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LEISURE-TIME PHYSICAL ACTIVITY AND THE ONSET OF TYPE 2 DIABETES IN THE MALMÖ DIET AND CANCER STUDY COHORT

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ABSTRACT

Aims/objectives: The study's aim was to assess the association between different levels of leisure time physical activity (LTPA) and the risk of type 2 diabetes mellitus (T2DM) and assess the association between socio-economic status (SES) and distribution of LTPA.

Methods: The study was based on the Malmo Diet and Cancer Study cohort that included participants aged 44-74 years at enrolment. Demographic and covariate data from the baseline questionnaire (1991-1996) and outcomes of interest (2014) linking the cohort data to various medical and population registers was used. LTPA was assessed using a standard questionnaire as a sum of products of 17 predefined individual activities (assessed as minutes spent weekly per activity in the previous year) with their intensity factors (Metabolic Equivalent or MET) and reported as MET-hours per week. Chi-square test was used to assess the proportions of different socioeconomic groups in the various LTPA categories and Cox regression utilized to model the association between LTPA and incidence of T2DM, adjusted for age, sex, body mass index (BMI), smoking, education level and occupation.

Results: There were significant differences in the distribution of LTPA levels across the different socioeconomic groups. Moderate LTPA (7.5-15 MET-hours/week) was not significantly associated with T2DM risk (HR=0.92, 95% CI 0.81-1.05), vigorous (15-25 MET-hours/week) and strenuous (25-50 MET-hours/week) levels of LTPA were associated with reduced incidence of T2DM (HR=0.83, 95% CI 0.74-0.94) and (HR=0.81,95% CI 0.72-0.91) respectively. LTPA beyond 50 MET-hours/week had no added benefit (HR=0.84, 95% CI 0.74-0.96).

Conclusion: The study demonstrated the benefits of different LTPA levels in reducing the risk of T2DM in the MDC cohort. Moderate activity was not significantly associated while vigorous activity and above was significantly associated with reduced risk but there was no added benefit for LTPA beyond 50 MET-hours per week. The amount of LTPA was significantly related to SES.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) which contributes to about 90-95% of all diabetes cases (1), is a chronic metabolic disease characterized by elevated glucose levels resulting from abnormalities in insulin metabolism, mainly; insulin resistance, inadequate insulin secretion and abnormal glucagon secretion (2). Poorly controlled T2DM is associated with life threatening and debilitating health complications. T2DM differs from type 1 diabetes mellitus (T1DM) that accounts for 5-10% of the cases (1) which is an autoimmune condition that leads to destruction of insulin-producing cells in the pancreas and subsequent lack of insulin (3) necessitating patients to be on insulin for the rest of their lives. Type-1 diabetes occurs mainly in children while the onset of T2DM mostly occurs in adulthood. Another variant, gestational diabetes mellitus (GDM), occurs in pregnancy and poses danger to both the child and mother even later in life (4). T2DM in the recent years has been occurring at younger ages due to childhood obesity and inactivity (2).

1.1 Global burden of diabetes

According to the International Diabetes Federation (4, 5), as of 2015, the global prevalence of diabetes was estimated to be 8.8% representing about 415 million cases among those aged 20-70 years old, with men (approximately 215 million) being more affected than women (approximately 199.5 million), and this number is expected to rise to 642 million in 2040 if the current trend of incidence persists (4). In the same year, there were 5 million diabetes-related deaths, more than HIV/AIDS, tuberculosis and malaria combined. It is estimated that worldwide about 193 million people have undiagnosed diabetes, meaning that one in every two adults with diabetes is undiagnosed (4). Further, it is estimated that one in 15 adults has impaired glucose tolerance, one in 11 adults has diabetes and one in seven births is affected by gestational diabetes (4). Urban areas reported more cases (269.7M) than rural areas (145.1M) and this difference is expected to almost triple (477.9M versus 163.9M) in 2040 due to more people living in urban areas (4). Table 1 below shows regional estimates of diabetes in 2015 and the projected estimates for the year 2040.

Diabetes places a huge financial and economic burden on individuals and households due to the cost of insulin and other related medicines and services and by extension exerts significant pressure on countries' economies and national health systems (4). The IDF estimates that diabetes and its related complications contribute to about 12% of the global expenditure on healthcare and that most countries spend between 5-20% of their total health expenditure on diabetes (4). The global expenditure on diabetes in 2015 was $673 billion. Low and middle-income countries experience higher out-of-pocket health expenditure than high-income countries due underdeveloped public health services and lack of health insurance (4) which further entrenches household poverty.

Table 1. 2015 regional estimates for diabetes and 2040 projected estimates

Region	2015 estimates	2040 estimates
North America and Caribbean	44.3 M	60.5 M
Europe	59.8 M	71.1 M
Middle East and North Africa	35.4 M	72.1 M
Western Pacific	153.2 M	214.8 M
Africa	14.2 M	34.2 M
South East Asia	78.3 M	140.2 M
South and Central America	29.6 M	48.8 M

Source: International Diabetes Federation, 2015

1.2 Diabetes in Europe and Sweden

As of 2015, there were about 60 million people with diabetes in the European region, approximately 23.5 million undiagnosed cases and about 627,000 related deaths reported (4). In addition, about 31.7 million people aged between 20-79 years were estimated to have impaired glucose tolerance and thus at an increased risk of developing diabetes (4). The regional prevalence, which varies in the constituent countries, has been increasing for all ages mainly due to overweight and obesity, unhealthy diet and physical inactivity (6). For instance Turkey has the highest prevalence (12.5% age-adjusted raw prevalence) and highest number of persons (6.3 million) with diabetes in the European region (4). To a greater extend the high prevalence in Europe is contributed by advanced age, an important risk factor, where about 31% of the general population is aged between 50-79 years (4). The health expenditure attributed to diabetes was about 9% of total health expenditure in Europe for 2015, approximately $156 billion (4).

