Received: 2 January 2024 | Accepted: 10 March 2024

DOI: 10.1111/dme.15317

DIABETIC Medicine

RESEARCH ARTICLE

Epidemiology

Association of physical activity and sports participation with insulin resistance and non-alcoholic fatty liver disease in people with type 1 diabetes

M. de Vries[1] | **J. Westerink**[2] | **H. A. H. Kaasjager**[1] | **H. W. de Valk**[1] | **on behalf of the UCC-SMART Study Group**

[1]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Department of Internal Medicine, Isala Hospital, Zwolle, the Netherlands

Correspondence
M. de Vries, Department of Internal Medicine, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.
Email: m.devries-19@umcutrecht.nl

Abstract

Aim: To evaluate the association between physical activity (PA) and sports participation with insulin resistance and non-alcoholic fatty liver disease (NAFLD) in people with type 1 diabetes (T1D).

Methods: People with T1D from a secondary and tertiary care centre were included. Questionnaire-derived PA was expressed in metabolic equivalent of task hours per week (METh/week). Insulin sensitivity was calculated with the estimated glucose disposal rate (eGDR). NAFLD was assessed by transient elastography (TE). Multivariate linear and logistic regression models were conducted, adjusted for age, sex, diabetes duration and BMI.

Results: In total, 254 participants were included (men 56%, age 44 ± 14 years, diabetes duration 24 ± 14 years, median BMI 24.8 kg/m^2), of which 150 participants underwent TE. Total PA (median 50.7 METh/week) was not significantly associated with insulin resistance (median eGDR 7.31 mg/kg/min) (beta −0.00, 95% CI −0.01 to 0.00) or with NAFLD (OR 1.00, 95% CI 0.99–1.01). Participating in sports was significantly associated with eGDR (beta 0.94, 95% CI 0.48–1.41) and with NAFLD (OR 0.21, 95% CI 0.08–0.56).

Conclusions: In our T1D population, we could not find any dose-dependent association between PA, insulin resistance and NAFLD. People participating in sports had a lower degree of insulin resistance and lower odds for NAFLD.

KEYWORDS

insulin resistance, NAFLD, non-alcoholic fatty liver disease, physical activity, sports participation, type 1 diabetes

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide.[1] Type 2 diabetes (T2D) and obesity are the most important risk factors for the development of NAFLD as well as its progression from isolated hepatic steatosis (HS) to more advanced stages including non-alcoholic steatohepatitis (NASH) and fibrosis through the pathway of insulin resistance.[2] Although mostly a hallmark of T2D,

the prevalence of NAFLD in people with type 1 diabetes (T1D) is considerable at 20%.[3,4] In people with T2D as well as T1D, the presence of NAFLD is associated with insulin resistance.[3,5]

Current NAFLD guidelines recommend lifestyle changes – consisting of weight reduction, healthy diet and promotion of physical activity (PA) – as first-line treatment.[6–8] A recent large study in individuals with and without T2D indeed showed beneficial effects of leisure-time PA (LTPA) on NAFLD.[9] LTPA had a dose-dependent protective effect on NAFLD and patients reaching the PA threshold as recommended in international guidelines suffered from NAFLD less often than patients not reaching this threshold.[9] Furthermore, reaching over two times the recommended level of LTPA was associated with a lower risk of significant fibrosis and cirrhosis.[9]

In clinical care for people with T1D, the focus is mainly on optimizing insulin therapy, while guidelines also stress PA as treatment target.[10] With the increasing amount of people suffering from T1D in combination with features of the metabolic syndrome ("double diabetes"), lifestyle modification might be beneficial in the prevention and treatment of diabetes-related complications.[11] In this study, we aim to evaluate the association of PA and sports participation with insulin resistance and prevalence of NAFLD in people with T1D.

What's new?

- Prevalence of non-alcoholic fatty liver disease (NAFLD) in type 1 diabetes (T1D) is considerable at 20%. Guidelines on NAFLD and T1D recommend lifestyle changes, including physical activity (PA), as treatment target.
- We did not find any dose-dependent association between self-reported PA and either insulin resistance or NAFLD. Still, people participating in sports, indicating a healthy lifestyle, had a lower degree of insulin resistance and lower odds for NAFLD.
- In people with T1D lifestyle management is pivotal, especially in those with NAFLD. Accelerometer-based studies could evaluate the effect of sedentary versus non-sedentary behaviour on insulin resistance and risk of NAFLD.

