Change in Cardiovascular Health and Incident Type 2 Diabetes and Impaired Fasting Glucose

Change in Cardiovascular Health and Incident Type 2 Diabetes and Impaired Fasting Glucose: The Whitehall II Study

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OBJECTIVE

Most previous studies on cardiovascular health (CVH) and incident type 2 diabetes (T2D) have used a single measure of CVH, and none have investigated the association with impaired fasting glucose (IFG). We examined the association between changes in CVH and incident T2D and IFG.

RESEARCH DESIGN AND METHODS

Within the Whitehall II study, CVH was examined every 5 years from 1991/93 until 2015/16. Subjects with 0–2, 3–4, and 5–6 ideal metrics of CVH from the American Heart Association were categorized as having low, moderate, or high CVH, respectively.

RESULTS

There were 6,234 participants (mean age 49.8 ± 6.0 years, 70% male) without prior cardiovascular disease and T2D, including 5,015 who were additionally free from IFG at baseline. Over a median follow-up of 24.8 (interquartile range 24.0–25.2) years, 895 and 1,703 incident cases of T2D and IFG occurred, respectively. Change in CVH between 1991/93 and 2002/04 was calculated among 4,464 participants free from CVD and T2D and among 2,795 participants additionally free from IFG. In multivariate analysis, compared with those with stable low CVH, risk of T2D was lower in those with initially high CVH (hazard ratio [HR] 0.21; 95% CI 0.09, 0.51), those who had persistently moderate CVH or changed from moderate to high CVH (moderate-moderate/high; HR 0.53; 95% CI 0.41, 0.69), low-moderate/high (HR 0.62; 95% CI 0.45, 0.86), and moderate-low (HR 0.74; 95% CI 0.56, 0.98). Results were similar for IFG, but the effect sizes were smaller.

CONCLUSIONS

Compared with stable low CVH, other patterns of change in CVH were associated with lower risk of T2D and IFG.

Diabetes affects an estimated 425 million people worldwide, and if current trends continue, ~693 million people (10% of the population) will have diabetes by 2045 (1). In addition, the prevalence of dysglycemia, or impaired fasting glucose (IFG), is increasing rapidly and projected to affect >470 million people by 2030. Of these individuals, up to 70% will develop type 2 diabetes (T2D) (1). Thus, identifying effective preventive strategies for T2D is a public health priority.

Primordial prevention (i.e., the prevention of risk factor onset) is increasingly recognized as a complimentary strategy for the prevention of cardiovascular disease

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(CVD). As such, the American Heart Association (AHA) developed a 7-item tool for primordial prevention of CVD risk factors. This tool assesses cardiovascular health (CVH) and considers diet, smoking, physical activity, BMI, blood pressure (BP), blood glucose, and cholesterol levels (2). There is accumulating evidence suggesting that higher CVH is related to lower risk of CVD (3−5), but also non-CVD outcomes such as dementia (6) and cancer (7). Given that CVD and T2D share common risk factors, including hypertension, dyslipidemia, and obesity, the concept of ideal CVH may be applicable to the prevention of T2D and IFG. Indeed, previous research has reported substantially lower risk of T2D in those with high CVH (8−11). Most (8−10) but not all previous studies (11) used a single measure of CVH; however, change in CVH has recently been related to incident CVD and mortality (12,13).

This study used several examinations of the Whitehall II Study (14) with the aim of quantifying the association between the change in CVH (main exposure) and baseline and time-dependent CVH (secondary exposure) with incident T2D (main outcome) and IFG (secondary outcome).

RESEARCH DESIGN AND METHODS

Study Participants

The Whitehall II Study is an ongoing prospective cohort study involving individuals recruited from the British Civil Service (14). At baseline, 10,308 individuals (6,895 men and 3,413 women, aged 35–55 years) were recruited, underwent a clinical examination, and completed a self-administered questionnaire. Subsequent clinical examinations involving anthropometric, cardiovascular and metabolic risk factor measures (including measures of CVH metrics), and self-administrated questionnaires occurred approximately every 5 years after baseline until 2016 (1991/93, 1997/99, 2002/04, 2007/09, 2012/13, and 2015/16). A fasting blood glucose measure was included in 1991/93, which forms the baseline for the current study. Participants with IFG, T2D, and/or CVD at baseline (1991/93) were excluded. Participant informed consent and ethical approval from the University College London Hospital Ethics Committee were obtained at each examination; the latest approval was provided by the Joint University College London/ University College London Hospital Committee on the Ethics of Human Research (Committee Alpha; reference number 85/0938).

