The Joint Public Health Impact of Family History of Diabetes and Cardiovascular Disease among Adults in the United States: A Population-Based Study

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Abstract

Introduction: Family history is an established risk factor for both cardiovascular disease (CVD) and diabetes; however, no study has presented population-based prevalence estimates of family histories of CVD and diabetes and examined their joint impact on prevalence of diabetes, CVD, cardiometabolic risk factors, and mortality risk. Methods: We analyzed data from a representative sample of the US adult population including 29,440 participants from the National Health and Nutrition Examination Survey (2007–2018) and assessed self-reported first-degree family history of diabetes and CVD (premature heart disease before age of 50 years) as well as meeting criteria and/or having risk factors for CVD and diabetes. Results: Participants with joint family history exhibit 6.5 greater odds for having both diseases and are diagnosed with diabetes 6.6 years earlier than participants without family history. Healthy participants without prevalent CVD or diabetes but with joint family history exhibit a greater prevalence of diabetes risk factors compared to no family history counterparts. Joint family history is associated with an increase in all-cause mortality, but with no interactive effect. Conclusion: Over 44% of the US adult population has a family history of CVD and/or diabetes that is comparable in risk to common cardiometabolic risk factors. This wide presence of high-risk family history and its simplicity of ascertainment suggests that clinical and public health efforts should collect and act on joint family history of CVD and diabetes to improve population efforts in the prevention and early detection of these common chronic diseases.

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the hypothesis that both arise from a “common soil,” supporting the clinical observation that both chronic conditions not only frequently co-exist in the same individual but may spring from shared pathophysiological features [3]. Patients with type 1 diabetes also have a much higher risk of CVD, contributed by common risk factors such as hypertension, obesity, HbA1c, lipid levels, and smoking and significantly increased all-cause and cardiovascular mortality when compared to their peers without diabetes [4, 5].

Developing diabetes at a younger age is associated with higher rates of cardiovascular risk factors than developing diabetes at a later age, as evidenced by a longitudinal Swedish study that identified individuals with early onset type 2 diabetes (diagnosis before the age of 45 years) were likely to have a worse adiposity, lipid, and glycemic risk factor profile than individuals diagnosed at an older age [6]. A range of genetic, environmental, and lifestyle risk factors have been shown to be associated with the development of early onset type 2 diabetes [7]. Genetic predisposition plays an important role in the development of early onset diabetes [8, 9], with multiple studies that have identified genetic variants associated with the development of early onset type 2 diabetes [10–12].

Family history, which reflects genetic susceptibility and shared environmental, behavioral, and lifestyle factors [13], can be used to investigate if individuals with joint family history (defined as having both family histories of diabetes and CVD) are at greater risk than individuals with only one family history (i.e., family history of diabetes or family history of CVD) for developing diabetes, CVD, or their risk factors. Examining the interaction of genetic, environmental, and lifestyle risk of diabetes and CVD, captured by their respective family histories, can suggest novel hypotheses on the mechanisms contributing to the incidence of diabetes and CVD and can help identify subsets of the population who may disproportionately benefit from early detection to prevent or delay the onset of complications. Given the shared genetic and environmental antecedents of diabetes and CVD, our hypothesis is that a joint family history is associated with cumulative effects on cardiometabolic disease risk and risk factors. In this study, we examined if the interaction between genetic, environmental, and lifestyle risk of diabetes and CVD as captured by their respective family histories leads to an increased risk for disease and cardiometabolic risk factors in an additive or multiplicative interaction – meaning, whether the effect of joint family history is greater than the sum of the individual effects of each family history (additive), or the effect of joint family history is greater than the product of the individual effects (multiplicative).

Clinical guidelines for the prevention of CVD incorporate family history of premature coronary heart disease (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative) to determine patient risk status [14]. Yet, commonly used multivariable risk algorithms for assessing general cardiovascular risk profile lack family history because of their short-term contribution to increased risk [15]. However, family history of premature CVD is associated with a persistent increase in CVD mortality risk across long-term follow-up, translating to a considerable accumulation of risk across an individual’s lifetime [16]. To our knowledge, no population-based investigation has assessed the combined influence of family history of premature CVD (under age of 50 years) and diabetes, denoted hereafter as “joint family history,” on the prevalence of CVD, diabetes, and their risk factors, and conducted a longitudinal study to determine their joint effect on the risk of all-cause and cardiovascular mortality. Understanding the impact of a family history of CVD, in combination with a family history of diabetes, can influence clinical practice guidelines for the identification of individuals at increased risk for these complex diseases.