2 | MATERIALS AND METHODS

2.1 | Study design and Setting

This cross-sectional study was conducted at University Medical Center Utrecht (UMC Utrecht), a secondary and tertiary (academic) care centre for people with T1D. In the Netherlands, all T1D care is hospital based, with UMC Utrecht serving as a representative centre for the regular T1D population. Participants from two different cohorts were combined, of which patient inclusion and data collection and measurements were described in detail in earlier reports.[3,12]

2.2 | Participants

One third of participants was derived from the Utrecht Cardiovascular Cohort – Second Manifestations of ARTerial disease (UCC SMART) cohort.[12] This is an ongoing prospective cohort, which includes people aged 18–80 years referred to UMC Utrecht for management of manifest vascular disease or cardiovascular risk factors. For the present study, people with known T1D at baseline included in the UCC SMART cohort between January 2002 and November 2018 were included ($n = 104$). In UCC SMART, T1D was defined as diagnosis of diabetes before or at the age of 30 and the use of insulin.[12] The diagnosis of T1D was checked in the electronic health records for all participants. Two thirds of participants were included in a cohort of patients who participated in a T1D and NAFLD study (DILIVER) ($n = 150$).[3] People were included between September and December 2019. In DILIVER, T1D was defined by the use of insulin, in combination with either the presence of anti-GAD or anti-islet cell auto-antibodies, and/or a clearly documented diagnosis of T1D. Exclusion criteria were known secondary causes of hepatic steatosis or fibrosis, including former or present excessive alcohol consumption, defined as >21 standard drinks per week in men and >14 standard drinks per week in women.[7] If people participated in both the UCC SMART cohort and the DILIVER cohort, the most recent patient data from the DILIVER cohort were used. The study was approved by the medical ethics committee of UMC Utrecht and written consent has been obtained from each patient.

2.3 | Outcomes

Insulin resistance was assessed with the formula of the estimated glucose disposal rate (eGDR): 21.158 + (−0.09*waist circumference (cm)) + (−3.407*hypertension (y/n)) + (−0.551*HbA1c (%)).[13,14] Hypertension was defined as blood pressure > 140/90 mmHg and/or the use of anti-hypertensive medication (0 = no, 1 = yes). We used the eGDR formula with waist circumference instead of waist-to-hip-ratio (WHR) because of the more comprehensive availability of data. In the original study by Williams et al., waist circumference demonstrated a

pattern of results similar to that of WHR.[13] Lower eGDR values reflect higher insulin resistance.

NAFLD was assessed by transient elastography (TE) controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) as previously described.[3] TE was performed only in the DILIVER cohort. NAFLD was defined as hepatic steatosis (CAP ≥274 dB/m), either with or without fibrosis (LSM ≥8.2 kPa for both M- and XL-probe).[15]

2.4 | Physical activity and participation in sports

PA was measured with the previously validated EPIC questionnaire considering the past 12 months, suitable for ranking subjects.[16] Patients reported number of hours spent on walking, cycling, gardening and sports were multiplied by a corresponding metabolic equivalent of task (MET) derived from the Compendium of Physical Activities, yielding an amount of MET hours (METh) per week per activity.[17] PA was reported as METh per week (METh/week) for (1) activity from sports, (2) activity from other activities (i.e. the sum of walking, cycling and gardening) and (3) total activities (i.e. the sum of activity from sports and other activities). The EPIC PA questionnaire also includes a question about sports participation (yes/no, definition of sports at the patient's discretion).[16] For the secondary analyses, intensity of activities was divided into low, moderate and vigorous (MET <3.0, 3.0–6.0 and ≥6.0) and PA was categorized into meeting PA guidelines or not. The American Diabetes Association and World Health Organisation PA guidelines recommend engaging in activities of moderate intensity for at least 150 minutes per week, in activities of vigorous intensity for at least 75 minutes per week or in an equivalent combination corresponding to at least 7.5 METh per week.[10,18]

2.5 | Statistical methods

Analyses were performed using SPSS software version 26.0.0.1. Data are mean ± SD, median [IQR] or frequencies (percentage), when appropriate. Missing values were imputed by multiple imputation, using logistic regression models for categorical variables, and linear regression models in combination with predictive mean matching for continuous variables. Five multiple imputed datasets were created per cohort. Primary analyses were performed with merged imputed datasets. In the DILIVER, cohort imputation was performed for waist circumference (36.7%), PA from sports (12.7%), PA from other activities (8.0%), lipids (0.7%), blood pressure (0.7%) and weight (0.7%). In the SMART cohort, imputation was performed for waist circumference (1.9%), PA from sports (11.5%), HbA1c (1.9%), LDL cholesterol (2.9%), TG, HDL cholesterol and total cholesterol (1.9%), MDRD (1.9%) and diastolic blood pressure (1.0%).