CVH Metrics

The AHA criteria were used to define poor, intermediate, and ideal levels for each metric of CVH at each examination (2) (Supplementary Table 1). Fasting blood glucose was not included as a CVH metric in the main analysis because blood glucose is used to define T2D and IFG (4,12). However, the analysis was systematically adjusted for baseline fasting glycemia. CVH status was categorized as poor, moderate, and high in subjects with 0–2, 3–4, and 5–6 CVH metrics, respectively, at the ideal level. The number of metrics at the ideal level (range 0–6) and a continuous 12-point CVH score based on a three-level categorization of each metric (poor = 0, intermediate = 1, and ideal = 2) were also calculated.

Change in CVH From 1991/93 to 2002/04

Change in CVH between 1991/93 and 2002/04 was examined in people with 6 metrics at both time points. For those with ≥1 missing CVH metrics in 2002/04, change in CVH was estimated between 1991/93 and 1997/99. Participants were included in these analyses if they were free of incident T2D, CVD, and IFG (for the IFG analysis only) between the 1991/93 and 2002/04 examinations.

Confounders

Confounders included age, sex, ethnicity (white, nonwhite), marital status (married/cohabiting, other), socioeconomic status assessed via occupation (categories of high, intermediate, and low based on income and work status), education (lower secondary school or less, higher secondary school, tertiary, and university or higher degree), family history of T2D, and fasting glycemia measured at baseline.

T2D and IFG

T2D was defined based on a fasting blood glucose level ≥126 mg/dL, reported doctor diagnosis or treatment for T2D at each follow-up examination, or hospitalization for T2D (date of hospitalization via linkage to hospital records), as described previously (15). IFG was defined based on a fasting blood glucose level of ≥100 mg/dL and <126 mg/dL. Glucose levels after a 2-h oral glucose tolerance test (OGTT) were available from 1991/93 to 2007/09 examination rounds, whereas glycated hemoglobin (HbA_{1c}) was measured in the 2002/04 and 2007/09 examination waves only and was, therefore, considered for outcome definitions in the sensitivity analysis. Blood glucose was measured using the glucose oxidase method throughout the study, as previously described (16).

Statistical Analysis

Analysis was conducted in two separate populations (see the flowchart in Supplementary Fig. 1), including the population at risk for incident T2D (main outcome) and those at risk for IFG (secondary outcome), but using exactly the same statistical approach. Comparisons between groups (included and excluded participants) were performed using *t* tests for continuous variables and the χ^2 test for categorical variables.

Association of Baseline and Time-Varying CVH With Incident T2D/IFG

The follow-up of events started after the 1991/93 baseline examination (Supplementary Fig. 1). Baseline and time-varying CVH status, the number of ideal metrics, and the 12-point CVH score between 1991/93 and 2015/16 were used in Cox proportional hazards regression. For the time-varying analysis, incidence of T2D/IFG at each examination (1997/99, 2002/04, 2007/09, 2012/13, and 2015/16) was identified, and CVH exposure at the examination just before diagnosis was used to examine associations. In the case of missing CVH exposure, the last observation carried forward approach was used.

Change in CVH Between 1991/93 and 2002/04 and Subsequent Risk of T2D/IFG

In this analysis, the follow-up of events started after the 2002/04 examination (Supplementary Fig. 1). As a result of low numbers of participants and events in some categories of CVH change, five categories of change (instead of nine possible categories) were considered: stable low (low-low); low-moderate and low-high combined (low-moderate/high); moderate-low; moderate-moderate and moderate-high combined (moderate-moderate/high); and high-high, high-low, and high-moderate combined (initially high CVH). Kaplan-Meier curves of incident T2D/IFG across the five categories of change in CVH were compared with

the log-rank test using follow-up time as the timescale. The hazard ratio (HR) for incident T2D/IFG for each combination of CVH change was computed in Cox proportional hazards model using the stable low CVH group as the reference category. The HRs of T2D/IFG per unit of change in the number of ideal metrics and in the 12-point CVH score were also estimated.

All Cox models used age as the time scale, were stratified by year of birth (5-year intervals) to account for any birth cohort effects, and were adjusted for baseline confounders, including sex, ethnicity, education, occupation, alcohol intake, fasting glycemia, and family history of T2D at baseline. The analysis of change in the number of ideal CVH metrics or in the 12-point CVH score was further adjusted for the corresponding baseline exposure. Time to event corresponded to the midpoint between the last visit without a diagnosis of T2D/IFG and the first visit with a diagnosis or to the date of hospitalization for T2D, whichever came first (for the cases), and to the date of the last examination (for the noncases). The proportional hazards assumption of the Cox models was ensured by the Schoenfeld residuals. The linearity assumption for the models with the number of ideal metrics and the 12-point CVH score as continuous exposures was assessed by comparing the Akaike information criterion of linear models with models including quadratic and cubic terms.