The Scandinavian region has a reportedly lower prevalence of diabetes than other parts of Europe (7). In Sweden, there were 446,900 cases of diabetes in 2015, a prevalence of 6.3% and 3,076 related deaths in persons aged 20-79 years. An estimated 168,700 had undiagnosed diabetes and the cost of treatment per person for the same year was $6,776 (5). Due to changes in the age structure of the population and improved survival, this prevalence is projected to rise to 10.4% by the year 2050 with the number of affected individuals being about 940,000 (8).

1.3 Risk factors for T2DM

The main risk factors for developing T2DM include excess body weight, physical inactivity, genetic predisposition/family history, poor nutrition, ethnicity, past history of gestational diabetes and advancing age (2, 4). Studies have also shown that persons of lower socioeconomic status are at a higher risk of diabetes compared to those of higher status, regardless of the assessment measure used (9, 10). Smoking is an important risk factor that is associated with higher risk of T2DM in current and former smokers compared to those who have never smoked and it has been shown that this effect on risk is reversible and cessation of smoking reduces the risk of diabetes in the long term (11). Overt T2DM differs from a "pre-diabetes" state characterized by high glucose levels that are not high enough for a diagnosis of diabetes (4, 12). Impaired glucose tolerance, impaired fasting glucose and insulin resistance are all pre-diabetic states that need intervention to prevent progression to full diabetes. Furthermore, metabolic syndrome characterized by insulin resistance, hypertension, obesity and hyperlipidemia increases the risk of T2DM (13). Management of T2DM involves lifestyle changes (diet and exercise) and use of medication. Not all cases will require medication and the pre-diabetic states are managed with lifestyle and diet modification (3).

1.4 Complications of T2DM

T2DM has long-term health complications affecting multiple organ systems and is associated with a double-fold increase in the overall risk of death in those affected compared to those who are not, therefore the aim of early diagnosis and treatment is to delay the onset of these complications (6). The disease can cause damages to the heart and blood vessels (cardiovascular complications), kidneys (diabetic nephropathy), eyes (diabetic retinopathy) and nerves (diabetic neuropathy). Cardiovascular complications lead to increased risk of stroke, myocardial infarction and micro-vascular disorders (12, 14) and it is estimated that 50% of diabetics die of cardiovascular disease (6). After 15 years approximately 2% of diabetics go blind and about 10% develop severe visual impairment due to diabetic retinopathy which is a result of damage to the small blood vessels (micro vascular complications) in the eyes (6). Diabetic nephropathy can lead to kidney failure requiring dialysis and/or renal transplants, and about 10-20% of diabetics die of kidney failure (4, 6). In about 50% of cases, diabetic neuropathy and a combination of impaired blood flow and poor sensation in the feet leads to increased risk of foot ulceration (diabetic foot) and eventual limb amputation (6, 13). Diabetes also complicates pregnancies and affects the unborn child and later in life (4).

1.5 Physical activity and the risk of T2DM

The relationship between physical activity and development of diabetes and other non-communicable diseases is well known. Physical activity improves insulin sensitivity independent of any effect on weight loss and fat distribution, even in the presence of overt T2DM and plays a role in improving the regulation of insulin secretion (1). Studies have shown that inflammation plays part in development of diabetes and other chronic diseases (15). Excess adiposity contributes to low-grade inflammation especially visceral adiposity in addition to insulin insensitivity and disorders in glucose homeostasis (2, 15). Increased physical activity is associated with the release of anti-inflammatory cytokines, improved insulin sensitivity partly by blocking inflammatory cytokines and also offering a protective effect on destruction of pancreatic beta cells as well as improved lipid metabolism, body composition (especially visceral adiposity) and cardiorespiratory fitness (15, 16).

Many studies have demonstrated the relationship between physical activity and incident T2DM. In the China Da Qing study (17), 577 individuals with impaired glucose tolerance were randomized in three groups for targeted interventions of exercise, diet and both exercise and diet. They were followed for six years during the intervention period and then for 14 more years post intervention to assess the individual impact of the interventions on the incidence of T2DM and cardiovascular disease. Participants in the diet and exercise group had a 43% reduction in the risk of incident T2DM than the controls (HR = 0.57, 95% CI 0.41−0.81) during the six years of intervention and this effect was seen to persist two decades later, diabetes onset was also delayed an average of 3.6 years. The study also showed that the risk of eventual diabetes in those with IGT remains high for many years sans interventions.

In the Diabetes Prevention Program (DPP) clinical trial (18), subjects were put in three intervention groups: standard lifestyle recommendations plus metformin, standard lifestyle recommendations plus placebo and an intense group/lifestyle intervention (the targets of the group were weight loss by 7%, low calorie and low fat diet, physical activity of at least 150 minutes per week and behavior modification taught by case managers) and followed up for 2.8 years. Compared to the placebo group, the incidence of diabetes was 58% (95% CI, 48% - 66%) and 31% lower (95% CI, 17% - 43%) in the intense and metformin groups respectively, while the intense group had a 39% (95% CI, 24% - 51%) lower incidence compared to the metformin group. This study showed that a combination of physical activity and other interventions was superior to pharmacotherapy (metformin) in reducing the risk of T2DM.

