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Cardiometabolic Benefit of Replacing Sedentary Time with Light-Intensity Physical Activity: Compositional Data Analysis of the Nijmegen Exercise Study

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ABSTRACT

Purpose: The cardiometabolic benefits of replacing sedentary time with light-intensity physical activity (LIPA) are unclear. We studied the associations of hypothetically reallocating sedentary time towards LIPA with changes in cardiometabolic risk factors using thigh-worn accelerometery. We also explored whether reallocation effects differed across subgroups with low, moderate, and high sedentary time and compared proportionally similar reallocations to either LIPA or moderate-to-vigorous physical activity (MVPA). **Methods:** We assessed physical behaviours across eight consecutive days using thigh-worn accelerometers among adults from the Nijmegen Exercise Study. Multiple cardiometabolic risk factors were assessed and categorised as: 1) anthropometrics, 2) cardiovascular biomarkers, and 3) glucose metabolism. Reallocation effects were estimated for each cardiometabolic risk factor using compositional isotemporal substitution models adjusted for confounders. Analyses were repeated in sedentary time subgroups, i.e. <8.5, 8.5-10, and >10 hours/day. **Results:** We included 1,041 participants (64 (standard deviation 11) years; 39.5% female). Reallocating sedentary time towards LIPA was associated with improvements in anthropometrics, some cardiovascular biomarkers, and glucose metabolism; e.g., replacing 60 minutes/day of sedentary time with LIPA was associated with improvements in BMI (-0.28 (-0.42, -0.13) kg/m^2), eGFR (0.68 (0.15, 1.20) $mL/min/1.73m^2$), and glucose (-0.05 (-0.08, -0.03) mmol/L). Trends suggested that reallocation benefits were strongest in those with >8.5 hours/day of sedentary time. Proportionally similar replacements of sedentary time with either LIPA or MVPA were associated with similar cardiometabolic benefits. **Conclusions:** Reallocation of sedentary time to LIPA was associated with improvements in cardiometabolic risk factors, predominantly in anthropometrics and glucose metabolism, with greater benefits in the most sedentary individuals. Time reallocation from sedentary time to LIPA may be an effective and

arguably feasible strategy to improve population-wide cardiometabolic health. **Key Words:** ANTHROPOMETRICS, CARDIOVASCULAR BIOMARKERS, GLUCOSE METABOLISM, GUIDELINES, PUBLIC HEALTH

INTRODUCTION

Several studies have demonstrated strong, independent associations between excessive sedentary time and the risk of chronic diseases, such as cardiometabolic diseases, cancer, dementia, and all-cause mortality (1-5). Engagement in regular physical activity, especially at a moderate-to-vigorous intensity, is known to reduce the risk of chronic diseases and can attenuate the detrimental effects of excessive sedentary time (5, 6). Accordingly, the World Health Organization advises children and adults to limit sedentary time and replace sitting with physical activity of any intensity (7). However, little is known about the duration of sedentary time that should be replaced and the intensity of physical activity to replace sitting with.

When investigating the independent effects of sedentary time on health, most studies adjust their models for time spent in moderate-to-vigorous physical activity (MVPA). This approach ignores the impact of light-intensity physical activity (LIPA) and time spent sleeping, which is important since these lifestyle behaviours are related to cardiometabolic disease development (1, 2, 5, 6). Simultaneous statistical adjustment for all behaviours of the physical behaviour spectrum is frequently omitted because of multicollinearity issues. These issues can be overcome by applying compositional data analysis, treating all physical behaviours (i.e. sedentary time, physical activity, and sleep) as one 24-hour composition. This approach takes the relative nature of the components into consideration, appreciating that spending more time in one behaviour necessarily requires fewer time to be spent in another behaviour. Compositional data analysis therefore provides a way to handle the co-dependency of the physical behaviours (8-10). In addition, compositional data analysis can be combined with isotemporal substitution modelling to examine the health effects of hypothetical time reallocation from one physical behaviour to another (11).

Previous research using compositional data analysis primarily focussed on hypothetical time reallocation from any physical behaviour to MVPA and reported such time reallocations to be beneficial for health outcomes (8). The health effects of substituting sedentary time with time spent in LIPA, however, are inconsistent (8, 12-14). A likely reason is that few studies employed thigh-worn accelerometery, which is the gold standard to differentiate between sedentary time, standing, and LIPA (15, 16). Therefore, this study used thigh-worn accelerometery to investigate how hypothetical reallocations from sedentary time to LIPA are associated with changes in cardiometabolic risk factors, in particular with regard to anthropometrics, cardiovascular biomarkers, and glucose metabolism. We also explored whether the magnitude of reallocation-induced changes differed across individuals with low, moderate, or high sedentary time. We expected that reallocations from sedentary time to LIPA would improve cardiometabolic risk factors, especially in those with the highest habitual sedentary time. Finally, to provide context for the magnitude of the reallocation effects, we also evaluated how replacing 30 minutes/day of sedentary time to LIPA compared to a proportionally similar replacement of sedentary time to MVPA.

METHODS

Study design and population

We recruited adult volunteers from the Nijmegen Exercise Study, a prospective cohort study among Dutch individuals that investigates the relationship between lifestyle and disease development (17). Participants for the current study were recruited by email and at selected random from the Nijmegen Exercise Study cohort with an oversampling of individuals with cardiovascular risk factors or cardiovascular disease. Participants completed online questionnaires about their

lifestyle and health status, and objective measurements of habitual physical behaviour patterns were conducted between May 2021 and March 2023. Inclusion criteria were Dutch residency and language proficiency, and pregnancy was an exclusion criterion for the current study. Based on mobility assessed by the EQ-5D-5L (18), participants who had severe mobility problems (N=2) were excluded for the current study. Participants visited our research centre at the Radboud university medical center (Radboudumc, Nijmegen, the Netherlands) once to undergo testing. All participants provided written informed consent. The local Medical Research Ethics Committee provided approval (NL36743.091.11), and the study was conducted in accordance with the Declaration of Helsinki.

Data collection

Demographics. Demographical data were collected via an online questionnaire and included age, sex, level of education, employment status, alcohol consumption, and smoking behaviour. Level of education was categorised as low-to-intermediate (i.e. primary school, basic vocational education, secondary school, or secondary vocational education) or high (i.e. higher vocational education or academic education). Moreover, participants were inquired about their cardiometabolic medical health status and use of cholesterol-lowering, antihypertensive, and antidiabetic medication.

