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Quantifying the relationship between physical activity energy expenditure and incident Type 2 Diabetes: a prospective cohort study of device-measured activity in 90,096 adults

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Short running title: Physical activity and incident type 2 diabetes

Twitter summary: Strain and colleagues found a strong linear relationship between physical activity energy expenditure and incident type 2 diabetes. A difference equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of type 2 diabetes.

Suggested twitter image: Graphical Abstract. Alt-text: Physical activity energy expenditure was estimated from wrist-worn accelerometers using data from 90,096 middle-aged UK Biobank participants. There were 2018 incident events. A 5 $kJ.kg^{-1}.d^{-1}$ difference in physical activity energy expenditure – equivalent to an additional daily 20-minute brisk walk – was associated with 11% lower odds of type 2 diabetes, adjusted for demographic, lifestyle factors, and BMI.

Keywords: Physical activity, Type 2 Diabetes, Adults, Epidemiology, Triaxial Accelerometer

Word count: 4389, 1 Table, 3 Figures

Abstract

Objective

To investigate the association between accelerometer-derived physical activity energy expenditure (PAEE) and incident type 2 diabetes (T2D) in a cohort of middle-aged adults and within subgroups.

Research Design and Methods

Data were from 90,096 UK Biobank participants without prevalent diabetes (mean age 62 years, 57% women) who wore a wrist accelerometer for 7 days. PAEE was derived from wrist acceleration using a population-specific method validated against doubly-labelled water. Logistic regressions were used to assess associations between PAEE, its underlying intensity, and incident T2D, ascertained using hospital episode and mortality data up to November 2020. Models were progressively adjusted for demographic, lifestyle factors, and body mass index (BMI).

Results

The association between PAEE and T2D was approximately linear (n=2018 events). We observed 19% (95% confidence interval 17-21%) lower odds of T2D per 5 $kJ.kg^{-1}.d^{-1}$ in PAEE without adjustment for BMI, and 11% (9-13%) with BMI adjustment. The association was stronger in men than women, and weaker in those with obesity and higher genetic susceptibility to obesity. There was no evidence of effect modification by genetic susceptibility to T2D or insulin resistance. For a given level of PAEE, odds of T2D were lower amongst those engaging in more moderate-to-vigorous activity.

Conclusions

There was a strong linear relationship between PAEE and incident T2D. A difference in PAEE equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of T2D. The association was broadly similar across population subgroups, supporting physical activity for diabetes prevention in the whole population.

Article highlights

- We aimed to investigate the association between accelerometer-derived physical activity energy expenditure and incident type 2 diabetes in a large (n=90,096) cohort of middle-aged adults.
- We found a strong linear relationship between physical activity energy expenditure and incident type 2 diabetes, broadly similar across population subgroups.
- A difference equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of type 2 diabetes.
- These results support physical activity for the prevention of diabetes in the whole population.

There is a well-established inverse association between self-reported physical activity and incident type 2 diabetes mellitus (T2D) in observational studies (1–5) which is supported by evidence of prevention in randomised controlled trials (6–8). However, quantification of the association between habitual physical activity energy expenditure (PAEE) has proven to be challenging because of the intrinsic limitations in translating self-reported participation in particular activities into accurate estimates of PAEE. For example, the recall and social desirability biases inherent to self-report methods may differ by weight status (9). Thus, there are remaining uncertainties about the dose-response between physical activity and incident T2D. These uncertainties impact on public health messaging as it remains unclear how much benefit would be obtained from small changes in population-level PAEE.

The importance of using PAEE to investigate dose-response relationships is that it allows public health recommendations to be framed in terms of the benefits of physical activity of any type, potentially informing more specific or targeted prevention strategies. The best method for estimating PAEE is using stable isotopes to assess total energy expenditure, from which a measure of resting energy expenditure is subtracted (10,11). However, applying this technique at sufficiently large scale to enable the study of disease incidence in the general population remains prohibitively expensive. The use of wearables such as accelerometers to measure physical activity offers a viable alternative to objectively quantify dose-response associations with health outcomes (12–15), complementing previous studies using self-report of behaviours (1,16–18). To date, few studies have investigated the association between accelerometer-measured physical activity and incident T2D (19–22) and none of these have parameterised PAEE using methods validated against gold-standard stable isotope measurements. In addition, previous studies had smaller sample sizes, limiting the investigation of effect modification by population stratification or exploration of volume-intensity interactions.

The aims of this study were to investigate the association between accelerometer-derived PAEE and incident T2D in a large (n=90,096) cohort of middle-aged adults without known diabetes at baseline. We also examined whether associations differ in sub-groups defined by a range of demographic and health-related characteristics. Finally, we investigated whether different intensity profiles are associated with incident T2D.

Research Design and Methods

Study population

The UK Biobank is a prospective study of over half a million adults aged 40-69 living in Great Britain when recruited in 2006-2010 as explained in detail elsewhere (23). Briefly, participants completed a touchscreen questionnaire, and undertook nurse interview and anthropometric assessment at a designated interview centre. A subsample (n=103,670) were invited to wear a wrist-worn accelerometer approximately 5 years after initial recruitment (24). Some participants (n=8,697) undertook one or two additional assessment centre visits in the interim (see Supplementary Figure 1 for an overview).

Accelerometry measurement & processing

Accelerometry subsample participants were requested to wear a triaxial accelerometer (AX3, Axivity, UK) on their dominant wrist continuously for seven days. Raw acceleration was collected at 100Hz resolution, calibrated to local gravity (25) and low-pass filtered at 20Hz to eliminate machine noise. Movement-related acceleration was calculated as vector magnitude minus gravitational acceleration in 5-second epochs and summarised into proportions of daily time spent at different movement intensity levels for each participant. Non-wear time (awake or sleep) was identified as extended periods of non-movement and imputed using the average of similar time-of-day vector magnitude and intensity distribution data points with one minute granularity on different days of the measurement. We excluded those with inadequate data for calibration (n=11), those that had insufficient wear time no wear data in each one-hour period of the 24-hour cycle from the whole period of wear or <72 hours of total wear; n=6,985), and those with an average acceleration >100 milli-gravities (m*g*) (n=13), as explained elsewhere (24).

As in our previous work (12), we used a population-specific equation (13) to convert time spent in each movement intensity category into physical activity energy expenditure (PAEE) in $kJ.kg^{-1}.d^{-1}$. This was derived in a separate validation study through regression to PAEE measured by individually calibrated combined heart rate and trunk acceleration in 1695 UK adults; the resulting wrist acceleration-based estimate of PAEE was subsequently validated against total PAEE, measured by the gold-standard stable isotope method and resting indirect calorimetry in 97 adults (Supplementary

Figure 2) (14). In addition, we derived the fraction of PAEE from moderate-to-vigorous physical activity (%MVPA; any activity with a movement intensity above 125 m*g* (equivalent to 3 METs from combined sensing), expressed as a percentage to enable the study of joint activity volume and intensity associations (12). A scatter plot between PAEE and %MVPA is shown in Supplementary Figure 3. We excluded one individual who was a clear outlier (PAEE>150kJ.kg^{-1}.d^{-1} and %MVPA>80%). We also derived time spent in MVPA (hours/day). Season of wear was parameterised as two sine functions.

Diabetes ascertainment

Participants were considered to have prevalent diabetes (any type) if they either self-reported any diabetes other than gestational diabetes, or self-reported diabetes medication at recruitment (insulin, sulfonylureas, glitazones, meglitinides, or acarbose), or had a hospital episode statistics (HES) event with ICD-10 codes E10-E14 prior to accelerometry (n=3,619) (26). We excluded those with prevalent diabetes of any type and those for whom no prevalent diabetes status could be inferred (n=5). Compared to the method developed by Eastwood et al. (27), we counted a further n=524 individuals as prevalent cases, primarily because we used self-reported (via touchscreen interview) diabetes diagnosis as evidence. Eastwood et al. (27) identified 10 individuals as prevalent cases that our algorithm did not; we excluded these in order to be conservative. Incident T2D was ascertained through HES and mortality records with ICD code E11 without E10, or E14 without E10-E13 (27). HES records were available until 30th November 2020 in England, 28th February 2018 in Wales, and 31st October 2020 in Scotland. Death records were available until 30th November 2020. We used Eastwood et al.'s method to infer diagnosis date by taking the mid-point between the last record without diabetes and the date of the first record with diabetes (27).

Potential confounders

Data were obtained at initial recruitment through a touchscreen questionnaire and anthropometric assessment. Blood samples were also collected at this point. For participants that took part in further in-person assessments prior to accelerometry (n=9,171), we used the data from the time-point closest

to the accelerometry measurement. Exceptions were sex and Townsend Index of deprivation (based on postcode) that were only obtained at baseline; ethnicity (assumed not to have changed), and family medical history where a condition was counted even if it was at any of the measurement points. We have previously shown that the majority of covariates are stable over this period with the exceptions of employment status and medication use where there were trends towards unemployment and greater medication use at later visits (12).

We considered the following variables to be potential confounders with plausible associations to both exposure and outcome: sex (men/women), age (in years), ethnicity (white/non-white), Townsend Index of deprivation, highest educational level achieved (degree or above/any other qualification/no qualification), employment status (unemployed/in paid or self-employment), smoking status (never/previous/current), alcohol consumption (never/< twice a week/at least three times a week), fruit and vegetable intake (a score from 0-4 taking into account questions on cooked and raw vegetables, fresh and dried fruit consumption), parental history of diabetes (yes/no) and sleep duration (<7 hours/7-8 hours/>8 hours); see Supplementary Figure 4. We considered body mass index (BMI) to be a potential confounder but also a potential mediator of the association between physical activity and T2D given the plausible bidirectional associations between obesity and activity (28); in sensitivity analyses we also considered abdominal obesity using waist circumference.

Those missing data in any potential confounder were excluded from the main analysis (n=2,940). Multiple imputation using chained equations (MICE) was used to impute these missing data for a sensitivity analysis. All potential confounders, PAEE, and incident T2D were included in the imputation model.

Potential effect modifiers

The following variables were investigated as potential effect modifiers: sex, age, ethnicity, BMI status, prevalent CVD status, prevalent cancer status, and tertiles of cardiorespiratory fitness, grip strength, genetic predisposition scores for T2D, insulin resistance, and BMI.

The association was not estimated in those with BMI <18.5 kg/m^2 as the sample size was too small. Prevalent CVD was determined using both self-reported data and HES records up to accelerometry.

CVD was classified as ICD-9 410-414, 430-439 or ICD-10 I20-25, I60-69 or self-reported angina, chest pain, leg pain while walking normally, heart attack, or stroke. Prevalent cancer was determined using both self-reported data and HES records (ICD-9 140-199, 201-208, 209.1-209.3, 209.7-209.9, 235-239 and ICD-10 C0-99). Cardio-respiratory fitness was estimated from resting heart rate measures taken during blood pressure measurements at the initial recruitment visit. Grip strength was measured at the same time point; we averaged the values from both hands. Age and sex-specific tertiles were derived. Genotyping was performed using the UK BiLEVE and UK Biobank Axiom arrays, and initial quality control performed by the UK Biobank (29). We used the 'v3' release of the genetic data, imputed to the full set of Haplotype Reference Consortium reference panel (30) and the merged UK10K and 1000 Genomes Phase III reference panels (31). Approximately 93 million directly genotyped and imputed autosomal genetic markers were available after quality control. From these, we derived genetic risk scores for T2D using 424 single-nucleotide polymorphisms (SNPs) (32), insulin resistance using 53 SNPs (33) and BMI using 97 SNPs (34), weighted by their relative effect size extracted from the reference genome-wide association studies. Participants were excluded from the specific analysis if they had a missing value of the stratification variable.

Statistical analysis

As likely date of T2D diagnosis was inferred rather than measured, our primary analysis used logistic. Cubic splines with four evenly-spaced knots were used to examine the shape of the dose-response relationship between PAEE and incident T2D. We fit three models progressively adjusting for covariates. Model 0 adjusted for age, sex, and season of accelerometry wear. Season of wear is not a confounder (not associated with the outcome) but explains considerable variance in the exposure and is included to improve the precision of estimates (35). Model 1 additionally adjusted for all other demographic and lifestyle variables, and parental history of diabetes; Model 2 additionally adjusted for BMI, which may be considered to partially be on the causal pathway between PA and T2D. All continuous covariates except BMI met the linearity assumption as assessed visually by fractional polynomials. The shape of the BMI association was best modelled by including both a linear and a log-transformed term, determined using likelihood ratio tests. The reference value was 25 $kJ.kg^{-1}.d^{-1}$, approximately the 5^{th} percentile of the PAEE distribution in the sample.

We estimated the linear association between PAEE (per 5 $kJ.kg^{-1}.d^{-1}$) and incident T2D using the same three levels of adjustment. We also estimated the association between PAEE and T2D within subgroups of the potential effect modifiers. P-values for interaction were reported based on a likelihood ratio test comparing models with and without an interaction term. Genetic risk score analyses were additionally adjusted for the UK Biobank genotyping arrays and 10 genetic principal components, but did not adjust for ethnicity as analyses were restricted to those of white European ancestry (the population in which the scores were derived).

Finally, we investigated the joint association of PAEE and %MVPA with T2D in the whole sample. Both exposures were included as linear terms alongside an interaction term in a logistic regression model. Odds ratios for selected values of %MVPA (10%, 20%, 30%, 40%) were displayed graphically across the corresponding observed range of PAEE, with tables showing the odds ratios for specific combinations.

We performed several sensitivity analyses on the linear association between PAEE and T2D in the whole sample: (1) a time-to-event analysis using Cox regression, (2) imputation of missing covariate data, (3) excluding participants whose estimated T2D event date occurred within the first two years post-accelerometry, (4) excluding participants who were underweight (BMI <18.5 kg/m^2), and (5) excluding participants with HbA1c > 48mmoL/mol at study baseline (n=386). HbA1c was obtained from blood samples collected at the initial recruitment visit. Further details on the assay used are provided on the UK Biobank website (36). We also repeated the PAEE-%MVPA analysis additionally adjusting for waist circumference to shed light on the potential role of abdominal adiposity (37), and using alternative cut points for MVPA (100m*g* and 150m*g*). We also included a supplementary analysis of the association between time spent in MVPA and incident T2D risk using cubic splines as described above.

All analyses performed in Stata v16.1 (StataCorp, TX). Figures were produced in R and Biorender.com.

Results

Sample descriptives

The main analytical sample consisted of n=90,096 individuals (57% women, mean age at accelerometry baseline 62 (SD 7.8) years). There were 2018 incident T2D events. Table 1 presents the descriptive characteristics of the sample by tertile of PAEE. Supplementary Table 1 presents these characteristics by incident T2D status.

Cubic spline modelled associations of PAEE and incident T2D

Figure 1 shows the cubic spline modelled association between PAEE and incident T2D for the three levels of model adjustment. The association was approximately linear; compared with a PAEE of 25 $kJ.kg^{-1}.d^{-1}$, the odds ratios adjusted for demographic, lifestyle, and health-related confounders except BMI (Model 1) were 0.78 (95% confidence interval: 0.75-0.82), 0.52 (0.46-0.59), and 0.36 (0.32-0.41) at 30, 40, and 50 $kJ.kg^{-1}.d^{-1}$, respectively. The comparable odds ratios after additional adjustment for BMI (Model 2) were 0.86 (0.82-0.90), 0.72 (0.63-0.82), and 0.59 (0.52-0.68), respectively (Supplementary Table 2).

Linear associations of PAEE and incident T2D

We observed 19% (17-21%) lower odds of incident T2D per 5 $kJ.kg^{-1}.d^{-1}$ higher PAEE in Model 1 (Supplementary Figure 5, Supplementary Table 3). With further adjustment for BMI (Model 2), odds were 11% (9-13%) lower(Figure 2).

The associations were stronger for men than for women. The Model 1 odds ratios were 0.79 (0.77-0.82) and 0.83 (0.81-0.86), respectively, with a borderline significant interaction (p-value for interaction, 0.033). The magnitude of the difference in the association between men and women was greater with further BMI adjustment (Model 2 odds ratios 0.86 (0.83-0.88) for men and 0.95 (0.91-0.98) for women, with a p-value for interaction <0.001).

The associations were weaker amongst the obese than the other BMI subgroups. The Model 2 odds ratios (including adjustment for BMI within subgroup) were 0.87 (0.82-0.93) for those of normal weight, 0.85 (0.82-0.89) for those who were overweight, and 0.93 (0.90-0.96) for those who were

obese (p-value for interaction 0.002). This pattern of association was also observed for the tertiles of BMI genetic risk score, i.e. weaker associations in those at higher genetic risk of obesity.

There was some evidence that the association was stronger in White compared to than non-White individuals but this analysis is underpowered because of the small size of the non-White population subgroup in UK Biobank. There was no evidence of an interaction by age group, prevalent CVD or cancer status, or genetic risk for T2D or insulin resistance. There were no differences in strength of association across tertiles of cardiorespiratory fitness or grip strength in the BMI adjusted models, although the association was slightly stronger in the higher tertile of cardiorespiratory fitness in Model 1.

There were negligible differences in the magnitude of the association between PAEE and incident T2D across the range of sensitivity analyses undertaken (Supplementary Table 4). The Model 2 hazard ratio from Cox regression was 0.89 (0.87-0.91). The Model 1 and Model 2 odds ratios ranged between 0.81-0.82 and 0.89-0.90 respectively when missing data were imputed, and for different exclusion criteria (events estimated to occur within 2 years of accelerometry, those with BMI <18.5 kg/m2 were excluded, and those with HbA1c >48 mmoL/mol).

Joint associations of PAEE and %MVPA with incident T2D

The association between %MVPA and incident T2D was approximately linear (Supplementary Figure 6).

In the confounder and BMI-adjusted model (Model 2), a fixed PAEE of 25 $kJ.kg^{-1}.d^{-1}$, a 20% contribution MVPA was associated with 21% (15%-26%) lower odds of incident T2D compared to a 10% contribution of MVPA (Figure 3, Supplementary Table 5). Meanwhile 30% and 40% MVPA were associated with 37% (27-46%) and 50% (38-60%) lower odds respectively. When %MVPA was fixed, higher volumes of PAEE were associated with lower odds of incident T2D. The greatest risk reductions were observed with a combination of high PAEE and higher %MVPA. For example, those with a PAEE of 50 $kJ.kg^{-1}.d^{-1}$ and 40% MVPA had 58% (52-64%) lower odds of incident T2D compared with those a PAEE 15 $kJ.kg^{-1}.d^{-1}$ and 10% MVPA. Supplementary Figure 7 presents the

BMI-adjusted odds ratios for further combinations of PAEE and %MVPA, grouping those with similar durations of MVPA.

The associations were stronger without adjustment for BMI (Model1; Supplementary Figure 8). This was evident both with regards to the slope of the association between PAEE and incident T2D for a given %MVPA, and for the slope of the %MVPA association for a given PAEE, when compared to Model 2. Also, for a given value of PAEE, the differences across selected %MVPA values were greater.

In sensitivity analyses, adjustment for waist circumference as well as BMI attenuated the odds ratios by up to 5 percentage points (Supplementary Table 5). The %MVPA associations tended to be slightly weaker using a lower movement intensity threshold for MVPA (100m*g*) and stronger using a higher threshold (150m*g*). The greatest differences in magnitude were evident at the higher end of the PAEE and %MVPA range (Supplementary Table 6).

Time spent in MVPA

Supplementary Figure 9 shows the cubic spline modelled association between time spent in MVPA and incident T2D for the three levels of model adjustment. The association was approximately linear. Compared to a reference value of 0.5 hours/day, the odds ratios for Model 1 were 0.57 (0.52-0.63), and 0.39 (0.34-0.44) at 1 and 1.5 hours/day, respectively. The comparable odds ratios after additional adjustment for BMI (Model 2) were 0.74 (0.67-0.81) and 0.60 (0.53-0.68), respectively (Supplementary Table 7).