In another multi-center randomized controlled trial, the Finnish Diabetes Prevention Study (19), that enrolled overweight or obese participants aged 40-65 years old with impaired glucose tolerance, post hoc analyses on 487 men and women on the effect of changes in amount of LTPA in the prevention of T2DM showed that, in the intervention group (the interventions were exercise for at least 30 minutes per day, targeted weight reduction, dietary changes - reduced fat intake and increased fiber - and endurance training, walking and lifestyle LTPA, and advise on how to achieve these goals) incremental changes in LTPA by those who already had prior higher levels of LTPA (i.e. vigorous and strenuous) led to decreased T2DM, than in controls who were only given general information verbally without individualized programs. Risk reduction, albeit much lower, was also observed in those who had incremental change from prior low intensity and lifestyle LTPA and walking for exercise (19). Moderate –to-vigorous LTPA was defined as 3.5 METs and LTPA was quantified as MET-hours per week. Change in LTPA was calculated by subtracting baseline total LTPA from corresponding measures of average LTPA during follow-up. Participant's whose total change in LTPA was in the upper third were 80% less likely to develop T2DM compared to those in the lower third (RR=0.20, 95% CI 0.10 - 0.41).

The effects of physical activity have also been shown to decrease the risk of T2DM in different populations and subgroups. In a prospective cohort study in high-risk Pima Indians, physical activity, overall, was related to low incidence of diabetes. However, physical activity was not significant in lowering the incidence of diabetes in those with a high BMI (20). Another cohort study conducted in Iran (21) showed that the incidence of diabetes was reduced by 50% in those with more than 150 minutes of physical activity per week (OR = 0.5, 95% CI 0.26 - 0.94). In Japan, a cohort study involving workers (N= 26,628, incident cases = 1770) aged 30-64 years, (22) that assessed physical activity using an aggregate measure of leisure time, occupational and commuting activities using MET-hours per week (inactive = 0 MET-hours; low = 0.1 to <7.5 MET-hours; Medium = 7.5 to <15.0 MET-hours; and high ≥ 15.0 MET-hours), showed that moderate physical activity alone was not significantly associated with reduced incidence of T2DM (HR= 0.92, 95% CI 0.78 - 1.08) but vigorous physical activity was (HR = 0.83, 95% CI 0.69 - 0.99), even below recommended doses and a combination of moderate and vigorous intensity PA was associated with much lower risk of developing T2DM (HR = 0.57, 95% CI 0.37 - 0.90). In the same study, occupational PA and walk commuting were not statistically significant.

Many meta-analyses conducted have shown that high amounts of physical activity are associated with low risk of diabetes. In one meta-analysis Cloostermans et al. (14) used a standardized protocol to reanalyze data for nine individual prospective cohort studies from different countries (two from Australia, three from the UK, and one each from USA, Canada, Netherlands and Finland) with 117,878 subjects and a total of 11,273 incident T2DM cases. In this study the unadjusted risk for T2DM was 64 % (95 % CI, 1.45 -1.85) higher in those who had low physical activity levels (measured in two domains: leisure time which included walking, gardening, shopping and home maintenance, and active commuting) compared to those who had high levels. After adjusting for confounders (age, gender, educational level, smoking, and BMI) the relative risk was 23% higher (95% CI, 1.09 -1.39) in the same group (5). Individuals who were both obese and had low physical activity had a 7.4-fold (95% CI, 3.47-15.89) increased risk of T2DM compared to those who had normal weight and high levels of activity. Huai et al. (23) conducted a meta-analysis of eight prospective cohort studies searched on Pubmed and Embase from their inception to June 13, 2014 that had a total population of 296,395 participants and 10,815 incident diabetes cases. Using fixed or random effects models to calculate pooled effect sizes based on between-study heterogeneity, this study showed that high-level LTPA (measured as MET-hours, kilocalories per week or hours/week) might reduce incidence of T2DM by 22-39% (HR = 0.69, 95% CI 0.61-0.78) and moderate LTPA by 11-30% (HR = 0.79, 95% CI 0.70-0.89) compared with the reference group with low level LTPA (23).

Studies conducted locally in Sweden have also demonstrated the inverse relationship between physical activity and incidence of T2DM. In Västerbotten County, a population-based study (24) on lifestyle behavior change (*n* = 2211) where participants were followed for ten years showed that being moderately active was associated with a lower risk of T2DM (RR= 0.84, 95% CI 0.77 – 0.92) compared to being inactive. In the same study those who had never smoked and those with BMI less than 25 kg/m^2 had lower risk of T2DM compared to current/former smokers and those with higher BMI respectively. In another population-based cohort study on women followed for over 34 years (*n* = 1448) in Gothenburg (25), subjects who had low physical activity were at increased risk of developing diabetes (HR = 1.79, 95% CI 1.15 – 2.79) compared to those who were a more active and non-obese. The risk was much higher for those who were obese and active and highest in those who were obese and inactive.

While numerous studies have shown the importance of physical activity, it is not yet known what exact amount of physical activity is beneficial and at what point is stops being beneficial in lowering the risk of T2DM. Despite earlier challenges in assessing physical activity due to precision and methodological objectivity (26, 27) current different methods and have been shown to be valid towards this end (28). According to Lamb and Brodie (29), LTPA is preferred because many jobs in developed countries are sedentary and the increasing availability of leisure time makes any LTPA valuable. In view of the importance of physical activity in reduction of T2DM incidence risk, understanding the dose-effect relationship is important. Some studies have shown that

150 minutes per week of moderate intensity physical activity is associated with lower prevalence of metabolic syndrome which is a key precursor of T2DM whether PA was measured using self-reports or exercise measures (30) but the exact upper cut-off level remains unclear (15). Although the role of physical activity has been extensively studied in relation to metabolic risk factors and T2DM risk, this association has not been studied in detail in the Malmö Diet and Cancer (MDC) study cohort and the ideal amount of LTPA has not been conclusively determined.