Materials and Methods

Study Sample

The National Health and Nutrition Examination Survey (NHANES) is conducted by the Centers for Disease Control and Prevention’s National Center for Health Statistics and consists of cross-sectional studies using stratified multistage probability samples designed to assess the health and nutritional status of noninstitutionalized, civilian residents from the US population [17]. We analyzed data for 29,440 males and nonpregnant females aged 20 years and over from six 2-year cycles of the 2007–2018 NHANES with available information on current disease status, first-degree family history of diabetes and CVD, and cardiovascular health risk factor measurements (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526242).

Measures

We identified survey participants with diabetes using (a) self-reported diagnosis of diabetes or (b) undiagnosed diabetes, identified in participants who do not self-report a diabetes diagnosis but who meet a fasting glucose or hemoglobin A1C level in accordance with American Diabetes Association guidelines [18]. Specifically, participants with diabetes met at least one of three criteria: (1) self-reported a physician diagnosis by an affirmative response to the question “have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes”; (2) a negative re-
response to the question and fasting glucose level 7.00 mmol/L (126 mg/dL) or greater following at least an 8-h fast; or (3) hemoglobin AIC concentration 6.5% or greater [18]. Since laboratory equipment for measuring glucose levels changed during the NHANES 2007–2018 period, we applied glucose regression equations as advised by NCHS for consistency among estimates. We identified participants diagnosed with CVD by an affirmative response to questions about the diagnosis of coronary heart disease, angina, heart attack, or stroke. Participants with missing current disease status or with missing glucose laboratory measures were removed (n = 255, 0.83%).

We identified participants who reported a positive family history as those who had a first-degree affected relative (parent and/or sibling). NHANES ascertained family history of diabetes with an affirmative response to “Including living and deceased, were any of your close biological, that is, blood relatives including father, mother, sisters, or brothers, ever told by a health professional that they had diabetes” in the Medical Conditions Questionnaire. NHANES ascertained family history of CVD by an affirmative response to the question “Including living and deceased, were any of your close biological, that is, blood relatives including father, mother, sisters, or brothers, ever told by a health professional that they had a heart attack or angina before the age of 50.” Participants who lacked knowledge or refused to respond were removed from further analyses (n = 1,027, 3.34%). We classified participants according to four family history categories: (1) no family history of diabetes or CVD, (2) family history of CVD and no family history of diabetes, (3) family history of diabetes and no family history of CVD, and (4) joint family history (family histories of both diabetes and CVD).

Demographic, Behavioral, and Clinical Risk Factors

We estimated associations between family history of CVD, diabetest, and joint family history with risk factors, including demographic characteristics (age group [20–39, 40–59, 60+], sex, and race and Hispanic ethnicity [non-Hispanic white, Mexican-American, non-Hispanic black, and other Hispanic]), as well as measures of socioeconomic status, including poverty-income-ratio, computed as the ratio of family income to poverty threshold, and educational status of the participants (less than high school completion, or high school completion or greater).

We additionally estimated associations between family history and CVD/diabetes risk factors based on criteria from the American Heart Association, including BMI (<25, 25–29.9, ≥30 kg/m²), smoking status, physical activity, total cholesterol, and blood pressure. We defined participants as current smokers if the participant responded to the question “Do you now smoke cigarettes?” with “every day” or “some days” and as a nonsmoker if the participant responded to the question with “Not at all.” We defined participants as physically active if the participant reported at least 150 min a week of moderate-intensity or 75 min a week of vigorous-intensity aerobic physical activity.

We also estimated associations between family history and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels in accordance with classifications set by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). We categorized participants with a total cholesterol of <200, 200–239, and ≥240 as low/desirable, borderline high, and high; LDL cholesterol levels of <100, 100–159, ≥160 as low/desirable, borderline high, and high; and HDL cholesterol levels of <40, 40–60, ≥60 as low, borderline high, and high/desirable, respectively. We classified participants as having a normal blood pressure by a systolic blood pressure ≤120 mm Hg and a diastolic blood pressure <80 mm Hg and as having hypertension by a systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥80 mm Hg, or if they have controlled hypertension, defined as having a normal blood pressure but self-reporting that a doctor or health professional has diagnosed them with a high blood pressure. We accounted for C-reactive protein (CRP), a marker of systemic inflammation known to be associated with glycemic control and increased risk of diabetes, and identified participants with normal serum CRP level (≤3.0 mg/L) and high CRP levels (>3.0 mg/L). Prior studies have shown an increase in the ratio of triglycerides to HDL cholesterol (TG/HDL-c) can be indicative of an increased atherogenic lipid profile and is positively associated with insulin resistance and CVD [19–21]. Therefore, we additionally determined TG/HDL-c ratio by dividing triglyceride levels (mg/dL) by HDL cholesterol (mg/dL) and categorized TG/HDL-c levels as ≤1.25, 1.26–1.98, 1.99–3.24, and ≥3.25.