Physical behaviours. Physical behaviours were assessed over a period of eight consecutive days using the triaxial activPAL3 micro accelerometer (PAL Technologies Ltd., Glasgow, UK). Participants were instructed to wear the accelerometer on the midline of their right thigh for 24 hours/day and were daily requested to fill out a sleep/wake diary to enable automated identification

of sleep periods. Data were extracted using PALbatch (PAL Software Suite version 8, PAL Technologies Ltd.) and analysed with a modified version of the script by Winkler et al. (19, 20) in SAS (Statistical Analysis System, RRID:SCR_008567, version 9.4; SAS Institute Inc., Cary, NC, USA). The script classified awake hours as sedentary time, LIPA, or MVPA, and it determined daily step count. Wear days were considered valid when data of >10 awake hours were available and >1,000 steps were measured. Measurements with <4 valid wear days were excluded from analysis (N=51). Sedentary time, LIPA, MVPA, and sleep time were expressed as proportions of the 24-hour cycle to create four-part physical behaviour compositions. For example, the composition (0.30, 0.25, 0.10, 0.35) describes a participant spending 30% of time sedentary whilst spending 25%, 10%, and 35% of time in LIPA, in MVPA, and sleeping, respectively.

Cardiometabolic risk factors. We evaluated multiple cardiometabolic risk factors when the participants visited the research centre. Risk factors were categorised into the following subsets: 1) anthropometrics (i.e. body mass index (BMI), body fat percentage, and fat-free mass), 2) cardiovascular biomarkers (i.e. total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity cardiac troponin I (hs-cTnI), amino-terminal pro-B-type-natriuretic-peptide (NT-proBNP), estimated glomerular filtration rate (eGFR (21)), systolic and diastolic blood pressure, carotid-femoral pulse wave velocity, and carotid stiffness index Beta), and 3) glucose metabolism (i.e. glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR (22))). Standard operating procedures were used to assess the cardiometabolic risk factors; a detailed description of the measurements can be found in Supplemental File 1 and Supplemental Figure 1, Supplemental Digital Content.

Statistical analysis

Group characteristics were reported as mean (standard deviation), median [first quartile, third quartile], or as number (percentage). Physical behaviour compositions were described using geometric means (9). Statistical analyses were performed in R (version 4.3.2, RRID:SCR_001905) using packages *compositions* (23), *codaredistlm* (24), and *ggtern* (25). Significance was assumed at *p*-values <0.05.

We used isometric log ratio (ilr) transformation to convert the four-part physical behaviour compositions to mathematically equivalent sets of three ilr coordinates (26-28). The first ilr coordinate describes the time spent sedentary relative to the time spent in the remaining three behaviours. We pivoted the physical behaviour composition to create a second set of ilr coordinates in which the first coordinate describes the time spent in LIPA relative to the remaining behaviours. Finally, we pivoted the physical behaviour composition another time to create a third set of ilr coordinates in which the first coordinate describes the time spent in MVPA relative to the remaining behaviours. Details on the ilr transformation can be found in Supplemental File 2, Supplemental Digital Content.

We performed linear regression analyses with the first set of ilr coordinates as independent variables to investigate the associations between sedentary time relative to the other physical behaviours and each cardiometabolic risk factor whilst adjusting for age and sex (model 1). Subsequently, we adjusted each model for additional confounders, i.e. level of education, employment status, alcohol consumption, smoking behaviour, and cholesterol-lowering, antihypertensive, and antidiabetic medication use (model 2). However, in models with cholesterol-

related, blood pressure-related, and glucose-related outcomes, we did not adjust for cholesterol-lowering, antihypertensive, and antidiabetic medication, respectively. In models with cholesterol-related and glucose-related outcomes, we excluded participants with hypercholesterolaemia and diabetes mellitus, respectively. In models with blood pressure-related outcomes, we modified systolic and diastolic blood pressure values by adding 10 mmHg in participants using antihypertensive medication, as previously recommended (29). An overview of the included participants and confounders per model is provided in Supplemental Figure 1, Supplemental Digital Content. We did not adjust for BMI in model 2 because we assumed that BMI lies in the causal pathway between the physical behaviours and cardiometabolic risk factors. Nevertheless, we performed sensitivity analyses in which we additionally adjusted for BMI to explore the mediating effect. We repeated the analyses with the second and third sets of ilr coordinates to examine how time spent in LIPA and MVPA, respectively, relative to the other physical behaviours are associated with each cardiometabolic risk factor.

Finally, we used compositional isotemporal substitution modelling to study the associations of hypothetically reallocating sedentary time to LIPA with changes in cardiometabolic risk factors (11). Using the fully adjusted models (model 2) and the geometric mean composition as reference, we modelled changes in cardiometabolic risk factors as a function of 0-60-minutes/day reallocations with 5-minutes/day intervals. To explore how the magnitude of reallocation-induced changes differs between subgroups of sedentary time, we stratified our sample into low (<8.5 hours/day, i.e. reference), moderate (8.5-10 hours/day), and high (>10 hours/day) sedentary time subgroups, based on a tertile split and subsequent rounding to well-interpretable cut-off values. We tested for interaction between the first ilr coordinate and sedentary

time subgroup (i.e. low versus moderate and low versus high) and repeated the time reallocation analyses per subgroup. To put the effect sizes of replacing sedentary time with LIPA in perspective, we estimated the effects of a reallocation towards MVPA that was proportionally similar in terms of the geometric means of the respective physical behaviours. More specifically, we reallocated 30 minutes/day of sedentary time towards LIPA or 10 minutes/day of sedentary time to MVPA.

RESULTS

Between May 2021 and May 2023, N=1,417 participants of the Nijmegen Exercise Study visited our research centre to undergo physical examinations. One or multiple exposure, outcome, or covariate variables were missing in N=376 participants, who were excluded from analyses. This resulted in an analytical sample of N=1,041 participants with complete exposure, outcome, and covariate data. Exceptions to this were outcome variables body fat percentage (N=671), fat free mass (N=665), carotid-femoral pulse wave velocity (N=595), and carotid stiffness index Beta (N=589), which were only measured in a subgroup of participants. Participants had a mean age of 64 (11) years and 411 (39.5%) were female (Table 1). The geometric mean composition of physical behaviours consisted of 9.2 hours (38.3%) of sedentary time, 4.6 hours (19.2%) of LIPA, 1.7 hours (7.2%) of MVPA, and 8.5 hours (35.3%) of sleeping (Supplemental Figure 2, Supplemental Digital Content). Descriptives of the cardiometabolic risk factors are displayed in Supplemental Figures 3-5, Supplemental Digital Content.