2. AIM

This study aimed to assess the association between LTPA measures in the Malmo Diet and Cancer Study (MDC) cohort and the risk of T2DM as well as the distribution of LTPA measures in different socioeconomic categories.

3. METHODS

3.1 Study Design

The study was based on data collected in a population-based prospective cohort study, Malmö Diet and Cancer (MDC), from 1991 to 1996 in Malmö, Sweden. Baseline assessment was done between 1991 and 1996 and it included two separate visits at the MDC Center in Malmö. The objectives of the study as well as the tools were explained to all participants who in turn gave written informed consent. The ethics committee in Lund University, Faculty of Medicine, and the Swedish Data Inspection Agency granted approval for the study. Baseline information (bio-demographics, exposure and covariate) was collected using a standardized 141-item questionnaire administered by trained professionals. Standard anthropometric measures were taken at baseline and blood samples collected from individuals, tested for baseline investigations and stored for future studies.

3.2 Study setting and population

The MDC participants were living in Malmö in southern Sweden whose population was about 230,000 at the time of initiation of the study. The age groups of the participants were 45-74 years of age. The study population and recruitment methods have been described in detail in earlier studies about this cohort (31, 32).

3.3 Eligibility and exclusion criteria

For this particular study we excluded subjects who did not show up for a second baseline screening as per the records (*n*=1870) and those who had diabetes at baseline (*n*=1380). We also excluded individuals who had unrealistically high self-reported hours (>50 hours) of LTPA per week (*n*=11) and those who were missing information on BMI (*n*=30). The final sample consisted of 26,450 persons.

3.4 Exposure assessment

Leisure time physical activity was assessed at baseline as the self-reported amount of minutes spent in a particular activity per week during each of the four seasons of the preceding year. The questions were adapted from the Minnesota LTPA questionnaire (33). Seventeen activities in total were assessed. The leisure time activities assessed ranged from sport to general activities like walking and gardening. A composite measure was computed by multiplying the time spent doing an activity per week and the activity's metabolic intensity equivalent (MET) or intensity factor and reported as MET-hours per week. One MET is described as the metabolic intensity when a person is at rest (26). The most intense activity assessed was playing football (9 METs) while the least intense was walking for pleasure (Table 2). Subjects were classified into five groups based on the amount of MET-hours per week (Low activity <7.5; moderate =7.5-14.99; vigorous = 15-29.99; strenuous = 25-49.99; over-strenuous > 50 MET-hours/week) to assess the effect of different activity levels on the outcome. The low activity group was used as the reference.

Table 2. Leisure time activities assessed, LTPA and T2DM in the MDC study cohort 1991-1996

***Moderate Intensity 3-6**	**METs**
PR = Walking	3.5 (for pleasure)
BO = Table tennis	4.0
CY = Cycling	4.0
TR = Gardening	4.0
MO = Gymnastics	4.0
GO = Golf	4.5
BA = Badminton	4.5
GR =Digging	5.0
SÄ = Dancing (folkdance)	5.5
GA = Dancing (ballroom)	5.5
GK =Mowing the lawn (with a manual mower)	6.0

Vigorous Intensity >6	**METs**
JO = Jogging	7.0
SI = Swimming	7.0
TE =Tennis	7.0
FO= Football	8.0
OR = Orienteering	9.0
GÅ= Climbing stairs	9.0

METs= Metabolic equivalent
*No activity was of low intensity, i.e. <3 METs

3.5 Covariate assessment

Information on age, sex, weight, height, smoking status, education and occupation was collected at baseline. Age was taken in years to the nearest two decimals while sex was classified as male or female. Smoking status was in three categories of smokers, ex-smokers and never smokers. Education was in 5 categories (elementary- EDU 1; primary and secondary – EDU 2; upper secondary - EDU 3; further education without a degree - EDU 4; and university degree - EDU 5) while occupation status was classified as employed, retired or other (student, unemployed and home worker). Body weight (kilograms) and height (centimeters) were measured using standardized instruments by trained nurses following standardized procedures. Body mass index (BMI) was calculated as kilograms per meters squared (kg/m^2) and individuals were placed in 3 categories, normal weight (BMI < 25kg/m^2), overweight (BMI 25-30 kg/m^2) and obese (BMI ≥ 30 kg/m^2).

3.6 Outcome assessment: Source of data

Information about outcomes (T2DM) was obtained from hospital inpatient and outpatient registers, Swedish National Diabetes Register (NDR), HBA1c register, cause of death register, Swedish prescribed drug register and post-baseline screening registers related to the study. Information on T2DM was also obtained from re-examination of subgroups of the participants and during other scheduled screenings for related studies. Information was updated in the study database, including other outcomes of death or loss to follow up. Censoring was done as the date of first diabetes event reported or diagnosed, date of emigration or loss to follow-up, death or date until last day of follow-up (December 31, 2014), whichever came first. All final diagnoses were determined using the International Classification of Diseases, (ICD-9).

3.7 Data analysis

Analysis was carried out using SPSS version 23 statistical software (IBM Inc.). Continuous variables that were normally distributed were reported as mean and standard deviation (± SD) and those not normally distributed as median and inter-quartile range (IQR). Chi square test of proportionality was used to assess the difference in distribution of LTPA in relation to the different subjects' characteristics and the distribution of diabetes outcome in the subjects. Cox proportional hazards regression was used to estimate the risk, in hazard ratios (HRs), of developing diabetes during the follow up time among the subjects. Stepwise adjustment for covariates was done and three sequential models were created. In the stepwise adjustment, further adjustment for occupation after all the other covariates did not result in any change in the HRs and thus occupation was not included in the final analysis. The first model was adjusted for age sex and smoking. The second model was adjusted for factors in model one and education status while the third and final model was adjusted for factors in model two and BMI. Sensitivity analysis was carried out by comparing the hazard ratios in the final model with those of a similar model without outliers (over-reporters and under-reporters of energy intake). $P < 0.05$ was used as the significance level.