Conclusions

In this large prospective cohort study with objective measurement of physical activity, we found that estimated PAEE was inversely associated with incident T2D. Both without and with adjustment for BMI, the relationship between PAEE and risk of T2D was linear with no observable attenuation in the association even at much higher PAEE levels. The magnitude of the association is that there is a 19% and 11% lower odds per 5 $kJ.kg^{-1}.d^{-1}$ for the models without and with adjustment of BMI; a difference in PAEE equivalent to an additional 20-min brisk walk per day. These results suggest that the benefits of higher physical activity on T2D risk are constant, whatever the initial level of activity (i.e. ‘some is

good but more is better'). The strength of the association differed by sex, BMI, and genetic susceptibility to obesity. However, a linear inverse association between PAEE and incident T2D was evident amongst all subgroups investigated, except those of non-white ethnicity, which was underpowered.

We also found an association for moderate physical activity intensity, over and above total activity volume, with incident T2D risk. In other words, accumulating the same volume through higher intensity activity was associated with lower odds of T2D than accumulating through lower intensity activity. This is in line with our findings for all-cause mortality and CVD (12,15). It highlights the key message that health benefits can be achieved through a variety of combinations of volume and intensity but that if practical and appealing, undertaking more intense activity should be encouraged.

Few studies have quantified the relationship between objectively measured physical activity and risk of T2D. Our estimates suggest a stronger association than has been typically observed in the literature. In a cohort of 16,415 Hispanic/Latino adults, Cuthbertson et al. (2022) estimated a 2% (0-5%) lower hazard of incident diabetes per 1,000 steps/day; with the association fully attenuated after adjustment for BMI (21). Similarly, Garduno et al. (2022) found their estimated 12% (0-22%) lower hazard of incident diabetes per 2,000 steps/day to be non-significant after BMI adjustment amongst a sample of 4,838 older US women (19). Ballin et al. (2020) found a non-linear association between daily step count and incident diabetes amongst 3,055 older Swedish men and women (22). Compared to the sample median of 7,445 steps/day, the lowest extreme of the distribution (~1000 steps/day) had a three-fold higher risk, and there were no differences in risk amongst the upper half of the exposure distribution. Both Cuthbertson et al. and Garduno et al. found the relationship to be approximately linear, while Ballin et al. observed a non-linear dose-response relationship typically observed between physical activity and other chronic health outcomes (19,21,22). Cuthbertson et al. also found lower incidence of T2D (21).

As BMI is a known mechanism through which physical activity may influence the risk of T2D (38), adjustment likely produces a conservative estimate of association. However, as BMI also acts as a confounder (28), not adjusting for it likely results in an overestimation of the association. Our results tentatively suggest that more of the association between PAEE and T2D is mediated through BMI amongst women, as we observed a greater difference between Models 1 and 2 than for men.

However, the finding of a stronger association amongst men than women needs confirmation in further studies. We note this finding is opposite to the sex-specific meta-analytical results of self-reported data by Smith et al. (1), and the trends observed by Cuthbertson et al. (21).

We found no evidence of an interaction of PAEE and incident T2D with genetic predisposition to T2D or insulin resistance. We did observe a smaller effect size in individuals who were obese at baseline and in those who had higher genetic susceptibility to obesity. However, it is absolute rather than relative risk which determines the benefits of targeted prevention. There is an extremely strong relationship between obesity and T2D risk, as demonstrated by the distribution of cases in the different obesity strata in Figure 2 (approximately 3- and 9-fold higher for overweight and obese compared with normal-weight). Therefore, the absolute risk difference for a difference in PAEE in the subgroup of obese individuals will still be much larger than in non-obese subgroups despite the lower relative risk. Therefore, these results suggest that population-level approaches to increasing PAEE in all individuals should remain a public health priority.

Our finding that activity intensity plays a role over and above volume in T2D risk is interesting to consider from a mechanistic perspective. Our sensitivity analysis additionally adjusting for waist circumference showed further attenuation, potentially indicating visceral fat as an important factor. Previous research has suggested that higher intensity activities may impact T2D risk through metabolic adaptations while lower intensity activities may be mediated through changes in BMI (37). This is plausible as higher intensities require greater reliance on carbohydrate oxidation (39), which may increase the expression and activity of proteins related to glucose metabolism and insulin signalling. It is also possible that the greater stimulation of cardiovascular related pathways (e.g. stroke volume, capillary density, red blood cell, mitochondrial density) (40), leads to improved cardiorespiratory fitness, which in turn lowers the risk of T2D (41). The main strength of this study is the accurate quantification of PAEE at a large scale. This allows the investigation of dose-response relationships within subgroups and identification of interactions. We have also undertaken several sensitivity analyses indicating that the analytical assumptions made have a negligible impact on overall conclusions. A key limitation is the reliance on hospital episode statistics and mortality data for the ascertainment of T2D. Although it would be preferable to enhance ascertainment with information from other sources, particularly primary care records, these are not currently available for the whole cohort. However, it is important to note that 58% of our sample attended hospital in the follow-up

period of approximately 6 years and that diabetes is routinely recorded when admitted to hospital for other reasons in the UK. Thus the under-ascertainment that might be presumed through use of secondary care data may not be as consequential as it may appear (27) and the bias diminishes over time. Under the assumption that errors in the outcome classification are not associated with the exposure, the implication for our results of ascertainment error is to increase the uncertainty around the estimate of the association (42). To mitigate the issue of the likely diagnosis date being earlier than the first secondary care record, we used logistic regression rather than a time-to-event analysis method. That being said, our sensitivity analysis using Cox regression produced very similar estimates of association. Another potential limitation is that our estimate of PAEE relies on the accurate reflection of energy expenditure from dominant wrist acceleration. Given the method's documented validity in a UK population (13,14), this is a reasonable assumption at a whole sample level. The distribution of estimated PAEE is narrower than PAEE measured with stable isotopes and resting metabolic rate assessment; this error would lead to the amplification of the dose-response relationship. However, individuals who engage primarily in activities such as resistance exercise or cycling may not be appropriately characterised by the wrist measure which was also only done at a single time-point, thus not accounting for variability in activity levels over time, all of which could attenuate the associations. Other limitations include the measurement of covariates 5 years prior to accelerometry which may increase residual confounding in our estimates. However, we have previously shown that the majority of covariates are stable over this period, the exceptions being employment status and medication use (12). Also, the UK Biobank is not a representative national survey with a 5.5% response rate and respondents shown to be healthier and more affluent than the general population (43). However, our sample median PAEE of 42 $kJ.kg^{-1}.d^{-1}$ is in line with nationally representative age-specific estimates (11).

In summary, we have shown a strong linear relationship between accelerometer-derived PAEE and incident T2D in a large sample of middle-aged adults. A difference in PAEE equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of T2D. The association was broadly similar across population subgroups although slightly stronger in men than women, and weaker in those with obesity and higher genetic susceptibility to obesity. These results support physical activity for the prevention of diabetes in the whole population. For a given level of PAEE, engaging in a greater proportion of moderate-to-vigorous activity was associated with additional benefits. Therefore,

the role of activity intensity, over and above its contribution to PAEE, appears to be important for incident T2D.

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Author contributions

NW, SB, CLa, TS, PD, KW, TG, and SJS all contributed to the analysis plan. TS, PD, NK, CLi, EW, TG, NW, CLa, SB contributed to the derivation of variables. TS takes responsibility for the data analysis with assistance and checks were undertaken by SJS. All authors contributed to the interpretation of the results. TS, PD, NW, and SB initially drafted the manuscript and all authors contributed subsequently. TS is the guarantor for this manuscript.

Conflict of interest statement

All authors declare no conflicts of interest.

Data availability

UK Biobank data were obtained under application number 44448. Analysis code is available upon request to datasharing@mrc-epid.cam.ac.uk. UK Biobank data are available to researchers with an approved request (https://www.ukbiobank.ac.uk/register-apply/).

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References

1. Smith AD, Crippa A, Woodcock J, Brage S. Physical activity and incident type 2 diabetes mellitus: a systematic review and dose–response meta-analysis of prospective cohort studies. Diabetologia. 2016 Dec;59(12):2527–45.

2. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis. Eur J Epidemiol. 2015 Jul;30(7):529–42.

3. World Health Organization. WHO guidelines on physical activity and sedentary behaviour. [Internet]. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/336656/9789240015128-eng.pdf

4. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016 Nov 1;39(11):2065–79.

5. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Medicine & Science in Sports & Exercise. 2022 Feb;54(2):353–68.

6. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med. 2002 Feb 7;346(6):393–403.

7. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N Engl J Med. 2001 May 3;344(18):1343–50.

8. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007 Feb 10;334(7588):299.

9. Warner ET, Wolin KY, Duncan DT, Heil DP, Askew S, Bennett GG. Differential Accuracy of Physical Activity Self-Report by Body Mass Index. am j health behav. 2012 Mar 1;36(2):168–78.

10. Westerterp KR. Doubly labelled water assessment of energy expenditure: principle, practice, and promise. Eur J Appl Physiol. 2017 Jul;117(7):1277–85.

11. Brage S, Lindsay T, Venables M, Wijndaele K, Westgate K, Collins D, et al. Descriptive epidemiology of energy expenditure in the UK: findings from the National Diet and Nutrition Survey 2008–15. International Journal of Epidemiology. 2020 Jun 1;49(3):1007–21.

12. Strain T, Wijndaele K, Dempsey PC, Sharp SJ, Pearce M, Jeon J, et al. Wearable-device-measured physical activity and future health risk. Nat Med. 2020 Sep;26(9):1385–91.

13. White T, Westgate K, Wareham NJ, Brage S. Estimation of Physical Activity Energy Expenditure during Free-Living from Wrist Accelerometry in UK Adults. Song H, editor. PLoS ONE. 2016 Dec 9;11(12):e0167472.

14. White T, Westgate K, Hollidge S, Venables M, Olivier P, Wareham N, et al. Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study. Int J Obes. 2019 Nov;43(11):2333–42.

15. Dempsey PC, Rowlands AV, Strain T, Zaccardi F, Dawkins N, Razieh C, et al. Association of Physical Activity Volume and Intensity with Incident Cardiovascular Disease: a UK Biobank Study [Internet]. Sports Medicine; 2022 Feb [cited 2022 Jun 1]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.02.23.22271386

16. Garcia L, Pearce M, Abbas A, Mok A, Strain T, Ali S, et al. Non-occupational physical activity and risk of 22 cardiovascular disease, cancer, and mortality outcomes: a dose-response meta-analysis of large prospective studies [Internet]. Epidemiology; 2022 Mar [cited 2022 Jul 15]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.03.02.22271753

17. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case–control studies. Br J Sports Med. 2022 Jun;56(12):701–9.

18. Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, et al. Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2022 Jun 1;79(6):550.

19. Garduno AC, LaCroix AZ, LaMonte MJ, Dunstan DW, Evenson KR, Wang G, et al. Associations of Daily Steps and Step Intensity With Incident Diabetes in a Prospective Cohort Study of Older Women: The OPACH Study. Diabetes Care. 2022 Feb 1;45(2):339–47.

20. Chen GC, Qi Q, Hua S, Moon JY, Spartano NL, Vasan RS, et al. Accelerometer-assessed physical activity and incident diabetes in a population covering the adult life span: the Hispanic Community Health Study/Study of Latinos. The American Journal of Clinical Nutrition. 2020 Nov 11;112(5):1318–27.

21. Cuthbertson CC, Moore CC, Sotres-Alvarez D, Heiss G, Isasi CR, Mossavar-Rahmani Y, et al. Associations of steps per day and step intensity with the risk of diabetes: the Hispanic Community Health Study / Study of Latinos (HCHS/SOL). Int J Behav Nutr Phys Act. 2022 Dec;19(1):46.

22. Ballin M, Nordström P, Niklasson J, Alamäki A, Condell J, Tedesco S, et al. Daily step count and incident diabetes in community-dwelling 70-year-olds: a prospective cohort study. BMC Public Health. 2020 Dec;20(1):1830.

23. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 2015 Mar 31;12(3):e1001779.

24. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. Buchowski M, editor. PLoS ONE. 2017 Feb 1;12(2):e0169649.

25. van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva ICM, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014 Oct 1;117(7):738–44.

26. Cai L, Gonzales T, Wheeler E, Kerrison N, Day FR, Langenberg C, et al. Causal associations between cardiorespiratory fitness and type 2 diabetes. In submission;

27. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. Herder C, editor. PLoS ONE. 2016 Sep 15;11(9):e0162388.

28. Jones PR, Ekelund U. Physical Activity in the Prevention of Weight Gain: the Impact of Measurement and Interpretation of Associations. Curr Obes Rep. 2019 Jun;8(2):66–76.

29. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. Genome-wide genetic data on ~500,000 UK Biobank participants [Internet]. Genetics; 2017 Jul [cited 2022 Jul 15]. Available from: http://biorxiv.org/lookup/doi/10.1101/166298

30. The Haplotype Reference Consortium. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016 Oct;48(10):1279–83.

31. UK10K Consortium, Huang J, Howie B, McCarthy S, Memari Y, Walter K, et al. Improved imputation of low-frequency and rare variants using the UK10K haplotype reference panel. Nat Commun. 2015 Nov;6(1):8111.

32. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet. 2020 Jul 2;52(7):680–91.

33. EPIC-InterAct Consortium, Cambridge FPLD1 Consortium, Lotta LA, Gulati P, Day FR, Payne F, et al. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. Nat Genet. 2017 Jan;49(1):17–26.

34. The LifeLines Cohort Study, The ADIPOGen Consortium, The AGEN-BMI Working Group, The CARDIOGRAMplusC4D Consortium, The CKDGen Consortium, The GLGC, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015 Feb 12;518(7538):197–206.

35. Schisterman EF, Cole SR, Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology. 2009 Jul;20(4):488–95.

36. UK Biobank. Data-Field 30750 Description: Glycated haemoglobin (HbA1c) [Internet]. Available from: https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30750

37. Lynch J. Moderately Intense Physical Activities and High Levels of Cardiorespiratory Fitness Reduce the Risk of Non-Insulin-Dependent Diabetes Mellitus in Middle-aged Men. Arch Intern Med. 1996 Jun 24;156(12):1307.

38. Gill JMR, Cooper AR. Physical Activity and Prevention of Type 2 Diabetes Mellitus: Sports Medicine. 2008;38(10):807–24.

39. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and Type 2 Diabetes. Diabetes Care. 2010 Dec 1;33(12):e147–67.

40. Booth FW, Thomason DB. Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. Physiological Reviews. 1991 Apr 1;71(2):541–85.

41. Zaccardi F, O'Donovan G, Webb DR, Yates T, Kurl S, Khunti K, et al. Cardiorespiratory fitness and risk of type 2 diabetes mellitus: A 23-year cohort study and a meta-analysis of prospective studies. Atherosclerosis. 2015 Nov;243(1):131–7.

42. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. BMJ. 2010 Jun 23;340(jun23 2):c2289–c2289.

43. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American Journal of Epidemiology. 2017 Nov 1;186(9):1026–34.

Table 1

Descriptive characteristics by tertile of physical activity energy expenditure; UK Biobank (n=90,096)

	Physical Activity Energy Expenditure			Whole sample
	Tertile 1	Tertile 2	Tertile 3	
Sample size (% of total analysis sample)	30032 (33.3%)	30032 (33.3%)	30032 (33.3%)	90096 (100.0%)
PAEE range ($kJ.kg^{-1}.d^{-1}$)	2.8-36.1	36.1-45.4	45.4-129.2	2.8-129.2
PAEE in $kJ.kg^{-1}.d^{-1}$, mean (SD)	29.9 (4.8)	40.6 (2.6)	54.1 (8.0)	41.5 (11.4)
MVPA in $hours.d^{-1}$, mean (SD)	0.7 (0.3)	1.2 (0.3)	1.9 (0.5)	1.2 (0.6)
Diabetes incident events (n, %)	1111 (3.7%)	578 (1.9%)	329 (1.1%)	2018 (2.2%)
Age in years, mean (SD)	64.5 (7.5)	62.3 (7.7)	60.1 (7.7)	62.3 (7.8)
Age group, (n, %)				
<60 years	7982 (26.6%)	11252 (37.5%)	14476 (48.2%)	33710 (37.4%)
60-70 years	14112 (47.0%)	13566 (45.2%)	12385 (41.2%)	40063 (44.5%)
>70 years	7938 (26.4%)	5214 (17.4%)	3171 (10.6%)	16323 (18.1%)
Female sex, (n, %)	15333 (51.1%)	17623 (58.7%)	18478 (61.5%)	51434 (57.1%)
Ethnicity, (n, %)				
White	29310 (97.6%)	29213 (97.3%)	28990 (96.5%)	87513 (97.1%)
Asian excl. Chinese	245 (0.8%)	253 (0.8%)	262 (0.9%)	760 (0.8%)
Chinese	43 (0.1%)	57 (0.2%)	97 (0.3%)	197 (0.2%)
Black	177 (0.6%)	219 (0.7%)	310 (1.0%)	706 (0.8%)
Mixed	136 (0.5%)	141 (0.5%)	189 (0.6%)	466 (0.5%)
Any other ethnic group	121 (0.4%)	149 (0.5%)	184 (0.6%)	454 (0.5%)
Townsend Index of Deprivation, mean (SD)	-1.7 (2.9)	-1.8 (2.8)	-1.8 (2.8)	-1.8 (2.8)
Highest education level achieved, (n, %)				
No qualification	2953 (9.8%)	2189 (7.3%)	1983 (6.6%)	7125 (7.9%)
Any other qualification	14328 (47.7%)	14364 (47.8%)	14606 (48.6%)	43298 (48.1%)
Degree level or above	12751 (42.5%)	13479 (44.9%)	13443 (44.8%)	39673 (44.0%)
Employment status, (n, %)				
Unemployed	14427 (48.0%)	11519 (38.4%)	9376 (31.2%)	35322 (39.2%)
In paid employment	15605 (52.0%)	18513 (61.6%)	20656 (68.8%)	54774 (60.8%)
Smoking status, (n, %)				
Never	16463 (54.8%)	17542 (58.4%)	17905 (59.6%)	51910 (57.6%)
Previous	11164 (37.2%)	10656 (35.5%)	10431 (34.7%)	32251 (35.8%)
Current	2405 (8.0%)	1834 (6.1%)	1696 (5.6%)	5935 (6.6%)
Alcohol drinking status, (n, %)				
Never	1838 (6.1%)	1558 (5.2%)	1538 (5.1%)	4934 (5.5%)
< Twice a week	14131 (47.1%)	13413 (44.7%)	13316 (44.3%)	40860 (45.4%)
At least three times a week	14063 (46.8%)	15061 (50.1%)	15178 (50.5%)	44302 (49.2%)
Sleep duration, (n, %)				
< 7 hours	6503 (21.7%)	6478 (21.6%)	6587 (21.9%)	19568 (21.7%)

7-8 hours	20981 (69.9%)	21732 (72.4%)	22123 (73.7%)	64836 (72.0%)
> 8 hours	2548 (8.5%)	1822 (6.1%)	1322 (4.4%)	5692 (6.3%)
Fruit and veg intake score, mean (SD)	1.6 (1.1)	1.7 (1.1)	1.8 (1.2)	1.7 (1.1)
Parental history of diabetes, (n, %)				
No	25088 (83.5%)	24934 (83.0%)	24938 (83.0%)	74960 (83.2%)
Yes	4944 (16.5%)	5098 (17.0%)	5094 (17.0%)	15136 (16.8%)
Body Mass Index (kg/m^2), mean (SD)	27.8 (4.8)	26.5 (4.2)	25.3 (3.8)	26.5 (4.4)
Body Mass Index, (n, %)				
Underweight (<18.5 kg/m^2)	111 (0.4%)	150 (0.5%)	282 (0.9%)	543 (0.6%)
Normal weight (18.5-25 kg/m^2)	8677 (28.9%)	11965 (39.8%)	15332 (51.1%)	35974 (39.9%)
Overweight (25-30 kg/m^2)	13217 (44.0%)	12874 (42.9%)	11175 (37.2%)	37266 (41.4%)
Obese (>30 kg/m^2)	8027 (26.7%)	5043 (16.8%)	3243 (10.8%)	16313 (18.1%)
Prevalent cardiovascular disease, (n, %)				
No	21144 (70.4%)	22835 (76.0%)	24240 (80.7%)	68219 (75.7%)
Yes	8647 (28.8%)	6960 (23.2%)	5598 (18.6%)	21205 (23.5%)
Prevalent cancer, (n, %)				
No	25695 (85.6%)	26514 (88.3%)	27203 (90.6%)	79412 (88.1%)
Yes	4334 (14.4%)	3515 (11.7%)	2829 (9.4%)	10678 (11.9%)
BMI genetic risk score tertile, (n, %)				
Lowest tertile	9386 (31.3%)	9361 (31.2%)	9334 (31.1%)	28081 (31.2%)
Middle tertile	9368 (31.2%)	9319 (31.0%)	9398 (31.3%)	28085 (31.2%)
Upper tertile	9430 (31.4%)	9465 (31.5%)	9190 (30.6%)	28085 (31.2%)
Insulin resistance risk score tertile (weighted), (n, %)				
Lowest tertile	9470 (31.5%)	9277 (30.9%)	9336 (31.1%)	28083 (31.2%)
Middle tertile	9457 (31.5%)	9454 (31.5%)	9173 (30.5%)	28084 (31.2%)
Upper tertile	9257 (30.8%)	9414 (31.3%)	9413 (31.3%)	28084 (31.2%)
Type 2 Diabetes genetic risk score tertile, (n, %)				
Lowest tertile	9366 (31.2%)	9394 (31.3%)	9323 (31.0%)	28083 (31.2%)
Middle tertile	9434 (31.4%)	9421 (31.4%)	9229 (30.7%)	28084 (31.2%)
Upper tertile	9384 (31.2%)	9330 (31.1%)	9370 (31.2%)	28084 (31.2%)

Season of wear was modelled as two orthogonal spline variables; a visualisation of these variables has been previously published in Strain et al. (2020) (12). Genetic risk scores were derived for those of white European ancestry only. PAEE: Physical activity energy expenditure; SD: standard deviation. A higher Townsend index score indicates greater deprivation.