Mortality Status

We determined all-cause mortality status and cardiovascular underlying cause of death from the NHANES-linked National Death Index public-use access files. These files are available for NHANES 2007–2014 and have been updated with mortality follow-up data through December 31, 2015. We identified cardiovascular mortality by using underlying cause of death information that had been recorded from the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and 10). We prospectively followed survey participants from the date of survey participation until December 31, 2015, or the documented date of death. We determined time to death from the date of survey interview through December 31, 2015, as person-months of follow-up by using the date of survey participation through December 31, 2015, for participants assumed to be alive. We calculated the follow-up time as person-years by dividing the number of months by 12.

Statistical Analyses

We used logistic regression to quantify the associations between family history and prevalent disease, adjusting by age, sex, and race and ethnic origin. We estimated the prevalence ratio (PR) for CVD and diabetes, which is inclusive of both undiagnosed and self-reported diagnosis of diabetes, given a family history. We used quasi-Poisson regression to model the association between disease and family history, adjusting for age, sex, race/ethnicity, BMI, education, poverty-income-ratio, smoking, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. One model was constructed for each of four outcomes: diabetes, CVD, both, and either/or. Here, a PR of 2.0 for “CVD family history only” and “CVD diagnosis,” for example, can be interpreted to mean that the proportion of participants with a CVD diagnosis is 2-fold greater if a participant has a CVD family history, compared to a participant with no family history of CVD or diabetes.

We treated the continuous variables, namely, age, income-to-poverty ratio, BMI, blood pressure, HDL cholesterol, LDL cholesterol, total cholesterol, C-reactive protein, and triglycerides as continuous variables in our analyses. For visualization purposes, we
categorized findings according to risk factor levels. We used survey-weighted Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality associated with an interaction term for family history of CVD and family history of diabetes, adjusted by demographic and clinical risk factors.

We estimated measures of interaction between the two family histories on an additive scale by calculating the relative excess risk due to interaction (RERI), the attributable proportion (AP), and synergy index (S) [22]. We conducted a relative importance analysis to examine the extent to which disease risk is attributable to family history rather than to modifiable risk factors, including BMI, education, and income-to-poverty ratio. We investigated varying sensitivity levels of family history recall with a simulation analysis rooted by prior reports of the sensitivities of family history of diabetes and CVD [23, 24]. In a simulation study in NHANES 2007–2018, based on prior reports of the sensitivities of family history of diabetes and CVD, we have analyzed our associations between family history and CVD and diabetes for a sensitivity of 70%, 80%, and 90% for family history of diabetes, and 80%, 85%, and 90% for a family history of CVD, as well as for combinations of sensitivities of 80% and 90% for family history of diabetes and 80% and 90% for family history of CVD. For each simulation, for a sensitivity s, we have reclassified, at random, (1-s)% of the participants who are not classified as having a family history to having a family history and determined PRs according to the family history categories.

In accordance with NHANES analytic guidelines, all analyses accounted for the complex sample design by using design variables and adjusting for mobile examination center exam sample weights. To correct for multiple hypothesis testing for our regression analyses, we calculated the false discovery rate and denoted significance by a false discovery rate threshold of 5%.

Results

Prevalence of Family History

Our study included 30,722 participants who met the inclusion criteria of having mobile examination center data items at the time of examination (online suppl. Fig. 1), of whom 255 (0.83%) and a further 1,027 (3.34%) participants were excluded due to no reported disease and family history information, respectively. The prevalence of self-reported first-degree family history of CVD only,

### Table 1. Crude prevalence of reported family history of CVD and diabetes by demographic characteristics, NHANES 2007–2018