Associations of physical behaviour compositions with cardiometabolic risk factors

Regression analyses demonstrated that an increase in sedentary time, and consequently a proportional decrease in the remaining behaviours, was associated with unfavourable changes in most anthropometrics (i.e. BMI and body fat percentage), some cardiovascular biomarkers (i.e. triglycerides and diastolic blood pressure), and glucose metabolism (i.e. insulin and HOMA-IR). Sensitivity analyses including BMI as additional confounder attenuated the magnitude of these associations (Supplemental Table 1, Supplemental Digital Content). An increase in LIPA, and a proportional decrease in the remaining behaviours, was associated with improvements in eGFR and glucose metabolism (i.e. glucose and HOMA-IR). Sensitivity analyses including BMI did not impact these associations (Supplemental Table 1, Supplemental Digital Content). An increase in MVPA, and a proportional decrease in the remaining behaviours, was associated with improvements in most anthropometrics (i.e. BMI and body fat percentage), some cardiovascular biomarkers (i.e. HDL cholesterol, triglycerides, NT-proBNP, and eGFR), and glucose metabolism (i.e. insulin and HOMA-IR). Sensitivity analyses including BMI attenuated most associations (Supplemental Table 1, Supplemental Digital Content).

Reallocating sedentary time to light-intensity physical activity

Replacing sedentary time with LIPA was associated with an improved BMI and body fat percentage and a decline in fat-free mass (Figure 1). Reallocation was also associated with improvements in some cardiovascular biomarkers (i.e. triglycerides and eGFR, Figure 2) and with improvements in all markers of glucose metabolism (i.e. glucose, insulin, and HOMA-IR, Figure 3). For example, replacing 60 minutes/day of sedentary time with LIPA was associated with estimated changes in BMI (-0.28 (-0.42, -0.13) kg/m^2), eGFR (0.68 (0.15, 1.20) $mL/min/1.73m^2$),

and glucose (-0.05 (-0.08, -0.03) mmol/L). Reallocation of sedentary time to LIPA was not associated with changes in total, HDL, or LDL cholesterol, blood pressure-related outcomes, hs-cTnI, and NT-proBNP (Figures 1-3).

Subgroup analyses indicated that the associations between time reallocation and changes in cardiometabolic risk factors differed across sedentary time subgroups. Compared to the subgroup with low sedentary time (i.e. reference), reallocation-induced benefits in cardiometabolic risk factors were greater in the moderate sedentary time subgroup, and the benefits were the greatest for the high sedentary time subgroup (Figure 4, Supplemental Figures 6-10, Supplemental Digital Content).

Reallocating sedentary time to moderate-to-vigorous physical activity

Replacing 10 minutes/day of sedentary time with MVPA was associated with an improved BMI and body fat percentage and a decline in fat-free mass (Figure 5A), improvements in HDL cholesterol, triglycerides, NT-proBNP, and eGFR (Figure 5B), and improvements in insulin and HOMA-IR (Figure 5C). Proportionally similar reallocations from sedentary time towards LIPA (i.e. +30 minutes/day; +10.8% of time spent in LIPA) or MVPA (i.e. +10 minutes/day; +9.6% of time spent in MVPA) were generally associated with similar cardiometabolic risk factor improvements.

DISCUSSION

In this study, we investigated how hypothetically reallocating sedentary time to time spent in LIPA is associated with changes in cardiometabolic risk factors, and we investigated whether

the magnitude of reallocation effects was different based on the volume of sedentary time. First, we found that replacing sedentary time with LIPA was generally associated with improvements in anthropometrics and glucose metabolism whilst reallocations were associated with only a few cardiovascular biomarker improvements. Second, subgroup analyses suggested that reallocation-induced benefits are strongest in those with moderate (i.e. 8.5-10 hours/day) or high sedentary time (i.e. >10 hours/day). Proportionally similar replacement of sedentary time with MVPA demonstrated similar cardiometabolic benefits. However, replacing sedentary time with LIPA may present a more feasible strategy for many individuals to improve their physical activity level. These findings underline that daily replacements of sedentary time with LIPA may provide valuable cardiometabolic health benefits at a population level.

We found that reallocating sedentary time to LIPA was beneficially associated with anthropometrics and glucose metabolism. Previous studies in the field largely reported similar results. Most studies reported improvements in anthropometrics following time reallocation, reinforcing our findings (26, 30-34). Few previous studies investigated the effects of reallocation on fat-free mass, yet our finding that replacing sedentary time with LIPA was associated with a decrease in fat-free mass was unexpected (35-38). This may have been caused by residual confounding, and further research is needed to investigate physiological mechanisms that may explain this observation. Furthermore, some (30, 33, 39), but not all (14, 26, 34) studies reported improvements in glucose metabolism after time reallocation. Thigh- and hip-worn devices were used in studies that reported positive associations but also in studies that reported no associations, so wear location may not explain the discrepancy in findings. With regard other to study characteristics, such as sample size, age, sex, BMI, and diabetes prevalence, no major

discrepancies were found between the studies reporting positive versus no associations. Hence, there does not seem to be an apparent explanation for the conflicting evidence in previous studies. Our findings, based on thigh-worn devices, add valuable insights suggesting that replacing sedentary time with LIPA does have beneficial effects on glucose metabolism.

Replacing sedentary time with LIPA was associated with marginal improvements in some cardiovascular biomarkers, but it was not associated with changes in the remaining cardiovascular biomarkers. Taking the potential issue of multiple hypothesis testing into consideration, the reallocation effects on cardiovascular biomarkers seem limited. Our observations align with previous studies, which reported that replacing sedentary time with LIPA was associated with improvement in some (i.e. one or two) (30, 31, 34, 40) or none of the cardiovascular biomarkers (26, 33, 41). Further supporting these observations, a recent review suggested that all physical behaviours, including MVPA, only marginally affect cholesterol-related measures (42). These observations contrast with the general observation that replacing sedentary time with LIPA improves anthropometrics and glucose metabolism. An explanation for the modest effects on cardiovascular biomarkers may relate to the intensity of the physical activity. Haemodynamic stimuli such as shear stress are known to improve vascular function and structural remodelling in a dose-dependent manner (43). LIPA may be insufficient to substantially alter haemodynamic stimuli. Although beneficial trends can be observed even for the biomarkers with non-significant associations, the effects of replacing sedentary time with LIPA seem limited. Nonetheless, previous work did reveal the potential of reducing sedentary time to improve endothelial function and inflammation (44), and engagement in LIPA is also associated with a reduced risk of all-cause mortality (6, 45). Time reallocation may thus provide improvements in cardiovascular biomarkers

involved in other pathways (e.g. endothelial function and inflammation). Furthermore, reallocation effects may possibly occur in high-risk groups, such as individuals with manifest cardiometabolic disease or with high sedentary time volumes.