Figure Titles and Legends

Figure 1: Cubic spline modelled association between PAEE and incident type 2 diabetes; UK Biobank (n=90,096)

Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases. PAEE: physical activity energy expenditure, BMI: body mass index.

Figure 2: Odds ratios for incident type 2 diabetes per 5 $kJ.kg^{-1}.d^{-1}$ PAEE for the whole sample and in subgroups adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)

Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Genetic risk score stratified analyses also adjusted for UK Biobank genotyping array and 10 genetic principal components but did not adjust for ethnicity as analyses were restricted to those of white European ancestry. PAEE: physical activity energy expenditure, CMI: Cumulative incidence, CVD: cardiovascular disease, BMI: body mass index, GRS: genetic risk score. p-value for interaction between subgroups.

Figure 3: The joint association of PAEE and %MVPA with the odds of incident type 2 diabetes adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)

Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, BMI: body mass index.

Quantifying the relationship between physical activity energy expenditure and incident Type 2 Diabetes: a prospective cohort study of device-measured activity in 90,096 adults

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Short running title: Physical activity and incident type 2 diabetes

Twitter summary: Strain and colleagues found a strong linear relationship between physical activity energy expenditure and incident type 2 diabetes. A difference equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of type 2 diabetes.

Suggested twitter image: Graphical Abstract. Alt-text: Physical activity energy expenditure was estimated from wrist-worn accelerometers using data from 90,096 middle-aged UK Biobank participants. There were 2018 incident events. A 5 kJ./kg^{-1}/.d^{-1} difference in physical activity energy expenditure – equivalent to an additional daily 20-minute brisk walk – was associated with 11% lower odds of type 2 diabetes, adjusted for demographic, lifestyle factors, and BMI.

Keywords: Physical activity, Type 2 Diabetes, Adults, Epidemiology, Triaxial Accelerometer

Word count: 42444389, 1 Table, 3 Figures

Abstract

Objective

To investigate the association between accelerometer-derived physical activity energy expenditure (PAEE) and incident type 2 diabetes (T2D) in a cohort of middle-aged adults and within subgroups.

Research Design and Methods

Data were from 90,096 UK Biobank participants without prevalent diabetes (mean age 62 years, 57% women) who wore a wrist accelerometer for 7 days. PAEE was derived from wrist acceleration using a population-specific method validated against doubly-labelled water. Logistic regressions were used to assess associations between PAEE, its underlying intensity, and incident T2D, ascertained using ~~secondary-care~~hospital episode and mortality data up to November 2020. Models were progressively adjusted for demographic, lifestyle factors, and body mass index (BMI).

Results

The association between PAEE and T2D was approximately linear (n=2018 events). We observed 19% (95% confidence interval 17-21%) lower odds of T2D per 5 $kJ.kg^{-1}.d^{-1}$ in PAEE without adjustment for BMI, and 11% (9-13%) with BMI adjustment. The association was stronger in men than women, and weaker in those with obesity and higher genetic susceptibility to obesity. There was no evidence of effect modification by genetic susceptibility to T2D or insulin resistance. For a given level of PAEE, odds of T2D were lower amongst those engaging in more moderate-to-vigorous activity.

Conclusions

There was a strong linear relationship between PAEE and incident T2D. A difference in PAEE equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of T2D. The association was broadly similar across population subgroups. ~~These results~~ supporting physical activity for ~~the prevention of~~ diabetes prevention in the whole population.

Article highlights

- We aimed to investigate the association between accelerometer-derived physical activity energy expenditure and incident type 2 diabetes in a large (n=90,096) cohort of middle-aged adults.
- We found a strong linear relationship between physical activity energy expenditure and incident type 2 diabetes, broadly similar across population subgroups.
- A difference equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of type 2 diabetes.
- These results support physical activity for the prevention of diabetes in the whole population.

There is a well-established inverse association between self-reported physical activity and incident type 2 diabetes mellitus (T2D) in observational studies (1–5) which is supported by evidence of prevention in randomised controlled trials (6–8). However, quantification of the association between habitual physical activity energy expenditure (PAEE) has proven to be challenging because of the intrinsic limitations in translating self-reported participation in particular activities into accurate estimates of PAEE. For example, the recall and social desirability biases inherent to self-report methods may differ by weight status (9). Thus, there are remaining uncertainties about the dose-response between physical activity and incident T2D. These uncertainties impact on public health messaging as it remains unclear how much benefit would be obtained from small changes in population-level PAEE.

The importance of using PAEE to investigate dose-response relationships is that it allows public health recommendations to be framed in terms of the benefits of physical activity of any type, potentially informing more specific or targeted prevention strategies. The best method for estimating PAEE is using stable isotopes to assess total energy expenditure, from which a measure of resting energy expenditure is subtracted (10,11). However, applying this technique at sufficiently large scale to enable the study of disease incidence in the general population remains prohibitively expensive. The use of wearables such as accelerometers to measure physical activity offers a viable alternative to objectively quantify dose-response associations with health outcomes (12–15), complementing previous studies using self-report of behaviours (1,16–18). To date, few studies have investigated the association between accelerometer-measured physical activity and incident T2D (19–22) and none of these have parameterised PAEE using methods validated against gold-standard stable isotope measurements. In addition, previous studies had smaller sample sizes, limiting the investigation of effect modification by population stratification or exploration of volume-intensity interactions.

The aims of this study were to investigate the association between accelerometer-derived PAEE and incident T2D in a large (n=90,096) cohort of middle-aged adults without known diabetes at baseline. We also examined whether associations differ in sub-groups defined by a range of demographic and health-related characteristics. Finally, we investigated whether different intensity profiles are associated with incident T2D.

Research Design and Methods

Study population

The UK Biobank is a prospective study of over half a million adults aged 40-69 living in Great Britain when recruited in 2006-2010 as explained in detail elsewhere (23). Briefly, participants completed a touchscreen questionnaire, and undertook nurse interview and anthropometric assessment at a designated interview centre. A subsample (n=103,6708) were invited to wear a wrist-worn accelerometer approximately 5 years after initial recruitment (24). Some participants (n=8,697) undertook one or two additional assessment centre visits in the interim (see Supplementary Figure 1 for an overview).

Accelerometry measurement & processing

Accelerometry subsample participants were requested to wear a triaxial accelerometer (AX3, Axivity, UK) on their dominant wrist continuously for seven days. Raw acceleration was collected at 100Hz resolution, calibrated to local gravity (25) and low-pass filtered at 20Hz to eliminate machine noise. Movement-related acceleration was calculated as vector magnitude minus gravitational acceleration in 5-second epochs and summarised into proportions of daily time spent at different movement intensity levels for each participant. Non-wear time (awake or sleep) was identified as extended periods of non-movement and imputed using the average of similar time-of-day vector magnitude and intensity distribution data points with one minute granularity on different days of the measurement. We excluded those with inadequate data for calibration (n=11), those that had insufficient wear time no wear data in each one-hour period of the 24-hour cycle from the whole period of wear or <72 hours of total wear(~~<72 hours or no wear data in each one-hour period of the 24-hour cycle~~; n=6,9857), and those with an average acceleration >100 milli-gravities (m*g*) (n=13), as explained elsewhere (24).

As in our previous work (12), we used a population-specific equation (13) to convert time spent in each movement intensity category into physical activity energy expenditure (PAEE) in $kJ.kg^{-1}.d^{-1}$. This was derived in a separate validation study through regression to PAEE measured by individually calibrated combined heart rate and trunk acceleration in 1695 UK adults;~~,~~ the resulting wrist acceleration-based estimate of PAEE was ~~and~~ subsequently validated against total PAEE, measured by the gold-standard stable isotope method and resting indirect calorimetry in 97 adults

(Supplementary Figure 2) (14). In addition, we derived the fraction of PAEE from moderate-to-vigorous physical activity (%MVPA; any activity with a movement intensity above 125 m*g* (equivalent to 3 METs from combined sensing), expressed as a percentage to enable the study of joint activity volume and intensity associations (12). A scatter plot between PAEE and %MVPA is shown in Supplementary Figure 3. We excluded one individual who was a clear outlier (PAEE>150kJ.kg^{-1}.d^{-1} and %MVPA>80%). We also derived time spent in MVPA (hours/day). Season of wear was parameterised as two sine functions.

Diabetes ascertainment

Participants were considered to have prevalent diabetes (any type) if they either self-reported any diabetes other than gestational diabetes, or self-reported diabetes medication at recruitment (insulin, sulfonylureas, glitazones, meglitinides, or acarbose), or had a hospital episode statistics (HES) event with ICD-10 codes E10-E14 prior to accelerometry (n=3,619) (26). We excluded those with prevalent diabetes of any type and those for whom no prevalent diabetes status could be inferred (n=5). Compared to the method developed by Eastwood et al. (27), we counted a further n=524 individuals as prevalent cases, primarily because we used self-reported (via touchscreen interview) diabetes diagnosis as evidence. Eastwood et al. (27) identified 10 individuals as prevalent cases that our algorithm did not; we excluded these in order to be conservative. Incident T2D was ascertained through HES and mortality records with ICD code E11 without E10, or E14 without E10-E13 (27). HES records were available until 30th November 2020 in England, 28th February 2018 in Wales, and 31st October 2020 in Scotland. Death records were available until 30th November 2020. We used Eastwood et al.'s method to infer diagnosis date by taking the mid-point between the last record without diabetes and the date of the first record with diabetes (27).

Potential confounders

Data were obtained at initial recruitment through a touchscreen questionnaire and anthropometric assessment. Blood samples were also collected at this point. For participants that took part in further in-person assessments prior to accelerometry (n=9,171), we used the data from the time-point closest

to the accelerometry measurement. Exceptions were sex and Townsend Index of deprivation (based on postcode) that were only obtained at baseline; ethnicity (assumed not to have changed), and family medical history where a condition was counted even if it was at any of the measurement points. We have previously shown that the majority of covariates are stable over this period with the exceptions of employment status and medication use where there were trends towards unemployment and greater medication use at later visits (12).

We considered the following variables to be potential confounders with plausible associations to both exposure and outcome: sex (men/women), age (in years), ethnicity (white/non-white), Townsend Index of deprivation, highest educational level achieved (degree or above/any other qualification/no qualification), employment status (unemployed/in paid or self-employment), smoking status (never/previous/current), alcohol consumption (never/< twice a week/at least three times a week), fruit and vegetable intake (a score from 0-4 taking into account questions on cooked and raw vegetables, fresh and dried fruit consumption), parental history of diabetes (yes/no) and sleep duration (<7 hours/7-8 hours/>8 hours); see Supplementary Figure 4. We considered body mass index (BMI) to be a potential confounder but also a potential mediator of the association between physical activity and T2D given the plausible bidirectional associations between obesity and activity (28); in sensitivity analyses we also considered abdominal obesity using waist circumference.

Those missing data in any potential confounder were excluded from the main analysis (n=2,940). Multiple imputation using chained equations (MICE) was used to impute these missing data for a sensitivity analysis. All potential confounders, PAEE, and incident T2D were included in the imputation model.

Potential effect modifiers

The following variables were investigated as potential effect modifiers: sex, age, ethnicity, BMI status, prevalent CVD status, prevalent cancer status, and tertiles of cardiorespiratory fitness, grip strength, genetic predisposition scores for T2D, insulin resistance, and BMI.

The association was not estimated in those with BMI <18.5 kg/m^2 as the sample size was too small. Prevalent CVD was determined using both self-reported data and HES records up to accelerometry.

CVD was classified as ICD-9 410-414, 430-439 or ICD-10 I20-25, I60-69 or self-reported angina, chest pain, leg pain while walking normally, heart attack, or stroke. Prevalent cancer was determined using both self-reported data and HES records (ICD-9 140-199, 201-208, 209.1-209.3, 209.7-209.9, 235-239 and ICD-10 C0-99). Cardio-respiratory fitness was estimated from resting heart rate measures taken during blood pressure measurements at the initial recruitment visit. Grip strength was measured at the same time point; we averaged the values from both hands. Age and sex-specific tertiles were derived. Genotyping was performed using the UK BiLEVE and UK Biobank Axiom arrays, and initial quality control performed by the UK Biobank (29). We used the 'v3' release of the genetic data, imputed to the full set of Haplotype Reference Consortium reference panel (30) and the merged UK10K and 1000 Genomes Phase III reference panels (31). Approximately 93 million directly genotyped and imputed autosomal genetic markers were available after quality control. From these, we derived genetic risk scores for T2D using 424 single-nucleotide polymorphisms (SNPs) (32), insulin resistance using 53 SNPs (33) and BMI using 97 SNPs (34), weighted by their relative effect size extracted from the reference genome-wide association studies. Participants were excluded from the specific analysis if they had a missing value of the stratification variable.

Statistical analysis

As likely date of T2D diagnosis was inferred rather than measured, our primary analysis used logistic. Cubic splines with four evenly-spaced knots were used to examine the shape of the dose-response relationship between PAEE and incident T2D. We fit three models progressively adjusting for covariates. Model 0 adjusted for age, sex, and season of accelerometry wear. Season of wear is not a confounder (not associated with the outcome) but explains considerable variance in the exposure and is included to improve the precision of estimates (35). Model 1 additionally adjusted for all other demographic and lifestyle variables, and parental history of diabetes; Model 2 additionally adjusted for BMI, which may be considered to partially be on the causal pathway between PA and T2D. All continuous covariates except BMI met the linearity assumption as assessed visually by fractional polynomials. The shape of the BMI association was best modelled by including both a linear and a log-transformed term, determined using likelihood ratio tests. The reference value was 25 $kJ.kg^{-1}.d^{-1}$, approximately the 5^{th} percentile of the PAEE distribution in the sample.

We estimated the linear association between PAEE (per 5 $kJ.kg^{-1}.d^{-1}$) and incident T2D using the same three levels of adjustment. We also estimated the association between PAEE and T2D within subgroups of the potential effect modifiers. P-values for interaction were reported based on a likelihood ratio test comparing models with and without an interaction term. Genetic risk score analyses were additionally adjusted for the UK Biobank genotyping arrays and 10 genetic principal components, but did not adjust for ethnicity as analyses were restricted to those of white European ancestry (the population in which the scores were derived).

Finally, we investigated the joint association of PAEE and %MVPA with T2D in the whole sample. Both exposures were included as linear terms alongside an interaction term in a logistic regression model. Odds ratios for selected values of %MVPA (10%, 20%, 30%, 40%) were displayed graphically across the corresponding observed range of PAEE, with tables showing the odds ratios for specific combinations.

We performed several sensitivity analyses on the linear association between PAEE and T2D in the whole sample: (1) a time-to-event analysis using Cox regression, (2) imputation of missing covariate data, (3) excluding participants whose estimated T2D event date occurred within the first two years post-accelerometry, (4) excluding participants who were underweight (BMI <18.5 kg/m^2), and (5) excluding participants with HbA1c > 48mmoL/mol at study baseline (n=386). HbA1c was obtained from blood samples collected at the initial recruitment visit. Further details on the assay used are provided on the UK Biobank website (36). We also repeated the PAEE-%MVPA analysis additionally adjusting for waist circumference to shed light on the potential role of abdominal adiposity (37), and using alternative cut points for MVPA (100m*g* and 150m*g*). We also included a supplementary analysis of the association between time spent in MVPA and incident T2D risk using cubic splines as described above.

All analyses performed in Stata v16.1 (StataCorp, TX). Figures were produced in R and Biorender.com.

Results

Sample descriptives

The main analytical sample consisted of n=90,096 individuals (57% women, mean age at accelerometry baseline 62 (SD 7.8) years). There were 2018 incident T2D events. Table 1 presents the descriptive characteristics of the sample by tertile of PAEE. Supplementary Table 1 presents these characteristics by incident T2D status.

Cubic spline modelled associations of PAEE and incident T2D

Figure 1 shows the cubic spline modelled association between PAEE and incident T2D for the three levels of model adjustment. The association was approximately linear; compared with a PAEE of 25 $kJ.kg^{-1}.d^{-1}$, the odds ratios adjusted for demographic, lifestyle, and health-related confounders except BMI (Model 1) were 0.78 (95% confidence interval: 0.75-0.82), 0.52 (0.46-0.59), and 0.36 (0.32-0.41) at 30, 40, and 50 $kJ.kg^{-1}.d^{-1}$, respectively. The comparable odds ratios after additional adjustment for BMI (Model 2) were 0.86 (0.82-0.90), 0.72 (0.63-0.82), and 0.59 (0.52-0.68), respectively (Supplementary Table 2).

Linear associations of PAEE and incident T2D

We observed 19% (17-21%) lower odds of incident T2D per 5 $kJ.kg^{-1}.d^{-1}$ higher PAEE in Model 1 (Supplementary Figure 5, Supplementary Table 3). With further adjustment for BMI (Model 2), odds were 11% (9-13%) lower(Figure 2).

The associations were stronger for men than for women. The Model 1 odds ratios were 0.79 (0.77-0.82) and 0.83 (0.81-0.86), respectively, with a borderline significant interaction (p-value for interaction, 0.033). The magnitude of the difference in the association between men and women was greater with further BMI adjustment (Model 2 odds ratios 0.86 (0.83-0.88) for men and 0.95 (0.91-0.98) for women, with a p-value for interaction <0.001).

The associations were weaker amongst the obese than the other BMI subgroups. The Model 2 odds ratios (including adjustment for BMI within subgroup) were 0.87 (0.82-0.93) for those of normal weight, 0.85 (0.82-0.89) for those who were overweight, and 0.93 (0.90-0.96) for those who were

obese (p-value for interaction 0.002). This pattern of association was also observed for the tertiles of BMI genetic risk score, i.e. weaker associations in those at higher genetic risk of obesity.

There was some evidence that the association was stronger in White compared to than non-White individuals but this analysis is underpowered because of the small size of the non-White population subgroup in UK Biobank. There was no evidence of an interaction by age group, prevalent CVD or cancer status, or genetic risk for T2D or insulin resistance. There were no differences in strength of association across tertiles of cardiorespiratory fitness or grip strength in the BMI adjusted models, although the association was slightly stronger in the higher tertile of cardiorespiratory fitness in Model 1.

There were negligible differences in the magnitude of the association between PAEE and incident T2D across the range of sensitivity analyses undertaken (Supplementary Table 4). The Model 2 hazard ratio from Cox regression was 0.89 (0.87-0.91). The Model 1 and Model 2 odds ratios ranged between 0.81-0.82 and 0.89-0.90 respectively when missing data were imputed, and for different exclusion criteria (events estimated to occur within 2 years of accelerometry, those with BMI <18.5 kg/m2 were excluded, and those with HbA1c >48 mmoL/mol).

Joint associations of PAEE and %MVPA with incident T2D

The association between %MVPA and incident T2D was approximately linear (Supplementary Figure 6).