| Reported family history of | CVD only, prevalence (%) | diabetes only, prevalence (%) | joint family history, prevalence (%) |
|----------------------------|--------------------------|-------------------------------|-------------------------------------|
| neither, prevalence (%)   |                          |                               |                                     |
| Overall population        | 55.60 (54.66–56.54)      | 5.48 (5.09–5.87)              | 31.64 (30.83–32.47)                |
| Age, years                |                          |                               |                                     |
| 20–39                     | 61.61 (60.34–62.88)      | 3.80 (3.34–4.25)              | 29.02 (27.84–30.19)                |
| 40–59                     | 51.98 (50.55–53.41)      | 5.61 (4.96–6.25)              | 33.81 (32.50–35.11)                |
| 60+                       | 52.50 (50.80–54.21)      | 7.61 (6.71–8.51)              | 32.17 (30.89–33.46)                |
| Sex                       |                          |                               |                                     |
| Males                     | 59.03 (57.89–60.15)      | 5.05 (4.60–5.51)              | 29.94 (28.94–30.93)                |
| Females                   | 52.97 (51.75–54.19)      | 5.80 (5.24–6.37)              | 32.96 (31.90–34.02)                |
| Race/ethnicity            |                          |                               |                                     |
| Non-Hispanic white        | 57.42 (56.27–58.57)      | 6.55 (5.97–7.13)              | 28.56 (27.57–29.54)                |
| Other Hispanic            | 59.17 (58.68–61.47)      | 3.22 (2.71–3.92)              | 31.51 (29.27–33.02)                |
| Non-Hispanic black        | 46.99 (45.30–48.70)      | 3.40 (2.79–4.00)              | 41.54 (40.10–42.98)                |
| BMI, kg/m²                 |                          |                               |                                     |
| <25                       | 63.67 (62.09–65.24)      | 5.49 (4.82–6.17)              | 25.78 (24.36–27.21)                |
| 25–29.9                   | 57.96 (56.70–59.21)      | 5.82 (5.21–6.43)              | 30.15 (28.98–31.32)                |
| 30+                       | 46.56 (45.13–47.98)      | 5.17 (4.64–5.68)              | 37.99 (36.64–39.33)                |
| Poverty-income-ratio      |                          |                               |                                     |
| <1                        | 52.29 (50.59–53.98)      | 5.10 (4.38–5.82)              | 33.33 (31.77–34.90)                |
| ≥1                        | 56.50 (55.53–57.48)      | 5.58 (5.15–6.01)              | 31.19 (30.31–32.06)                |
| Education                 |                          |                               |                                     |
| < High school             | 51.93 (50.18–53.68)      | 6.13 (5.18–7.09)              | 32.59 (31.08–34.09)                |
| ≥ High school             | 56.31 (55.35–57.28)      | 5.35 (4.94–5.76)              | 31.46 (30.60–32.32)                |

1 A reported family history of “CVD only” denotes a family history of CVD and no family history of diabetes. 2 A reported family history of “diabetes only” denotes a family history of diabetes and no family history of CVD.
diabetes only, and joint family history was 5.5% (95% CI, 5.1–5.9%), 31.6% (95% CI, 30.8–32.5%), and 7.3% (95% CI, 6.8–7.8%), respectively (Table 1), and trends in prevalence of family history during the period of 2007–2018 exhibited relative stability over time (online suppl. Fig. 2).

Participants with a family history of either CVD or diabetes were more likely to have the other condition. We identified a 2.36-fold (95% CI, 2.12–2.63) increase of having a family history of CVD among participants with a family history of diabetes, adjusted by age, sex, and race/ethnicity.

**PR for CVD and Diabetes by Family History**

We found PRs of 2.67 (95% CI, 2.30–3.12), 2.53 (95% CI, 2.23–2.87), 5.04 (95% CI, 4.07–6.23), and 2.03 (1.82–2.27) for having CVD, diabetes, both, and either/or, respectively, for participants with joint family history (Table 2). Figure 1 presents the adjusted odds ratios (aORs) for having CVD, diabetes, and both CVD and diabetes by family history status. The aOR for having both CVD and diabetes was 3.01 (95% CI, 2.44–3.71), 2.10 (95% CI, 1.36–3.24), and 6.30 (95% CI, 4.89–8.09) in association with a family history of diabetes only, CVD only, and joint family history, respectively (Fig. 1). Online supplementary Table 1 presents the aOR for CVD and diabetes according to family history, adjusting for age, sex, race and ethnic origin, BMI, income-to-poverty-ratio, and education. The aOR for having a diagnosis of CVD, given a family history of CVD and not diabetes was 3.04 (95% CI, 2.65–3.50) and 3.37 (95% CI, 2.74–4.14) given joint family history.

**Family History-Associated Prevalence and PRs Differ by Cardiometabolic Risk Factors**

The prevalence and PR for CVD and diabetes given the family history categories differed by levels of established risk factors for CVD and diabetes (Fig. 2, online suppl. Fig. 3, 4). Surprisingly, we found that the prevalence and PRs for CVD according to a family history of CVD was similar across low/desirable, borderline high, and high LDL cholesterol levels (Fig. 2a; online suppl. Fig. 3). Further, we also found that the PR for CVD according to a family history of diabetes was also similar across low/desirable, borderline high, and high total cholesterol levels (online suppl. Fig. 3). The PR for CVD according to joint family history remained similar across hypertensive and normal blood pressure levels (online suppl. Fig. 3). For joint family history, we found that the prevalence and PR for CVD according to joint family history remained similar across hypotensive and normal blood pressure levels (online suppl. Fig. 3).