4. RESULTS

4.1 Participants' characteristics

Overall there were more women than men in the study and on average the men were heavier, taller and older than the women. The participants' characteristics for men and women are presented in Table 3. Walking was the most popular leisure time activity (87% of the participants walked) followed by cycling (62%) while orienteering (0.4%) and table tennis (1.1%) were the least popular (additional information). Total LTPA in MET-hours/week was not normally distributed; the median was 26.75 (IQR=25.8). Men had higher LTPA, median 27 (IQR=27.5) than women, median 26.5, (IQR=24.75). However, upon log transformation to normalize the distribution, the mean total MET-hours/week was 24.56 (SD=2.24), Men 24.57(SD=2.3), and women 24.13 (SD=2.2).

The participants' characteristics according to LTPA categories are presented in Table 4. Those under 50 years of age exercised the most compared to the other age groups. Obese and overweight individuals formed a higher proportion of those who had low levels LTPA. Smokers exercised less than ex-smokers and nonsmokers in general. Persons with low education exercised less compared to the higher educated. Participants with elementary school level education constituted 51% of all persons classified as having low LTPA.

Table 3. Participants' characteristics, men and women in the MDC study cohort 1991-1996

Variable	Men	Women	Total
	Mean (SD)	Mean (SD)	
N	10219	16188	26407
Age at screening	59.09(7.07)	57.18(7.89)	57.92(7.64)
Height (cm)	176.44(6.61)	163.71(6.04)	168.64(8.82)
Weight (kg)	81.49(11.89)	67.75(11.43)	73.07(13.40)
BMI	26.16(3.40)	25.29(4.13)	25.63(3.89)
Body fat %	20.64(4.93)	30.63(4.94)	26.76(6.93)
Waist (cm)	93.36(9.83)	77.46(10.18)	83.61(12.69)
HIP (cm)	99.1(6.93)	97.61(9.42)	98.19(8.58)
Waist hip ratio	0.94(0.06)	0.79(0.05)	0.85(0.09)
LTPA	27.00(27.5)*	26.5(24.75)*	26.75(25.79)*
Categorical var.			
LTPA[&]			
Low	825(40.7%)	1201(59.3%)	2026
Moderate	1550(38.6%)	2461(61.4%)	4011
Vigorous	2301(37.2%)	3891(62.8%)	6192
Strenuous	3677(37.3%)	6176(62.7%)	9853
Over-strenuous	1866(43.2%)	2458(56.8%)	4324
BMI (Kg/m^2)			
<24.9	3924(31.0%)	8746(69.0%)	12670
25.0-29.99	5074(48.7%)	5337(51.3%)	10411
>30.0	1220(37.2%)	2057(62.8%)	3277
Age groups			
<50 years	1079(20.5%)	4181(79.5%)	5260
50-60 years	4458(43.2%)	5854(56.8%)	10312
>60years	4678(43.2%)	6150(56.8%)	10828
Smoking			
Smokers	2919(39.2%)	4528(60.8%)	7447
Ex-smokers	4379(49.4%)	4494(50.6%)	8873
Never	2919(28.9%)	7164(71.1%)	10083
Education[#]			
EDU-1	4635(42.8%)	6201(57.2%)	10836
EDU-2	2008(28.9%)	4932(71.1%)	6940
EDU-3	1225(51.4%)	1157(48.6%)	2382
EDU-4	959(40.7%)	1398(59.3%)	2357
EDU-5	1392(35.8%)	2500(64.2%)	3892
Occupation			
Employed	5989(37.8%)	9871(62.2%)	15860
Retired	3596(42.1%)	4941(57.9%)	8537
Other	634(31.5%)	1376(68.5%)	2010

*Median (IQR)

[#]EDU-1: Elementary
EDU-2: Primary and secondary
EDU-3: Upper secondary
EDU-4: Further education without a degree
EDU-5: University degree

[&]Low LTPA - <7.5 MET-hours per week
Moderate LTPA - 7.5 -14.99 MET-hours per week
Vigorous LTPA - 15 -24.99 MET-hours per week
Strenuous LTPA - 25-49.99 MET-hours per week
Over-strenuous LTPA - >50 MET-hours per week

Table 4. Distribution of LTPA* (MET-Hours/week) categories according to covariates in the MDC study cohort 1991-1996