A relevant observation was that replacing sedentary time with LIPA was more strongly associated with improvements in cardiometabolic risk factors in those with moderate or high sedentary time. Caution is required since the confidence intervals indicate non-significance for some outcomes due to the smaller sample size of these stratified analyses. Nonetheless, time reallocation was associated with the largest improvements in anthropometrics and glucose metabolism in the moderate (i.e. 8.5-10 hours/day) and high (i.e. >10 hours/day) sedentary time subgroups. Moreover, and in contrast to the total sample, trends showed that reallocation in the high sedentary time subgroup was also associated with improvements in certain cardiovascular biomarkers (i.e. total and LDL cholesterol and blood pressure). These findings suggest that the largest cardiometabolic improvements can be achieved by those who are most sedentary whilst substantial improvements may already be obtained by moderately sedentary individuals. The mean sedentary time in most Western countries currently exceeds 8.5 hours/day (6, 46-48). The moderate and high sedentary time subgroups of the current study therefore represent tens of millions of individuals, highlighting the large health benefits that can be achieved by small changes in habitual routines.

The benefits of replacing sedentary time with LIPA are especially relevant from a public health perspective. Prevalence of physical inactivity is increasing globally (49), and replacement of sedentary time with LIPA appears to be an effective strategy to combat this pandemic. At an

individual level, the estimated benefit of a single risk factor may appear limited. However, at a population level, the effects may translate to valuable improvements in overall public health levels, especially since multiple risk factors were associated with significant changes. This could translate to a lower incidence of cardiometabolic diseases and a slower progression in those already diagnosed, resulting in lower healthcare demands and costs. Similar to previous studies (8, 26), our findings demonstrated that replacing sedentary time with MVPA provides significant cardiometabolic improvements, possibly greater than the improvements induced by replacing sedentary time with LIPA. However, from a practical perspective, replacing 30 minutes of sedentary time with LIPA on a daily basis is much more feasible than structurally replacing sedentary time with MVPA. LIPA can easily be integrated in daily life, e.g. by doing (office) work at a standing desk, by getting off public transport one stop early, or by socialising whilst standing or strolling. Given the feasibility of such replacements without the need for equipment and/or supervision, such strategies can be adopted by a majority of the general population, including older, diseased, and/or unfit individuals. This underlines that replacing sedentary time with LIPA seems to be an effective, feasible, and widely applicable method to improve cardiometabolic health at a population level.

Strengths and limitations

An important strength of the Nijmegen Exercise Study is the use of thigh-worn accelerometery data because, in contrast to most previous studies (8), these devices accurately distinguish sedentary time from time spent in LIPA (15, 16). Another strength is including multiple traditional and novel risk factors, resulting in a comprehensive overview of reallocation effects. A limitation of this study is the cross-sectional design. The reallocation-induced health benefits are

therefore hypothetical, and evidence shows that observed, longitudinal reallocation effects tend to be weaker than cross-sectional estimations (8). Repeated measurements or intervention studies would be needed to investigate whether within-person time reallocations are truly associated with changes in cardiometabolic risk factors. Moreover, the cross-sectional design does not offer insight into causal relationships between time reallocation and changes in the outcome measures. Another limitation is that body composition and arterial stiffness data were missing in approximately 40% of the participants. However, these data were missing at random rather than being related to individual characteristics. Whilst participants with body composition data were slightly older and more often had hypertension and hypercholesterolaemia than participants without body composition data, no substantial differences between these subgroups were apparent. Similarly, no differences between individuals with versus without arterial stiffness measurements were observed, suggesting that the missing data did not influence the results (Supplemental Tables 2-3, Supplemental Digital Content). Finally, residual confounding (e.g. by diet) may have occurred despite adjustment for major confounders.

CONCLUSIONS

Reallocations from sedentary time towards LIPA were associated with improvements in anthropometrics, glucose metabolism, and marginally, in some cardiovascular biomarkers. Individuals with moderate (>8.5 hours/day) or high (>10 hours/day) volumes of sedentary time, who are most at risk of developing cardiometabolic diseases, seem to benefit most from time reallocation into physical activity in terms of risk factor improvement. At a population level, replacing sedentary time with LIPA could be an effective and feasible strategy to improve cardiometabolic health. This emphasises the importance for international physical activity

guidelines to combat excessive sitting whilst promoting LIPA to enhance worldwide cardiometabolic health.

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Conflicts of Interest and Source of Funding

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Data Availability Statement

The datasets generated during and/or analysed during the current study are not publicly available due to information that could compromise the privacy of research participants but are available on request from the corresponding author (EAB, email: Esmee.Bakker@radboudumc.nl) or the principal investigator of the Nijmegen Exercise Study (TMHE, email: Thijs.Eijsvogels@radboudumc.nl).

Authors' contributions

Drafting, conception and design: KMvdS, DHJT, TMHE, and EAB. Collection and assembly of data: KMvdS, JIAV, and EAB. Analysis and interpretation of data: KMvdS and EAB. Drafting of the manuscript: KMvdS. Critical revision of the manuscript: JIAV, DHJT, TMHE, and EAB. Final approval of the manuscript: all authors.

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FIGURE LEGENDS

Figure 1. Estimated changes in A) body mass index, B) body fat percentage, and C) fat-free mass induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. LIPA: light-intensity physical activity, ST: sedentary time.

Figure 2. Estimated changes in A) total cholesterol, B) HDL cholesterol, C) LDL cholesterol, D) triglycerides, E) log(hs-cTnI), F) log(NT-proBNP), G) eGFR, H) systolic BP, I) diastolic BP, J) cfPWV, and K) stiffness index Beta induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. BP: blood pressure, cfPWV: carotid-femoral pulse wave velocity, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, hs-cTnI: high-sensitivity cardiac troponin I, LDL: low-density lipoprotein, LIPA: light-intensity physical activity, NT-proBNP: amino-terminal pro-B-type-natriuretic peptide, ST: sedentary time.

Figure 3. Estimated changes in A) glucose, B) log(insulin), and C) log(HOMA-IR) induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. HOMA-IR: homeostasis model assessment of insulin resistance, LIPA: light-intensity physical activity, ST: sedentary time.

Figure 4. Estimated changes in A-C) body mass index, D-F) total cholesterol, G-I) systolic BP, and J-L) glucose induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). BP: blood pressure, LIPA: light-intensity physical activity, ST: sedentary time.