| CVD or diabetes diagnosis, n = 5,603 | Prevalence, % | PR Reference | PR | Prevalence, % | PR Reference | PR | Prevalence, % | PR Reference | PR | Prevalence, % | PR Reference | PR |
|-------------------------------------|-------------|-------------|-----|-------------|-------------|-----|-------------|-------------|-----|-------------|-------------|-----|
| No family history of CVD or diabetes, n = 15,693 | 5.37 (4.95–5.79) | 2.16 (1.84–2.55) | 1.12 (0.90–1.39) | 18.89 (16.41–21.36) | 1.51 (1.32–1.73) | 1.72 (1.58–1.86) | 2.03 (1.82–2.27) | 15.43 (12.83–18.02) | 3.17 (1.94–4.45) | 1.97 (1.34–2.89) | 2.67 (2.22–3.21) |
| CVD family history only, n = 1,430 | 7.11 (6.49–7.73) | 9.89 (8.03–11.56) | 1.10 (0.90–1.39) | 20.00 (18.85–21.16) | 2.31 (2.09–2.54) | 2.53 (2.23–2.87) | 2.16 (1.84–2.55) | 9.89 (8.03–11.56) | 1.10 (0.90–1.39) | 20.00 (18.85–21.16) | 2.31 (2.09–2.54) |
| Joint family history, n = 1,084 | 1.26 (1.06–1.45) | 3.74 (3.28–4.21) | 3.74 (3.28–4.21) | 20.09 (18.96–21.22) | 1.72 (1.58–1.86) | 2.03 (1.82–2.27) | 1.26 (1.06–1.45) | 3.74 (3.28–4.21) | 3.74 (3.28–4.21) | 20.09 (18.96–21.22) | 1.72 (1.58–1.86) |
| CVD and diabetes diagnosis, n = 2,190 | 2.67 (2.30–3.12) | 5.04 (4.07–6.23) | 5.04 (4.07–6.23) | 25.58 (23.44–27.71) | 1.97 (1.34–2.89) | 2.67 (2.22–3.21) | 2.67 (2.30–3.12) | 5.04 (4.07–6.23) | 5.04 (4.07–6.23) | 25.58 (23.44–27.71) | 1.97 (1.34–2.89) |

PR, prevalence ratio. 1 Prevalence ratios are adjusted by age, sex, race/ethnicity, BMI, education, poverty-income-ratio, smoking, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides. 2 Diabetes here is inclusive of diagnosed (self-reported a diagnosis by a doctor or other health professional) and undiagnosed (fasting glucose value greater than 126 mg/dL or glycated hemoglobin value greater than 6.5% in the laboratory testing panels for participants who did not self-report a diabetes diagnosis).
across the various TG/HDL-c levels (online suppl. Fig. 5a, 6a), but that for a family history of CVD, the prevalence of diabetes in the high-risk TG/HDL-c category of 3.25+ was 16.09% (95% CI, 8.85–23.35) compared to 2.24% (95% CI, 0.18–4.67%) in the lower risk 1.26–1.98 category (online suppl. Fig. 5b).

In the relative importance analysis, we found for a dual diagnosis of CVD and diabetes; the t-statistic values for joint family history (t = 14.5, p value <0.05) were much higher than that of BMI (t = 6.1, p value <0.05), income-to-poverty ratio (t = −5.0, p value <0.05), and education (t = −0.7, p value = 0.52), indicating the greater importance of joint family history in the dual diagnosis of CVD and diabetes compared to these modifiable risk factors. This finding was also reflected in the analysis for CVD, where the t-statistic values for family history (t = 13.21, p value <0.05) exceeded that of BMI (t = 2.70, p value <0.05), income-to-poverty ratio (t = −6.80, p value <0.05), and education (t = −1.46, p value = 0.15), and also for diabetes, where the t-statistic values for family history (t = 14.92, p value <0.05) greatly exceeded that of income-to-poverty ratio (t = −3.40, p value <0.05) and education (t = −3.70, p value <0.05).

**Fig. 1.** aORs for CVD and diabetes according to family history. Presented are estimates of aORs (95% CI) for CVD, diabetes, and both CVD and diabetes (labeled at the top of the figure) according to family history of CVD, diabetes, joint family history, and either family history of CVD or diabetes, adjusted by age, sex, race/ethnicity, BMI, poverty-income-ratio, education, smoking, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides in the NHANES 2007–2018. The reference group is the cohort of participants with no family history of CVD or diabetes. Diabetes is inclusive of diagnosed (self-reported a diagnosis by a doctor or other health professional) and undiagnosed (fasting glucose value greater than 126 mg/dL or glycated hemoglobin value greater than 6.5% in the laboratory testing panels for participants who did not self-report a diabetes diagnosis).