Characteristic	<7.5	7.5-14.99 (%)	15-24.99 (%)	25-49.99 (%)	>50 (%)	P-value
Age groups						<0.05
<50 years	397(7.5%)	829(15.8%)	1249(23.7%)	2041(38.8%)	744(14.1%)	
50-60 years	890(8.6%)	1627(15.8%)	2489(24.1%)	3780(36.7%)	1526(14.8%)	
>60years	738(6.8%)	1554(14.4%)	2454(22.7%)	4028(37.2%)	2053(19.0%)	
Sex						<0.05
0=Female	1201(7.4%)	2461(15.2%)	3891(24.0%)	6176(38.2%)	2458(15.2%)	
1=male	825(8.1%)	1550(15.2%)	2301(22.5%)	3677(36.0%)	1866(18.3%)	
BMI						<0.05
<24.9	853(6.7%)	1775(14.0%)	2998(23.7%)	4970(39.2%)	2074(16.4%)	
25.0-29.99	810(7.8%)	1603(15.4%)	2395(23.0%)	3799(36.5%)	1803(17.3%)	
>30.0	359(11.0%)	623(19.0%)	784(23.9%)	1068(32.6%)	443(13.5%)	
Smoking						<0.05
Smokers	742(10.0%)	1248(16.8%)	1754(23.6%)	2577(34.6%)	1126(15.1%)$_c$	
Ex-smokers	593(6.7%)	1274(14.4%)	2047(23.1%)$_b$	3390(38.2%)$_c$	1569(17.7%)	
Never smokers	690(6.8%)	1488(14.8%)	2391(23.7%)	3884(38.5%)	1629(16.2%)	
Education						<0.05
EDU-1	1043(9.6%)	1779(16.4%)	2442(22.5%)	3744(34.6%)	1828(16.9%)	
EDU-2	473(6.8%)	1038(15.0%)	1691(24.4%)	2619(37.7%)	1118(16.1%)	
EDU-3	160(6.7%)	364(15.3%)	525(22.0%)	942(39.5%)	391(16.4%)	
EDU-4	124(5.3%)	323(13.7%)	552(23.4%)	977(41.5%)	381(16.2%)	
EDU-5	226(5.8%)	507(13.0%)	982(25.2%)	1571(40.4%)	606(15.6%)	
Occupation						<0.05
Employed	1267(8.0%)	2537(16.0%)	3892(24.5%)	5992(37.8%)	2172(13.7%)	
Retired	620(7.3%)	1187(13.9%)	1863(21.8%)	3113(36.5%)	1753(20.5%)	
Other	139(6.9%)	287(14.3%)	437(21.7%)	748(37.2%)	399(19.9%)	

*Low LTPA - <7.5 MET-hours per week

Moderate LTPA - 7.5 -14.99 MET-hours per week

Vigorous LTPA - 15 -24.99 MET-hours per week

Strenuous LTPA - 25-49.99 MET-hours per week

Over-strenuous LTPA - >50 MET-hours per week

4.2 Cox regression results for association between LTPA and T2DM

The average follow-up time was 17.38 (SD=5.62) years and the total amount of follow-up time was 458,782.9 person-years. During this time 3869 (14.7%) people developed T2DM (men= 1892 (18.5%), women=1977 (12.2%). The incidence rate was 8.43 per 1000 person-years. Men had higher incidence (11.3) rate than women (8.43). Cox regression was done with stepwise adjustment of covariates each of which resulted in changes in the hazard ratios (HRs) of the different levels of LTPA (Table 5). In the unadjusted crude model, there was reduction of T2DM incident risk across all the categories of LTPA compared to the first (referent) group (<7.5MET-hrs/week). The greatest effect of LTPA in reducing the risk of developing T2DM was seen in those with strenuous LTPA (25-50 MET-hours/week) who had about 32% reduction in risk (HR=0.68, 95% CI 0.60 – 0.76). The least impact was seen in the moderately active group (7.5-15 MET-hours/week) who were 14% less likely to develop T2DM than the referent group (HR=0.86, 95% CI, 0.76-1.0). In the first adjusted model (for age, sex, and smoking) there was minimal attenuation of risk reduction (average 1% across all LTPA categories).

In the following model we adjusted additionally for education. Here, the risk attenuation was higher (average 3%) in each category of LTPA compared to the previous model however the same pattern was observed. The risk reduction in the moderate group was not significant while the strenuous group had the highest risk reduction (HR= 0.72, 95% CI 0.64 - 0.81). In the final model we adjusted additionally for BMI. There was further attenuation of risk reduction across all the categories of LTPA, which shows that BMI has a large effect on the model. The highest attenuation (14%) was observed in the >50MET-hours group and the lowest in the moderate group (5%). The pattern observed in previous models was also seen in the final model where the risk reduction in the moderate group was lowest compared to the reference group and insignificant (HR=0.94, 95% CI, 0.83 -1.07). In the strenuous group, the risk reduction was 17% (HR=0.83, 95% CI 0.74-0.93) compared to the referent group. The risk was not further reduced in LTPA amounts higher than strenuous and risk reduction was actually attenuated in the over-strenuous group to 12% (HR=0.88, 95% CI 0.77-1.00) compared to the reference category.

Table 5. HR and 95% CI for risk of diabetes according to level of LTPA and BMI in the MDC study cohort, 1991-1996

	Crude HR	**Model 1**	**Model 2**	**Model 3**
LTPA*	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95% CI)
Low	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Moderate	0.86(0.76-1.0)	0.87(0.77-1.0)	0.89(0.79-1.01)	0.94(0.83-1.07)
Vigorous	0.72(0.64-0.81)	0.73(0.65-0.83)	0.77(0.68-0.87)	0.86(0.76-0.97)
Strenuous	0.68(0.60-0.76)	0.69(0.61-0.77)	0.72(0.64-0.81)	0.83(0.74-0.93)
Over-strenuous	0.73(0.65-0.84)	0.71(0.62-0.81)	0.74(0.65-0.84)	0.88(0.77-1.00)

Model 1- adjusted for age and sex and smoking

Model 2- adjusted as model 1 and education

Model 3-adjusted as model 2 and BMI

*Low LTPA - <7.5 MET-hours per week

Moderate LTPA - 7.5 -14.99 MET-hours per week

Vigorous LTPA - 15 -24.99 MET-hours per week

Strenuous LTPA - 25-49.99 MET-hours per week

Over-strenuous LTPA - >50 MET-hours per week

In the overall final model (not shown), factoring all covariates, an increase in age by one year was associated with a 1% (HR=1.01, 95% CI 1.00-1.01) increase in the risk of developing T2DM. Men had a 60% higher risk of developing T2DM compared to women (HR=1.6, 95% CI 1.50-1.71). Smokers were had a 39% (HR=1.39, 95% CI 1.28-1.51) higher risk compared to never smokers while former smokers had 8% higher risk (HR= 1.08, 95% CI 1.004-1.17). Lower education was associated with increased risk of T2DM, as those with a university degree were 31% (HR= 0.69, 95% CI 0.62-0.77) less likely to develop T2DM compared to those who had elementary school education, the referent. An increase in BMI by one unit was associated with a 16% increase in the risk of T2DM (HR=1.16, 95% CI 1.15-1.16).

