Journal of Clinical & Translational Endocrinology 9 (2017) 8–14

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Physical inactivity and cardiac events: An analysis of the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study

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ARTICLE INFO

Article history:
Received 7 December 2016
Received in revised form 1 May 2017
Accepted 16 May 2017

Keywords:
Type 2 diabetes
Physical activity
Coronary artery disease

ABSTRACT

Aims: Diabetes affects 29 million adults, and the majority have type 2 diabetes (T2D). Coronary artery disease (CAD) is the leading cause of death, and physical inactivity is an important risk factor. The aims of this study were to examine the contribution of physical inactivity to CAD events, and to identify the independent predictors of CAD events in a sample of older adults with T2D.
Method: A secondary data analysis of the prospective randomized screening trial "Detection of Ischemia in Asymptomatic Diabetics (DIAD)" study. Cox proportional hazard modeling was used to examine the outcome of CAD events.
Results: During the five years of follow-up, the CAD event rate for all subjects ($n = 1119$) was 8.4% ($n = 94$). In unadjusted analysis, physical inactivity was significantly associated with development of a CAD event. In the final model, nine baseline variables were significant predictors ($p < 0.05$) of a CAD: physical inactivity, race, diabetes duration, hemoglobin A1c (HbA1c), peripheral numbness, insulin use, increasing waist-to-hip ratio, family history of premature CAD, and a higher pulse pressure. In men only, there were five predictors ($p < 0.05$) of a CAD event: diabetes duration, peripheral numbness, HbA1c, increasing waist-to-hip ratio, and higher pulse pressure. The final model in women included three independent predictors ($p < 0.05$) of a CAD event: diabetes duration, a family history of premature CAD, and higher pulse pressure.
Conclusion: Several variables predicted CAD events in this sample of older adults with T2D. Understanding baseline characteristics that heighten risk may assist providers in intervening early to prevent its occurrence.

Introduction

Diabetes mellitus affects 422 million adults worldwide [1] and 29 million adults in the United States (U.S.). Approximately 90–95% of these cases are type 2 diabetes (T2D) [2]. Complications of diabetes include heart disease and stroke, blindness, kidney failure, and lower-limb amputation [2] and the majority (68%) of people > 65 years old with diabetes will die of some form of heart disease [3]. Several self-management practices are recommended for the primary prevention of cardiovascular disease in the presence of diabetes, including blood pressure and lipid management, tobacco cessation, low-dose aspirin therapy, glycemic control of hemoglobin A1c (HbA1c) < 7%, as well as 150 min of moderate intensity physical activity per week [4–7]. Upon diagnosis of T2D, clinical care focuses on lifestyle management, including the component of physical activity [5].

In individuals with T2D, regular physical activity leads to improvements in HbA1c, blood glucose, insulin sensitivity, cardiorespiratory fitness, and importantly, the reduction of cardiovascular risk factors including hypertension, hyperlipidemia, body mass index, insulin resistance, and inflammatory markers[8,9]. In a recent *meta*-epidemiological study, physical activity interventions showed mortality benefits similar to drug interventions, except in heart failure, where diuretics were superior [10]. In the presence of stroke rehabilitation, physical activity outperformed drug interventions. Similarly, in a *meta*-analysis of 11 studies examining the association between physical activity and cardiovascular disease (CVD) in adults with diabetes, the highest level of physical activity in each study was associated with a lower relative risk of CVD (RR = 0.71; 95% CI 0.60–0.84) as compared to the lowest level of physical activity for that study [11]. In a prospective study that examined the combined effect of diabetes and physical activity on cardiovascular mortality in a large ($n = 53{,}587$)

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http://dx.doi.org/10.1016/j.jcte.2017.05.005
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population-based study, inactive adults with diabetes had a higher risk of CVD mortality (HR = 2.81; 95% CI: 1.93–4.07) as compared to inactive adults without diabetes [12]. In a pooled analysis of adults with diabetes in Great Britain, individuals who reported some physical activity, although it was below the recommended amount, had a lower risk of CVD mortality (HR = 0.68, 95% CI 0.51–0.92), as did those who met recommendations for physical activity (HR = 0.60, 95% CI 0.44–0.82) [13].

Previous studies have looked at the relationship between physical activity and a variety of fatal and non-fatal CVD outcomes in adults with diabetes and have assessed the contribution of some diabetes-related factors such as diabetes duration, HbA1c, microalbuminuria, and diabetes medications [14,15]. However, they have not included other diabetes-related complications such as neuropathy and retinopathy, which along with older age and higher body mass index (BMI), may affect not only CVD outcomes, but also engagement in physical activity.