**Fig. 2.** Prevalence of CVD and diabetes by risk factors and family history. Presented are the survey-adjusted prevalence of CVD (a) and diabetes (b) within cohorts of participants by selected risk factors and family history of neither CVD nor diabetes, diabetes only, CVD only, and both CVD and diabetes in the NHANES 2007–2018. Race/ethnicity groups are labeled as “black” for non-Hispanic black, “Hispanic,” and “white” for non-Hispanic white. (For figure see next page.)
Interaction between Family History of Diabetes and Family History of CVD

The interaction between family history of diabetes and family history of CVD in the diagnosis of CVD (interaction beta = −0.09 SE 0.11; p value = 0.41), diabetes (beta = −0.0087 SE 0.13; p value = 0.95), and both (beta = −0.025 SE 0.23; p value = 0.91) were nonsignificant. We measured the interaction of the family histories on an additive scale and found that for a diagnosis of CVD and diabetes, the RERI was 0.82, the AP was 0.16, and the S was 1.24, all indicating a positive or more than exactly additive interaction. For a diagnosis of CVD only, RERI, AP, and S were −0.41, −0.21, and 0.70, indicating a less than additive or negative interaction, while for a diagnosis of diabetes only, the measures were 0.03, 0.01, and 1.01, respectively, indicating a near exactly additive interaction. Our findings based on our RERI analysis suggest that the relationship between family history of diabetes and family history of CVD is closer to additive than to multiplicative for an outcome of both diabetes and CVD, near exactly additive for an outcome of diabetes only, and less than additive for an outcome of CVD only.

Earlier Age of Diabetes Diagnosis for Participants with Joint Family History

For participants diagnosed with diabetes, the weighted mean age of diabetes diagnosis for participants with joint family history was 44.07 years, or on average, 6.62 years earlier (p < 0.0001) than participants with no family history of CVD and diabetes. Furthermore, for participants diagnosed with diabetes, participants with a family history of diabetes and no family history of CVD were diagnosed with diabetes, on average, at 48.16 years, or 2.53 years earlier (p < 0.0001) than participants with neither family history and participants with a family history of CVD and no family history of diabetes were diagnosed with diabetes, on average, at 51.31 years, or 0.62 years later (p < 0.0001) than participants with neither family history.

Joint Family History Associated with an Increase in All-Cause Mortality but with No Significant Interactive Effect

In multivariate analysis adjusted by age, sex, race/ethnicity, BMI, education, and poverty-to-income ratio, joint family history of CVD and diabetes was associated with an increase in all-cause mortality (hazard ratio 1.67; 95% CI, 1.25–2.24, p = 0.007), compared to participants with neither family history of CVD or diabetes (online suppl. Fig. 7). We observed no significant interaction between family history of CVD and diabetes in association with all-cause mortality (interaction p = 0.39) and cardiovascular mortality (interaction p = 0.62), suggesting that the joint effect of family history of CVD and diabetes on the risk of all-cause and cardiovascular mortality is not statistically larger than the sum of their individual effects.

Family History Associated with Increased Prevalence of Cardiometabolic Risk Factors in Participants Not Reporting Diabetes or CVD

Among participants without prevalent CVD or diabetes and who did not have abnormal glucose or hemoglobin A1C levels, a positive family history of CVD and/or diabetes was significantly associated with CVD and diabetes risk factors. Joint family history was significantly associated with a BMI greater than 30 (aOR 1.70; 95% CI, 1.48–1.94), a poverty-income-ratio less than 1.3 (aOR of 1.51; 95% CI, 1.31–1.73), smoking (aOR 2.15; 95% CI, 1.81–1.56), and low HDL levels (aOR 1.36; 95% CI, 1.20–1.54) (online suppl. Table 2).

Sensitivity Analyses

Simulation analyses based on prior reports of the sensitivity thresholds for family history of diabetes and CVD showed that even at conservative estimates for the reclassification of joint family history, the PRs for CVD, diabetes, and both remain high (online suppl. Fig. 8). We found that the PRs for a diagnosis of CVD and a family history of diabetes as well as diagnosis of diabetes and a family history of CVD given various sensitivity levels of family history remained consistent in their association direction (online suppl. Fig. 8A left; online suppl. Fig. 8B right); however, the associations between diabetes and family history of diabetes as well as CVD and family history of CVD were attenuated (online suppl. Fig. 8A right; online suppl. Fig. 8B left). We have also found that the PRs for combinations of sensitivities of family history of diabetes and CVD were attenuated (online suppl. Fig. 8C). However, as we are not taking the correlation between family history of diabetes and CVD into account, our sensitivity analyses present more conservative estimates than expected. Therefore, while attenuated, even at a conservative estimate of 20% reclassification of family history of diabetes and 20% reclassification of family history of CVD, the PRs for CVD (PR 1.49, 95% CI, 1.33–1.66), diabetes (PR 1.99; 95% CI, 1.78–2.21), and both (PR 2.56; 95% CI, 2.12–3.10) associated with joint family history remain high.
Discussion