In the confounder and BMI-adjusted model (Model 2), a fixed PAEE of 25 $kJ.kg^{-1}.d^{-1}$, a 20% contribution MVPA was associated with 21% (15%-26%) lower odds of incident T2D compared to a 10% contribution of MVPA (Figure 3, Supplementary Table 5). Meanwhile 30% and 40% MVPA were associated with 37% (27-46%) and 50% (38-60%) lower odds respectively. When %MVPA was fixed, higher volumes of PAEE were associated with lower odds of incident T2D. The greatest risk reductions were observed with a combination of high PAEE and higher %MVPA. For example, those with a PAEE of 50 $kJ.kg^{-1}.d^{-1}$ and 40% MVPA had 58% (52-64%) lower odds of incident T2D compared with those a PAEE 15 $kJ.kg^{-1}.d^{-1}$ and 10% MVPA. Supplementary Figure 7 presents the

BMI-adjusted odds ratios for further combinations of PAEE and %MVPA, grouping those with similar durations of MVPA.

The associations were stronger without adjustment for BMI (Model1; Supplementary Figure 8). This was evident both with regards to the slope of the association between PAEE and incident T2D for a given %MVPA, and for the slope of the %MVPA association for a given PAEE, when compared to Model 2. Also, for a given value of PAEE, the differences across selected %MVPA values were greater.

In sensitivity analyses, adjustment for waist circumference as well as BMI attenuated the odds ratios by up to 5 percentage points (Supplementary Table 5). The %MVPA associations tended to be slightly weaker using a lower movement intensity threshold for MVPA (100m*g*) and stronger using a higher threshold (150m*g*). The greatest differences in magnitude were evident at the higher end of the PAEE and %MVPA range (Supplementary Table 6).

Time spent in MVPA

Supplementary Figure 9 shows the cubic spline modelled association between time spent in MVPA and incident T2D for the three levels of model adjustment. The association was approximately linear. Compared to a reference value of 0.5 hours/day, the odds ratios for Model 1 were 0.57 (0.52-0.63), and 0.39 (0.34-0.44) at 1 and 1.5 hours/day, respectively. The comparable odds ratios after additional adjustment for BMI (Model 2) were 0.74 (0.67-0.81) and 0.60 (0.53-0.68), respectively (Supplementary Table 7).

Conclusions

In this large prospective cohort study with objective measurement of physical activity, we found that estimated PAEE was inversely associated with incident T2D. Both without and with adjustment for BMI, the relationship between PAEE and risk of T2D was linear with no observable attenuation in the association even at much higher PAEE levels. The magnitude of the association is that there is a 19% and 11% lower odds per 5 $kJ.kg^{-1}.d^{-1}$ for the models without and with adjustment of BMI; a difference in PAEE equivalent to an additional 20-min brisk walk per day. These results suggest that the benefits of higher physical activity on T2D risk are constant, whatever the initial level of activity (i.e. ‘some is

good but more is better'). The strength of the association differed by sex, BMI, and genetic susceptibility to obesity. However, a linear inverse association between PAEE and incident T2D was evident amongst all subgroups investigated, except those of non-white ethnicity, which was underpowered.

We also found an association for moderate physical activity intensity, over and above total activity volume, with incident T2D risk. In other words, accumulating the same volume through higher intensity activity was associated with lower odds of T2D than accumulating through lower intensity activity. This is in line with our findings for all-cause mortality and CVD (12,15). It highlights the key message that health benefits can be achieved through a variety of combinations of volume and intensity but that if practical and appealing, undertaking more intense activity should be encouraged.

Few studies have quantified the relationship between objectively measured physical activity and risk of T2D. Our estimates suggest a stronger association than has been typically observed in the literature. In a cohort of 16,415 Hispanic/Latino adults, Cuthbertson et al. (2022) estimated a 2% (0-5%) lower hazard of incident diabetes per 1,000 steps/day; with the association fully attenuated after adjustment for BMI (21). Similarly, Garduno et al. (2022) found their estimated 12% (0-22%) lower hazard of incident diabetes per 2,000 steps/day to be non-significant after BMI adjustment amongst a sample of 4,838 older US women (19). Ballin et al. (2020) found a non-linear association between daily step count and incident diabetes amongst 3,055 older Swedish men and women (22). Compared to the sample median of 7,445 steps/day, the lowest extreme of the distribution (~1000 steps/day) had a three-fold higher risk, and there were no differences in risk amongst the upper half of the exposure distribution. Both Cuthbertson et al. and Garduno et al. found the relationship to be approximately linear, while Ballin et al. observed a non-linear dose-response relationship typically observed between physical activity and other chronic health outcomes (19,21,22). Cuthbertson et al. also found lower incidence of T2D (21).

As BMI is a known mechanism through which physical activity may influence the risk of T2D (38), adjustment likely produces a conservative estimate of association. However, as BMI also acts as a confounder (28), not adjusting for it likely results in an overestimation of the association. Our results tentatively suggest that more of the association between PAEE and T2D is mediated through BMI amongst women, as we observed a greater difference between Models 1 and 2 than for men.

However, the finding of a stronger association amongst men than women needs confirmation in further studies. We note this finding is opposite to the sex-specific meta-analytical results of self-reported data by Smith et al. (1), and the trends observed by Cuthbertson et al. (21).

We found no evidence of an interaction of PAEE and incident T2D with genetic predisposition to T2D or insulin resistance. We did observe a smaller effect size in individuals who were obese at baseline and in those who had higher genetic susceptibility to obesity. However, it is absolute rather than relative risk which determines the benefits of targeted prevention. There is an extremely strong relationship between obesity and T2D risk, as demonstrated by the distribution of cases in the different obesity strata in Figure 2 (approximately 3- and 9-fold higher for overweight and obese compared with normal-weight). Therefore, the absolute risk difference for a difference in PAEE in the subgroup of obese individuals will still be much larger than in non-obese subgroups despite the lower relative risk. Therefore, these results suggest that population-level approaches to increasing PAEE in all individuals should remain a public health priority.

Our finding that activity intensity plays a role over and above volume in T2D risk is interesting to consider from a mechanistic perspective. Our sensitivity analysis additionally adjusting for waist circumference showed further attenuation, potentially indicating visceral fat as an important factor. Previous research has suggested that higher intensity activities may impact T2D risk through metabolic adaptations while lower intensity activities may be mediated through changes in BMI (37). This is plausible as higher intensities require greater reliance on carbohydrate oxidation (39), which may increase the expression and activity of proteins related to glucose metabolism and insulin signalling. It is also possible that the greater stimulation of cardiovascular related pathways (e.g. stroke volume, capillary density, red blood cell, mitochondrial density) (40), leads to improved cardiorespiratory fitness, which in turn lowers the risk of T2D (41). The main strength of this study is the accurate quantification of PAEE at a large scale. This allows the investigation of dose-response relationships within subgroups and identification of interactions. We have also undertaken several sensitivity analyses indicating that the analytical assumptions made have a negligible impact on overall conclusions. A key limitation is the reliance on hospital episode statistics and mortality data for the ascertainment of T2D. Although it would be preferable to enhance ascertainment with information from other sources, particularly primary care records, these are not currently available for the whole cohort. However, it is important to note that 58% of our sample attended hospital in the follow-up

period of approximately 6 years and that diabetes is routinely recorded when admitted to hospital for other reasons in the UK. Thus the under-ascertainment that might be presumed through use of secondary care data may not be as consequential as it may appear (27) and the bias diminishes over time. Under the assumption that errors in the outcome classification are not associated with the exposure, the implication for our results of ascertainment error is to increase the uncertainty around the estimate of the association (42). To mitigate the issue of the likely diagnosis date being earlier than the first secondary care record, we used logistic regression rather than a time-to-event analysis method. That being said, our sensitivity analysis using Cox regression produced very similar estimates of association. Another potential limitation is that our estimate of PAEE relies on the accurate reflection of energy expenditure from dominant wrist acceleration. Given the method's documented validity in a UK population (13,14), this is a reasonable assumption at a whole sample level. The distribution of estimated PAEE is narrower than PAEE measured with stable isotopes and resting metabolic rate assessment; this error would lead to the amplification of the dose-response relationship. However, individuals who engage primarily in activities such as resistance exercise or cycling may not be appropriately characterised by the wrist measure which was also only done at a single time-point, thus not accounting for variability in activity levels over time, all of which could attenuate the associations. Other limitations include the measurement of covariates 5 years prior to accelerometry which may increase residual confounding in our estimates. However, we have previously shown that the majority of covariates are stable over this period, the exceptions being employment status and medication use (12). Also, the UK Biobank is not a representative national survey with a 5.5% response rate and respondents shown to be healthier and more affluent than the general population (43). However, our sample median PAEE of 42 $kJ.kg^{-1}.d^{-1}$ is in line with nationally representative age-specific estimates (11).

In summary, we have shown a strong linear relationship between accelerometer-derived PAEE and incident T2D in a large sample of middle-aged adults. A difference in PAEE equivalent to an additional daily 20-minute brisk walk was associated with 19% lower odds of T2D. The association was broadly similar across population subgroups although slightly stronger in men than women, and weaker in those with obesity and higher genetic susceptibility to obesity. These results support physical activity for the prevention of diabetes in the whole population. For a given level of PAEE, engaging in a greater proportion of moderate-to-vigorous activity was associated with additional benefits. Therefore,

the role of activity intensity, over and above its contribution to PAEE, appears to be important for incident T2D.

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Author contributions

NW, SB, CLa, TS, PD, KW, TG, and SJS all contributed to the analysis plan. TS, PD, NK, CLi, EW, TG, NW, CLa, SB contributed to the derivation of variables. TS takes responsibility for the data analysis with assistance and checks were undertaken by SJS. All authors contributed to the interpretation of the results. TS, PD, NW, and SB initially drafted the manuscript and all authors contributed subsequently. TS is the guarantor for this manuscript.

Conflict of interest statement

All authors declare no conflicts of interest.

Data availability

UK Biobank data were obtained under application number 44448. Analysis code is available upon request to datasharing@mrc-epid.cam.ac.uk. UK Biobank data are available to researchers with an approved request (https://www.ukbiobank.ac.uk/register-apply/).

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References

1. Smith AD, Crippa A, Woodcock J, Brage S. Physical activity and incident type 2 diabetes mellitus: a systematic review and dose–response meta-analysis of prospective cohort studies. Diabetologia. 2016 Dec;59(12):2527–45.

2. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose–response meta-analysis. Eur J Epidemiol. 2015 Jul;30(7):529–42.

3. World Health Organization. WHO guidelines on physical activity and sedentary behaviour. [Internet]. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/336656/9789240015128-eng.pdf

4. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care. 2016 Nov 1;39(11):2065–79.

5. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Medicine & Science in Sports & Exercise. 2022 Feb;54(2):353–68.

6. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med. 2002 Feb 7;346(6):393–403.

7. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N Engl J Med. 2001 May 3;344(18):1343–50.

8. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007 Feb 10;334(7588):299.

9. Warner ET, Wolin KY, Duncan DT, Heil DP, Askew S, Bennett GG. Differential Accuracy of Physical Activity Self-Report by Body Mass Index. am j health behav. 2012 Mar 1;36(2):168–78.

10. Westerterp KR. Doubly labelled water assessment of energy expenditure: principle, practice, and promise. Eur J Appl Physiol. 2017 Jul;117(7):1277–85.

11. Brage S, Lindsay T, Venables M, Wijndaele K, Westgate K, Collins D, et al. Descriptive epidemiology of energy expenditure in the UK: findings from the National Diet and Nutrition Survey 2008–15. International Journal of Epidemiology. 2020 Jun 1;49(3):1007–21.

12. Strain T, Wijndaele K, Dempsey PC, Sharp SJ, Pearce M, Jeon J, et al. Wearable-device-measured physical activity and future health risk. Nat Med. 2020 Sep;26(9):1385–91.

13. White T, Westgate K, Wareham NJ, Brage S. Estimation of Physical Activity Energy Expenditure during Free-Living from Wrist Accelerometry in UK Adults. Song H, editor. PLoS ONE. 2016 Dec 9;11(12):e0167472.

14. White T, Westgate K, Hollidge S, Venables M, Olivier P, Wareham N, et al. Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study. Int J Obes. 2019 Nov;43(11):2333–42.

15. Dempsey PC, Rowlands AV, Strain T, Zaccardi F, Dawkins N, Razieh C, et al. Association of Physical Activity Volume and Intensity with Incident Cardiovascular Disease: a UK Biobank Study [Internet]. Sports Medicine; 2022 Feb [cited 2022 Jun 1]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.02.23.22271386

16. Garcia L, Pearce M, Abbas A, Mok A, Strain T, Ali S, et al. Non-occupational physical activity and risk of 22 cardiovascular disease, cancer, and mortality outcomes: a dose-response meta-analysis of large prospective studies [Internet]. Epidemiology; 2022 Mar [cited 2022 Jul 15]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.03.02.22271753

17. Iso-Markku P, Kujala UM, Knittle K, Polet J, Vuoksimaa E, Waller K. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case–control studies. Br J Sports Med. 2022 Jun;56(12):701–9.

18. Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, et al. Association Between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2022 Jun 1;79(6):550.

19. Garduno AC, LaCroix AZ, LaMonte MJ, Dunstan DW, Evenson KR, Wang G, et al. Associations of Daily Steps and Step Intensity With Incident Diabetes in a Prospective Cohort Study of Older Women: The OPACH Study. Diabetes Care. 2022 Feb 1;45(2):339–47.

20. Chen GC, Qi Q, Hua S, Moon JY, Spartano NL, Vasan RS, et al. Accelerometer-assessed physical activity and incident diabetes in a population covering the adult life span: the Hispanic Community Health Study/Study of Latinos. The American Journal of Clinical Nutrition. 2020 Nov 11;112(5):1318–27.

21. Cuthbertson CC, Moore CC, Sotres-Alvarez D, Heiss G, Isasi CR, Mossavar-Rahmani Y, et al. Associations of steps per day and step intensity with the risk of diabetes: the Hispanic Community Health Study / Study of Latinos (HCHS/SOL). Int J Behav Nutr Phys Act. 2022 Dec;19(1):46.

22. Ballin M, Nordström P, Niklasson J, Alamäki A, Condell J, Tedesco S, et al. Daily step count and incident diabetes in community-dwelling 70-year-olds: a prospective cohort study. BMC Public Health. 2020 Dec;20(1):1830.

23. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 2015 Mar 31;12(3):e1001779.

24. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. Buchowski M, editor. PLoS ONE. 2017 Feb 1;12(2):e0169649.

25. van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva ICM, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014 Oct 1;117(7):738–44.

26. Cai L, Gonzales T, Wheeler E, Kerrison N, Day FR, Langenberg C, et al. Causal associations between cardiorespiratory fitness and type 2 diabetes. In submission;

27. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. Herder C, editor. PLoS ONE. 2016 Sep 15;11(9):e0162388.

28. Jones PR, Ekelund U. Physical Activity in the Prevention of Weight Gain: the Impact of Measurement and Interpretation of Associations. Curr Obes Rep. 2019 Jun;8(2):66–76.

29. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. Genome-wide genetic data on ~500,000 UK Biobank participants [Internet]. Genetics; 2017 Jul [cited 2022 Jul 15]. Available from: http://biorxiv.org/lookup/doi/10.1101/166298

30. The Haplotype Reference Consortium. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016 Oct;48(10):1279–83.

31. UK10K Consortium, Huang J, Howie B, McCarthy S, Memari Y, Walter K, et al. Improved imputation of low-frequency and rare variants using the UK10K haplotype reference panel. Nat Commun. 2015 Nov;6(1):8111.

32. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet. 2020 Jul 2;52(7):680–91.

33. EPIC-InterAct Consortium, Cambridge FPLD1 Consortium, Lotta LA, Gulati P, Day FR, Payne F, et al. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. Nat Genet. 2017 Jan;49(1):17–26.

34. The LifeLines Cohort Study, The ADIPOGen Consortium, The AGEN-BMI Working Group, The CARDIOGRAMplusC4D Consortium, The CKDGen Consortium, The GLGC, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015 Feb 12;518(7538):197–206.

35. Schisterman EF, Cole SR, Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology. 2009 Jul;20(4):488–95.

36. UK Biobank. Data-Field 30750 Description: Glycated haemoglobin (HbA1c) [Internet]. Available from: https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30750

37. Lynch J. Moderately Intense Physical Activities and High Levels of Cardiorespiratory Fitness Reduce the Risk of Non-Insulin-Dependent Diabetes Mellitus in Middle-aged Men. Arch Intern Med. 1996 Jun 24;156(12):1307.

38. Gill JMR, Cooper AR. Physical Activity and Prevention of Type 2 Diabetes Mellitus: Sports Medicine. 2008;38(10):807–24.

39. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and Type 2 Diabetes. Diabetes Care. 2010 Dec 1;33(12):e147–67.

40. Booth FW, Thomason DB. Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. Physiological Reviews. 1991 Apr 1;71(2):541–85.

41. Zaccardi F, O'Donovan G, Webb DR, Yates T, Kurl S, Khunti K, et al. Cardiorespiratory fitness and risk of type 2 diabetes mellitus: A 23-year cohort study and a meta-analysis of prospective studies. Atherosclerosis. 2015 Nov;243(1):131–7.

42. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. BMJ. 2010 Jun 23;340(jun23 2):c2289–c2289.

43. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American Journal of Epidemiology. 2017 Nov 1;186(9):1026–34.