In an analysis of older adults with diabetes, only 21% met the recommendations for 150 min of moderate physical activity per week [16]. Previous analyses of subjects with T2D enrolled in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study found that 24% of the sample were physically inactive at baseline which rose to 33% at 5-year follow-up ($p < 0.0001$) and mean hours of weekly physical activity decreased from 3.94 ± 5.30 to 2.63 ± 2.74 ($p < 0.0001$) [17]. Baseline factors predictive of physical inactivity at 5-year follow-up included lower level of education, higher HbA1c, presence of peripheral pain, BMI, and being physically inactive at baseline. Factors predictive of physical inactivity differed by sex when men and women were analyzed separately: levels of high-density lipoprotein and the presence of peripheral neuropathy symptoms were predictive for men, while the level of education, waist circumference and Black ethnicity were predictive for women. In separate analyses, physical inactivity, along with other clinical and diabetes-related factors, was associated with poorer quality of life [18]. We have also previously analyzed the role of cardiac autonomic neuropathy in the DIAD cohort, and identified predictors of subsequent cardiac events [19]. However, the role of physical activity was not accounted for in these analyses.

In a previous analysis, women in DIAD were found to be more likely classified as low risk by the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine ($p < 0.0001$) [20]. Women were significantly less likely to experience a cardiac death (HR = 0.17; 95% CI 0.04–0.77) or the composite endpoint (myocardial infarction or cardiac death) (HR = 0.44; 95% CI 0.20–0.96). However, outcomes for individual or composite secondary events (HR 1.03; 95% CI 0.53–2.01; $p = 0.1$)[20], as well as when all events were considered together [19], were similar in men and women. Currently, there are limited data on sex differences in adults with T2D when examined within racial/ethnic groups, and the data available are mixed in regards to the impact of sex on cardiovascular outcomes [21]. Furthermore, exactly how much physical activity is needed in diabetes to reduce CVD risk is unclear, but the consensus remains any physical activity level lowers CVD risk [22]. Despite the known benefits few adults, particularly those with T2D, meet recommendations for daily physical activity. Therefore, the aims of this secondary data analysis in subjects enrolled in the DIAD study were to:

1. Examine the contribution of physical inactivity to subsequent coronary artery disease (CAD) events (a composite endpoint including myocardial infarction (MI), cardiac death, acute coronary syndromes (ACS), heart failure (HF), and revascularization); and
2. Identify predictors of subsequent CAD events in all subjects, and individually in men and women, excluding the contribution of cardiac autonomic neuropathy measures

We hypothesize that physical inactivity will remain a significant contributor to CAD events, after controlling for other diabetes-related factors in the model.

Methods

Design

This is a secondary data analysis of the DIAD study, a five-year prospective randomized screening trial that assessed the prevalence of silent ischemia in asymptomatic patients with T2D [23]. The appropriate institutional review board approvals were obtained from each center. Patients (n = 1123) from 14 outpatient practices in the United States and Canada were randomized to screening with stress testing and follow-up, or to follow-up only. Four subjects did not complete the first six-month follow-up and are excluded from this analysis. DIAD inclusion criteria were (1) history of T2D with onset at age $\geq$ 30 years on no history of ketoacidosis; and (2) age between 50 and 75 years. Exclusion criteria included (1) angina pectoris or anginal equivalent symptoms; (2) stress test or coronary angiography in the three years prior to entry into the study; (3) history of MI, HF, or coronary revascularization; (4) electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST-segment or T-wave changes, or complete left bundle branch block; (5) any clinical indication for stress testing; (6) active bronchospasm, precluding the use of adenosine; (7) pregnancy; and (8) limited life expectancy due to the cancer or end-stage renal or liver disease [23].

Measures

Participants were contacted by telephone every 6 months for five years to assess the development of CAD events which included MI, cardiac death, ACS, HF, and revascularization [24]. Data collection has been described previously [19,23,24]. Four subjects did not complete the first six-month follow-up and were excluded from the analysis.

The Framingham Physical Activity Index (FPAI) was used to assess physical activity. The interviewer also asked the individual about the average hours of sleep, rest, occupation and extracurricular activities over a 24-h period [25]. Intensity of physical activity (sedentary, slight, moderate, or heavy) was also obtained. A composite score was obtained by summing the number of hours spent in each activity intensity level and multiplying by a weighting factor which was derived from the estimated oxygen consumption requirement for each level of intensity. As a reference, sleep or resting for 24 h would yield a score of 24. Reliability (test-re-test r = 0.3–0.59) and validity have been established and the scale has been used extensively in epidemiological studies [26]. In addition, one question asked subjects how many hours of physical activity they participated in on a weekly basis. Physical activity was assessed several ways: FPAI score, quartiles of FPAI scores, hours of physical activity, and hours categorized into 3 (none, some but < 150 min per week, and $\geq$ 150 min per week) and 2 (none or any) levels.