Sensitivity Analysis

The results of the sensitivity analysis focused on the main exposure (CVH change) and the main outcome (incident T2D), but very similar findings were obtained for incident IFG. Missing CVH metrics and covariates were imputed by multiple imputation using the fully conditional specification method SAS MI procedure (n = 10 imputations). Given the known difference in risk of T2D by ethnicity, the modification effect of ethnicity in the association between change in categories of CVH and T2D was explored by including a corresponding interaction term in the models. The analyses were rerun after including 2-h OGTT glucose levels and HbA_{1c} in the definition of T2D. To account for the possible influence of incident CVD events (coronary heart disease and stroke) and to assess competing risk by death, we repeated the analysis by excluding incident CVD events on one hand and by estimating subdistribution HRs with the Fine and Gray method (17) on the other. Finally, given that the incident T2D and IFG status was known every 5 years on average at examination waves (i.e., the time-to-disease onset is interval censored), we repeated the main analysis, accounting simultaneously for interval-censored time-to event data and competing risk by death using an illness death model (18,19). All statistical analyses were performed using SAS 9.4 software, except for the illness death

Table 1—Baseline characteristics by pattern of change in CVH status between 1991/93 and 2002/04, T2D analysis

	Low CVH-low CVH (n = 1,596)	Low CVH-moderate/high CVH (n = 589)	Moderate CVH-low CVH (n = 729)	Moderate CVH-moderate/high CVH (n = 1,397)	Initially high CVH (n = 153)
Age (years), mean (SD)	50.16 (5.90)	50.87 (5.84)	48.88 (5.78)	48.98 (5.80)	46.57 (5.20)
Men	1,109 (69.49)	433 (73.51)	534 (73.25)	1,001 (71.65)	104 (67.97)
Education level					
University or higher degree	397 (24.87)	164 (27.84)	224 (30.73)	511 (36.58)	59 (38.56)
Higher secondary school	423 (26.50)	172 (29.20)	197 (27.02)	358 (25.63)	32 (20.92)
Lower secondary school or less	776 (48.62)	253 (42.95)	308 (42.25)	528 (37.80)	62 (40.52)
Occupation					
Administrative	593 (37.16)	264 (44.82)	313 (42.94)	690 (49.39)	75 (49.02)
Professional/executive	743 (46.55)	269 (45.67)	326 (44.72)	606 (43.38)	65 (42.48)
Clerical/support	260 (16.29)	56 (9.51)	90 (12.35)	101 (7.23)	13 (8.50)
Marital status					
Married/cohabiting	1,218 (76.32)	483 (82.00)	567 (77.78)	1,094 (78.31)	120 (78.43)
Single	240 (15.04)	77 (13.07)	107 (14.68)	199 (14.24)	18 (11.76)
Divorced	112 (7.02)	24 (4.07)	44 (6.04)	84 (6.01)	12 (7.84)
Widowed	26 (1.63)	5 (0.85)	11 (1.51)	20 (1.43)	3 (1.96)
Ethnicity (white)	1,469 (92.04)	552 (93.72)	687 (94.24)	1,332 (95.35)	148 (96.73)
Family history of diabetes	175 (10.96)	55 (9.34)	70 (9.6)	124 (8.88)	11 (7.19)
Alcohol, units/week					
0	284 (17.79)	93 (15.79)	106 (14.54)	208 (14.89)	23 (15.03)
1–13	815 (51.07)	321 (54.50)	422 (57.89)	822 (58.84)	104 (67.97)
≥14	497 (31.14)	175 (29.71)	201 (27.57)	367 (26.27)	26 (16.99)
Fasting glycemia (mg/dL), mean (SD)	96.84 (15.12)	94.78 (11.20)	95.33 (10.63)	93.34 (8.83)	93.36 (11.31)

Data are n (%), unless otherwise stated. CVH status was categorized as low, moderate, and high in subjects with 0–2, 3–4, and 5–6 CVH metrics at the ideal level, respectively. The low CVH-low CVH category corresponds to participants who had a low CVH status both at baseline (1991/93) and in 2002/04; the low CVH-moderate/high CVH category corresponds to participants who had a low CVH status at baseline (1991/93) but a moderate/high CVH in 2002/04; the moderate CVH-low CVH category corresponds to participants who had a moderate CVH status at baseline (1991/93) but a low CVH status in 2002/04; the moderate CVH-moderate CVH/high CVH category corresponds to participants who had a moderate CVH status at baseline (1991/93) and a moderate/high CVH in 2002/04; and the initially high CVH category corresponds to participants who had a high CVH status at baseline (1991/93) and either a low, moderate, or high CVH status in 2002/04.