Table 1

Descriptive characteristics by tertile of physical activity energy expenditure; UK Biobank (n=90,096)

	Physical Activity Energy Expenditure			Whole sample
	Tertile 1	Tertile 2	Tertile 3	
Sample size (% of total analysis sample)	30032 (33.3%)	30032 (33.3%)	30032 (33.3%)	90096 (100.0%)
PAEE range (kJ.kg^{-1}.d^{-1})	2.8-36.1	36.1-45.4	45.4-129.2	2.8-129.2
PAEE in kJ.kg^{-1}.d^{-1}, mean (SD)	29.9 (4.8)	40.6 (2.6)	54.1 (8.0)	41.5 (11.4)
MVPA in hours.d^{-1}, mean (SD)	0.7 (0.3)	1.2 (0.3)	1.9 (0.5)	1.2 (0.6)
Diabetes incident events (n, %)	1111 (3.7%)	578 (1.9%)	329 (1.1%)	2018 (2.2%)
Age in years, mean (SD)	64.5 (7.5)	62.3 (7.7)	60.1 (7.7)	62.3 (7.8)
Age group, (n, %)				
<60 years	7982 (26.6%)	11252 (37.5%)	14476 (48.2%)	33710 (37.4%)
60-70 years	14112 (47.0%)	13566 (45.2%)	12385 (41.2%)	40063 (44.5%)
>70 years	7938 (26.4%)	5214 (17.4%)	3171 (10.6%)	16323 (18.1%)
Female sex, (n, %)	15333 (51.1%)	17623 (58.7%)	18478 (61.5%)	51434 (57.1%)
Ethnicity, (n, %)				
White	29310 (97.6%)	29213 (97.3%)	28990 (96.5%)	87513 (97.1%)
Asian excl. Chinese	245 (0.8%)	253 (0.8%)	262 (0.9%)	760 (0.8%)
Chinese	43 (0.1%)	57 (0.2%)	97 (0.3%)	197 (0.2%)
Black	177 (0.6%)	219 (0.7%)	310 (1.0%)	706 (0.8%)
Mixed	136 (0.5%)	141 (0.5%)	189 (0.6%)	466 (0.5%)
Any other ethnic group	121 (0.4%)	149 (0.5%)	184 (0.6%)	454 (0.5%)
Townsend Index of Deprivation, mean (SD)	-1.7 (2.9)	-1.8 (2.8)	-1.8 (2.8)	-1.8 (2.8)
Highest education level achieved, (n, %)				
No qualification	2953 (9.8%)	2189 (7.3%)	1983 (6.6%)	7125 (7.9%)
Any other qualification	14328 (47.7%)	14364 (47.8%)	14606 (48.6%)	43298 (48.1%)
Degree level or above	12751 (42.5%)	13479 (44.9%)	13443 (44.8%)	39673 (44.0%)
Employment status, (n, %)				
Unemployed	14427 (48.0%)	11519 (38.4%)	9376 (31.2%)	35322 (39.2%)
In paid employment	15605 (52.0%)	18513 (61.6%)	20656 (68.8%)	54774 (60.8%)
Smoking status, (n, %)				
Never	16463 (54.8%)	17542 (58.4%)	17905 (59.6%)	51910 (57.6%)
Previous	11164 (37.2%)	10656 (35.5%)	10431 (34.7%)	32251 (35.8%)
Current	2405 (8.0%)	1834 (6.1%)	1696 (5.6%)	5935 (6.6%)
Alcohol drinking status, (n, %)				
Never	1838 (6.1%)	1558 (5.2%)	1538 (5.1%)	4934 (5.5%)
< Twice a week	14131 (47.1%)	13413 (44.7%)	13316 (44.3%)	40860 (45.4%)
At least three times a week	14063 (46.8%)	15061 (50.1%)	15178 (50.5%)	44302 (49.2%)
Sleep duration, (n, %)				
< 7 hours	6503 (21.7%)	6478 (21.6%)	6587 (21.9%)	19568 (21.7%)

7-8 hours	20981 (69.9%)	21732 (72.4%)	22123 (73.7%)	64836 (72.0%)
> 8 hours	2548 (8.5%)	1822 (6.1%)	1322 (4.4%)	5692 (6.3%)
Fruit and veg intake score, mean (SD)	1.6 (1.1)	1.7 (1.1)	1.8 (1.2)	1.7 (1.1)
Parental history of diabetes, (n, %)				
No	25088 (83.5%)	24934 (83.0%)	24938 (83.0%)	74960 (83.2%)
Yes	4944 (16.5%)	5098 (17.0%)	5094 (17.0%)	15136 (16.8%)
Body Mass Index (kg/m^2), mean (SD)	27.8 (4.8)	26.5 (4.2)	25.3 (3.8)	26.5 (4.4)
Body Mass Index, (n, %)				
Underweight (<18.5 kg/m^2)	111 (0.4%)	150 (0.5%)	282 (0.9%)	543 (0.6%)
Normal weight (18.5-25 kg/m^2)	8677 (28.9%)	11965 (39.8%)	15332 (51.1%)	35974 (39.9%)
Overweight (25-30 kg/m^2)	13217 (44.0%)	12874 (42.9%)	11175 (37.2%)	37266 (41.4%)
Obese (>30 kg/m^2)	8027 (26.7%)	5043 (16.8%)	3243 (10.8%)	16313 (18.1%)
Prevalent cardiovascular disease, (n, %)				
No	21144 (70.4%)	22835 (76.0%)	24240 (80.7%)	68219 (75.7%)
Yes	8647 (28.8%)	6960 (23.2%)	5598 (18.6%)	21205 (23.5%)
Prevalent cancer, (n, %)				
No	25695 (85.6%)	26514 (88.3%)	27203 (90.6%)	79412 (88.1%)
Yes	4334 (14.4%)	3515 (11.7%)	2829 (9.4%)	10678 (11.9%)
BMI genetic risk score tertile, (n, %)				
Lowest tertile	9386 (31.3%)	9361 (31.2%)	9334 (31.1%)	28081 (31.2%)
Middle tertile	9368 (31.2%)	9319 (31.0%)	9398 (31.3%)	28085 (31.2%)
Upper tertile	9430 (31.4%)	9465 (31.5%)	9190 (30.6%)	28085 (31.2%)
Insulin resistance risk score tertile (weighted), (n, %)				
Lowest tertile	9470 (31.5%)	9277 (30.9%)	9336 (31.1%)	28083 (31.2%)
Middle tertile	9457 (31.5%)	9454 (31.5%)	9173 (30.5%)	28084 (31.2%)
Upper tertile	9257 (30.8%)	9414 (31.3%)	9413 (31.3%)	28084 (31.2%)
Type 2 Diabetes genetic risk score tertile, (n, %)				
Lowest tertile	9366 (31.2%)	9394 (31.3%)	9323 (31.0%)	28083 (31.2%)
Middle tertile	9434 (31.4%)	9421 (31.4%)	9229 (30.7%)	28084 (31.2%)
Upper tertile	9384 (31.2%)	9330 (31.1%)	9370 (31.2%)	28084 (31.2%)

Season of wear was modelled as two orthogonal spline variables; a visualisation of these variables has been previously published in Strain et al. (2020) (12). Genetic risk scores were derived for those of white European ancestry only. PAEE: Physical activity energy expenditure; SD: standard deviation. A higher Townsend index score indicates greater deprivation.

Figure Titles and Legends

Figure 1: Cubic spline modelled association between PAEE and incident type 2 diabetes; UK Biobank (n=90,096)

Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases. PAEE: physical activity energy expenditure, BMI: body mass index.

Figure 2: Odds ratios for incident type 2 diabetes per 5 $kJ.kg^{-1}.d^{-1}$ PAEE for the whole sample and in subgroups adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)

Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Genetic risk score stratified analyses also adjusted for UK Biobank genotyping array and 10 genetic principal components but did not adjust for ethnicity as analyses were restricted to those of white European ancestry. PAEE: physical activity energy expenditure, CMI: Cumulative incidence, CVD: cardiovascular disease, BMI: body mass index, GRS: genetic risk score. p-value for interaction between subgroups.

Figure 3: The joint association of PAEE and %MVPA with the odds of incident type 2 diabetes adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)

Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, BMI: body mass index.

Supplementary Tables and Figures

Supplementary Figure 1

Timeline of measurements and sample sizes for those included in the present study.

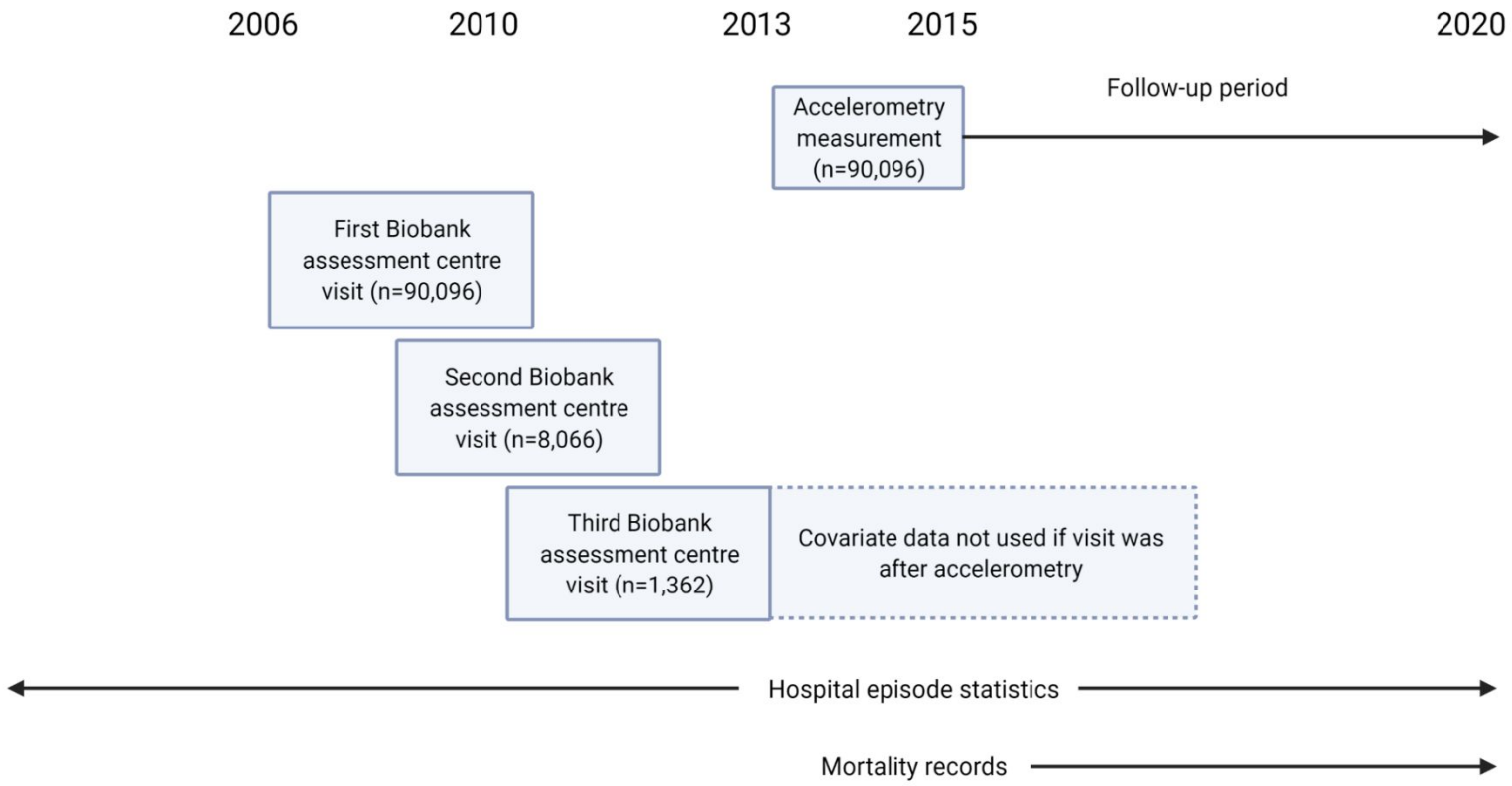
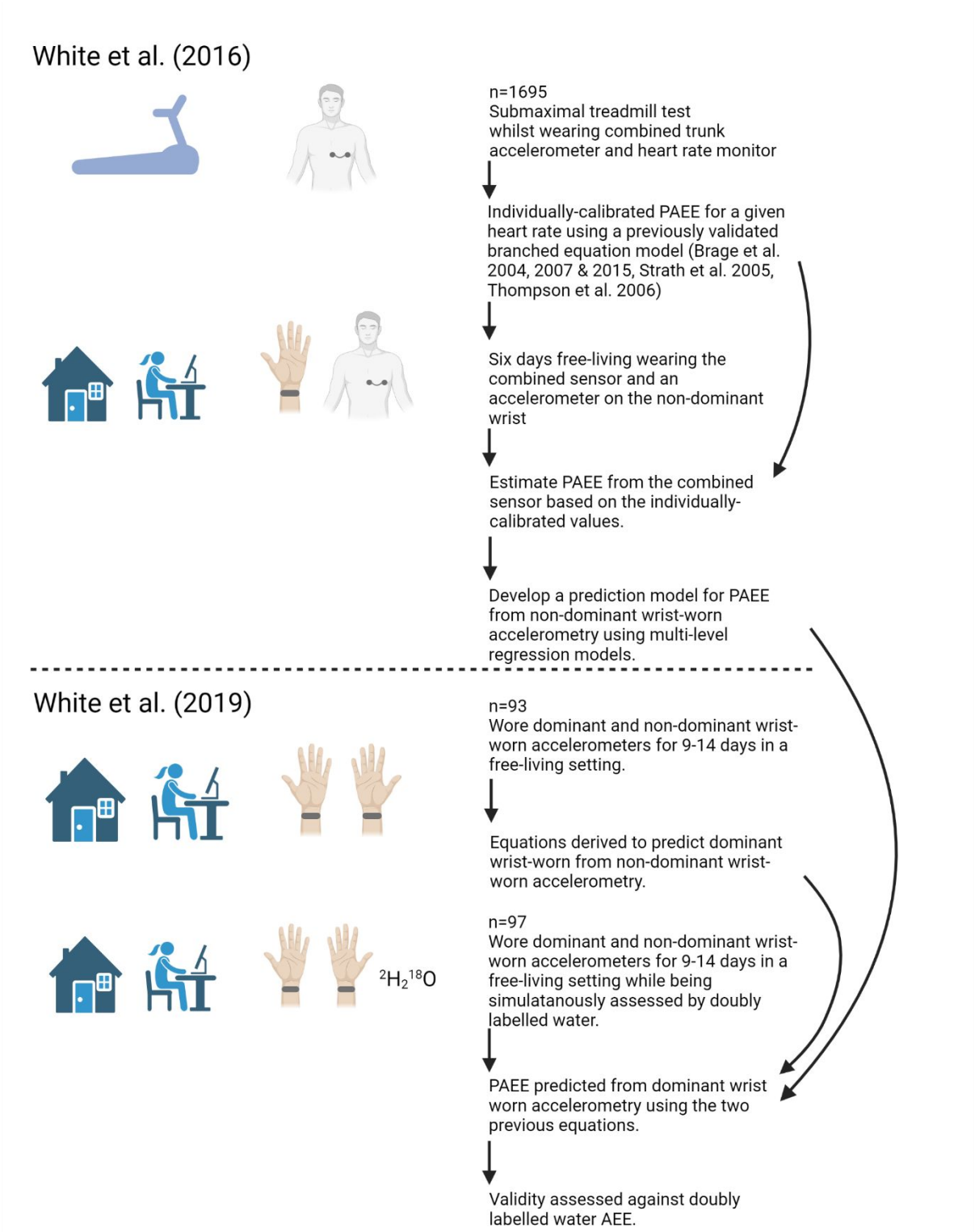


Figure created using Biorender.com. Covariate data was obtained at assessment centre visits with the data provided at the closest time point prior to accelerometry used (unless otherwise stated in the Methods). Hospital episode statistics were used to inform prevalent disease status prior to accelerometry and were one method of incident Type 2 diabetes diagnosis ascertainment in the follow up period alongside mortality records.

Supplementary Figure 2

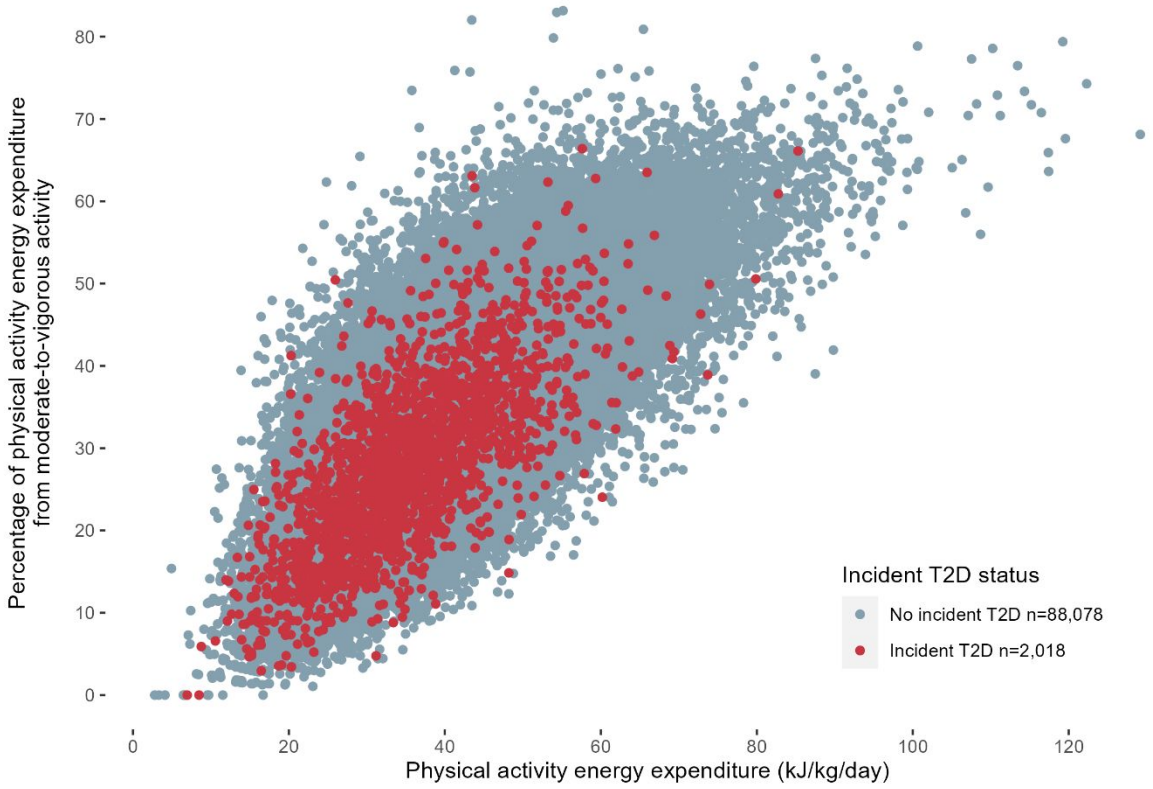
Derivation and validation of PAEE from dominant wrist-worn accelerometry



Created with biorender.com. PAEE: physical activity energy expenditure; AEE: activity energy expenditure. References provided at the end of the Supplementary Materials.

Supplementary Figure 3

Scatter plot showing PAEE and the percentage of PAEE from MVPA by incident type 2 diabetes status; UK Biobank (n=90,096)



PAEE: Physical Activity Energy Expenditure, MVPA: moderate-to-vigorous physical activity. Pearson's correlation coefficient between PAEE and the percentage of PAEE from MVPA = 0.72

Supplementary Figure 4

A simplified diagram displaying the rationale for covariate adjustment

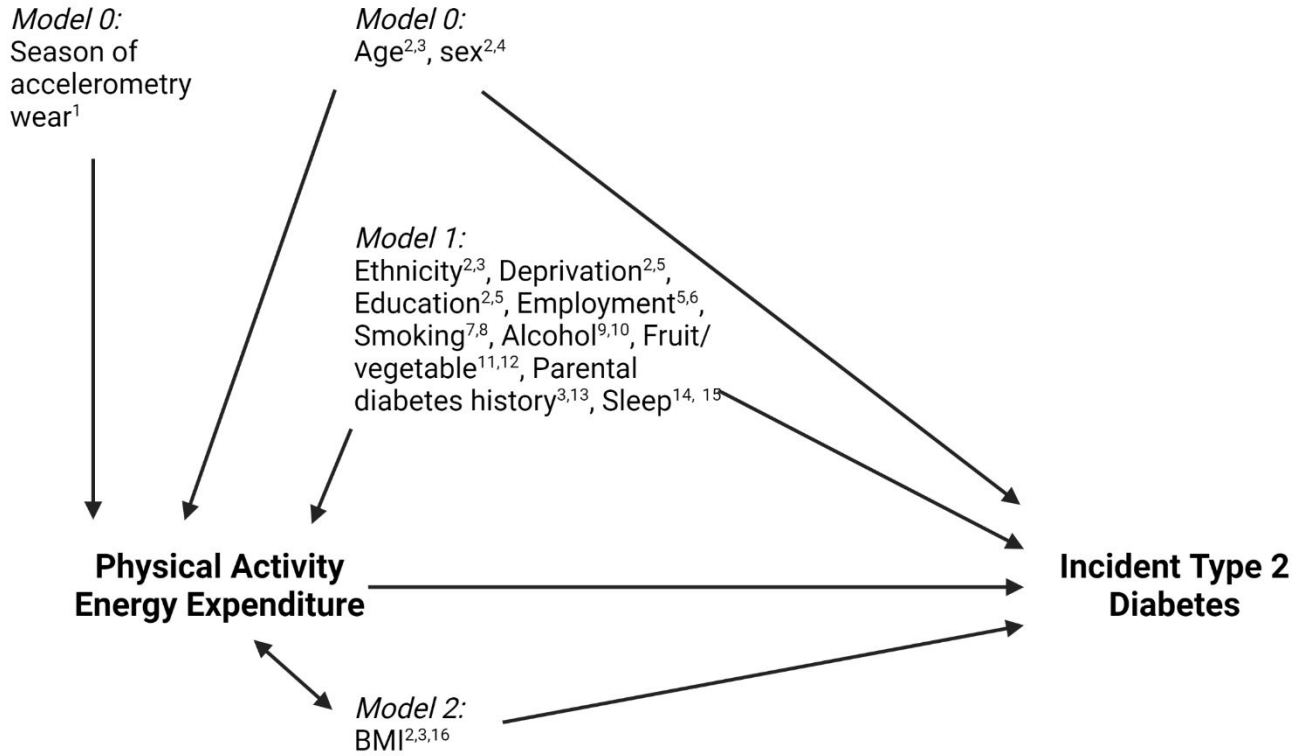
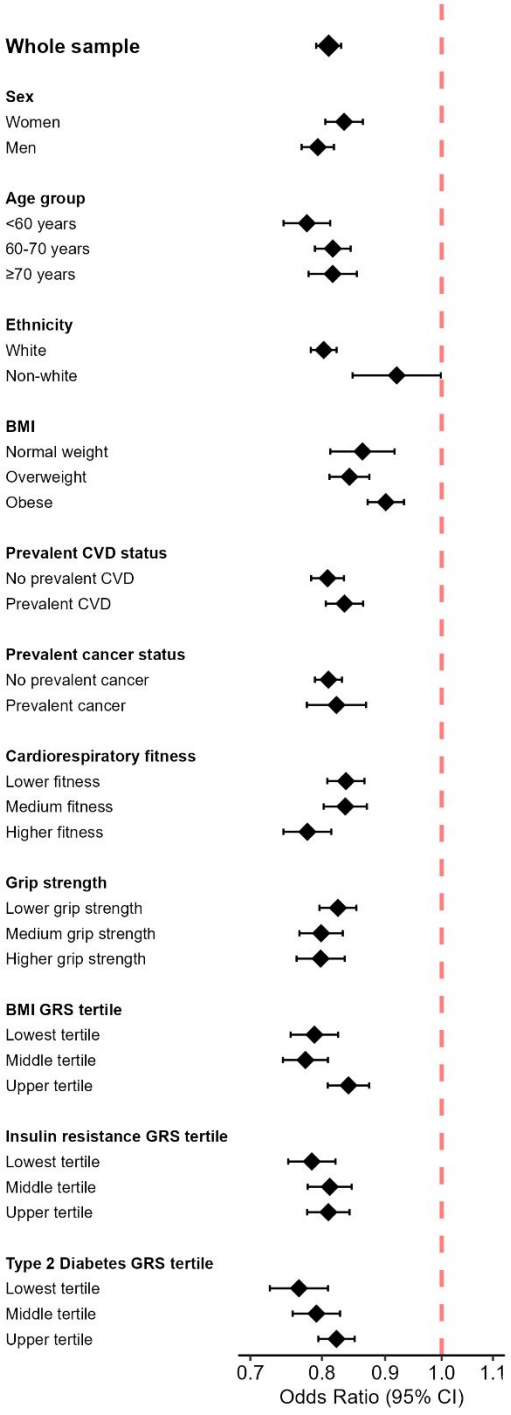


Figure created using Biorender.com. Models progressively adjusted for variables listed above i.e. Model 2 also adjusted for variables listed under Models 0 and 1. References are provided at the end of the Supplementary Materials.