Statistical analysis

Analyses, conducted using SAS (Version 9.3), included descriptive statistics for baseline characteristics followed by chi-square and independent t-tests to compare men and women individually, and then to compare all subjects with or without a CAD, as well as according to sex. Variables significantly associated with a CAD event at $p < 0.10$ in the bivariate analyses were included in the multivariate analysis to determine independent predictors of a

CAD event. In our previous analysis of factors associated with CAD events, we identified predictors in the presence of cardiac autonomic neuropathy, which was strongly associated with CAD events [19]. Given the difficulty of performing cardiac autonomic testing in clinical practice, the present analysis did not consider these measures. After testing the proportionality assumption, Cox proportional hazard modeling was used to examine the outcome of CAD events in all subjects, as well as women (n = 519) and men (n = 600) separately, first in unadjusted analyses and then in multivariate analyses, with the model identified in all subjects as a guide in the sex-specific analyses. Addition of physical inactivity to the final Cox models in men and women was done to assess if its inclusion improved model fit or changed other parameter estimates. A level of $p \leq 0.05$ was considered significant.

Results

Baseline subject characteristics

Subject characteristics are shown in Table 1. There was no significant sex difference in relation to age (p = 0.33), duration of T2D (p = 0.53), insulin use (p = 0.18), HbA1c (p = 0.94), presence of retinopathy (p = 0.13), microalbuminuria (p = 0.66), or peripheral neuropathy symptoms (p = 0.69). There was a higher percentage of Black women (23%) as compared to men (11%; p < 0.0001). In addition, women tended to be less likely to work (p=<0.0001), had lower incomes (p < 0.0001), were more likely to live alone (p < 0.0001) and have fewer years of education (p < 0.0001). Women had higher body mass index (p < 0.0001), higher HDL levels (p < 0.0001) and pulse pressure (p < 0.0001), and were more likely to have a history of PVD (p = 0.02). Men were more likely to have symptoms of autonomic neuropathy (p < 0.0001), higher serum creatinine levels (p < 0.0001), and waist-to-hip ratio (p < 0.0001). Men had higher mean hours of physical activity hours per week (p = 0.01), as well when categorized into quartiles (p = 0.05) or mean FPAI scores (p = 0.04), but not when considered according to none/any (p = 0.71) or into three levels based on 150 min per week (p = 0.07). Differences were not observed in regard to FPAI quartile scores (data not shown).

Predictors of cardiac outcomes for all subjects

During the five years of follow-up, the CAD event rate for all subjects (n = 1119) was 8.4% (n = 94). Bivariate associations in all subjects, as well as in men and women separately are shown in Table 2, with a significant difference noted between those who had some level of activity versus those who had none, but not the other measures of physical activity. In unadjusted analysis, physical inactivity (no physical activity as compared to any physical activity), was significantly associated with development of a CAD event (HR = 1.60; 95% CI 1.05–2.46; p = 0.03). In the final Cox proportional hazard model for all subjects, in addition to physical inactivity (HR = 1.53; 95% 1.00–2.36; p = 0.05), eight baseline variables were significant predictors of a CAD event at five years (Table 3). These included: White race, as compared to Black or other races (HR = 2.63; 95% CI: 1.22–5.67; p = 0.01); each 1-year increase in diabetes duration (HR = 1.07; 95% CI: 1.04–1.10; p < 0.0001); each 1-point increase in HbA1c (HR = 1.27; 95% CI:1.11–1.45; p = 0.0004); the presence of peripheral numbness (HR = 1.97; 95% CI:1.30–2.99; p = 0.0003); the use of insulin (HR = 0.52; 95% CI: 0.30-0.89; p = 0.02); each 0.1 increase in waist-to-hip ratio (HR = 1.04; 95% CI:1.01–1.07; p = 0.0094); a family history of premature CAD (HR = 1.74; 95% CI 1.09–2.77; p = 0.02) and the highest quartile of pulse pressure (HR = 2.18; 95% CI:1.42–3.35; p = 0.0004). As previously noted, men tended to be more likely to experience a MI or cardiac death (p = 0.04), as well as undergo coronary artery bypass surgery (p = 0.02) more frequently than women, yielding an overall higher rate of all CAD events (p = 0.04) in unadjusted analysis (HR = 1.52; 95% CI 1.00–2.32; p = 0.05). However, sex was not a significant predictor of composite cardiac events in the final multivariate model (HR = 1.17; 95% CI: 0.72–1.93; p = 0.51).