For the primary analyses, to assess the association between PA and insulin resistance, linear regression analyses were performed with PA in METh/week as independent variable and eGDR as dependent variable. To assess the association between PA and hepatic steatosis and liver stiffness, linear regression analyses were performed with PA in METh/week as independent variable and CAP and LSM as dependent variables. To assess the association between PA and the presence of NAFLD, multivariate binary logistic regression analyses were performed with PA in METh/week as independent variable and NAFLD as dichotomous dependent variable. For both linear and logistic regression analyses, three determinants were used separately: (1) PA from sports, (2) PA from other activities and (3) total PA. All models were adjusted for potential confounders age, sex, diabetes duration and BMI. Results were expressed as regression coefficient (B) or as odds ratio (OR), with a 95% confidence interval (CI). *p*-value <0.05 was considered statistically significant. To assess the possible effect modification of age and sex on the association between PA and the outcome, interaction analysis for age and sex was performed in all models. *p*-value of the interaction term <0.05 was considered statistically significant. Assumptions of linear regression analysis – linearity between independent variable and outcome, normal distribution of residuals and homogeneity of variance – were checked visually.

Secondary exploratory analyses were performed with similar outcomes and confounders as in the primary analyses. Additionally, in the NAFLD models, eGDR was added as a confounder instead of BMI. Subsequently, a model was created for three dichotomous independent variables: (1) meeting PA guidelines or not, (2) performing sports or not and (3) within participants performing sports: engaging in activities of vigorous intensity or only in activities of low/moderate intensity.

3 | RESULTS

3.1 | Participants' characteristics

Baseline characteristics are shown in Table 1. In total, 254 participants were included, of which 150 underwent TE. Mean age was 44 ± 14 years, 56% were men, mean diabetes duration was 24 ± 14 years and median glycaemic control was moderate (HbA1c 62 mmol/mol (7.8%)). Median BMI was 24.8 kg/m^2 [22.6–27.8]. Thirteen per cent of participants had cardiovascular disease at inclusion. Baseline data on determinants and outcomes are shown in Table 2.

TABLE 1 Baseline characteristics of total type 1 diabetes population.

	Participants with T1D ($n=254$)
Age, years	43.7 ± 13.9
Sex, men	142 (55.9)
Diabetes duration, years	23.9 ± 13.7
Current smoking	51 (20.1)
Metabolic syndrome[a]	84 (33.2)
Weight, kg	79.1 ± 14.2
Height, m	1.76 ± 0.10
BMI, kg/m^2	24.8 [22.6-27.8]
Waist circumference, cm	88.8 ± 13.6
Systolic blood pressure, mmHg	133 ± 17
Diastolic blood pressure, mmHg	81 ± 10
Total cholesterol, mmol/L	4.53 ± 1.05
Triglycerides, mmol/L	0.96 [0.70-1.40]
HDL cholesterol, mmol/L	1.53 ± 0.44
LDL cholesterol, mmol/L	2.50 ± 0.87
eGFR (MDRD), ml/min/1.73 m^2	90 [88-90]
HbA1c, mmol/mol	62 [55-68]
HbA1c, %	7.8 [7.2-8.4]
Anti-hypertensive medication	87 (34.3)
Lipid-lowering medication	73 (28.7)
Retinopathy[b]	51 (34.0)
Neuropathy[b]	43 (28.7)
Nephropathy[b]	19 (12.7)
Cardiovascular disease[c]	32 (12.7)

Note: *n* (%), mean ± SD, median [IQR].

Abbreviation: T1D, type 1 diabetes.

[a]Metabolic syndrome was defined according to an adapted version of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria.[36,37]

[b]$n=150$, only available in DILIVER cohort.

[c]Coronary artery disease, stroke or peripheral arterial disease.