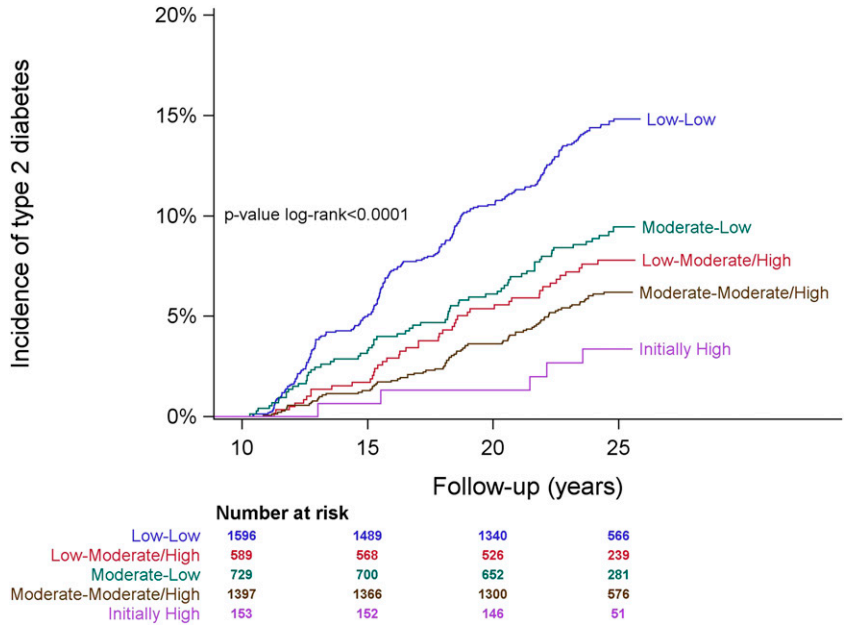

Figure 1—Kaplan-Meier curves for incident T2D by patterns of change in CVH between 1991/93 and 2002/04. The follow-up of T2D started after 2002/04 (i.e., 11 years after the baseline examination). The median follow-up duration after 2002/04 was 13.5 years (IQR 13.0–14.0). Curves are ordered from highest to lowest risk for incident T2D. CVH status was categorized as low, moderate, and high in subjects with 0–2, 3–4, and 5–6 CVH metrics at the ideal level, respectively. The low-low category corresponds to participants who had a low CVH status at baseline (1991/93) and in 2002/04; the low-moderate/high category corresponds to participants who had a low CVH status at baseline (1991/93) but a moderate/high CVH in 2002/04; the moderate-low category corresponds to participants who had a moderate CVH status at baseline (1991/93) but a low CVH status in 2002/04; the moderate-moderate/high category corresponds to participants who had a moderate CVH status at baseline (1991/93) and a moderate/high CVH in 2002/04; and the initially high category corresponds to participants who had a high CVH status at baseline (1991/93) and either a low or moderate or high CVH status in 2002/04.

model analysis, which was performed using the SmoothHazard package for R software.

RESULTS

Analytic Samples

The study flowchart for the T2D and IFG analyses is shown in Supplementary Fig. 1*A* and *B*. Of the initial 10,308 recruited participants in 1985/88, 8,815 returned to the examination in 1991/93 (baseline of the current analysis). For the T2D analysis, 226 had prior diabetes, 281 had prior CVD, 1,924 had missing CVH data, and 150 had missing confounding data, leaving 6,234 participants (mean age 49.8 ± 6.0 years at baseline, 70% male) for the analysis. For the IFG analysis, an additional 1,516 participants had IFG at baseline and were excluded, leaving 5,015 participants (mean age 49.6 ± 6.0 at baseline years, 67% male) for the analysis. The baseline characteristics of those included compared with those excluded are reported in Supplementary Tables 2 and 3.

Participant Characteristics

The characteristics of the participants at each examination are reported in Supplementary Table 4 for the T2D analysis and in Supplementary Table 5 for the IFG analysis. The proportion of subjects with high CVH ranged from 3% in 1991/93 (baseline) to 5.1% at the following waves for participants included in the T2D analysis, with similar trends in participants included in the IFG analysis.

Association of Baseline and Time-Varying CVH With Incident T2D/IFG

T2D

After a median follow-up of 24.8 (interquartile range [IQR] 24.0–25.2) years starting from the baseline examination in 1991/93, 895 incident cases of T2D occurred, yielding an overall incidence rate of 6.38 (95% CI 5.97, 6.81) per 1,000 person-years. An inverse association was found between baseline and time-varying CVH status, the number of ideal metrics, and the CVH score with incident T2D (Supplementary Table 6).