Sensitivity analysis

We conducted sensitivity analyses by comparing the hazard ratios of the final model with those of a similar comparative model that excluded energy intake over-reporters and under reporters (i.e. potential misreporters of LTPA) (Table 6).

There was no significant difference in the HRs between the two models. In the comparative model there was a slight increase in risk protection but in all the categories of LTPA this was less than 5% with the highest category being a change of 3.2% in the strenuous group. As such the model predicts the effects of LTPA adequately without the effects being affected by the under or over-reporters.

Table 6. Sensitivity analysis HRs and 95% CI, association of LTPA and T2DM in the MDC cohort, 1991-1996

LTPA#	Original final model* HR (95% CI)	Comparative model*, HR (95% CI)	HR difference
Low	1	1	
Moderate	0.94(0.83-1.07)	0.93(0.83-1.07)	0.01
Vigorous	0.86(0.76-0.97)	0.84(0.74-0.97)	0.01
Strenuous	0.83(0.74-0.93	0.80(0.70-0.91)	0.03
Over-strenuous	0.88(0.77-1.00)	0.86(0.74-1.00)	0.02

*Adjusted for Age, sex, smoking, education, and BMI

#Low LTPA - <7.5 MET-hours per week

Moderate LTPA - 7.5 -14.99 MET-hours per week

Vigorous LTPA - 15 -24.99 MET-hours per week

Strenuous LTPA - 25-49.99 MET-hours per week

Over-strenuous LTPA - >50 MET-hours per week

5. DISCUSSION

In this study, LTPA was associated with a decreased risk of diabetes especially for those who undertook vigorous (15-25 MET-hours per week) activity or more. Moderate LTPA (7.5-15 MET-hours per week) was not significantly associated with reduced incidence of diabetes in this cohort and over-strenuous activity (>50 MET hours per week) conferred no added benefits. Our findings are similar to others that have shown that higher levels of physical activity are beneficial in reducing the risk of incident T2DM (22, 23, 34). This study further reinforces the importance of increased physical activity in decreasing the risk of developing diabetes, which has also been demonstrated in other studies (17, 18, 35). Other studies have also shown that moderate levels of LTPA are not significantly associated with a decreased risk of T2DM (22, 36). Increased physical activity confers more benefits that improve body composition and metabolic health of individuals as well as mitigation of low-grade inflammation that is associated with development of chronic diseases including diabetes (15). These benefits have been observed even in advanced age and in one study it was shown that moderate physical activity was effective in reducing the risk of T2DM in those over 70 years (34).

While this study has demonstrated clear benefits of LTPA in reducing the risk of T2DM, the ceiling for LTPA amount adequate for such risk protection or even overall health is unknown and it is hard to explain why in this cohort there was no added benefits above 50 MET-hours per week of LTPA. One possible explanation is that the maximum overall physiologic changes due to PA have been reached and pushing the body beyond that limit does not lead to any physiological changes and may actually be harmful. Not many studies have demonstrated a cut off point for LTPA yet the American College of Sports Medicine (ACSM) recommends about 500-1000 MET-minutes per week (1), a range that falls within the range of moderate activity (7.5-15 MET-hours/week), which was not significant in this study and others (22). It however remains to be determined what the exact dose-response relationship between LTPA and diabetes risk reduction is.

Obesity remains an important risk factor for T2DM and was associated with a highly significant risk (HR=1.16, 95% CI, 1.15-1.16) for T2DM in this study as observed in other studies (11, 20, 22, 37). Increased physical activity leads to weight loss that further reduces the risk of diabetes (35). Other studies have shown that LTPA is more effective in reducing the risk of diabetes onset in overweight and obese than in normal weight individuals, which we were not able to demonstrate. In this study however, a high proportion of participants with obesity had low amounts of LTPA. It is not known whether obesity limited the exercise or lack of exercise led to obesity since both measures were assessed at baseline and we did not have a way of objectively assessing changes during follow-up. In this study, current smokers were associated with a high risk of T2DM compared to non-smokers, which has been shown in related studies (11). Smoking remains a key risk factor in other non-communicable diseases and cancers especially lung cancer and as such efforts to reduce smoking will have wider health benefits, not only reducing the incidence of diabetes.

Low socioeconomic status, whether assessed using education level or occupational class, is associated with a greater risk of T2DM. This has been demonstrated before in this cohort (9) and elsewhere in Sweden where it was shown low socioeconomic status is a risk for T2DM independent of other risk factors (38). In this study, low education levels were shown to be associated with high risk of T2DM irrespective of LTPA amount and further reinforces what is already known, that poor socioeconomic status is a major determinant of poor health (39).

Strengths and weaknesses

A major strength of the study is that outcome assessment was done using verified multiple patient registers as opposed to self-reports or a single register. The study also utilized a population-based prospective cohort design, a large sample size that ensured statistical power and factored in the follow-up time by using cox regression. We also classified the exposure in categories that allowed for assessment of effect at different levels and also to approximately establish an effectiveness range. The tools used in the study had been validated in this cohort (40) and the measures for LTPA have also been validated elsewhere (26).