Median eGDR was 7.31 mg/kg/min [4.95–9.25]. Twenty per cent of participants ($n=30/150$) had NAFLD. Median PA from sports in the total group was 5.9 METh/week [0–20.1], respectively, and 16.5 METh/week [10.7–26.8] in participants engaging in sports activities. Median PA from other activities (walking, cycling and gardening) was 35.9 METh/week [20.2–63.8] and total PA was 50.7 METh/week [28.4–82.0]. The great majority of participants (97%) fulfilled the PA guideline recommendation of engaging in moderate or vigorous PA for at least ≥7.5 METh/week. Fifty-six per cent of the total group and two third of participants who underwent TE performed sports. Within participants performing sports, one third of participants engaged in activities of vigorous intensity.

TABLE 2 Baseline data on physical activity, insulin resistance and NAFLD.

	Participants with T1D	
	Total group ($n=254$)	DILIVER cohort ($n=150$)
PA sports, METh/week	5.9 [0.0–20.1]	11.2 [0–23.2]
PA sports (within pts performing sports), METh/week	16.5 [10.7–26.8]	17.6 [11.0–27.6]
PA other, METh/week	35.9 [20.2–63.8]	38.2 [20.7–66.1]
PA total, METh/week	50.7 [28.4–82.0]	58.6 [32.6–88.2]
PA guideline yes	245 (96.5)	146 (97.3)
Performing sports yes	143 (56.3)	103 (68.7)
Performing PA vigorous intensity yes (within pts performing sports)	48 (33.6)	35 (34.0)
eGDR, mg/kg/min	7.31 [4.95–9.25]	7.25 [4.84–9.23]
CAP, dB/m[a]	—	231 ± 53
LSM, kPa[a]	—	5.0 [3.7-6.2]
Men	-	5.6 [4.8–6.9]
Women	-	3.8 [3.3–5.1]
NAFLD present [a]	—	30 (20.0)

Note: *n* (%), mean ± SD, median [IQR]. PA other, physical activity from walking, cycling and gardening.

Abbreviations: CAP, controlled attenuation parameter; LSM, liver stiffness measurement; METh/week, metabolic equivalent of task hours per week; NAFLD, non-alcoholic fatty liver disease; PA, physical activity; pts, patients; T1D, type 1 diabetes; TE, transient elastography.

[a]$n=150$, only available in DILIVER cohort.

3.2 | Association between physical activity, insulin resistance and NAFLD

Results from linear and logistic regression analysis are shown in Tables 3 and 4. There was no significant association between PA from sports, other activities or total PA and insulin resistance (resp. B 0.01, 95% CI −0.02 to 0.02, B −0.01, 95% CI −0.01 to 0.00, B −0.00, 95% CI −0.01 to 0.00). For the association between PA from sports and eGDR, the interaction term of PA from sports and sex was statistically significant ($p=0.040$) in the total group, but not if the analysis was conducted in the group participating in sports only ($p=0.216$). None of the PA variables was associated with CAP (PA sports, B −0.41, 95% CI −0.98 to 0.15; PA other, B 0.19, 95% CI −0.00 to 0.38; PA total, B 0.11, 95% CI −0.08 to 0.29). For the LSM regression analysis, assumptions of linear regression strictly were met, but the residuals plot showed a pattern suggestive of two central tendencies. LSM indeed had a bimodal distribution caused by sex. In order to report a reliable

TABLE 3 Association between physical activity (METh/week), sports participation and insulin resistance (eGDR).

	eGDR	
	B (95% CI)	***p*-value**
PA sports		
In total group	0.01 (−0.00 to 0.03)	0.118
Within pts performing sports	−0.00 (−0.02 to 0.02)	0.702
PA other	−0.01 (−0.01 to 0.00)	0.119
PA total	−0.00 (−0.01 to 0.00)	0.446
Sports participation (yes vs. no)	0.94 (0.48 to 1.41)	<0.001
PA vigorous intensity (yes vs. no)	0.68 (0.01 to 1.34)	0.048

Note: Linear regression, adjusted for age, sex, diabetes duration and BMI. PA per 1 METh/week. PA other: physical activity from walking, cycling and gardening.

Abbreviations: B, regression coefficient; PA, physical activity; pts, patients; METh/week, metabolic equivalent of task hours per week.

regression coefficient, the analysis was performed for men and women separately. No significant association was found between PA and LSM in both groups. With logistic regression analyses, no significant association was found between PA and the presence of NAFLD (PA sports, OR 0.99, 95% CI 0.95–1.02; PA other, OR 1.00, 95% CI 0.99–1.01; PA total, OR 1.00, 95% CI 0.99–1.01). For the association between PA from sports and NAFLD, the interaction term of PA from sports and age was statistically significant ($p=0.030$) in the total group, but not if the analysis was conducted in people participating in sports only ($p=0.161$). Conducting the analysis using increments of 5 METh/week instead of 1 METh/week yielded consistent results (data not shown).