IFG

After a median follow-up of 24.2 (IQR 9.5–25.0) years starting from the baseline examination in 1991/93, 1,703 incident cases of IFG occurred, yielding an overall incidence rate of 18.45 (95% CI 17.59, 19.34) per 1,000 person-years. An inverse association was also found between baseline and time-varying CVH with incident IFG, but of a lower magnitude than with T2D (Supplementary Table 7).

Change in CVH (1991/93 to 2002/04)

T2D

Change in CVH was examined between 1991/93 and 2002/04 over a median follow-up of 11.2 (IQR 10.7–11.5) years in 4,464 participants who had complete data, were alive, and were free from T2D and CVD between these two time points. Supplementary Table 8 reports the baseline characteristics of those included compared with those excluded from this analysis. The participant characteristics at baseline by patterns of change in CVH are reported in Table 1. Supplementary Fig. 2*A* shows that 35.8% remained at low CVH, 13.2% improved from low to moderate/high CVH, 16.3% worsened from moderate to low CVH, 31.3% remained at moderate/improved from moderate to high, and 3.4% had initially high CVH. Those who remained moderate or improved to high CVH or were initially high were most likely to be white and younger at baseline (Supplementary Figs. 2*B* and *D*).

IFG

Change in CVH status from 1991/93 to 2002/04 was computed in 2,795 participants who were additionally free of IFG during this interval. Supplementary Table 9 reports the baseline characteristics of those included compared with those excluded from this analysis. The participant characteristics at baseline by patterns of change in CVH are reported in Supplementary Table 10. The patterns of change in CVH according to age, sex, and ethnicity were similar to those for T2D analysis (Supplementary Fig. 2*E*–*H*).

Change in CVH (1991/93 to 2002/04) and Subsequent Incident T2D/IFG (2002/04 to 2015/16)

T2D

After a median follow-up of 13.5 (IQR 13.0–14.0) years starting after the 2002/04 assessment, incident T2D occurred in

Table 2—Change in CVH between 1991/93 and 2002/04 and association with subsequent incident T2D

	n/N	Incidence rate per 1,000 PY (95% CI)	Adjusted HR (95% CI)
Change in CVH status	425/4,464	4.01 (3.65, 4.41)	
Low CVH-low CVH	226/1,596	6.11 (5.36, 6.96)	1 (Ref)
Moderate CVH-low CVH	66/729	3.80 (2.99, 4.84)	0.74 (0.56, 0.98)
Low CVH-moderate/high CVH	44/589	3.14 (2.34, 4.22)	0.62 (0.45, 0.86)
Moderate CVH-moderate/high CVH	84/1,397	2.49 (2.01, 3.08)	0.53 (0.41, 0.69)
Initially high CVH	5/153	1.34 (0.56, 3.21)	0.21 (0.09, 0.51)
Change in the number of ideal metrics (per 1 additional ideal metric)	425/4,464		0.81 (0.73, 0.91)
Change in the cardiovascular health score[a] (per 1-point increase in the score)	425/4,464		0.89 (0.83, 0.95)

HRs and 95% CIs were estimated by Cox proportional hazards models over a median follow-up of 13.5 (IQR 13.0–14.0) years. The Cox proportional hazards model was stratified by year of birth (5-year intervals) and used age as the time scale. HRs were adjusted for sex, ethnicity, education, occupation, marital status, alcohol, fasting glycemia, and family history of diabetes at baseline and were further adjusted for baseline number of ideal CVH metrics and baseline CVH score where appropriate. The linearity assumption of the model per additional ideal metric and per 1-point increase in the 12-point CVH score was evaluated by comparing the Akaike information criterion of a linear model with a quadratic and a cubic model. CVH status was categorized as low, moderate, and high in subjects with 0–2, 3–4, and 5–6 CVH metrics at the ideal level, respectively. The low CVH-low CVH category corresponds to participants who had a low CVH status at baseline (1991/93) and in 2002/04; the low CVH-moderate/high CVH category corresponds to participants who had a low CVH status at baseline (1991/93) but a moderate/high CVH in 2002/04; the moderate CVH-low CVH category corresponds to participants who had a moderate CVH status at baseline (1991/93) but a low CVH status in 2002/04; the moderate CVH-moderate CVH/high CVH category corresponds to participants who had a moderate CVH status at baseline (1991/93) and a moderate/high CVH in 2002/04; and the initially high CVH category corresponds to participants who had a high CVH status at baseline (1991/93) and a low, moderate, or high CVH status in 2002/04. PY, person-years. [a]For definition of the 12-point CVH score, see Supplementary Table 4.