The weaknesses were that the exposure and covariate information was collected at baseline and it was not ascertained whether the amount of exercise and alterable covariates like BMI had changed during the follow-up time, so lifestyle LTPA patterns and changes after baseline are unknown. In this study we did not evaluate the effect of comorbid conditions of importance in the development of T2DM like glucose intolerance/glycemic control (HBA1c) at baseline or presence of other chronic diseases or their risk factors like cardiovascular disease (hypertension), metabolic syndrome or other conditions that reduced the participants' ability to participate in LTPA. Participants who engaged in high LTPA may also have been more conscious about their health and ate healthier hence having additional protective factors apart from LTPA and subsequently lower incidence of T2DM. Dietary habits and energy intake could have affected the results. However, in a sensitivity analysis we excluded individuals that reported to high or too low energy intake in relation and there was no significant change in the hazard ratios. High alcohol consumption is associated with increased risk of developing T2DM (41, 42) and as such might be an important confounding factor and that was not adjusted for and may result in residual confounding. Like any other study, this one is also susceptible to errors at the point of assessment of exposure and covariates, despite tight control. Imprecise assessment using the detailed questionnaire may thus contribute to this.

6. CONCLUSION

In conclusion, this study demonstrated the importance of LTPA in reducing the risk of T2DM. The study showed that moderate LTPA was not significantly associated with reduced risk of T2DM and that there is no added benefit with over-strenuous activity. This has public health implications in recommending exercise amounts to populations in addition to other measures of preventing T2DM. Further studies in this cohort and elsewhere that investigate physical activity limits for different groups are warranted to better understand the limits of LTPA in conferring maximum health benefits and also guide in rolling out related public health policies. It also needs to be investigated whether changes in exposure and other alterable covariates over the course of follow-up affects the outcome, risk of T2DM.

Generalizability

The basic mechanisms that lead to the onset of T2DM are the same for all humans despite differences in predisposition due to ethnicity and other genetic differences. As such, even despite this study having been conducted in a Swedish population, the findings can probably be generalized to other different populations because the effects of LTPA do not differ per se in the human physiology.

Policy recommendations

The biggest question for public health policy makers, as relates to this study, might be how much physical activity is enough to ward off diabetes. To date recommendations have been a range of the amount of activity but with studies refining these boundaries, policy needs to shift to updated ranges in reference to these new insights. It is not easy to arrive at a definite cut off point though since many factors are involved and so the aim would be to be as clear and consistent as possible. By and large, increased physical activity, as demonstrated in this study, remains an important population level intervention that should be encouraged and supported with relevant initiatives. The poor outlook of lower socioeconomic groups highlights a worldwide problem of disparities in quality of life that are further worsened by disproportionate disease burden. Many low-income groups face poor health outcomes than their counterparts in the higher income brackets. This calls for improvement of socioeconomic welfare as a way of improving health. Therefore, direct efforts to tackle diabetes and other related diseases should also be accompanied by larger scale socioeconomic enhancement efforts especially for the majority that are economically vulnerable or already affected. The fact that those who are retired can engage in health-improving LTPA saves governments and health systems considerable healthcare costs by delaying potential onset of diabetes and other age related diseases. As such policy should also focus on and continue enabling active post-retirement lives.

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8. APPENDICES

8.1 Additional information

Table A1. Distribution of different activities among participants. LTPA and T2DM in the MDC study cohort 1991-1996

	Women		**Men**		**Total**	
Activity (Hr/wk)	**N**	**Median (IQR)**	**N**	**Median (IQR)**	**N (Median)**	**IQR**
Moderate Intensity						
Walking	14428	2.75(3.17)	8535	2.17(3.00)	22963(2.5)	3.13
Table tennis	51	0.5(0.75)	245	0.75(1.25)	296(0.625)	1.25
Cycling	10254	1.96(2.46)	6214	1.67(2.58)	16468(1.83)	2.50
Gardening	6997	1.5(1.93)	5475	1.25(1.88)	12472(1.36)	1.88
Gymnastics	4608	0.75(0.69)	1571	1.00(1.00)	6179(0.75)	0.94
Golf	1077	3.94(4.00)	918	4(3.75)	1995(4.00)	4.06
Badminton	200	0.375(0.63)	428	0.75(0.63)	625 (0.75)	0,72
Digging	2622	0.50(0.83)	3227	0.46(0.79)	5849(0.5)	0.75
Folk dancing	629	1.5(1.47)	423	1.5(1.5)	1052(1.5)	1.5
Ballrm dancing	1594	1.00(1.58)	1148	1.00(1.58)	2742(1.00)	1.5
Grass cutting	3115	0.33(0.46)	4913	0.42(0.50)	8028(0.38)	0.50
Vigorous intensity						
Jogging	1205	0.58(0.79)	1489	0.875(1.00)	2694(0.75)	1.00
Swimming	3561	0.50(0.63)	1737	0.42(0.58)	5298(0.5)	0.63
Lawn Tennis	187	0.75(1.17)	501	1(1.25)	688(0.98)	1.25
Soccer	31	0.75(1.42)	259	0.75(1.17)	290(0.75)	1.17
Orienteering	50	0.55(0.75)	63	0.50(1.06)	113(0.5)	0.90
Walking stairs	9077	0.50(0.58)	5221	0.33(0.5)	14298(0.42)	0.52

8.2 Popular Science Summary

This research was conducted to help understand how being active helps prevent diabetes and also how differently people from different social classes participate in leisure activities. The research showed that light activity (referred to moderate in the study) was not effective in preventing diabetes. However, vigorous and strenuous levels of activity were shown to help prevent diabetes but there was no added benefit of being active above strenuous levels. Exercise even in little amounts is beneficial to those who are overweight and obese. Social class affects people's ability to participate in leisure activities and a low social class increases one risk to get diabetes. People who smoke or are former smokers also have a high risk of having diabetes compare to those who have never smokes. In conclusion, we found that being active is beneficial for health.