Sex specific predictors

Over five years, the CAD event rate for men (n = 600) was 10% (n = 60). The unadjusted estimate for physical inactivity was HR = 1.47 (95% CI: 0.85–2.53; p = 0.17). The final model in men included five independent predictors of a CAD event: each 1-year increase in diabetes duration (HR = 1.04; 95% CI: 1.01–1.07; p = 0.01); the presence of peripheral numbness (HR = 2.03; 95% CI: 1.22–3.83; p = 0.007); each 1-point increase in HbA1c (HR = 1.18; 95% CI: 1.04–1.34; p = 0.009); each 0.1 increase in waist-to-hip ratio (HR = 1.04; 95% CI:1.00–1.08; p = 0.05); and highest quartile of pulse pressure (HR = 1.86; 95% CI:1.07–3.25; p = 0.02) (Table 3). When added to this model, the hazard ratio for physical activity (HR = 1.38; 95% CI: 0.80–2.40; p = 0.25) did not improve model fit, change other parameters, or result in a statistically significant effect.

Over five years the event rate for women (n = 519) was 6.6% (n = 34). The unadjusted estimate for physical inactivity was HR = 1.87 (95% CI 0.94–3.74; p = 0.08) and physical inactivity was not significant (HR = 1.64; 95% CI: 0.82–3.28; p = 0.16) in the final model, which included three independent predictors of a CAD event: each 1-year increase in diabetes duration (HR = 1.08; 95% CI:1.04–1.13; p = 0.0001); a family history of premature CAD (HR = 2.32; 95% CI 1.16–4.63;p = 0.02); and the highest quartile of pulse pressure (HR = 2.57; 95% CI:1.31–5.03; p = 0.006) (Table 3).

Discussion

Diabetes-related complications, including myocardial infarction, have declined in the past twenty years, while the prevalence of T2D continues to increase [27,28], and remains an important contributor to CVD risk. In this sample of older adults with T2D, several baseline factors were strongly predictive of CAD events, including several diabetes-related factors such as diabetes duration, HbA1c, the use of insulin, the presence of peripheral numbness (a surrogate measure of peripheral neuropathy), waist-to-hip ratio, and elevated pulse pressure. We have also highlighted the different factors predictive of an event in women as compared to men. Although as compared to men, in this study women were more likely to be on antihypertensive medication and equally likely to be on lipid lowering, it is known that women with diabetes have an unhealthier cardiovascular risk profile than men, which may be the result of treatment disparities [22]. Importantly, while the manifestations of CAD differed between men and women, with women being less likely to experience MI or cardiac death, as reported by others [29], women were just as likely to develop CAD, highlighting the importance of prevention and early detection of CAD in women with diabetes.

In the unadjusted analysis, physical inactivity was associated with having a CAD event, although this relationship was attenuated once other diabetes-related factors were controlled for in the model, supporting our hypothesis. While other studies have found an association between physical inactivity and cardiac events, diabetes-specific factors, such as disease duration, HbA1c, measures of peripheral neuropathy were often not assessed. In a *meta*-analysis of 11 studies examining the association between

Table 1
Characteristics of Study Participants according to Sex (n = 1119).