425. The Kaplan-Meier curve (Fig. 1) indicates a stepwise decrease in the incidence of T2D across the patterns of change in CVH categories. Table 2 reports the incidence rates of T2D and multivariable HRs of T2D by categories of change in CVH. Compared with those with stable low CVH, risk of T2D was significantly lower in those with initially high CVH (HR 0.21; 95% CI 0.09, 0.51) and those who had persistently moderate CVH or changed from moderate to high CVH (moderate-moderate/high; HR 0.53; 0.41, 0.69), low-moderate/high (HR 0.62; 0.45, 0.86), and moderate-low (HR 0.74; 0.56, 0.98). Accordingly, the risk of T2D was lower per 1-unit increase in change in the number of ideal metrics and per 1-unit increase in change in the 12-point CVH score, even after adjusting for the corresponding baseline number of ideal metrics and baseline value in the 12-point CVH score. Figure 2 shows the HRs of T2D by patterns of change in the number of ideal metrics.

IFG

After a median follow-up of 13.4 years (IQR 10.6–13.9 years) starting after 2002/04, incident IFG occurred in 498. The Kaplan-Meier curves (Supplementary Fig. 3) and the multivariable HRs of IFG by pattern of change in CVH (Supplementary Table 11 and Supplementary Fig. 4) show similar trends as for T2D, although of lower magnitude.

Sensitivity Analysis

Additional analyses were conducted for the main outcome (T2D) and for the main exposure (change in CVH). Multiple imputations to account for missing CVH metrics and covariates provided results that were consistent with the complete case analyses (Supplementary Table 12). The association between change in CVH categories and the risk of T2D did not differ in white versus nonwhite (*P* for interaction = 0.32). Consistent findings were found when additional incident T2D cases, identified by OGTT (*n* = 49) or by HbA_{1c} levels (*n* = 67), were added (Supplementary Table 13). Similarly, when incident CVD events that occurred from 2002/04 onward were excluded from the analysis and death were accounted for as competing events, the corresponding HRs and subdistribution HRs for T2D did not change (Supplementary Table 14). Finally, when accounting for interval-censored time-to-event data in the illness death model, the results also remained unchanged (Supplementary Table 15).

CONCLUSIONS

In this prospective study with repeat assessments of CVH, change in CVH over 11 years was associated with risk of T2D and IFG. Compared with the stable low CVH group, the risk of T2D was lower among those with initially high CVH and those who had persistently moderate CVH or changed from moderate to high CVH, low-moderate/high, and moderate-low CVH.

Three previous studies conducted in American populations—the Jackson Heart Study (8), the Multi-Ethnic Study of Atherosclerosis (9), and the Strong Heart Family Study (10)—have consistently reported that higher baseline CVH is associated with lower incidence of T2D. The current analysis on baseline CVH confirms these findings in a European population. However, these previous studies used a single measure of CVH. Only one other study (11) examined the association between change in CVH, albeit only over 2 years, and incident T2D and found improvement in CVH (assessed in categories) was associated with a lower incidence of T2D. Our study adds to these findings by considering the change in CVH over 11 years and with a longer follow-up for T2D (3.8 years vs. 13.5 years in the current study). Other studies have shown that baseline (20−22) or repeated assessment (23,24) of one CVD risk factor or combinations of some CVD risk factors (e.g., less than optimal dietary intake, body weight, waist circumference, physical activity, fitness, smoking, alcohol, and glucose levels) are associated with an increased risk of incident T2D. The results for IFG were consistent with those for T2D; that is, higher baseline and time-varying CVH and change in CVH were associated with lower risk of incident IFG. However, the effect sizes for IFG were of lower magnitude compared with T2D. The smaller sample size of the IFG population may contribute to this.

The current study findings have important public health implications. On one hand, the significantly lower risk of T2D in participants who improved their CVH from low to moderate/high CVH compared with those where CVH remained low suggests that promotion

