–2.30)	**1.69 (0.87–3.30)**
Not obese (BMI < 30 kg/m^2)					
# events	463	253	194	1163	1327
HR (95% CI)	0.71 (0.44–1.13)	–	**1.55 (0.93–2.59)**	0.97 (0.76–1.24)	1.01 (0.81–1.26)
Obese (BMI ≥ 30 kg/m^2)					
# events	411	441	264	970	910
HR (95% CI)	0.82 (0.38–1.74)	**0.77 (0.50–1.19)**	0.80 (0.25–2.56)	0.78 (0.47–1.31)	1.07 (0.68–1.70)
Not hyperthyroid					
# events	94	80	60	267	255
HR (95% CI)	0.87 (0.27, 2.81)	–	1.24 (0.38, 4.04)	0.74 (0.35, 1.59)	1.02 (0.54, 1.95)
Hyperthyroid					
# events	32	21	20	85	56
HR (95% CI)	1.13 (0.15, 8.69)	2.10 (0.26, 17.15)	1.20 (0.15, 9.41)	1.58 (0.56, 4.43)	0.64 (0.09, 4.76)
No cancer					
# events	817	663	420	2001	2087
HR (95% CI)	0.72 (0.48, 1.08)	0.73 (0.48, 1.13)	**1.37 (0.86, 2.18)**	0.94 (0.95, 1.17)	1.02 (0.82, 1.25)
Cancer					
# events	41	27	**30**	108	105
HR (95% CI)	0.46 (0.06, 3.15)	–	–	0.67 (0.21, 2.14)	0.71 (0.22, 2.26)
No diabetes medication					
# events	739	619	344	1827	1956
HR (95% CI)	0.70 (0.47, 1.04)	0.69 (0.45, 1.07)	**1.29 (0.81, 2.05)**	0.91 (0.73, 1.13)	1.01 (0.83, 1.24)
Diabetes medication use					
# events	135	68	114	300	274
HR (95% CI)	–	–	–	–	–
No HT					
# events	414	312	220	933	1026
HR (95% CI)	0.73 (0.41, 1.31)	0.78 (0.42, 1.44)	0.63 (0.25, 1.54)	0.82 (0.58, 1.17)	0.91 (0.67, 1.23)
HT use					
# events	433	359	230	1156	1111
HR (95% CI)	0.51 (0.27, 0.97)	0.67 (0.36, 1.22)	**2.07 (1.20, 3.58)**	0.92 (0.69, 1.24)	1.09 (0.82, 1.44)
Never smokers					
# events	453	341	183	1058	991
HR (95% CI)	0.77 (0.46, 1.30)	0.81 (0.46, 1.42)	0.57 (0.21, 1.55)	0.92 (0.68, 1.25)	0.91 (0.67, 1.25)
Ever smokers					
# events	408	348	265	1051	1207
HR (95% CI)	0.58 (0.31, 1.10)	0.58 (0.30, 1.13)	**1.97 (1.16–3.35)**	0.91 (0.66, 1.26)	1.07 (0.82,1.41)
No family history					
# events	249	228	127	670	703
HR (95% CI)	0.84 (0.45–1.55)	0.55 (0.24–1.25)	0.88 (0.35–2.18)	0.97 (0.67–1.39)	0.93 (0.66–1.33)
CVD family history					

Table 3 (*continued*)

Analytic approach	Coronary heart disease	Stroke	Heart failure	All cardiovascular disease	All-cause mortality
# events	625	466	331	1463	1534
HR (95% CI)	0.62 (0.37–1.05)	0.77 (0.47–1.28)	1.52 (0.89–2.60)	0.88 (0.67–1.16)	1.05 (0.82–1.35)

Bold for the subgroups indicates a significant difference from primary model results at $p < 0.05$ level, except for race/ethnicity where the comparator is Caucasian. Paired subgroups are mutually exclusive. For example, the cancer analysis includes only participants with a diagnosis of cancer.
Abbreviations: CVD (cardiovascular disease), CI (confidence intervals), HR (hazard ratio), HT (hormone therapy).
* Primary analysis is from the age adjusted survival model (model 1 in Table 2). Bold indicates significant difference from zero at $p < 0.05$ level.

allows us to help fill the gap in the literature about these associations specifically in postmenopausal women.

In the WHI cohort, low fasting glucose at baseline was not significantly associated with survival from specific cardiovascular disease events or all-cause mortality, except for an inverse association between low fasting glucose and coronary heart disease. While these results do not support the hypothesis that low fasting glucose is associated with increased risk for CVD and mortality, heterogeneity by age suggests that further investigation of the relationship with heart failure in younger populations is warranted.

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Author Contributions

MMC developed the hypothesis and designed the study. MMC designed the analysis and analyzed the data. All authors interpreted data for the manuscript, wrote and revised the manuscript, approved the final version for publication, and agree to be accountable for all aspects of the work.

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Disclosures

Dr. Philips wishes to disclose:

With regard to potential conflicts of interest, within the past several years, Lawrence Phillips has served on Scientific Advisory Boards for Boehringer Ingelheim and Janssen, and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, Abbvie, Vascular Pharmaceuticals, Janssen, Glaxo SmithKline, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the last several years. He is also a co-founder of a company, Diasyst, which aims to develop and commercialize diabetes management software programs.

The other authors have nothing to disclose.

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