	Men N = 600 (54%)	Women N = 519 (46%)	p	All
Age – yr (mean ± sd)	61 ± 6.7	61 ± 6.4	0.33	60.7 ± 6.6
Ethnicity - No. (%)				
White	492 (82%)	379 (73%)		871 (78%)
Black	70 (12%)	120 (23%)		190 (17%)
Other	38 (6%)	20 (4%)	<0.0001	38 (6%)
Employment				
Work full or part time	369 (62%)	248 (47%)		617 (55%)
Retired	198 (33%)	201 (39%)		399 (36%)
Other	33 (5%)	79 (13%)	<0.0001	103 (9%)
Income				
<$25,000	53 (9%)	117 (23%)		170 (15%)
$25,000 – 49,999	113 (19%)	132 (25%)		245 (22%)
> = $50,000	312 (52%)	152 (29%)		464 (41%
Refused	122 (20%	118 (23%)	<0.0001	240 (21%)
Marital Status				
Lives alone	116 (19%)	250 (48%)		366 (33%)
Lives with significant other	484 (81%)	269 (52%)	<0.0001	753 (67%)
Education (years)	15.7 ± 3.5	13.9 ± 3.7	<0.0001	14.7 ± 3.67
Diabetes-Related Factors				
Diabetes duration – yrs (mean ± sd)	8.6 ± 7.2	8.4 ± 6.8	0.53	8.5 ± 7.0
HbA1C - % (mean ± sd)	7.1 ± 1.5	7.1 ± 1.5	0.94	7.1 ± 1.5
Insulin - No. (%)	130 (22%)	130 (25%)	0.18	260 (23%)
Albuminuria - No. (%)				
<30 μg/mg	443 (75%)	391 (77%)		834 (75%)
30–299 μg/mg	121 (21%)	94 (19%)		215 (20%)
> = 299 μg/mg	26 (4%)	20 (4%)	0.66	58 (4%)
Serum creatinine mg/dL	1.06 ± 0.30	0.86 ± 0.28	<0.0001	0.97 ± 0.31
Retinopathy - No. (%)	102 (17%)	71 (14%)	0.13	173 (15%)
Peripheral numbness	201 (34%)	190 (37%)	0.27	450 (40%)
Cardiac-Risk Factors				
Body Mass Index – kg/m^2 (mean ± sd)	29.9 ± 5.2	32.5 ± 7.2	<0.0001	31.1 ± 6.3
Waist:hip ratio	0.98 ± 0.07	0.89 ± 0.08	<0.0001	0.94 ± 0.09
LDL - mg/dL - No. (%)	113 ± 32	115 ± 34	0.44	114 ± 33
HDL - mg/dL	46 ± 12	54 ± 16	<0.0001	49.6 ± 15
Lipid treatment - No. (%)	296 (49%)	231 (45%)	0.11	527 (47%)
Statin use - No. (%)	243 (41%)	194 (37%)	0.29	437 (39%)
SBP	130.5 ± 15.4	131.9 ± 17.5	0.16	131.2 ± 16.4
DBP	79.6 ± 8.4	77.8 ± 8.3	.0002	78.8 ± 8.4
Pulse pressure	50.9 ± 12.4	54.1 ± 14.3	<0.0001	52.4 ± 13.4
Hypertension treatment - No. (%)	313 (52%)	321 (62%)	0.001	634 (57%)
PVD	44 (7%)	59 (11%)	0.02	103 (9%)
Current smoking	59 (10%)	48 (9%)	.74	107 (10%)
Family history	103 (17%)	111 (21%)	0.07	214 (19%)
Physical Activity – M ± SD	3.96 ± 4.0	3.4 ± 3.4	0.01	3.7 ± 3.77
FPAI	33.9 ± 6.6	33.1 ± 6.2		33.5 ± 6.4
Hours of physical activity (quartiles)				
None	148 (25%)	133 (34%)		281 (25%)
≤3	156 (26%)	156 (29%)		312 (28%)
>3 - < 0.5.5	122 (20%)	117 (16%)		239 (21%)
≥5.5	174 (29%)	113 (21%)	0.05	287 (26%)
Hours of physical activity				
None	148 (25%)	133 (26%)		281 (25%)
Some - < 150 mins/week	156 (26%)	116 (22%)		312 (28%)
≥150 min per week	296 (49%)	270 (52%)	0.07	526 (47%)
Hours of physical activity				
None	148 (25%)	133 (26%)		281 (25%)
Any	452 (75%)	386 (74%)	0.71	838 (75%)
Outcomes				
Cardiac death or MI	23 (3.8%)	9 (1.7%)	0.04	32 (2.9%)
Unstable angina or HF	10 (1.7%)	10 (1.9%)	0.74	20 (1.7%)
CABG	26 (4.3%)	10 (1.9%)	0.02	36 (3.2%)
PCI	24 (4.0%)	18 (3.5%)	0.64	42 (3.8%)
All cardiac events	60 (10%)	34 (6.6%)	0.04	94 (8.4%)

CABG = coronary artery bypass surgery; BP = diastolic blood pressure; HDL = high-density lipoprotein cholesterol; FPAI = Framingham Physical Activity Index; HF = heart failure; HTN = hypertension; LDL = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; SBP = systolic blood pressure.

physical activity and CVD in adults with diabetes, higher levels of physical activity were associated with a lower relative risk of CVD [11]. However, the authors note less than half of the studies adjusted for the classic CVD risk factors of age, sex, smoking, dyslipidemia and hypertension, with the only diabetes-related factor accounted for, in just three studies, was diabetes severity [30–32].

Table 2
Factors Associated With CAD Events.