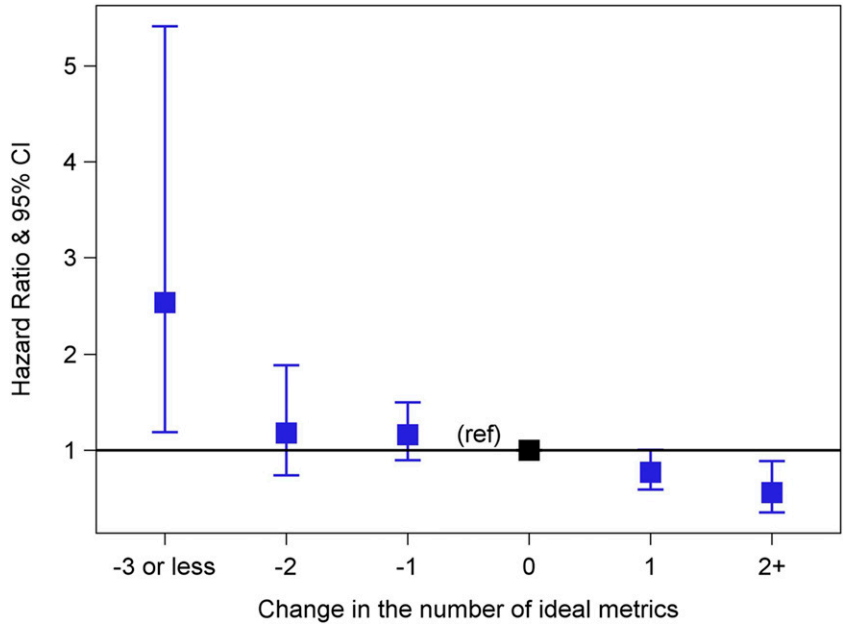

Figure 2—HRs for incident T2D by patterns of change in the number of ideal CVH metrics between 1991/93 and 2002/04. The *x* axis refers to the absolute difference (i.e., change) in the number of ideal CVH metrics between 1991/93 and 2002/04. A positive number indicates that the participant gained additional ideal metrics between 1991/93 and 2002/04, whereas a negative number indicates that the participant lost ideal metrics between 1991/93 and 2002/04, respectively. HRs and 95% CIs were estimated by a Cox proportional hazards model stratified by year of birth (5-year intervals) and using age as the timescale. The median follow-up duration after 2002/04 was 13.5 (IQR 13.0–14.0) years. The group with no change was the reference category. Results are adjusted for sex, race/ethnicity, depression, education, occupation, fasting glycemia, family history of T2D, and number of ideal metrics at baseline. HRs are ordered from highest to lowest risk for incident diabetes compared with the reference category.

of higher CVH is valuable even in midlife. On the other hand, those who worsened from moderate or high to low CVH were still at reduced risk of T2D compared with those remaining with low CVH. Although speculative, this may suggest that initial attainment of moderate or high CVH buffers the deleterious consequences of future worsening in CVH, although the effect size was lower in this group than in those whose CVH improved. A similar pattern of results was observed for IFG, which also has important implications given that a large number of those with IFG will go on to develop T2D (1) and that IFG itself is associated with an increased risk of CVD (25). Taken together, these findings suggest that promoting moderate and high CVH might be one strategy for the prevention of T2D and IFG.

Although lifestyle modification (improvements in nutrition and increased physical activity) has long been a cornerstone in the management and prevention of T2D and its associated complications, focusing on improving CVH as a whole (i.e., by targeting the AHA ideal CVH metrics) may help to reduce the burden of T2D and IFG worldwide. This requires a concerted effort from the individuals, caregivers, health policy and education, and engagement with industry to influence population health. Recent community-based intervention trials have demonstrated the effectiveness and efficacy of promoting CVH in preschoolers (26,27) and in adults (28). The long-term effect of these interventions on outcomes that include T2D and IFG, however, remain to be evaluated. Importantly, change in CVH is associated with health outcomes beyond CVD, including mortality (12), and our study suggests that these extend to T2D and IFG. Thus, improving and maintaining moderate or high CVH may represent a pertinent target for global health.

Limitations

Our study has limitations that should be considered. Firstly, some groups of CVH change were small in size (low-to-high and high-high) and had to be combined, precluding more detailed analysis of the association between change in CVH categories and incident T2D/IFG. Secondly, as a result of the observational nature of the study, conclusions regarding causality cannot be drawn. Thirdly, the exact date of T2D/IFG was not ascertained, and thus, the assessments of time to T2D/IFG may have been subject to misclassifications. That said, when using interval-censored time-to-event data methods, the results were very similar to when using the midpoint interval to define the date of events. Further, changes in CVH across repeated examinations might have partly been explained by aging, temporal trends, and cohort attrition. Also, 2-h plasma glucose and OGTT measures could only be investigated in sensitivity analysis because they were not available at each examination wave. The Whitehall II Study is based on government employees, and the study population may have been subject to the healthy worker effect, although the association between cardiovascular risk factors and CVD has been shown to be similar to that in the general population (29). Finally, the Whitehall II Study cohort is mostly composed of middle-aged individuals and Caucasians; thus, our findings may not apply to other populations.