3.3 | Secondary analyses

Because almost all participants met the PA guideline recommendation of 7.5 METh/week, no further linear or logistic regression analyses could be performed using this measure as independent variable. Engaging in PA from sports was significantly positively associated with eGDR (B 0.94, 95% CI 0.48–1.41), and inversely associated with CAP, LSM and the presence of NAFLD (respectively, B −34.02, 95% CI −48.98 to −19.05; B −0.98, 95% CI −1.53 to −0.43; OR 0.21, 95% CI 0.08–0.56) (Tables 3 and 4). The statistical significance of these associations persisted after incorporating total PA into the model (data not shown). The association of sports participation with NAFLD parameters remained significant also after adjustment for eGDR instead of BMI. Within participants performing sports, engaging in activities of vigorous intensity was significantly associated with eGDR (B 0.68, 95% CI 0.01–1.34), but not with the NAFLD parameters (Tables 3 and 4).

4 | DISCUSSION

In our type 1 diabetes (T1D) population, a higher degree of physical activity (PA) was not associated with lower insulin resistance or a lower odds for non-alcoholic fatty liver disease (NAFLD). Still, participants engaging in sports activities – which might be a proxy for healthy lifestyle – were less insulin resistant and had lower odds for NAFLD than people not participating in sports.

Contrary to our expectations, in the present study, there was no dose-dependent relationship between PA and insulin resistance. Few studies on daily PA and insulin resistance in T1D have been conducted with varying results. One study did find active patients (leisure time PA (LTPA) >40 METh/week) to be less insulin resistant (higher eGDR) than sedentary patients (LTPA <10 METh/week), and reported a significant correlation between LTPA and eGDR, indicating that higher LTPA comes with lower insulin resistance.[19] The same research group showed that lower LTPA was associated with higher prevalence of metabolic syndrome, which can be interpreted as an expression of insulin resistance.[20] In another study, physical activity did not correlate with insulin dose as surrogate marker of insulin resistance.[21] One study in people with newly diagnosed T2D found that habitual daily PA was associated with higher hyperinsulinaemic euglycaemic clamp-derived insulin sensitivity.[22] Of note, the reported regression and correlation coefficients in all the above-mentioned studies were very small. Possibly there are other factors contributing to insulin resistance more strongly than PA, such as peripheral hyperinsulinaemia and hyperglycaemia.[23]

We did not find any significant association between PA and hepatic steatosis, liver stiffness or the presence of NAFLD in our T1D population. Previous studies in individuals with and without T2D have shown that LTPA comes with decreased odds for NAFLD.[9,24] In one study, there was no clear linear association of increased PA with TE-assessed NAFLD, but participants in the middle PA tertile had significantly lower odds for NAFLD as compared to those in the lowest PA tertile.[24] In another recent large general population study, LTPA had a significant dose-dependent protective effect on TE-assessed NAFLD and patients meeting LTPA guidelines (≥7.5 METh/week) had a 44% lower odds for the presence of NAFLD.[9] An important difference between those studies and ours was the BMI of study participants (median 30 vs. 25 kg/m^2).

TABLE 4 Association between physical activity (METh/week), sports participation and CAP, LSM and the presence of NAFLD.

	CAP		LSM		NAFLD yn	
	B (95% CI)	***p*-value**	**B (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
PA sports in total group	−0.41 (−0.98 to 0.15)	0.148			0.99 (0.95-1.02)	0.336
Men			−0.00 (−0.03 to 0.02)	0.800		
Women			0.01 (−0.03 to 0.04)	0.735		
Within pts performing sports	0.19 (−0.44 to 0.82)	0.552			1.01 (0.98-1.05)	0.414
Men			0.01 (−0.02 to 0.05)	0.402		
Women			0.02 (−0.02 to 0.07)	0.294		
PA other	0.19 (−0.00 to 0.38)	0.054			1.00 (0.99-1.01)	0.903
Men			0.01 (−0.00 to 0.02)	0.167		
Women			0.01 (−0.00 to 0.02)	0.156		
PA total	0.11 (−0.08 to 0.29)	0.254			1.00 (0.99-1.01)	0.666
Men			0.01 (−0.00 to 0.02)	0.220		
Women			0.01 (−0.00 to 0.02)	0.156		
Sports participation (yes vs. no)						
Model 1	−34.02 (−48.98 to −19.05)	<0.001	−0.98 (−1.53 to −0.43)	0.001	0.21 (0.08-0.56)	0.002
Model 2	−25.46 (−41.09 to −9.82)	0.001	−0.91 (−1.48 to −0.34)	0.002	0.29 (0.11-0.76)	0.012
PA vigorous intensity (yes vs. no)	6.05 (−14.10 to 26.20)	0.556	−0.37 (−0.98 to 0.25)	0.242	0.48 (0.10-2.32)	0.478