Supplementary Figure 5

Odds ratios for incident type 2 diabetes per 5 kJ.kg^{-1}.d^{-1} PAEE for the whole sample and in subgroups with adjustment for confounding factors but not BMI (Model 1); UK Biobank (n=90,096)

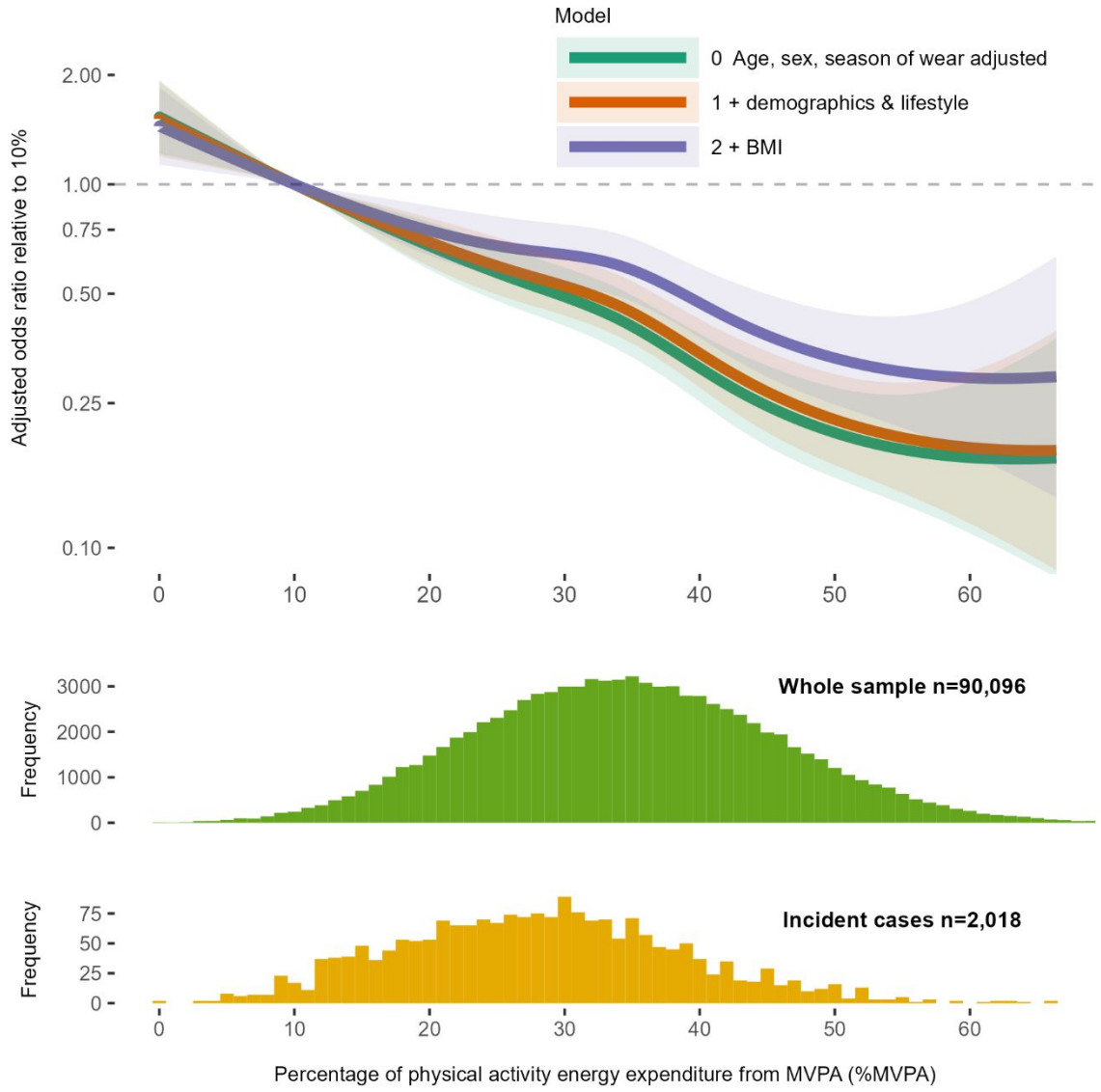


	n	Events	CMI	Odds Ratio (95% CI)	p-value
Whole sample	**90096**	**2018**	**2.24%**	**0.81 (0.79-0.83)**	
Sex					
Women	51434	831	1.62%	0.83 (0.81-0.86)	
Men	38662	1187	3.07%	0.79 (0.77-0.82)	0.033
Age group					
<60 years	33710	489	1.45%	0.78 (0.74-0.81)	
60-70 years	40063	931	2.32%	0.82 (0.79-0.84)	
≥70 years	16323	598	3.66%	0.82 (0.78-0.85)	0.175
Ethnicity					
White	87513	1901	2.17%	0.80 (0.78-0.82)	
Non-white	2583	117	4.53%	0.92 (0.85-1.00)	0.002
BMI					
Normal weight	35974	242	0.67%	0.86 (0.81-0.92)	
Overweight	37266	780	2.09%	0.84 (0.81-0.87)	
Obese	16313	994	6.09%	0.90 (0.87-0.93)	0.024
Prevalent CVD status					
No prevalent CVD	68219	1122	1.65%	0.81 (0.78-0.83)	
Prevalent CVD	21205	879	4.15%	0.83 (0.81-0.86)	0.172
Prevalent cancer status					
No prevalent cancer	79412	1665	2.10%	0.81 (0.79-0.83)	
Prevalent cancer	10678	353	3.31%	0.82 (0.78-0.87)	0.623
Cardiorespiratory fitness					
Lower fitness	20180	618	3.06%	0.84 (0.81-0.87)	
Medium fitness	22745	425	1.87%	0.84 (0.80-0.87)	
Higher fitness	23805	349	1.47%	0.78 (0.74-0.81)	0.022
Grip strength					
Lower grip strength	22975	586	2.55%	0.82 (0.80-0.85)	
Medium grip strength	22445	443	1.97%	0.80 (0.77-0.83)	
Higher grip strength	21102	360	1.71%	0.80 (0.76-0.83)	0.380
BMI GRS tertile					
Lowest tertile	28081	543	1.93%	0.79 (0.75-0.82)	
Middle tertile	28085	604	2.15%	0.78 (0.74-0.81)	
Upper tertile	28085	669	2.38%	0.84 (0.81-0.87)	0.012
Insulin resistance GRS tertile					
Lowest tertile	22250	419	1.88%	0.78 (0.75-0.82)	
Middle tertile	22234	465	2.09%	0.81 (0.78-0.85)	
Upper tertile	22289	512	2.30%	0.81 (0.78-0.84)	0.472
Type 2 Diabetes GRS tertile					
Lowest tertile	22294	277	1.24%	0.77 (0.73-0.81)	
Middle tertile	22228	410	1.85%	0.79 (0.76-0.83)	
Upper tertile	22251	709	3.19%	0.82 (0.79-0.85)	0.072

Model 1 displayed; adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Genetic risk score stratified analyses also adjusted for UK Biobank genotyping array and 10 genetic principal components but did not adjust for ethnicity as analyses were restricted to those of white European ancestry. PAEE: physical activity energy expenditure, CMI: Cumulative incidence, CVD: cardiovascular disease, BMI: body mass index, GRS: genetic risk score.

Supplementary Figure 6

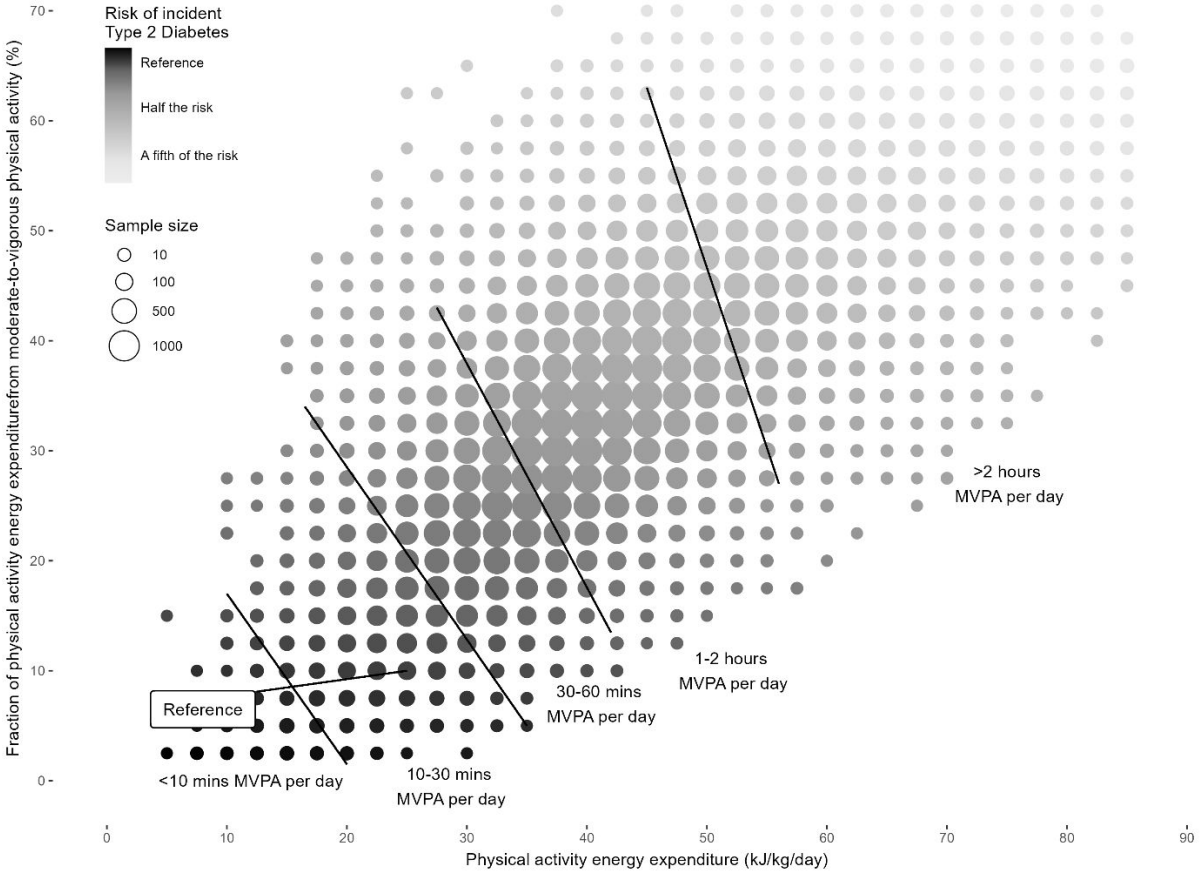
Cubic spline modelled association between the percentage of PAEE from MVPA and incident type 2 diabetes; UK Biobank (n=90,096)



Model 0 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), and PAEE; Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of %MVPA amongst incident cases. PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, BMI: body mass index.

Supplementary Figure 7

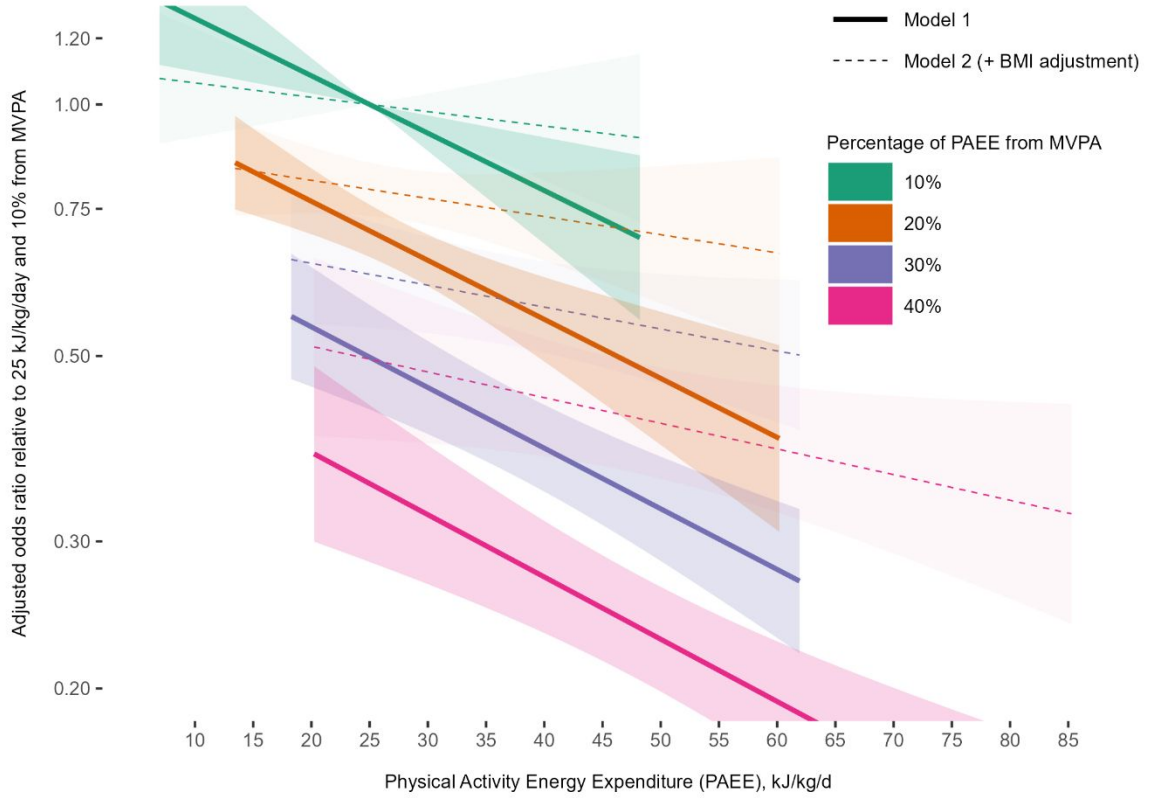
The relative risk of incident Type 2 diabetes for combinations of PAEE and %MVPA adjusted for BMI; UK Biobank (n=90,096).



PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA. BMI-adjusted odds ratio for type 2 diabetes represented by the colour gradient with 25 kJ/kg/day and 10% as reference values. Size of the points represents sample size and segments indicate the approximate average minutes of unbouted MVPA for each combination. Lines divide groups of similar observed median values of MVPA time, as indicated by the text. Each data point represents categories of dimensions 2.5 kJ/kg/day * 2.5%. Data points are placed at the midpoint of these categories. Points are not shown if there were no observations for that combination. Data are shown within the observed range of PAEE and %MVPA amongst incident type 2 diabetes cases.

Supplementary Figure 8

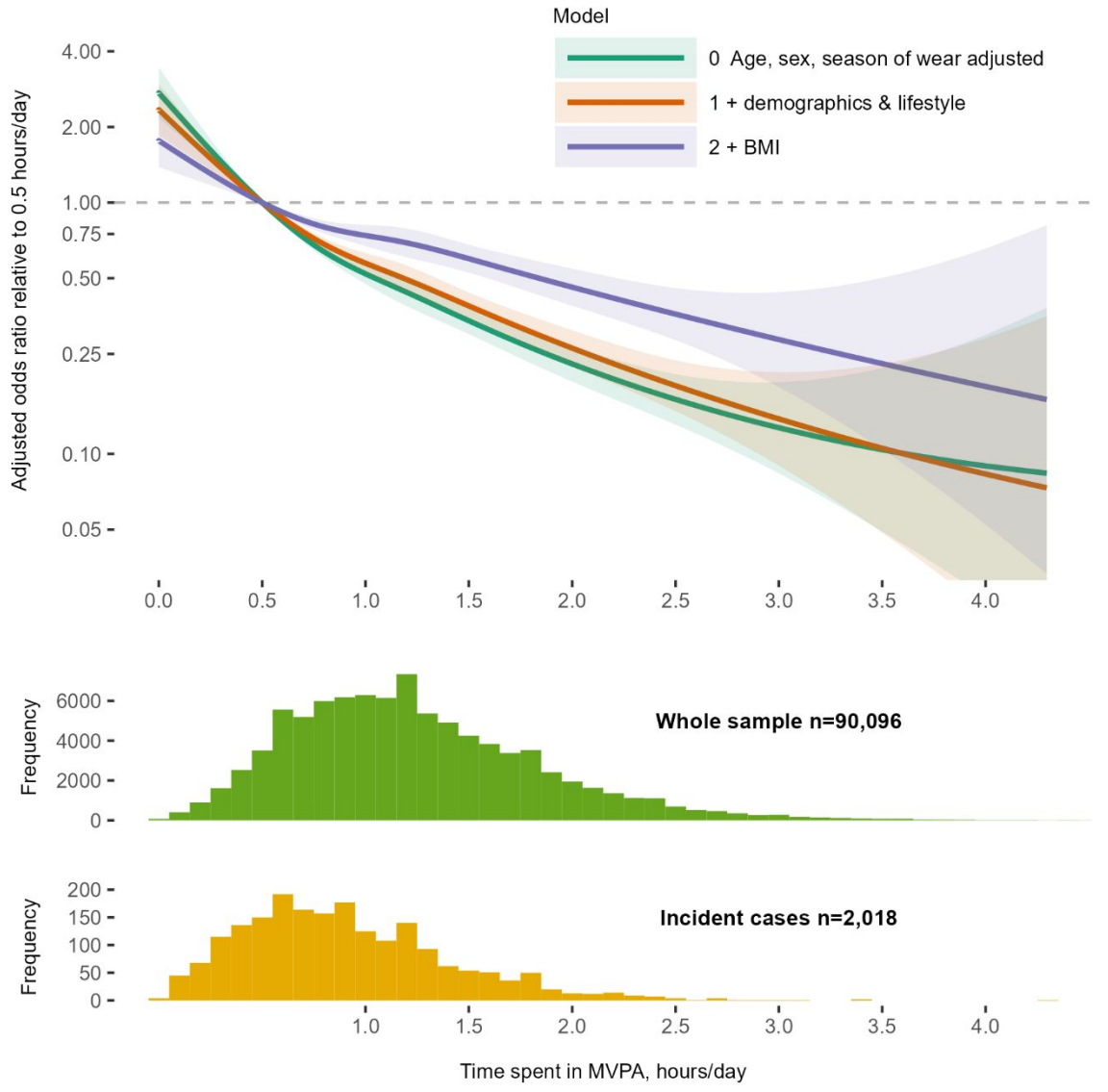
The joint association of PAEE and %MVPA with the odds of incident type 2 diabetes (Model 1 emphasised); UK Biobank (n=90,096)



Model 1 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA.