In a large population-based study, we document the combined impact of family histories of CVD and diabetes on the population prevalence of CVD, diabetes, and risk factors, and in a longitudinal study, we examined their joint effect on the risk of mortality. Our analyses suggest that the relationship between family history of diabetes and family history of CVD is closer to additive than to multiplicative, for an outcome of diagnosis of CVD and diabetes, as well as diabetes only, and less than additive for CVD only. We find that participants with joint family history are diagnosed with diabetes, on average, 6.6 years earlier than participants without either family history, and that joint family history is associated with an increase in all-cause mortality but with no interactive effect. We found that participants with joint family history, who were not diagnosed with either disease and who have normal fasting glucose and HbA1C levels, were at a 1.5-fold increased odds (OR 1.45 95% CI, 1.09–1.94, p < 0.05) of having a high CRP level, suggesting that the targeted assessment of C reactive-protein levels, a biomarker of inflammation demonstrated to predict cardiovascular events [25], can potentially improve CVD risk discrimination in individuals with joint family history. In addition to shared genetics, factors such as diet, smoking, physical activity, anthropometric, and behavioral characteristics, as well as environmental factors such as air pollution can influence the association between family history and risk of CVD and diabetes. We found our results remained unchanged when adjusted by self-reported smoking status, and cotinine (a metabolite of nicotine and a biomarker of both primary and secondary smoking), and lead and cadmium, heavy metals that are common air pollutants emitted from industrial production (online suppl. Fig. 9), suggesting environmental level family effects of tobacco smoke and air pollutants may not be influencing the magnitude of our associations.

In a large prospective case-control study of European individuals, a genetic risk score and prominent lifestyle and anthropometric factors such as waist circumference and BMI explained only a marginal proportion of the family history-associated excess risk of type 2 diabetes, indicative of the strong, independent risk that family history confers [26]. A greater magnitude of family history (number and type of family members having type 2 diabetes) confers a stronger association with type 2 diabetes and CVD [27], independently, supporting the notion that joint family histories may confer a substantially increased genetic and/or shared environmental risk. Joint family history can result in a greater total number of inherited diabetogenic and CVD-associated genes, manifesting in a greater risk of both diseases. While epidemiological studies have established a higher cardiovascular and atherosclerotic burden in participants with diabetes, there is also evidence for vascular abnormalities being present prior to diabetes onset, leading to the “common soil” hypothesis that both arise from a shared antecedent [3, 28–30]. Our study builds on these findings by examining the interaction between total shared genetic variations (e.g., GWAS single nucleotide polymorphisms and other sources of genetic variation) at multiple loci as well as shared environmental, behavioral, and lifestyle factors of diabetes and CVD, captured by their respective family histories.

Study Limitations

This study has several limitations. First, NHANES is a cross-sectional survey and therefore cannot be used to establish causal relationships between family history, risk factors, and diagnosis of CVD and diabetes. Second, the family history data collected by the NHANES do not allow us to differentiate between family history of type 1 and type 2 diabetes. However, approximately 90–95% of US adults with diabetes have type 2 diabetes [31, 32]; therefore, the presented findings are mostly reflective of the impact of type 2 diabetes. Third, as in previous studies examining family history of CVD and diabetes using the NHANES [33, 34], we used self-reported family history and disease diagnosis information, which is prone to recall biases that may contribute to measurement error. However, the Newcastle Family History Study I found that the net recall bias for family history of CVD is toward the null [35], suggesting our results represent a conservative risk estimate for CVD associated with family history. Further, studies examining the accuracy of reported family history to that of physician-assessed status of close relatives or status reported by parents have found a sensitivity and specificity of 78.5% and 94.9% for family history of diabetes and 85% and 93% for family history of coronary heart disease, which may attenuate the magnitude of our associations [23, 24]. Reports from the Framingham Offspring Study and the NHLBI Family Heart Study suggest that the accuracy of a self-reported parental family history of CVD is not affected by CVD risk factors in the offspring reporter, and the accuracy of parental history reports for diabetes and CVD do not differ in offspring reporters with and without the condition [24, 36]. Based on these prior reports of the sensitivities of family history of diabetes and CVD and to further examine this limita-
Joint Impact of Family History of Diabetes and CVD