Note: Linear and logistic regression: adjusted for age, sex, diabetes duration and BMI. Analysis of sports participation adjusted for age, sex, diabetes duration and BMI (model 1) or eGDR (model 2). PA per 1 METh/week. PA other: physical activity from walking, cycling and gardening.

Abbreviations: B, regression coefficient; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; METh/week, metabolic equivalent of task hours per week; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; PA, physical activity; pts, patients.

However, in one former study, the inverse relationship between PA and NAFLD was present even in those with a BMI below 25 kg/m^2.[25] Possibly, the relatively high overall PA level in our group explains the absence of an association between PA and NAFLD in our population.[19,24] This hypothesis is supported by a previous report in which a curvilinear dose–response relationship between accelerometer-measured PA and NAFLD was found.[26]

Current literature consequently describes a beneficial effect of aerobic and resistance exercise training on insulin sensitivity in healthy subjects, as well as in people with type 1 or T2D.[27–30] Also, it has been shown that structured exercise training reduces intrahepatic triglyceride content, independent of weight loss and dietary intervention.[31,32] In line with these findings, in our cohort people participating in sports, that is, regular exercise training, were less insulin resistant and had lower odds for NAFLD than people not engaging in sports activities. Furthermore, participation in vigorous PA as compared to only low or moderate-intensity PA came with lower insulin resistance, which has also been suggested in a previous study.[33] Of interest, sports participation remained statistically significantly associated with insulin resistance and NAFLD also when adjusted for total PA. These findings support the hypothesis that sports participation itself is acting here. Probably, in the Netherlands, sports participation is a proxy of healthy lifestyle; people regularly engaging in sports more often also have a higher socioeconomic status and a healthy diet. Unfortunately, we did not have any data on these demographics, and could not further test this hypothesis. Not adjusting for these confounders may have led to an overestimation of the effect of sports participation on NAFLD, but our results still support the idea of choosing a multilevel lifestyle approach in NAFLD management.[34]

Even though strictly speaking we cannot use our questionnaire-derived PA data as absolute values, it is remarkable that median PA is high as compared to previous

studies in people with T1D.[19,20,35] In our study, only a small minority was inactive (PA <7.5 METh/week), while in older studies roughly one- to two third of participants had an inactive lifestyle.[19,20,35] This difference possibly reflects the evolution of T1D management in the past decade with integration of lifestyle management into the standard treatment, hereby following the PA guidelines and using the opportunities of advances in diabetes technology. In our study, we could not distinguish between sedentary versus non-sedentary behaviour and did have only limited information on PA intensity. In order to further specify PA guidelines in people with T1D and to tailor lifestyle treatment with respect to influencing insulin resistance and the risk of NAFLD, future prospective accelerometer PA-measured studies should focus on these issues.

To our knowledge, this is the first study examining the association between PA and NAFLD in people with T1D. A strength of the study is the separate assessment of PA from sports and PA from walking, cycling and gardening. One potential limitation includes the use of a questionnaire to measure PA. Recall bias in combination with social desirability bias may play a role, with people reporting a higher amount of PA than truly engaged in. However, if we assume that overestimation of PA is distributed equally over participants, we do not expect this to influence the investigated associations. The questionnaire-derived PA data were only suitable for ranking subjects, and not using them as absolute values. Therefore, we were unable to categorize our participants as being active or inactive. Furthermore, the degree of insulin resistance was calculated with the eGDR formula, which should be considered a crude measurement of insulin resistance. Performing the gold standard of the euglycaemic hyperinsulinaemic clamp is not feasible in a large population as ours, because of its invasive and time-consuming character. Lastly, there might exist residual confounding from dietary status and social-economic status, for which we could not adjust in our analyses.