Figure 5. Estimated changes in A) anthropometrics, B) cardiovascular biomarkers, and C) glucose metabolism induced by daily reallocations from sedentary time to light-intensity physical activity or moderate-to-vigorous physical activity of similar proportion with regard to the respective geometric means. BP: blood pressure, cfPWV: carotid-femoral pulse wave velocity, CI: confidence interval, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, hs-cTnI: high-sensitivity cardiac troponin I, LDL: low-density lipoprotein, LIPA: light-intensity physical activity, MVPA: moderate-to-vigorous physical activity, NT-proBNP: amino-terminal pro-B-type-natriuretic peptide, ST: sedentary time.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Supplemental Digital Content 1. pdf

Figure 1

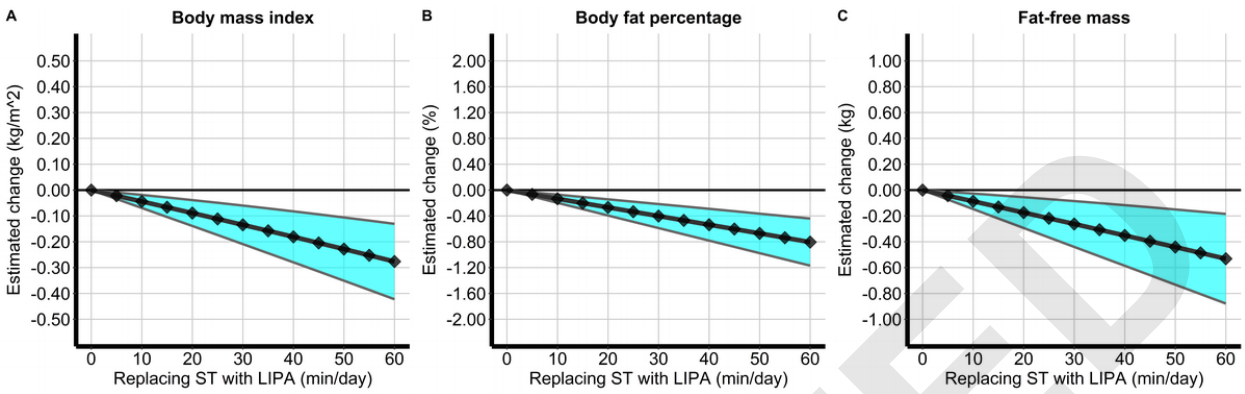

Figure 2

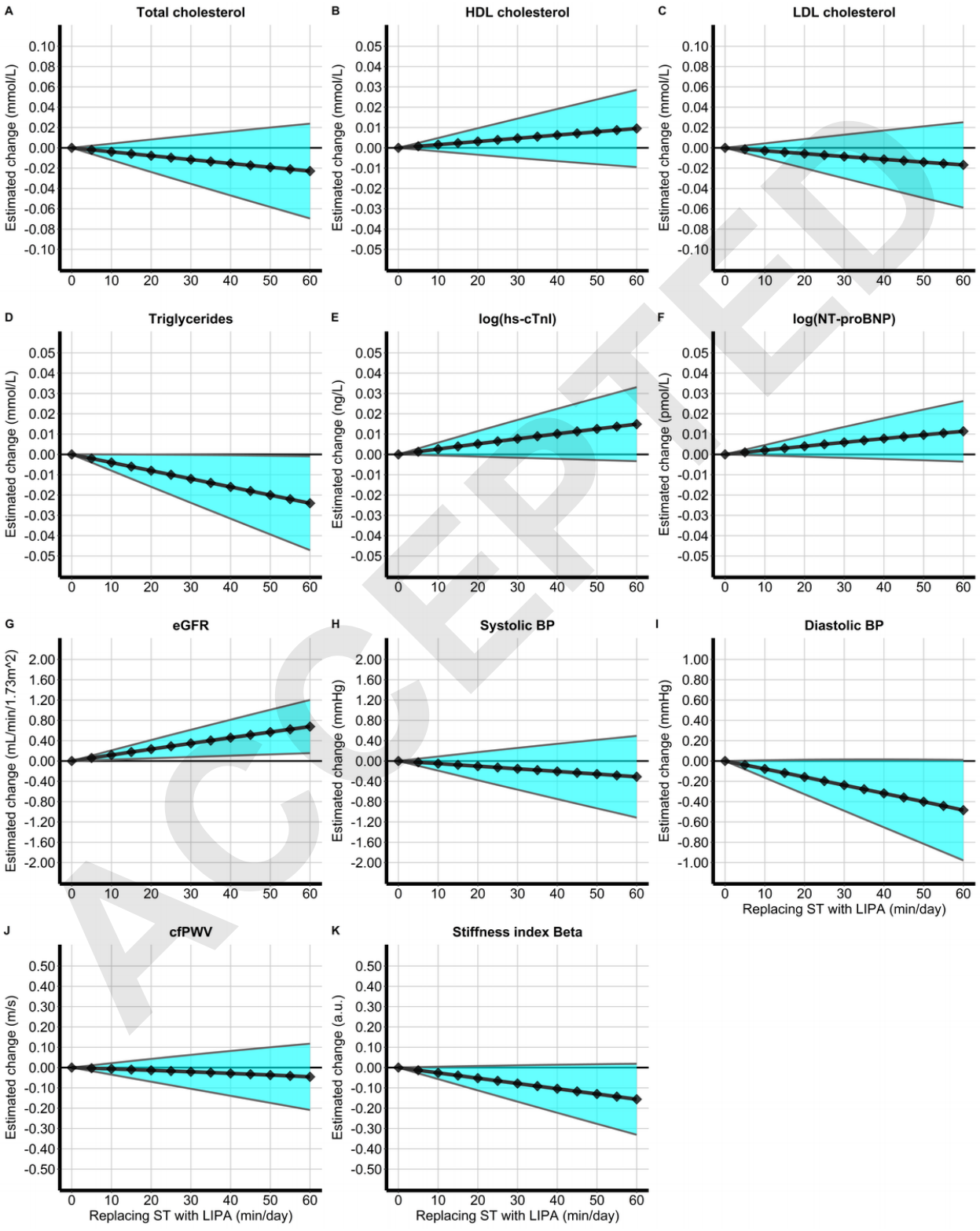

Figure 3

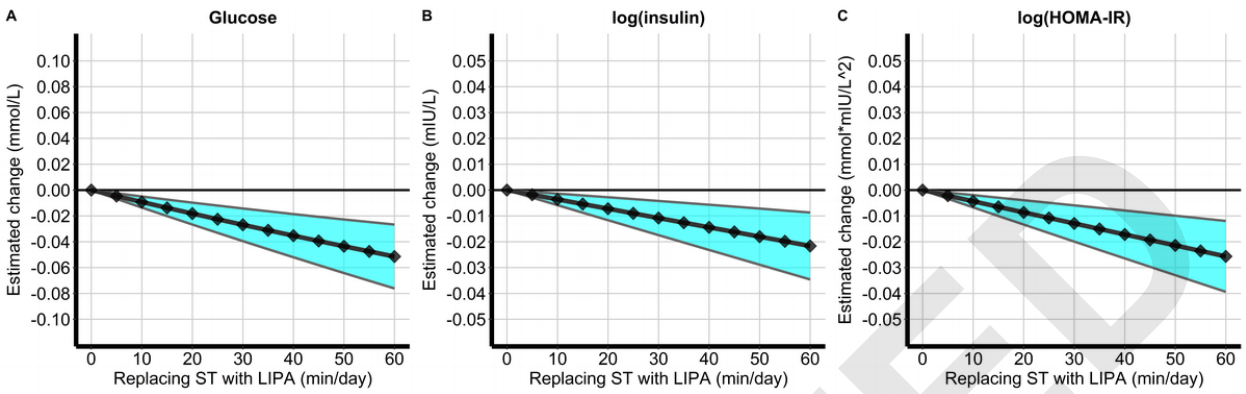

Figure 4

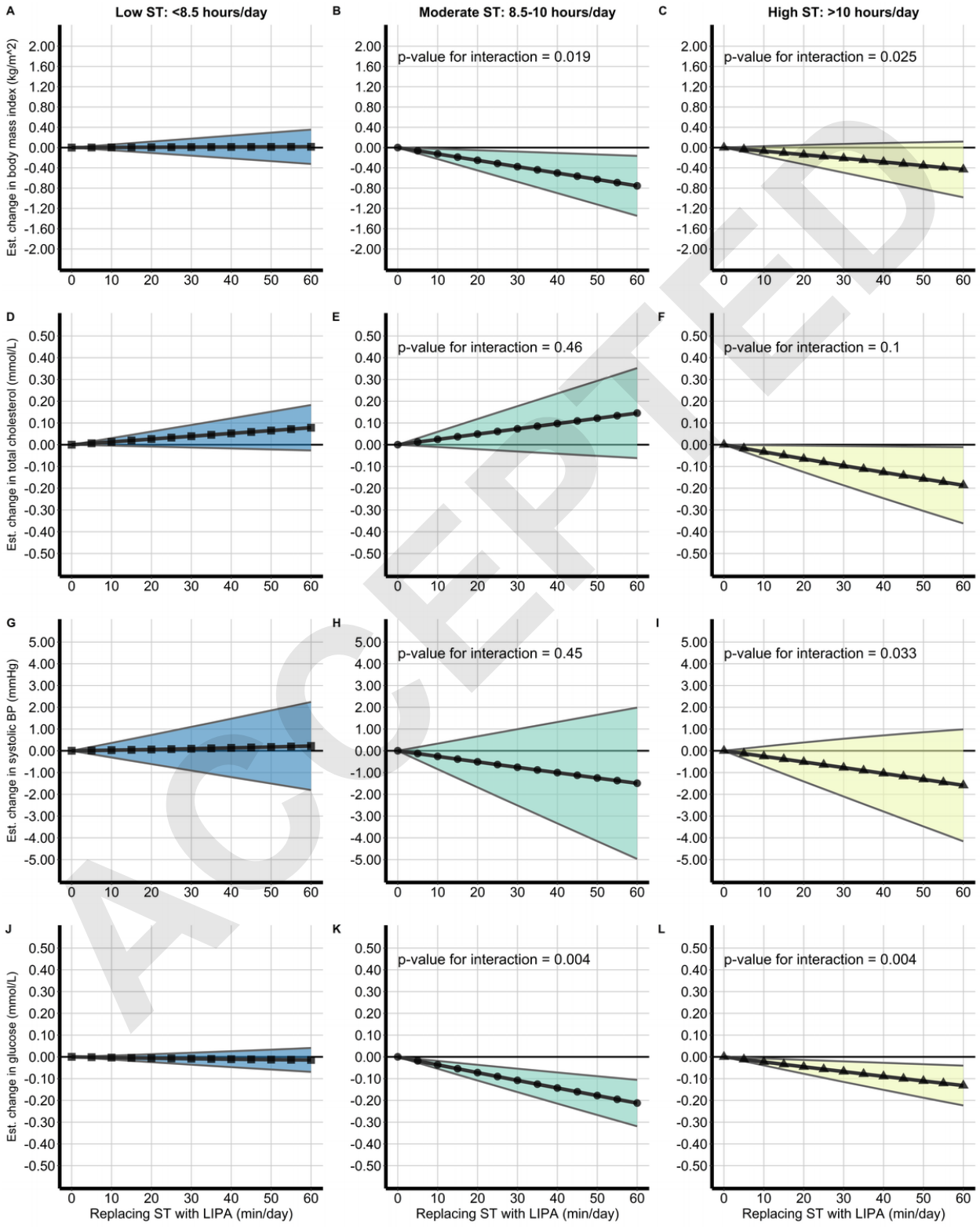

Figure 5

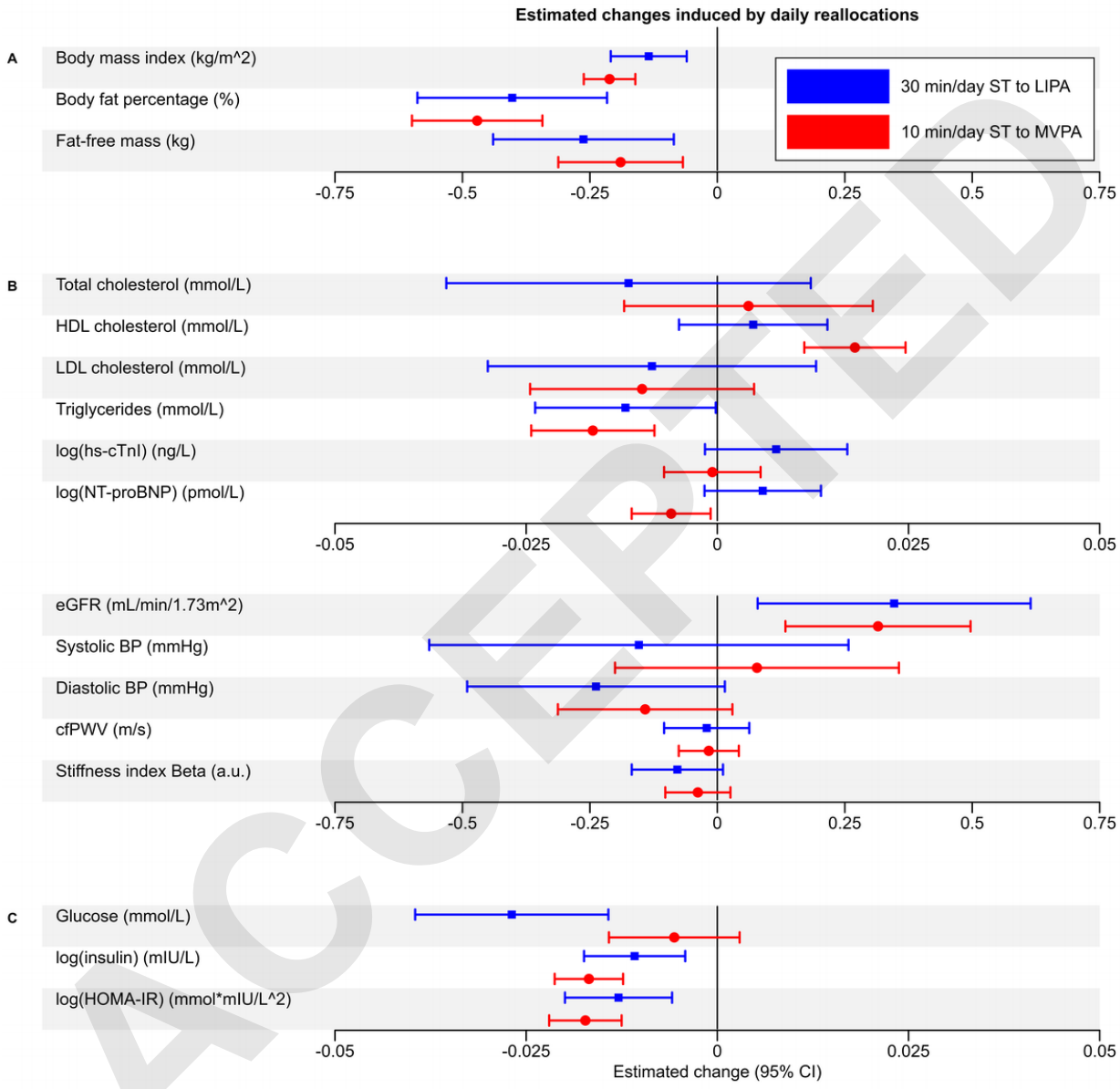

Table 1. Participant characteristics of the total sample and by subgroups of sedentary time.

	Total sample	**Low ST**	**Moderate ST**	**High ST**	***p*-value**
		<8.5 h/d	*8.5-10 h/d*	*>10 h/d*	
	N=1,041	N=350	N=381	N=310	
Age, years	64 (11)	64 (11)	64 (12)	64 (11)	0.88
Female sex	411 (39.5)	180 (51.4)	154 (40.4)	77 (24.8)	<0.001
Level of education					<0.001
Low-to-intermediate	483 (46.4)	204 (58.3)	154 (40.4)	125 (40.3)	
High	558 (53.6)	146 (41.7)	227 (59.6)	185 (59.7)	
Employed	539 (51.8)	167 (47.7)	190 (49.9)	182 (58.7)	0.012
Alcohol consumption, glasses/week	4 [1, 8]	3 [1, 7]	4 [2, 8]	4 [2, 10]	0.024
Smoking behaviour					0.007