In this study, we have conducted a simulation study in NHANES 2007–2018, where we have found that at a conservative sensitivity estimate of joint family history, the PRs for CVD, diabetes, and both remain high, suggesting the associations between family history and CVD or diabetes remain robust to conservative recall bias (online suppl. Fig. 8) and different socioeconomic levels (online suppl. Fig. 10). Studies have found the sensitivity of self-reported diabetes and heart disease were 96% and 78%, respectively, and specificity ranged from 95% to 99% [37, 38]. To ensure we were thorough in our identification of participants with indicators of CVD in the NHANES, we included all participants with coronary heart disease, angina, heart attack, and stroke, following the inclusion criteria in a prior study on the cardiovascular health impact of family history of CVD in the NHANES [34]. Lastly, we were unable to investigate the separate effects of maternal and paternal history due to lack of stratified family history data according to lineage in the NHANES 2007–2018. Prior studies have compared disease risk conferred by paternal from maternal family history. For example, one study identified a stronger maternal than paternal transmission for CVD risk [39] and another identified excess maternal transmission of type 2 diabetes in a multi-ethnic cohort [40]. A study on parental burden to the risk of joint CVD and diabetes family history merits future investigation.

Conclusion

Public health efforts in the prevention of common chronic diseases tend to be disease oriented. For example, the identification of individuals at high risk of diabetes typically starts with asking about family history of diabetes. On the other hand, efforts to reduce the burden of heart disease have used family history of heart disease [34]. Clinical guidelines for standards of medical care published by the American Diabetes Association screen for a family history of diabetes in first- and second-degree relatives; however, given the much greater odds for having both diseases among individuals with joint family history, awareness of joint family history can help identify high-risk individuals who would benefit most from early screening and promotion of healthy lifestyle in order to reduce the overall risk of diabetes and heart disease.

The strong association between family history and prevalence of CVD and/or diabetes revealed by our study warrants further investigation into the genetic and environmental factors that compose family history, beyond the common risk factors considered here. Through public educational offerings, the Center for Disease Control hosts the Surgeon General’s My Family Health Portrait, an online tool for collecting family health history for multiple disease conditions, with a focus on heart disease, diabetes, and cancer [41]. Our findings underscore the public health impact and utility of family history as a tool for screening and identifying high-risk populations across chronic diseases.

Statement of Ethics

The National Health and Nutrition Examination Survey (NHANES) is a publicly available dataset. All participants of the NHANES study provided written informed consent to participate in the study, and the NHANES study was approved by the National Center of Health Statistics Research Ethics Review Board (NCHS ERB), per NCHS IRB/ERB Protocol Number #2005-06 for NHANES 2007–2008 and 2009–2010, NCHS IRB/ERB Protocol Number #2011-17 for NHANES 2011–2012, 2013-2014, 2015–2016, and NCHS IRB/ERB Protocol Number #2011-17 effective through October 26, 2017, and NCHS IRB/ERB Protocol Number #2018-01 effective beginning October 26, 2017, for NHANES 2017–2018 (available at: https://www.cdc.gov/nchs/nhanes/irb98.htm, last accessed January 27, 2022). Our analysis of the de-identified NHANES data is exempt from ethics approval as a secondary analysis of existing NHANES publicly available data under the US Health & Human Services (HHS) regulations at 45 CFR 46.101(b)(4) (available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html, last accessed January 27, 2022). Written informed consent to participate in the NHANES was obtained by all adult participants of the NHANES both before the household interview and before the health examinations. The consent documents as part of the protocol for the NHANES conducted by the National Center for Health Statistics are available for each survey year at: https://www.cdc.gov/nchs/nhanes (last accessed January 27, 2022). Our analysis of the anonymized and publicly available NHANES data is exempt from written informed consent as it is not human subjects research in accordance with the US Health & Human Services (HHS) regulations at 45 CFR 46.101(b)(4). By using the public-use data files of the NHANES, we signify our agreement to comply with the statutorily based requirements found in the Data User Agreement by the National Center for Health Statistics. The Data User Agreement can be found at: https://www.cdc.gov/nchs/data_access/restrictions.htm (last accessed January 27, 2022).

Conflict of Interest Statement

Chirag J. Patel is consultant and cofounder of XY Health, Inc. No other potential conflicts. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
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Author Contributions

Danielle Rasooly contributed to conceptualization, methodology, formal analysis, investigation, visualization, writing – original draft, and writing – review and editing. Quanhe Yang and Ramal Moonesinghe have contributed to methodology, formal analysis, and writing – review and editing. Muin J. Khoury and Chirag J. Patel have contributed to conceptualization, methodology, supervision, writing – original draft, and writing – review and editing.

Data Availability Statement

Publicly available datasets were analyzed in this study. Data can be downloaded from the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm).

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