Factor	Men (*n* = 600) No event *n* = 540	Event *n* = 60	*p*	Women (*n* = 519) No Event *n* = 485	Event *n* = 34	*p*	All (*n* = 1119) No event *n* = 1025	Event *n* = 94	*p*
Age (yrs)	60.8 ± 6.8	61.7 ± 6.1	0.35	60.4 ± 6.5	61.9 ± 6.0	0.18	60.6 ± 6.6	61.8 ± 6.0	0.11
Sex									
Male	–	–	–	–	–	–	540 (53)	60 (64)	
Female							485 (47)	34 (36)	0.04
Race									
White	441 (82)	51 (85)		349 (72)	30 (88)		790 (77)	81 (86)	
Black	65 (12)	5 (8)	0.70	117 (24)	3 (9)	0.11	182 (18)	8 (9)	
Other	34 (6)	4 (7)		19 (4)	1 (3)		53 (5)	5 (5)	0.07
Diabetes-related Factors									
T2D duration (yrs)	8.28 ± 7.0	11.8 ± 7.7	0.0002	8.05 ± 6.6	12.97 ± 8.1	<0.0001	8.2 ± 6.8	12.3 ± 7.8	<0.0001
Age at T2D diagnosis (yrs)	52.6 ± 8.4	49.9 ± 7.7	0.02	52.4 ± 9.1	49 ± 9.9	0.04	52 ± 8.7	50 ± 8.6	0.002
HbA1c (%)	7.02 ± 1.5	7.7 ± 1.4	.001	7.07 ± 1.5	7.22 ± 1.6	.58	7.0 ± 1.5	7.5 ± 1.5	.004
Insulin use	110 (20)	20 (33)	0.02	123 (25)	7 (21)	0.53	233 (23)	27 (29)	0.19
MCR									
<30 µg/mg	409 (77)	34 (59)		371 (78)	20 (61)		780 (78)	54 (59)	
30–299 µg/mg	103 (19)	18 (31)		84 (18)	10 (30)		187 (18)	28 (31)	
>299 µg/mg	20 (4)	6 (10)	0.0004	17 (4)	3 (9)	0.04	37 (4)	9 (10)	0.0002
Serum creatinine (mg/dL)	1.05 ± 0.27	1.1 ± 0.49	0.35	.86 ± 0.28	0.91 ± 0.35	0.46	0.96 ± 0.29	1.04 ± 0.45	0.11
Retinopathy	86 (16)	16 (27)	0.04	63 (13)	8 (24)	0.08	149 (15)	24 (26)	0.005
Peripheral numbness	170 (31)	31 (52)	0.002	173 (36)	17 (50)	0.09	343 (33)	48 (51)	0.0006
Cardiac Risk Factors									
Waist: hip ratio	0.98 ± 0.67	0.99 ± 0.62	0.03	0.89 ± 0.08	0.91 ± 0.08	0.28	0.94 ± 0.09	0.96 ± 0.08	0.002
LDL-mg/dL	112 ± 31	124 ± 37	0.008	115 ± 34	114 ± 32	0.88	120 ± 35	113 ± 32	0.06
HDL-mg/dL	46 ± 12	44 ± 11	0.31	54 ± 16	51 ± 16	0.26	50 ± 15	47 ± 13	0.04
Triglycerides	170 ± 113	176 ± 117	0.72	166 ± 104	215 ± 102	0.008	168 ± 109	190 ± 113	0.06
Lipid treatment	264 (49)	32 (53)	0.51	211 (44)	20 (59)	0.08	475 (46)	52 (55)	0.10
SBP	130 ± 15	136 ± 17	0.008	132 ± 17	136 ± 18	0.15	131 ± 16	136 ± 17	0.005
PP > 60.3 mmHg	109 (20)	22 (37)	0.003	131 (27)	17 (50)	0.004	51.9 ± 13.3	57.5 ± 14.4	0.0001
HTN treatment	278 (51)	35 (58)	0.31	98 (61)	23 (68)	0.47	576 (56)	58 (62)	0.30
Family history	90 (17)	13 (22)	0.33	98 (20)	13 (38)	0.01	188 (18)	26 (28)	0.03
PVD	34(6)	10 (17)	0.004	52 (11)	7 (21)	0.08	86 (8)	17 (18)	0.002
Current smoking	52 (10)	7 (12)	0.62	43 (9)	5 (15)	0.26	95 (9)	12 (13)	0.27
Hours of PA									
None	129 (24)	19 (32)		120 (25)	13 (38)		249 (24)	32 (34)	
Any	411 (76)	41 (68)	0.19	365 (75)	21 (62)	0.08	776 (76)	62 (66)	0.04

Note. Data presented as mean±sd or *n* (%); CAD = coronary artery disease; yrs=years; T2D=type 2 diabetes; HbA1c=hemoglobin A1c; MCR=microalbumin creatinine ratio;µg/mg=micrograms/milligram; mg/dL=milligrams/deciliter; LDL= low-density lipoprotein; HDL= high-density lipoprotein; SBP=systolic blood pressure; PP=pulse pressure; HTN=hypertension; PVD=peripheral vascular disease; FPAI= Framingham Physical Activity Index; PA=physical activity.