Supplementary Figure 9

Cubic spline modelled association between time spent in MVPA and incident type 2 diabetes; UK Biobank (n=90,096)



Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of MVPA amongst incident cases. MVPA: moderate-to-vigorous physical activity, BMI: body mass index.

Supplementary Table 1

Descriptive characteristics by incident Type 2 Diabetes status; UK Biobank (n=90,096)

	Incident Type 2 Diabetes status		Whole sample
	Non-cases	Cases	
Sample size (% of total analysis sample)	88078 (97.8%)	2018 (2.2%)	90096 (100.0%)
PAEE range (kJ/kg/d)	2.8-129.2	7.0-85.3	2.8-129.2
PAEE in kJ/kg/d, mean (SD)	41.7 (11.3)	35.5 (10.3)	41.5 (11.4)
Percentage of PAEE from MVPA, mean (SD)	34.7 (11.1)	28.2 (10.5)	34.6 (11.1)
Age in years, mean (SD)	62.2 (7.8)	65.2 (7.4)	62.3 (7.8)
Age group, (n, %)			
<60 years	33221 (37.7%)	489 (24.2%)	33710 (37.4%)
60-70 years	39132 (44.4%)	931 (46.1%)	40063 (44.5%)
>70 years	15725 (17.9%)	598 (29.6%)	16323 (18.1%)
Female sex, (n, %)	50603 (57.5%)	831 (41.2%)	51434 (57.1%)
Ethnicity, (n, %)			
White	85612 (97.2%)	1901 (94.2%)	87513 (97.1%)
Asian excl. Chinese	714 (0.8%)	46 (2.3%)	760 (0.8%)
Chinese	194 (0.2%)	3 (0.1%)	197 (0.2%)
Black	668 (0.8%)	38 (1.9%)	706 (0.8%)
Mixed	454 (0.5%)	12 (0.6%)	466 (0.5%)
Any other ethnic group	436 (0.5%)	18 (0.9%)	454 (0.5%)
Townsend Index of Deprivation, mean (SD)	-1.8 (2.8)	-1.1 (3.1)	-1.8 (2.8)
Highest education level achieved, (n, %)			
No qualification	6797 (7.7%)	328 (16.3%)	7125 (7.9%)
Any other qualification	42227 (47.9%)	1071 (53.1%)	43298 (48.1%)
Degree level or above	39054 (44.3%)	619 (30.7%)	39673 (44.0%)
Employment status, (n, %)			
Unemployed	34284 (38.9%)	1038 (51.4%)	35322 (39.2%)
In paid employment	53794 (61.1%)	980 (48.6%)	54774 (60.8%)
Smoking status, (n, %)			
Never	51009 (57.9%)	901 (44.6%)	51910 (57.6%)
Previous	31341 (35.6%)	910 (45.1%)	32251 (35.8%)
Current	5728 (6.5%)	207 (10.3%)	5935 (6.6%)
Alcohol drinking status, (n, %)			
Never	4735 (5.4%)	199 (9.9%)	4934 (5.5%)
< Twice a week	39852 (45.2%)	1008 (50.0%)	40860 (45.4%)
At least three times a week	43491 (49.4%)	811 (40.2%)	44302 (49.2%)
Sleep duration, (n, %)			
< 7 hours	19001 (21.6%)	567 (28.1%)	19568 (21.7%)
7-8 hours	63573.0 (72.2)	1263.0 (62.6)	64836.0 (72.0)
> 8 hours	5504 (6.2%)	188 (9.3%)	5692 (6.3%)
Fruit and veg intake score, mean (SD)	1.7 (1.1)	1.5 (1.1)	1.7 (1.1)
Parental history of diabetes, (n, %)			
No	73481.0 (83.4)	1479.0 (73.3)	74960.0 (83.2)
Yes	14597 (16.6%)	539 (26.7%)	15136 (16.8%)

BMI (kg/m^2), mean (SD)	26.4 (4.3)	30.7 (5.6)	26.5 (4.4)
Body Mass Index, (n, %)			
Underweight	541 (0.6%)	2 (0.1%)	543 (0.6%)
Normal weight	35732 (40.6%)	242 (12.0%)	35974 (39.9%)
Overweight	36486 (41.4%)	780 (38.7%)	37266 (41.4%)
Obese	15319 (17.4%)	994 (49.3%)	16313 (18.1%)
Prevalent CVD, (n, %)			
No	67097 (76.2%)	1122 (55.6%)	68219 (75.7%)
Yes	20326 (23.1%)	879 (43.6%)	21205 (23.5%)
Missing	655 (0.7%)	17 (0.8%)	672 (0.7%)
Prevalent cancer, (n, %)			
No	77747 (88.3%)	1665 (82.5%)	79412 (88.1%)
Yes	10325 (11.7%)	353 (17.5%)	10678 (11.9%)
Missing	6 (0.0%)	0 (0.0%)	6 (0.0%)
BMI genetic risk score tertile, (n, %)			
Lowest tertile	27538 (31.3%)	543 (26.9%)	28081 (31.2%)
Middle tertile	27481 (31.2%)	604 (29.9%)	28085 (31.2%)
Upper tertile	27416 (31.1%)	669 (33.2%)	28085 (31.2%)
Missing	5643 (6.4%)	202 (10.0%)	5845 (6.5%)
Insulin resistance risk score tertile, (n, %)			
Lowest tertile	27537 (31.3%)	546 (27.1%)	28083 (31.2%)
Middle tertile	27472 (31.2%)	612 (30.3%)	28084 (31.2%)
Upper tertile	27426 (31.1%)	658 (32.6%)	28084 (31.2%)
Missing	5643 (6.4%)	202 (10.0%)	5845 (6.5%)
Type 2 Diabetes genetic risk score tertile, (n, %)			
Lowest tertile	27728 (31.5%)	355 (17.6%)	28083 (31.2%)
Middle tertile	27543 (31.3%)	541 (26.8%)	28084 (31.2%)
Upper tertile	27164 (30.8%)	920 (45.6%)	28084 (31.2%)
Missing	5643 (6.4%)	202 (10.0%)	5845 (6.5%)
Fitness tertile, (n, %)			
Lower fitness	26446 (30.0%)	876 (43.4%)	27322 (30.3%)
Medium fitness	30032 (34.1%)	634 (31.4%)	30666 (34.0%)
Higher fitness	31548 (35.8%)	503 (24.9%)	32051 (35.6%)
Missing	52 (0.1%)	5 (0.2%)	57 (0.1%)
Grip strength tertile, (n, %)			
Lower grip strength	30717 (34.9%)	849 (42.1%)	31566 (35.0%)
Medium grip strength	29380 (33.4%)	632 (31.3%)	30012 (33.3%)
Higher grip strength	27649 (31.4%)	526 (26.1%)	28175 (31.3%)
Missing	332 (0.4%)	11 (0.5%)	343 (0.4%)

Supplementary Table 2

Odds ratios for incident type 2 diabetes for selected values of PAEE based on the cubic-spline models; UK Biobank (n=90,096)

	Model 0	Model 1	Model 2
PAEE ($kJ.kg^{-1}.d^{-1}$)	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**	**Odds ratio (95% CI)**
20	1.41 (1.31-1.53)	1.31 (1.21-1.41)	1.20 (1.11-1.30)
25	1.00	1.00	1.00
30	0.74 (0.70-0.77)	0.78 (0.75-0.82)	0.86 (0.82-0.90)
40	0.46 (0.40-0.52)	0.52 (0.46-0.59)	0.72 (0.63-0.82)
50	0.31 (0.27-0.35)	0.36 (0.32-0.41)	0.59 (0.52-0.68)
60	0.21 (0.17-0.25)	0.24 (0.20-0.29)	0.45 (0.37-0.55)

Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. PAEE: physical activity energy expenditure, CI: confidence interval.

Supplementary Table 3

Linear associations between PAEE (per 5 kJ.kg^{-1}.d^{-1}) and incident type 2 diabetes for the whole sample and in subgroups; UK Biobank (n=90,096)

	n / cases	Cumulative incidence	Model 0 OR (95% CI)	Model 1 OR (95% CI)	p value for interaction (Model 1)	Model 2 OR (95% CI)	p value for interaction (Model 2)
Whole sample	90096 / 2018	2.24%	0.78 (0.77-0.80)	0.81 (0.79-0.83)		0.89 (0.87-0.91)	
Sex							
Women	51434 / 831	1.62%	0.81 (0.78-0.83)	0.83 (0.81-0.86)		0.95 (0.91-0.98)	
Men	38662 / 1187	3.07%	0.77 (0.75-0.79)	0.79 (0.77-0.82)	*0.033*	0.86 (0.83-0.88)	*0.000*
Age group							
<60 years	33710 / 489	1.45%	0.76 (0.72-0.79)	0.78 (0.74-0.81)		0.85 (0.81-0.88)	
60-70 years	40063 / 931	2.32%	0.79 (0.76-0.82)	0.82 (0.79-0.84)		0.90 (0.87-0.93)	
≥70 years	16323 / 598	3.66%	0.79 (0.76-0.83)	0.82 (0.78-0.85)	*0.175*	0.90 (0.86-0.94)	*0.062*
Ethnicity							
White	87513 / 1901	2.17%	0.77 (0.76-0.79)	0.80 (0.78-0.82)		0.88 (0.86-0.91)	
Non-white	2583 / 117	4.53%	0.92 (0.84-1.00)	0.92 (0.85-1.00)	*0.002*	0.98 (0.91-1.07)	*0.018*
BMI							
Normal weight	35974 / 242	0.67%	0.84 (0.79-0.89)	0.86 (0.81-0.92)		0.87 (0.82-0.93)	
Overweight	37266 / 780	2.09%	0.83 (0.80-0.86)	0.84 (0.81-0.87)		0.85 (0.82-0.89)	
Obese	16313 / 994	6.09%	0.89 (0.86-0.92)	0.90 (0.87-0.93)	*0.024*	0.93 (0.90-0.96)	*0.002*
Prevalent CVD status							
No prevalent CVD	68219 / 1122	1.65%	0.79 (0.76-0.81)	0.81 (0.78-0.83)		0.89 (0.86-0.92)	
Prevalent CVD	21205 / 879	4.15%	0.81 (0.78-0.84)	0.83 (0.81-0.86)	*0.172*	0.91 (0.88-0.94)	*0.353*
Prevalent cancer status							
No prevalent cancer	79412 / 1665	2.10%	0.78 (0.76-0.80)	0.81 (0.79-0.83)		0.89 (0.87-0.91)	
Prevalent cancer	10678 / 353	3.31%	0.80 (0.75-0.84)	0.82 (0.78-0.87)	*0.623*	0.90 (0.85-0.95)	*0.660*

BMI genetic risk score tertile							
Lowest tertile	28081 / 543	1.93%	0.76 (0.73-0.80)	0.79 (0.75-0.82)		0.87 (0.83-0.91)	
Middle tertile	28085 / 604	2.15%	0.75 (0.72-0.78)	0.78 (0.74-0.81)		0.86 (0.82-0.89)	
Upper tertile	28085 / 669	2.38%	0.81 (0.78-0.85)	0.84 (0.81-0.87)	*0.012*	0.93 (0.90-0.97)	*0.006*
Insulin resistance genetic risk score tertile							
Lowest tertile	22250 / 419	1.88%	0.76 (0.73-0.79)	0.78 (0.75-0.82)		0.87 (0.83-0.91)	
Middle tertile	22234 / 465	2.09%	0.78 (0.75-0.81)	0.81 (0.78-0.85)		0.90 (0.86-0.94)	
Upper tertile	22289 / 512	2.30%	0.78 (0.75-0.81)	0.81 (0.78-0.84)	*0.472*	0.89 (0.85-0.92)	*0.598*
Type 2 Diabetes genetic risk score tertile							
Lowest tertile	22294 / 277	1.24%	0.73 (0.69-0.78)	0.77 (0.73-0.81)		0.85 (0.81-0.90)	
Middle tertile	22228 / 410	1.85%	0.76 (0.73-0.80)	0.79 (0.76-0.83)		0.88 (0.84-0.92)	
Upper tertile	22251 / 709	3.19%	0.80 (0.77-0.82)	0.82 (0.79-0.85)	*0.072*	0.90 (0.87-0.93)	*0.191*
Cardiorespiratory fitness							
Lower fitness	20180 / 618	3.06%	0.81 (0.78-0.84)	0.84 (0.81-0.87)		0.91 (0.88-0.94)	
Medium fitness	22745 / 425	1.87%	0.81 (0.78-0.85)	0.84 (0.80-0.87)		0.91 (0.87-0.95)	
Higher fitness	23805 / 349	1.47%	0.76 (0.72-0.79)	0.78 (0.74-0.81)	*0.022*	0.86 (0.82-0.90)	*0.072*
Grip strength							
Lower fitness	22975 / 586	2.55%	0.80 (0.77-0.83)	0.82 (0.80-0.85)		0.91 (0.88-0.94)	
Medium fitness	22445 / 443	1.97%	0.77 (0.74-0.80)	0.80 (0.77-0.83)		0.88 (0.85-0.92)	
Higher fitness	21102 / 360	1.71%	0.77 (0.74-0.81)	0.80 (0.76-0.83)	*0.380*	0.87 (0.83-0.91)	*0.325*

Model 0 adjusted for age, sex and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Genetic risk score stratified analyses also adjusted for UK Biobank genotyping array and 10 genetic principal components but did not adjust for ethnicity as analyses were restricted to those of white European ancestry. PAEE: physical activity energy expenditure, OR: odds ratio, CI: confidence interval, BMI: body mass index, CVD: cardiovascular disease.

Supplementary Table 4

Sensitivity analyses for the linear associations per 5 kJ.kg^{-1}.d^{-1} of PAEE and incident Type 2 Diabetes; UK Biobank (n=93,036)

	n / cases	Model 1	Model 2
		Hazard Ratio (95% CI)	**Hazard Ratio (95% CI)**
Cox Regression	90096 / 2014	0.81 (0.80-0.83)	0.89 (0.87-0.91)
	n / cases	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Missing data imputed	93036 / 2131	0.81 (0.79-0.83)	0.89 (0.87-0.91)
Excluding early incident events (first 2 years)	89539 / 1461	0.82 (0.80-0.84)	0.90 (0.87-0.92)
Excluding underweight (BMI<18.5 kg/m^2)	89553 / 2016	0.81 (0.79-0.83)	0.89 (0.87-0.91)
Excluding those with HbA1c>48 mmoL/mol	89710 / 1806	0.81 (0.79-0.83)	0.89 (0.87-0.91)

Model 1 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake. Model 2 additionally adjusted for body mass index. *Hazard ratio. PAEE: physical activity energy expenditure, CI: confidence interval.

Supplementary Table 5

Associations between PAEE and %MVPA and incident Type 2 Diabetes for selected values of PAEE and %MVPA; UK Biobank (n=90,096)

PAEE ($kJ.kg^{-1}.d^{-1}$)	%MVPA	Model 0	Model 1	Model 2	Additional adjustment for waist circumference
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
20	10	1.12 (1.07-1.18)	1.08 (1.03-1.14)	1.02 (0.97-1.07)	1.02 (0.97-1.07)
25	10	1.00	1.00	1.00	1.00
30	10	0.89 (0.85-0.93)	0.92 (0.88-0.97)	0.98 (0.93-1.03)	0.98 (0.93-1.03)
40	10	0.70 (0.61-0.81)	0.79 (0.68-0.91)	0.94 (0.81-1.09)	0.95 (0.82-1.10)
50	10	N/A	N/A	N/A	N/A
60	10	N/A	N/A	N/A	N/A
20	20	0.76 (0.69-0.83)	0.77 (0.70-0.84)	0.81 (0.74-0.89)	0.83 (0.76-0.92)
25	20	0.68 (0.63-0.73)	0.71 (0.66-0.76)	0.79 (0.74-0.85)	0.81 (0.76-0.88)
30	20	0.60 (0.56-0.65)	0.65 (0.61-0.70)	0.77 (0.72-0.83)	0.79 (0.74-0.85)
40	20	0.48 (0.43-0.54)	0.55 (0.49-0.62)	0.73 (0.65-0.83)	0.75 (0.67-0.85)
50	20	0.39 (0.32-0.46)	0.47 (0.39-0.56)	0.70 (0.58-0.84)	0.72 (0.59-0.87)
60	20	0.31 (0.24-0.40)	0.40 (0.31-0.52)	0.66 (0.51-0.86)	0.68 (0.52-0.89)
20	30	0.51 (0.43-0.60)	0.54 (0.46-0.64)	0.65 (0.55-0.76)	0.68 (0.58-0.81)
25	30	0.46 (0.40-0.53)	0.50 (0.43-0.58)	0.63 (0.54-0.73)	0.66 (0.57-0.77)
30	30	0.41 (0.36-0.47)	0.46 (0.40-0.52)	0.61 (0.53-0.69)	0.64 (0.56-0.73)
40	30	0.33 (0.30-0.37)	0.39 (0.34-0.44)	0.57 (0.50-0.65)	0.60 (0.53-0.68)
50	30	0.27 (0.23-0.31)	0.33 (0.28-0.38)	0.54 (0.46-0.63)	0.56 (0.48-0.66)
60	30	0.22 (0.18-0.26)	0.28 (0.23-0.34)	0.51 (0.42-0.62)	0.53 (0.43-0.64)
20	40	0.34 (0.27-0.43)	0.38 (0.30-0.49)	0.51 (0.40-0.66)	0.56 (0.44-0.72)
25	40	0.31 (0.25-0.38)	0.35 (0.28-0.44)	0.50 (0.40-0.62)	0.54 (0.43-0.67)
30	40	0.28 (0.23-0.34)	0.32 (0.27-0.39)	0.48 (0.39-0.58)	0.52 (0.43-0.63)
40	40	0.23 (0.20-0.27)	0.27 (0.23-0.32)	0.45 (0.38-0.52)	0.48 (0.41-0.56)
50	40	0.19 (0.16-0.22)	0.23 (0.20-0.26)	0.42 (0.36-0.48)	0.44 (0.38-0.52)
60	40	0.15 (0.13-0.18)	0.19 (0.16-0.23)	0.39 (0.33-0.46)	0.41 (0.34-0.49)

N/A indicates this combination of PAEE and %MVPA not observed in this sample amongst incident cases. Model 0 adjusted for age, sex and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake; Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, CI: confidence interval.