Current smoker	49 (4.7)	10 (2.9)	14 (3.7)	25 (8.1)	
Former smoker	435 (41.8)	137 (39.1)	170 (44.6)	128 (41.3)	
Never smoked	557 (53.5)	203 (58.0)	197 (51.7)	157 (50.6)	
Medical history					
Obesity	65 (6.2)	8 (2.3)	25 (6.6)	32 (10.3)	<0.001
Myocardial infarction †	49 (4.7)	18 (5.2)	18 (4.7)	13 (4.2)	0.86
Heart failure ‡	34 (3.3)	10 (2.9)	9 (2.4)	15 (4.9)	0.19
Stroke ˣ	46 (4.5)	17 (4.9)	12 (3.2)	17 (5.6)	0.27
Thrombosis ˆ	26 (2.5)	6 (1.7)	11 (2.9)	9 (2.9)	0.52
Kidney disease *	17 (1.6)	3 (0.9)	8 (2.1)	6 (1.9)	0.36
Hypercholesterolaemia ˜	209 (20.4)	53 (15.3)	90 (24.2)	66 (21.6)	0.010

Hypertension *	240 (23.3)	66 (19.0)	98 (26.1)	76 (24.6)	0.06
Diabetes mellitus *	46 (4.5)	13 (3.8)	16 (4.3)	17 (5.5)	0.57
Medication use					
Cholesterol-lowering	156 (15.0)	39 (11.1)	68 (17.8)	49 (15.8)	0.034
Antihypertensive	215 (20.7)	60 (17.1)	81 (21.3)	74 (23.9)	0.10
Antidiabetic	28 (2.7)	7 (2.0)	11 (2.9)	10 (3.2)	0.59

Results are presented as mean (standard deviation), median [first quartile, third quartile], or number (percentage). Variables marked with symbols describe †N=1,036, ‡N=1,032, xN=1,033, ˆN=1,029, *N=1,031, ˜N=1,024 participants. h/d: hours/day, ST: sedentary time.

Supplemental Digital Content 1

Cardiometabolic benefit of replacing sedentary time with light-intensity physical activity: compositional data analysis of the Nijmegen Exercise Study

Short title: Replacing sitting with activity time

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Table of content

Supplementary File S1.

Supplementary File S1. Measurement of cardiometabolic risk factors.