Table 3
Predictors of Cardiac Events in Final Cox Proportional Model.

Factor	Men (n = 600) HR	95% CI	*p*	Women (n = 519) HR	95% CI	*p*	All (n = 1119) HR	95% CI	*p*
White race							2.63	1.22–5.67	0.01
Diabetes duration[1]	1.04	1.01–1.07	0.01	1.08	1.04–1.13	0.0001	1.07	1.04–1.10	<0.0001
HbA1c[2]	1.18	1.04–1.34	0.009				1.27	1.11–1.45	0.0004
Insulin use							0.52	0.30–0.89	0.02
Peripheral numbness	2.03	1.22–3.83	0.007				1.97	1.30–2.99	0.0003
Waist:hip ratio[3]	1.04	1.00–1.08	0.05				1.04	1.01–1.07	0.0094
Pulse pressure—highest quartile	1.86	1.07–3.25	0.02	2.57	1.31–5.03	0.006	2.18	1.42–3.35	0.0004
Family history				2.32	1.16–4.63	0.02	1.74	1.09–2.77	0.02
Physical inactivity							1.53	1.00–2.36	0.05

Note. CI=confidence interval; HbA1c=hemoglobin A1c; CAD=coronary artery disease; [1]=Each 1-year increase; [2]=Each 1-point increase; [3]=Each 0.1 increase.

Alternately, a prospective study examined the combined effect of diabetes and physical activity on CVD mortality in a large (n = 53,587) population-based study [12]. Compared to inactive adults without diabetes, inactive adults with diabetes had a higher risk of cardiovascular mortality (HR = 2.81; 95% CI: 1.93–4.07). Additionally, those with diabetes who reported at least three hours of light activity per week had a lower risk of cardiovascular mortality than those who were inactive (HR = 0.89; 95% CI: 0.48–1.63; $p < 0.001$). All models were adjusted for age, education, smoking status, alcohol consumption, systolic blood pressure, and cholesterol, but not diabetes-associated factors. Overall, levels of physical activity were low in the DIAD population, with less than half engaging in physical activity for 150 or minutes or more a week. Our findings are in agreement with others who demonstrated that some amount of activity, even if it did not meet the recommended level, is important in reducing CVD risk and reinforces the importance of physical inactivity in a sample with T2D, although this relationship was attenuated once the effect of other diabetes-related factors, which are stronger predictors, are considered.

An increase in diabetes duration was a strong predictor of a cardiac event. This result is consistent with those in a previous study with over 11,000 participants with T2D enrolled in the Action in

Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [33]. In those participants, every five-year increase in duration of T2D increased the adjusted risk of macrovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 13% when adjusting for age, and 49% when adjusting for age at diagnosis. Given the increased risk of CVD with longer duration of T2D, interventions to prevent CVD are critical. The intensive lifestyle intervention arm of the Diabetes Prevention Program for individuals at risk of developing diabetes focused on two of the modifiable risk factors for T2D: weight loss and sedentary behavior, with the goals of weight loss of 7% of body weight and 150 min per week of moderate physical activity per week [34]. The physical activity goal was thought to be achievable, and help prevent the onset of diabetes. Indeed, the intervention reduced the risk of T2D by 58% [35]. Prevention of T2D allows individuals to not only decrease their risk of diabetes, but also of associated risk factors for CVD.

Increases in HbA1c also predicted an increased risk of cardiac events. An recent analysis of a large cohort of patients with diabetes (n = 859,617) enrolled in 11 healthcare organizations in the U.S. examined the effects of inadequately controlled HbA1c, high LDL-cholesterol, high blood pressure, and current smoking on the incidence of major cardiovascular events [36]. In adults (45% were between ages 50–64) with diabetes, but without baseline CVD, an HbA1c $\geq$ 9% was associated with an elevated risk of MI/ACS (OR = 1.18; 95% CI: 1.14–1.23), stroke (OR = 1.29; 95% CI: 1.23–1.34), and HF (OR = 1.37; 95% CI: 1.31–1.44). Furthermore, inadequately controlled HbA1c was associated with 10% of heart failure deaths [36]. Our findings regarding the presence of peripheral numbness reflect poor long-term control of blood glucose. Of note, while use of insulin in our unadjusted analysis was associated with an increased risk a CAD event, once duration and HbA1c were included, insulin use was associated was associated with a lower risk.