In conclusion, we could not find any dose-dependent association between PA and insulin resistance or between PA and NAFLD in people with T1D. Nevertheless, participants performing regular exercise training – a possible proxy for healthy lifestyle – had a lower degree of insulin resistance and lower odds for NAFLD compared to those not participating in sports. This underlines the relevance of lifestyle management in T1D clinical care.

AUTHOR CONTRIBUTIONS

MV conceived the study. All authors contributed to the study design. MV performed the data collection and statistical analysis and drafted the manuscript. JW, HV and KK provided critical revision. All authors read, provided feedback and approved the final version of the manuscript. MV is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

We would like to thank Mariska Vreken, a biomedical student, for her help in completing the physical activity data.

FUNDING INFORMATION

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

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

ORCID

M. de Vries https://orcid.org/0000-0002-9802-921X

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84. doi:10.1002/hep.28431
2. Marjot T, Moolla A, Cobbold JF, Hodson L, Tomlinson JW. Nonalcoholic fatty liver disease in adults: current concepts in etiology, outcomes, and management. *Endocr Rev*. 2020;41(1):66-117. doi:10.1210/endrev/bnz009
3. de Vries M, Westerink J, El-Morabit F, Kaasjager H, de Valk HW. Prevalence of non-alcoholic fatty liver disease (NAFLD) and its association with surrogate markers of insulin resistance in patients with type 1 diabetes. *Diabetes Res Clin Pract*. 2022;186:109827. doi:10.1016/j.diabres.2022.109827
4. de Vries M, Westerink J, Kaasjager K, de Valk HW. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2020;105(12):3842-3853. doi:10.1210/clinem/dgaa575
5. de Vries M, El-Morabit F, van Erpecum KJ, et al. Non-alcoholic fatty liver disease: identical etiologic factors in patients with type 1 and type 2 diabetes. *Eur J Intern Med*. 2022;100:77-82. doi:10.1016/j.ejim.2022.03.025
6. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Obes Facts*. 2016;9(2):65-90. doi:10.1159/000443344
7. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of