We evaluated cardiometabolic risk factors of the participants during their visit to our research centre. Participants were instructed to fast for at least 4 hours, refrain from strenuous exercise for 24 hours, and refrain from alcohol and caffeine for 18 hours.

Height and body mass were measured (Seca GmbH & Co. KG, Hamburg, Germany), and we computed body mass index (BMI). Body composition was assessed using multi-frequency bioelectrical impedance analysis (770, InBody, Seoul, South Korea) and quantified as body fat percentage and fat-free mass. Body composition data have been collected since 2022, so these variables were only available in a subgroup of participants.

Venous blood was sampled (SST II Advance, BD Vacutainer, Franklin Lakes, NJ, USA) and coagulated for 45 to 60 minutes before being centrifuged at 3,000 revolutions/minute for 10 minutes at 4 °C. Serum was then transferred to 2-mL microtubes and stored at -80 °C until analysis. Concentrations of the following biomarkers were determined: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, high-sensitivity cardiac troponin I (hs-cTnI), amino-terminal pro-B-type-natriuretic-peptide (NT-proBNP), creatinine, glucose hexokinase, and insulin. Analyses were performed batchwise on Atellica™ (and IMMULITE® 2000 for insulin) analysers (Siemens Healthcare, Erlangen, Germany) in the Gelderse Vallei Hospital, Ede, the Netherlands. Age, sex, and creatinine serum concentration were used to compute the estimated glomerular filtration rate (eGFR) according to the 2021 CKD-EPI creatinine equation (1). The homeostasis model assessment of insulin resistance (HOMA-IR) was computed as follows: $HOMA\text{-}IR = (glucose \times insulin)/22.5$ (2). Log-transforms of hs-cTnI, NT-proBNP, insulin, and HOMA-IR were used in the analysis.