Supplementary Table 6

Sensitivity analyses using different thresholds for MVPA to estimate the association between PAEE and %MVPA and incident Type 2 Diabetes; UK Biobank (n=90,096)

PAEE	%MVPA	100mg		150mg	
		Model 1	Model 2	Model 1	Model 2
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
20	10	1.05 (0.99-1.12)	1.00 (0.93-1.06)	1.11 (1.06-1.15)	1.04 (1.00-1.08)
25	10	1.00	1.00	1.00	1.00
30	10	0.95 (0.89-1.01)	1.00 (0.94-1.07)	0.90 (0.87-0.94)	0.96 (0.92-1.00)
40	10	N/A	N/A	0.74 (0.65-0.83)	0.89 (0.79-1.01)
50	10	N/A	N/A	0.60 (0.49-0.73)	0.83 (0.68-1.01)
60	10	N/A	N/A	N/A	N/A
20	20	0.78 (0.71-0.85)	0.81 (0.74-0.89)	0.76 (0.69-0.84)	0.82 (0.74-0.90)
25	20	0.73 (0.69-0.78)	0.80 (0.75-0.86)	0.69 (0.63-0.75)	0.78 (0.72-0.85)
30	20	0.69 (0.64-0.74)	0.80 (0.74-0.86)	0.62 (0.58-0.67)	0.75 (0.70-0.81)
40	20	N/A	N/A	0.51 (0.47-0.56)	0.69 (0.63-0.76)
50	20	N/A	N/A	0.42 (0.36-0.48)	0.64 (0.55-0.74)
60	20	N/A	N/A	0.34 (0.28-0.42)	0.59 (0.48-0.72)
20	30	0.58 (0.49-0.67)	0.66 (0.56-0.77)	0.52 (0.43-0.63)	0.64 (0.53-0.78)
25	30	0.54 (0.47-0.61)	0.65 (0.57-0.74)	0.48 (0.40-0.56)	0.61 (0.52-0.73)
30	30	0.50 (0.44-0.57)	0.64 (0.56-0.72)	0.43 (0.37-0.50)	0.59 (0.51-0.68)
40	30	0.44 (0.38-0.50)	0.62 (0.54-0.72)	0.36 (0.32-0.40)	0.54 (0.48-0.61)
50	30	0.38 (0.31-0.46)	0.60 (0.49-0.74)	0.29 (0.26-0.33)	0.49 (0.43-0.56)
60	30	N/A	N/A	0.24 (0.20-0.28)	0.45 (0.38-0.53)
20	40	0.43 (0.34-0.53)	0.53 (0.43-0.67)	N/A	N/A
25	40	0.39 (0.32-0.48)	0.52 (0.43-0.64)	0.33 (0.26-0.42)	0.48 (0.37-0.62)
30	40	0.36 (0.31-0.44)	0.51 (0.42-0.61)	0.30 (0.24-0.37)	0.46 (0.37-0.57)
40	40	0.31 (0.27-0.37)	0.49 (0.41-0.57)	0.25 (0.21-0.29)	0.42 (0.35-0.50)
50	40	0.27 (0.23-0.32)	0.47 (0.39-0.56)	0.20 (0.17-0.24)	0.38 (0.32-0.45)
60	40	0.23 (0.19-0.28)	0.45 (0.36-0.55)	0.17 (0.14-0.20)	0.35 (0.28-0.42)

Model 1 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, CI: confidence interval.

Supplementary Table 7

Odds ratios for incident type 2 diabetes for selected values of time spent in MVPA based on the cubic-spline models; UK Biobank (n=90,096)

MVPA (hours/d)	Model 0	Model 1	Model 2
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
0.5	1.00	1.00	1.00
1	0.52 (0.47-0.57)	0.57 (0.52-0.63)	0.74 (0.67-0.81)
1.5	0.34 (0.30-0.38)	0.39 (0.34-0.44)	0.60 (0.53-0.68)
2	0.23 (0.19-0.27)	0.26 (0.22-0.31)	0.46 (0.39-0.55)

Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. MVPA: moderate-to-vigorous physical activity, CI: confidence interval.

Supplementary References

1. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. Buchowski M, editor. PLoS ONE. 2017 Feb 1;12(2):e0169649.

2. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW. Correlates of physical activity: why are some people physically active and others not? The Lancet. 2012 Jul;380(9838):258–71.

3. Fletcher B, Gulanick M, Lamendola C. Risk Factors for Type 2 Diabetes Mellitus: The Journal of Cardiovascular Nursing. 2002 Jan;16(2):17–23.

4. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocrine Reviews. 2016 Jun 1;37(3):278–316.

5. Robbins JM, Vaccarino V, Zhang H, Kasl SV. Socioeconomic status and diagnosed diabetes incidence. Diabetes Research and Clinical Practice. 2005 Jun;68(3):230–6.

6. Van Domelen DR, Koster A, Caserotti P, Brychta RJ, Chen KY, McClain JJ, et al. Employment and Physical Activity in the U.S. American Journal of Preventive Medicine. 2011 Aug;41(2):136–45.

7. Kaczynski A. Smoking and Physical Activity: A Systematic Review. ajhb [Internet]. 2008 [cited 2022 Sep 16];32(1). Available from: http://www.ingentaconnect.com/content/png/ajhb/2008/00000032/00000001/art00009

8. Maddatu J, Anderson-Baucum E, Evans-Molina C. Smoking and the risk of type 2 diabetes. Translational Research. 2017 Jun;184:101–7.

9. Leasure JL, Neighbors C, Henderson CE, Young CM. Exercise and Alcohol Consumption: What We Know, What We Need to Know, and Why it is Important. Front Psychiatry [Internet]. 2015 Nov 2 [cited 2022 Sep 16];6. Available from: http://journal.frontiersin.org/Article/10.3389/fpsyt.2015.00156/abstract

10. Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S, et al. Alcohol as a Risk Factor for Type 2 Diabetes. Diabetes Care. 2009 Nov 1;32(11):2123–32.

11. Vries H de, Kremers S, Smeets T, Reubsaet A. Clustering of diet, physical activity and smoking and a general willingness to change. Psychology & Health. 2008 Apr;23(3):265–78.

12. Wu Y, Zhang D, Jiang X, Jiang W. Fruit and vegetable consumption and risk of type 2 diabetes mellitus: A dose-response meta-analysis of prospective cohort studies. Nutrition, Metabolism and Cardiovascular Diseases. 2015 Feb;25(2):140–7.

13. Choi J, Choi JY, Lee SA, Lee KM, Shin A, Oh J, et al. Association between family history of diabetes and clusters of adherence to healthy behaviors: cross-sectional results from the Health Examinees-Gem (HEXA-G) study. BMJ Open. 2019 Jun;9(6):e025477.

14. Sherrill DL, Kotchou K, Quan SF. Association of Physical Activity and Human Sleep Disorders. Arch Intern Med. 1998 Sep 28;158(17):1894.

15. Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, et al. Sleep Duration and Risk of Type 2 Diabetes: A Meta-analysis of Prospective Studies. Diabetes Care. 2015 Mar 1;38(3):529–37.

16. Jones PR, Ekelund U. Physical Activity in the Prevention of Weight Gain: the Impact of Measurement and Interpretation of Associations. Curr Obes Rep. 2019 Jun;8(2):66–76.

17. White T, Westgate K, Wareham NJ, Brage S. Estimation of Physical Activity Energy Expenditure during Free-Living from Wrist Accelerometry in UK Adults. Song H, editor. PLoS ONE. 2016 Dec 9;11(12):e0167472.

18. White T, Westgate K, Hollidge S, Venables M, Olivier P, Wareham N, et al. Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study. Int J Obes. 2019 Nov;43(11):2333–42.

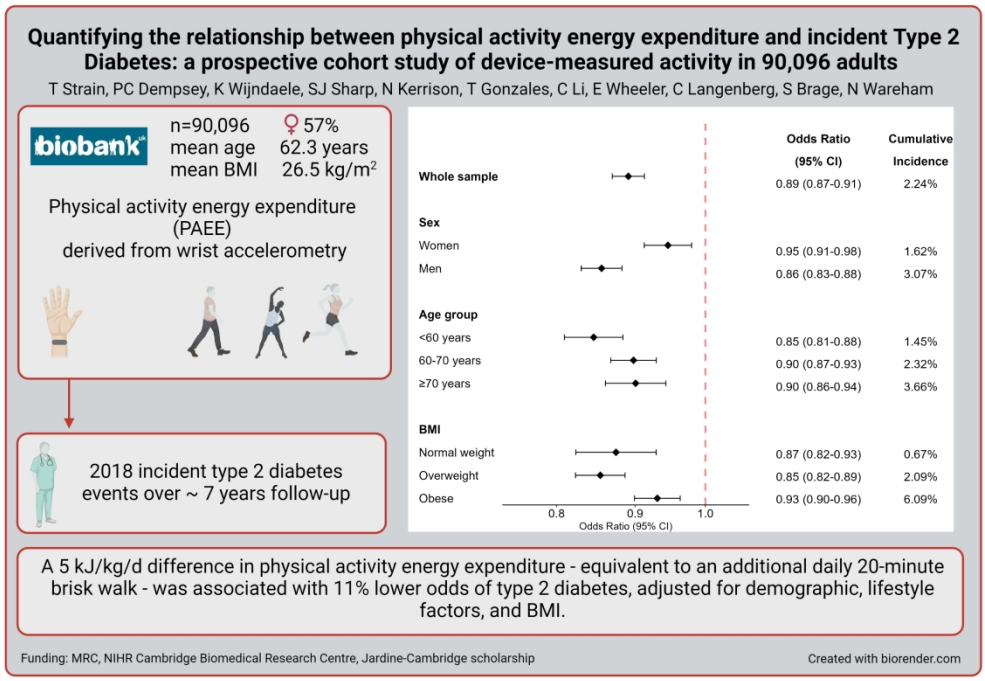
19. Brage S, Brage N, Franks PW, Ekelund U, Wong MY, Andersen LB, et al. Branched equation modeling of simultaneous accelerometry and heart rate monitoring improves estimate of directly measured physical activity energy expenditure. Journal of Applied Physiology. 2004 Jan;96(1):343–51.

20. Brage S, Ekelund U, Brage N, Hennings MA, Froberg K, Franks PW, et al. Hierarchy of individual calibration levels for heart rate and accelerometry to measure physical activity. Journal of Applied Physiology. 2007 Aug;103(2):682–92.

21. Brage S, Lindsay T, Venables M, Wijndaele K, Westgate K, Collins D, et al. Descriptive epidemiology of energy expenditure in the UK: findings from the National Diet and Nutrition Survey 2008–15. International Journal of Epidemiology. 2020 Jun 1;49(3):1007–21.

22. Strath SJ, Brage S, Ekelund U. Integration of Physiological and Accelerometer Data to Improve Physical Activity Assessment. Medicine & Science in Sports & Exercise. 2005 Nov;37(11):S563–71.

23. Thompson D, Batterham AM, Bock S, Robson C, Stokes K. Assessment of Low-to-Moderate Intensity Physical Activity Thermogenesis in Young Adults Using Synchronized Heart Rate and Accelerometry with Branched-Equation Modeling. The Journal of Nutrition. 2006 Apr 1;136(4):1037–42.



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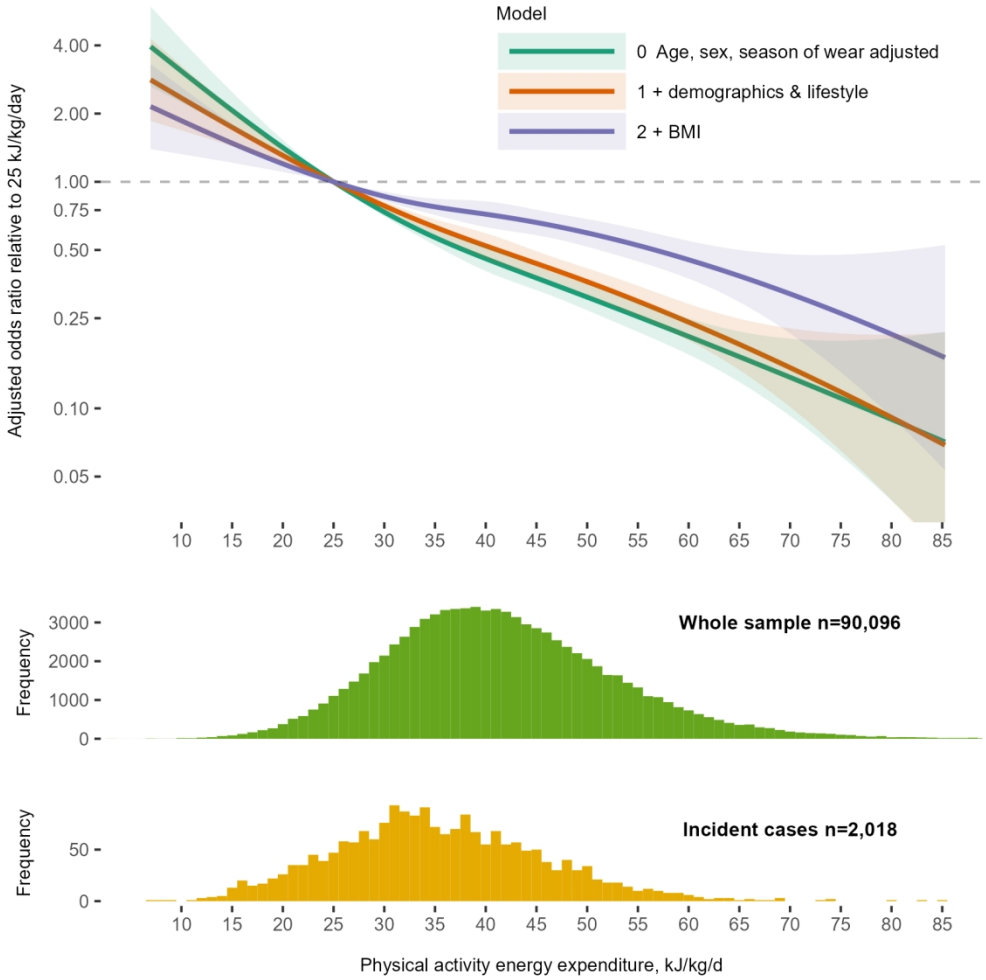

Figure 1: Cubic spline modelled association between PAEE and incident type 2 diabetes; UK Biobank (n=90,096)
Model 0 adjusted for age, sex, and season of accelerometry wear (using two orthogonal sine functions); Model 1 additionally adjusted for ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, and fruit and vegetable intake. Model 2 additionally adjusted for body mass index. Data presented for the observed range of PAEE amongst incident cases. PAEE: physical activity energy expenditure, BMI: body mass index.

152x152mm (300 x 300 DPI)

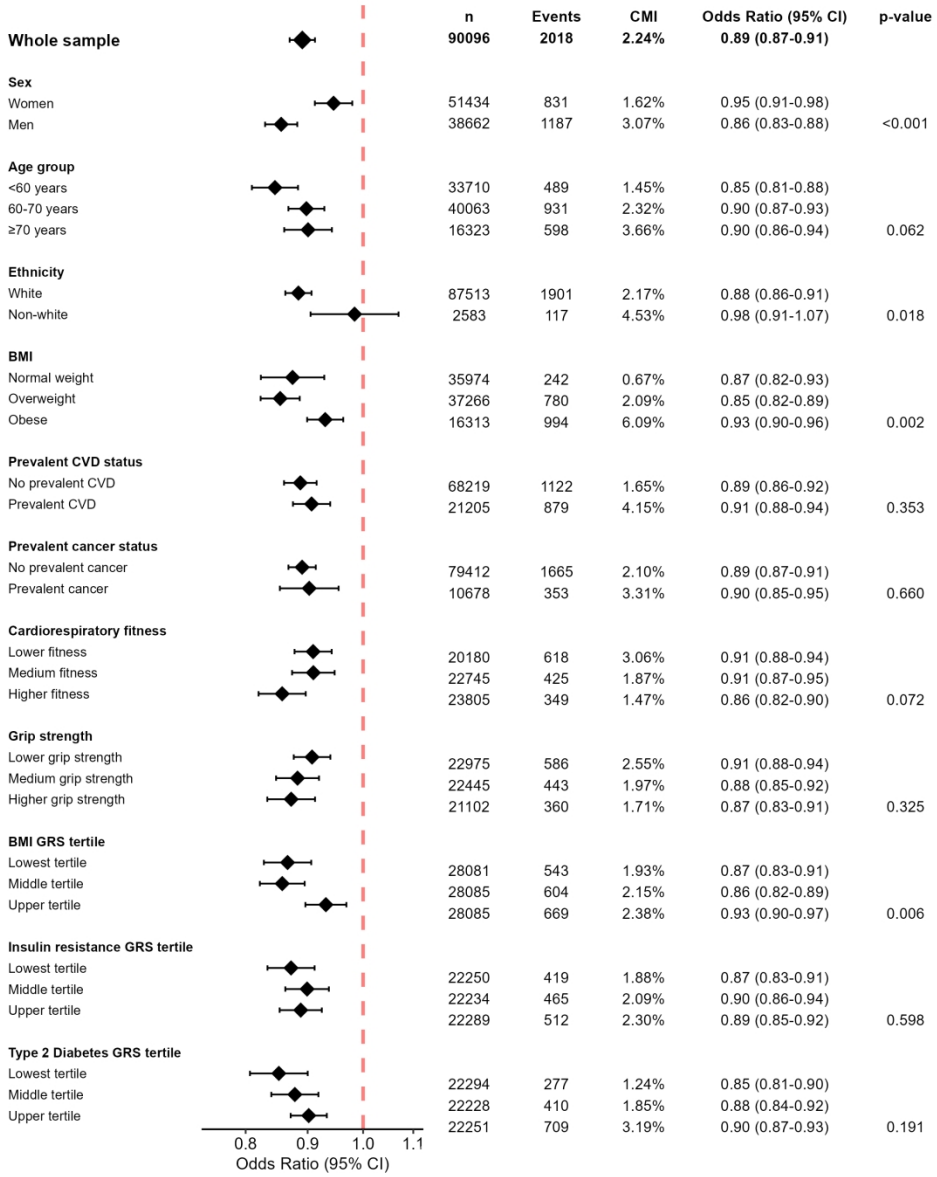

Figure 2: Odds ratios for incident type 2 diabetes per 5 kJ.kg-1.d-1 PAEE for the whole sample and in subgroups adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)
Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Genetic risk score stratified analyses also adjusted for UK Biobank genotyping array and 10 genetic principal components but did not adjust for ethnicity as analyses were restricted to those of white European ancestry. PAEE: physical activity energy expenditure, CMI: Cumulative incidence, CVD: cardiovascular disease, BMI: body mass index, GRS: genetic risk score. p-value for interaction between subgroups.

203x254mm (300 x 300 DPI)

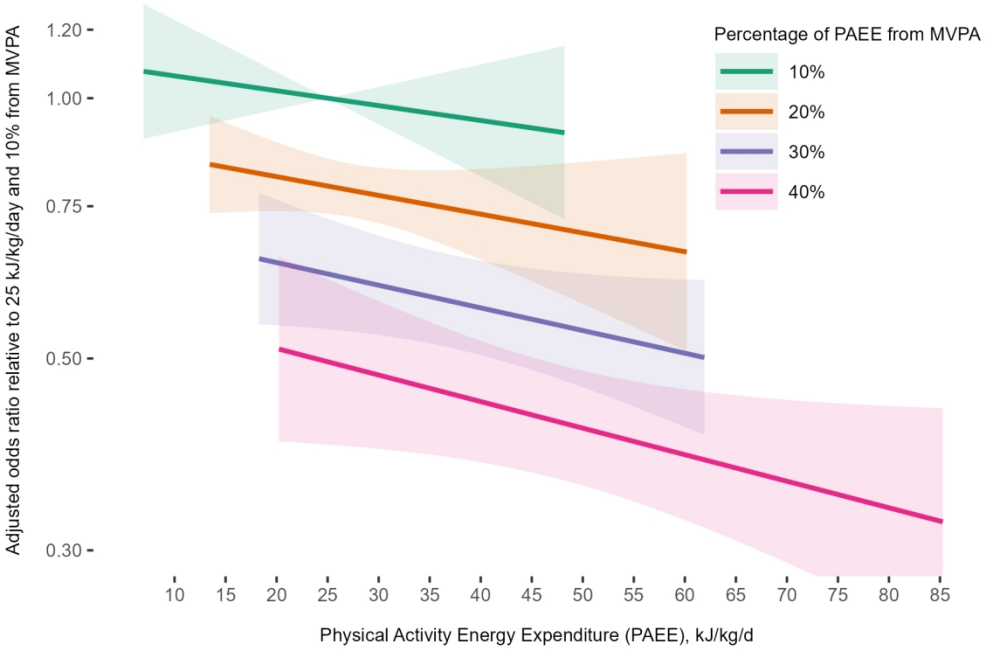

Figure 3: The joint association of PAEE and %MVPA with the odds of incident type 2 diabetes adjusted for BMI and other confounding factors (Model 2); UK Biobank (n=90,096)
Model 2 adjusted for age, sex, season of accelerometry wear (using two orthogonal sine functions), ethnicity, Townsend Index of deprivation, highest educational level achieved, employment status, parental history of diabetes, smoking status, alcohol drinking status, sleep duration, fruit and vegetable intake, and body mass index. Data presented for the observed range of PAEE amongst incident cases for a range around the %MVPA value (±5%, extending to respective end of distributions for 10% and 40%). PAEE: physical activity energy expenditure, %MVPA: percentage of PAEE from MVPA, BMI: body mass index.

152x101mm (300 x 300 DPI)