Liver Diseases. *Hepatology*. 2018;67(1):328-357. doi:10.1002/hep.29367
8. National Guideline Centre (UK). *Non-Alcoholic Fatty Liver Disease: Assessment and Management*. National Institute for Health and Care Excellence (NICE); 2016.
9. Kim D, Konyn P, Cholankeril G, Ahmed A. Physical activity is associated with nonalcoholic fatty liver disease and significant fibrosis measured by Fibroscan. *Clin Gastroenterol Hepatol*. 2021;20(6):e1438-e1455. doi:10.1016/j.cgh.2021.06.029
10. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39(11):2065-2079. doi:10.2337/dc16-1728
11. Khawandanah J. Double or hybrid diabetes: a systematic review on disease prevalence, characteristics and risk factors. *Nutr Diabetes*. 2019;9(1):33. doi:10.1038/s41387-019-0101-1
12. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y. Second manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol*. 1999;15(9):773-781. doi:10.1023/a:1007621514757
13. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes*. 2000;49(4):626-632. doi:10.2337/diabetes.49.4.626
14. Epstein EJ, Osman JL, Cohen HW, Rajpathak SN, Lewis O, Crandall JP. Use of the estimated glucose disposal rate as a measure of insulin resistance in an urban multiethnic population with type 1 diabetes. *Diabetes Care*. 2013;36(8):2280-2285. doi:10.2337/dc12-1693
15. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2019;156(6):1717-1730. doi:10.1053/j.gastro.2019.01.042
16. Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC physical activity questionnaire. *Int J Epidemiol*. 1997;26(Suppl 1):S181-S189. doi:10.1093/ije/26.suppl_1.s181
17. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 Suppl):S498-S504. doi:10.1097/00005768-200009001-00009
18. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour*. World Health Organization; 2020 Licence: CC BY-NC-SA 3.0 IGO.
19. Wadén J, Tikkanen H, Forsblom C, et al. Leisure time physical activity is associated with poor glycemic control in type 1 diabetic women: the FinnDiane study. *Diabetes Care*. 2005;28(4):777-782. doi:10.2337/diacare.28.4.777
20. Waden J, Thorn LM, Forsblom C, et al. Leisure-time physical activity is associated with the metabolic syndrome in type 1 diabetes: effect of the PPARgamma Pro12Ala polymorphism: the FinnDiane study. *Diabetes Care*. 2007;30(6):1618-1620. doi:10.2337/dc06-2467
21. Brazeau AS, Leroux C, Mircescu H, Rabasa-Lhoret R. Physical activity level and body composition among adults with type 1 diabetes. *Diabet Med*. 2012;29(11):e402-e408. doi:10.1111/j.1464-5491.2012.03757.x
22. Temple KA, Tjaden AH, Atkinson KM, et al. Association of Habitual Daily Physical Activity with Glucose Tolerance and β-cell function in adults with impaired glucose tolerance or recently diagnosed type 2 diabetes from the restoring insulin secretion (RISE) study. *Diabetes Care*. 2019;42(8):1521-1529. doi:10.2337/dc19-0538
23. Riddell MC, Li Z, Gal RL, et al. Examining the acute glycemic effects of different types of structured exercise sessions in type 1 diabetes in a real-world setting: the type 1 diabetes and exercise initiative (T1DEXI). *Diabetes Care*. 2023;46(4):704-713. doi:10.2337/dc22-1721
24. Heredia NI, Zhang X, Balakrishnan M, et al. Physical activity and diet quality in relation to non-alcoholic fatty liver disease: a cross-sectional study in a representative sample of U.S. adults using NHANES 2017–2018. *Prev Med*. 2021;154:106903. doi:10.1016/j.ypmed.2021.106903
25. Ryu S, Chang Y, Jung HS, et al. Relationship of sitting time and physical activity with non-alcoholic fatty liver disease. *J Hepatol*. 2015;63(5):1229-1237. doi:10.1016/j.jhep.2015.07.010
26. Tsunoda K, Kitano N, Kai Y, Jindo T, Uchida K, Arao T. Dose-response relationships of accelerometer-measured sedentary behaviour and physical activity with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2021;54:1330-1339. doi:10.1111/apt.16631
27. Battista F, Ermolao A, van Baak MA, et al. Effect of exercise on cardiometabolic health of adults with overweight or obesity: focus on blood pressure, insulin resistance, and intrahepatic fat-a systematic review and meta-analysis. *Obes Rev*. 2021;22:e13269. doi:10.1111/obr.13269
28. Conn VS, Koopman RJ, Ruppar TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin sensitivity following exercise interventions: systematic review and meta-analysis of outcomes among healthy adults. *J Prim Care Community Health*. 2014;5(3):211-222. doi:10.1177/2150131913520328
29. Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia*. 2012;55(3):542-551. doi:10.1007/s00125-011-2403-2
30. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. *Int J Sports Med*. 2000;21(1):1-12. doi:10.1055/s-2000-8847
31. Sargeant JA, Gray LJ, Bodicoat DH, et al. The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis. *Obes Rev*. 2018;19(10):1446-1459. doi:10.1111/obr.12719
32. Orci LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol*. 2016;14(10):1398-1411. doi:10.1016/j.cgh.2016.04.036
33. Paldus B, Morrison D, Zaharieva DP, et al. A randomized crossover trial comparing glucose control during moderate-intensity, high-intensity, and resistance exercise with hybrid closed-loop insulin delivery while profiling potential additional signals in adults with type 1 diabetes. *Diabetes Care*. 2022;45(1):194-203. doi:10.2337/dc21-1593
34. Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. *J Hepatol*. 2017;67(4):829-846. doi:10.1016/j.jhep.2017.05.016

35. Leroux C, Gingras V, Desjardins K, et al. In adult patients with type 1 diabetes healthy lifestyle associates with a better cardiometabolic profile. *Nutr Metab Cardiovasc Dis*. 2015;25(5):444-451. doi:10.1016/j.numecd.2015.01.004
36. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112(17):2735-2752. doi:10.1161/circulationaha.105.169404
37. Franssens BT, Westerink J, van der Graaf Y, Nathoe HM, Visseren FLJ. Metabolic consequences of adipose tissue dysfunction and not adiposity per se increase the risk of cardiovascular events and mortality in patients with type 2 diabetes. *Int J Cardiol*. 2016;222:72-77. doi:10.1016/j.ijcard.2016.07.081

How to cite this article: de Vries M, Westerink J, Kaasjager HAH, de Valk HW, . Association of physical activity and sports participation with insulin resistance and non-alcoholic fatty liver disease in people with type 1 diabetes. *Diabet Med*. 2024;41:e15317. doi:10.1111/dme.15317