Conclusion

In this study, baseline, time-varying, and change in CVH were associated with the risk of T2D and IFG. These findings support the promotion of, and adherence to, moderate to high CVH for the prevention of T2D and IFG.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium, International Diabetes Federation, 2017
2. Lloyd-Jones DM, Hong Y, Labarthe D, et al.; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586–613
3. Gaye B, Canonico M, Perier M-C, et al. Ideal cardiovascular health, mortality, and vascular events in elderly subjects: the three-city study. J Am Coll Cardiol 2017;69:3015–3026
4. Guo L, Zhang S. Association between ideal cardiovascular health metrics and risk of cardiovascular events or mortality: a meta-analysis of prospective studies. Clin Cardiol 2017;40:1339–1346
5. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol 2011;57:1690–1696
6. Samieri C, Perier M-C, Gaye B, et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 2018;320:657–664
7. Rasmussen-Torvik LJ, Shay CM, Abramson JG, et al. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk In Communities study. Circulation 2013;127:1270–1275
8. Effoe VS, Carnethon MR, Echouffo-Tcheugui JB, et al. The American Heart Association ideal cardiovascular health and incident type 2 diabetes mellitus among blacks: the Jackson Heart Study. J Am Heart Assoc 2017;6:e005008
9. Joseph JJ, Echouffo-Tcheugui JB, Carnethon MR, et al. The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Diabetologia 2016;59:1893–1903
10. Fretts AM, Howard BV, McKnight B, et al. Life's simple 7 and incidence of diabetes among American Indians: the Strong Heart Family Study. Diabetes Care 2014;37:2240–2245
11. Liu X, Shi J, Wang A, et al. Changes in ideal cardiovascular health status and risk of new-onset type 2 diabetes: the Kailuan prospective study. Medicine (Baltimore) 2016;95:e4571
12. van Sloten TT, Tafflet M, Périer M-C, et al. Association of change in cardiovascular risk factors with incident cardiovascular events. JAMA 2018;320:1793–1804
13. Enserro DM, Vasan RS, Xanthakis V. Twenty-year trends in the American Heart Association cardiovascular health score and impact on subclinical and clinical cardiovascular disease: the Framingham Offspring Study. J Am Heart Assoc 2018;7:e008741
14. Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. Lancet 1991;337:1387–1393
15. Vistisen D, Witte DR, Tabák AG, Brunner EJ, Kivimäki M, Færch K. Sex differences in glucose and insulin trajectories prior to diabetes diagnosis: the Whitehall II study. Acta Diabetol 2014;51:315–319
16. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509
18. Touraine C, Helmer C, Joly P. Predictions in an illness-death model. Stat Methods Med Res 2016;25:1452–1470
19. Leffondré K, Touraine C, Helmer C, Joly P. Interval-censored time-to-event and competing risk with death: is the illness-death model more accurate than the Cox model? Int J Epidemiol 2013;42:1177–1186
20. Reis JP, Loria CM, Sorlie PD, Park Y, Hollenbeck A, Schatzkin A. Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. Ann Intern Med 2011;155:292–299
21. Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE; Diabetes Prevention Program Research Group. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. Lancet 2012;379:2243–2251
22. Bantle AE, Chow LS, Steffen LM, et al. Association of Mediterranean diet and cardiorespiratory fitness with the development of pre-diabetes and diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) study. BMJ Open Diabetes Res Care 2016;4:e000229
23. Mozaffarian D, Kamineni A, Carnethon M, Djoussé L, Mukamal KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med 2009;169:798–807
24. Chow LS, Odegaard AO, Bosch TA, et al. Twenty year fitness trends in young adults and incidence of prediabetes and diabetes: the CARDIA study. Diabetologia 2016;59:1659–1665
25. Di Angelantonio E, Gao P, Khan H, et al.; Emerging Risk Factors Collaboration. Glycated hemoglobin measurement and prediction of cardiovascular disease. JAMA 2014;311:1225–1233
26. Céspedes J, Briceño G, Farkouh ME, et al. Targeting preschool children to promote cardiovascular health: cluster randomized trial. Am J Med 2013;126:27–35.e3
27. Peñalvo JL, Santos-Beneit G, Sotos-Prieto M, et al. The SI! Program for cardiovascular health promotion in early childhood: a cluster-randomized trial. J Am Coll Cardiol 2015;66:1525–1534
28. Gómez-Pardo E, Fernández-Alvira JM, Vilanova M, et al. A comprehensive lifestyle peer group–based intervention on cardiovascular risk factors: the Randomized Controlled Fifty-Fifty Program. J Am Coll Cardiol 2016;67:476–485
29. Batty GD, Shipley M, Tabák A, et al. Generalizability of occupational cohort study findings. Epidemiology 2014;25:932–933