Of interest are data from over 65,000 patients treated for T2D, which showed an association between physical inactivity, glycemic control (as measured by HbA1c) and cardiovascular risk profile [37]. The subjects were divided into two age groups: younger (age 20–59) and older (age 60–80). Physical activity levels were categorized as inactive, 1–2 days per week, or $\geq$2 days per week. In both the younger and older subjects, three indices of cardiovascular risk (body mass index, HbA1c and triglycerides) were lower in the most active group. Additionally, mean pulse pressure was significantly lower in the most active as compared to inactive, but only in the younger subjects.

Our study also found an increase in pulse pressure was associated with an increased risk of cardiac events. In another longitudinal study with older adults with T2D (n = 2911), pulse pressure, as compared to systolic or diastolic blood pressure, was found to be the strongest predictor of coronary heart disease events [38]. Similar outcomes were also found in a large observational study of adults (n = 5521) age 50–74 with T2D but without previous history of CVD [39]. Mean pulse pressure $\geq$ 75 mmHg, as compared to a mean pulse pressure < 75 mmHg, was associated with an increased risk of coronary heart disease (adjusted HR = 1.32; 95% CI: 1.07–1.62; p = 0.009) and CVD (adjusted HR = 1.28; 95% CI: 1.07–1.52; p = 0.007), after accounting for clinical characteristics and several cardiovascular risk factors. The authors concluded that significant reduction in CVD risk is possible with a lower pulse pressure, highlighting the need for reduction of this parameter. In a systematic review of randomized controlled trials, structured exercise has been shown to reduce both systolic and diastolic blood pressure in adults with T2D as compared to controls [40], providing one more incentive for promoting regular physical activity in this population. The combination of being physically active, treated with appropriate pharmacological agents, and having glycemic control has been shown to reduce CVD mortality risk to a level similar to that of a normoglycemic adult [41].

Differences in CAD predictors were found between men and women. Whether this was the result of the specific outcomes observed in each – hard CAD events in men and softer events in women – is unknown. Of note, the presence of peripheral numbness, a symptom of underlying peripheral neuropathy, while found similarly in both men and women, contributed to risk prediction in men, but not in women. In women, the presence of a family history of premature CAD was strongly associated with CAD risk. While we limited family history to a first-degree, research has shown that a family history in other relatives is also associated with an increase risk relative [42]. Nonetheless, these two readily available risk factors should be routinely assessed.

Despite the attenuated risk associated with physical inactivity overall and it not remaining an independent predictor of CAD events in either men or women, once other diabetes-related factors were accounted for in the model, its importance should not be underestimated, particularly in women, where in unadjusted analysis it was a stronger predictor than in men. Men had significantly more hours of physical activity per week than women, and consistent with the findings of others, women were slightly less likely to achieve American Diabetes Association recommendations for physical activity (adjusted OR = 0.76; 95% CI: 0.68–0.84) [16]. Over time physical activity may be an important strategy for maintaining appropriate body weight, blood glucose control, and blood pressure, the very factors that were independently associated with CAD events.

Limitations and strengths

There were several limitations to this study. Predictors were only measured at baseline and at the 5-year follow-up and may have varied in the interim. Additionally, physical activity data were obtained by self-report and the duration and intensity may have been over- or underestimated. Because of our low hard cardiac event rate we needed to rely on additional outcomes, such as development of heart failure and revascularization. Our relatively small sample size, particularly in sex-specific analyses, resulted in limited statistical power. But the study strengths include a large cohort study with five years of follow-up that included an extensive assessment of diabetes-related factors, and their contribution to cardiovascular events.

Conclusion

In this analysis, we identified several variables that were predictive of the onset of cardiac events in this sample of older adults with T2D. Understanding baseline characteristics that heighten risk may assist providers in identifying those who are at high risk for development of CAD and intervening early to prevent its occurrence.

Author contributions

Dr. McCarthy – data analysis and manuscript preparation.

Dr. Chyun – study design and data analysis; manuscript preparation.

Dr. Wackers – study design; manuscript review and critical revisions.

Ms. Davey – study recruitment and follow-up; study coordinator; manuscript review and critical revisions.

Acknowledgements

Conflicts of interest: None.

Source of Funding for original DIAD study: General Clinical Research Centers at Yale University (National Institutes of Health M01-RR-00125), University of Rochester (NIH 5M01-RR-00847), and Tulane University (NIH 6M01-RR-05096).

The DIAD study was supported by grants from Bristol Myers-Squibb Medical Imaging (North Billerica, Massachusetts, USA) and Astellas Pharma (Deerfield, Michigan, USA), who also provided Technetium-99 m Sestamibi (Cardiolite®) and Adenosine (Adenoscan®) for study patients.

For current analysis: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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