We measured non-invasive left brachial blood pressure using an automatic sphygmomanometer (M3, OMRON, Kyoto, Japan). We performed two measurements after at least five minutes of rest in supine position, and we used the average values for analysis. In participants using antihypertensive medication, we adjusted systolic and diastolic blood pressure by adding 10 mmHg, following standard practice (3). We assessed central and local arterial stiffness using ARTSENS Plus (Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, Chennai, India) after at least ten minutes of rest in supine position (4). Left brachial blood pressure and heart rate were acquired by the integrated blood pressure monitor for the acquisition of local arterial stiffness parameters. Amplitude mode (A-mode) ultrasound was used to track movement of the left common carotid arterial wall, from which the dimensionless stiffness index Beta was computed, a measure of local arterial stiffness (4). Simultaneously, the femoral artery pressure waveform was monitored using a thigh cuff to estimate the pulse transit time. Carotid-femoral pulse wave velocity, a measure of central arterial stiffness (5), was computed through combination of the pulse transit time and the estimated effective path length (6). Arterial stiffness data could not be collected in all participants because of limited availability of the measurement devices, so arterial stiffness data were only available in a subgroup of participants.

Supplementary File S2.

Supplementary File S2. Description of isometric log transformations.

The physical behaviours sedentary time, light-intensity physical activity (LIPA), moderate-to-vigorous physical activity (MVPA), and sleep time were expressed as proportions of the 24-hour cycle to create four-part physical behaviour compositions. Closure was ensured so that the four compositions add up to 1 for all participants. R (version 4.3.2, RRID:SCR_001905) with package *codaredistlm* was used to perform isometric log ratio (ilr) transformations (7). Using ilr, the four-part physical behaviour composition was converted into a mathematically equivalent three-part set of ilr coordinates (*ilr*1, *ilr*2, *ilr*3):

$$ilr1 = \sqrt{\frac{3}{4}} ln \sqrt{\frac{sedentary}{(LIPA * MVPA * sleep)^{1/3}}}$$

$$ilr2 = \sqrt{\frac{2}{3}} ln \sqrt{\frac{LIPA}{(MVPA * sleep)^{1/2}}}$$

$$ilr3 = \sqrt{\frac{1}{2}} ln \sqrt{\frac{MVPA}{sleep}}$$

The first ilr coordinate (*ilr*1) describes the time spent in the first behaviour of the composition (i.e. sedentary time) relative to the time spent in the remaining three physical behaviours (i.e. LIPA, MVPA, and sleep). We created an equivalent variant of the behaviour composition by switching the positions of sedentary time and time spent in LIPA (i.e. pivoting). The corresponding ilr transformation produces ilr coordinates:

$$ilr1 = \sqrt{\frac{3}{4}} ln \sqrt{\frac{LIPA}{(sedentary * MVPA * sleep)^{1/3}}}$$

$$ilr2 = \sqrt{\frac{2}{3}} ln \sqrt{\frac{sedentary}{(MVPA * sleep)^{1/2}}}$$

$$ilr3 = \sqrt{\frac{1}{2}} ln \sqrt{\frac{MVPA}{sleep}}$$

Here, *ilr*1 describes the time spent in LIPA relative to the time spent sedentary, in MVPA, and sleeping.

Supplementary Table S1.

Supplementary Table S1. Associations of increasing sedentary time, time spent in light-intensity physical activity, or time spent in moderate-to-vigorous physical activity whilst proportionally decreasing the remaining physical behaviours with cardiometabolic risk factors.

Cardiometabolic risk factor	Model 1 β (95% CI), p-value	Model 2 β (95% CI), p-value	Sensitivity analyses β (95% CI), p-value
Increase in sedentary time and a proportional decrease in the remaining physical behaviours			
Body mass index	**2.79 (1.83, 3.74), p<0.001**	**2.69 (1.75, 3.64), p<0.001**	N/A
Body fat percentage	**5.2 (2.77, 7.64), p<0.001**	**5.17 (2.73, 7.6), p<0.001**	N/A
Fat free mass	**4.25 (1.95, 6.55), p<0.001**	**4.16 (1.84, 6.48), p<0.001**	N/A
Total cholesterol ‡	0.15 (-0.16, 0.45), p=0.35	0.1 (-0.21, 0.4), p=0.54	0.1 (-0.21, 0.41), p=0.53
HDL cholesterol ‡	-0.07 (-0.19, 0.05), p=0.27	-0.08 (-0.2, 0.05), p=0.22	0.01 (-0.11, 0.13), p=0.92
LDL cholesterol ‡	0.12 (-0.15, 0.4), p=0.38	0.07 (-0.2, 0.35), p=0.60	0.01 (-0.26, 0.29), p=0.93
Triglycerides ‡	**0.18 (0.03, 0.33), p=0.017**	**0.15 (0, 0.3), p=0.05**	0.06 (-0.09, 0.21), p=0.42
log(hs-cTnI)	-0.02 (-0.13, 0.1), p=0.79	-0.03 (-0.15, 0.09), p=0.63	-0.01 (-0.13, 0.11), p=0.85
log(NT-proBNP)	-0.02 (-0.12, 0.08), p=0.67	-0.01 (-0.1, 0.09), p=0.88	0.01 (-0.08, 0.11), p=0.77
eGFR	-2.25 (-5.62, 1.12), p=0.19	-2.28 (-5.68, 1.13), p=0.19	-1.04 (-4.48, 2.39), p=0.55
Systolic BP †	1.75 (-3.44, 6.94), p=0.51	2.31 (-2.92, 7.53), p=0.39	-0.58 (-5.8, 4.64), p=0.83
Diastolic BP †	**4.13 (0.94, 7.33), p=0.011**	**4.08 (0.87, 7.29), p=0.013**	1.06 (-2.04, 4.16), p=0.50
cfPWV †	0.59 (-0.47, 1.65), p=0.28	0.78 (-0.29, 1.84), p=0.15	0.91 (-0.17, 1.99), p=0.10
Stiffness index Beta †	0.75 (-0.38, 1.89), p=0.19	0.9 (-0.25, 2.05), p=0.12	0.65 (-0.51, 1.81), p=0.27
Glucose *	0.04 (-0.12, 0.2), p=0.61	0.02 (-0.14, 0.18), p=0.78	-0.04 (-0.21, 0.12), p=0.59
log(Insulin) *	**0.14 (0.06, 0.22), p=0.001**	**0.14 (0.05, 0.22), p=0.001**	0.04 (-0.04, 0.11), p=0.38
log(HOMA-IR) *	**0.14 (0.05, 0.23), p=0.002**	**0.14 (0.05, 0.23), p=0.002**	0.03 (-0.05, 0.11), p=0.46
Increase in time spent in LIPA and a proportional decrease in the remaining physical behaviours			
Body mass index	0.12 (-0.61, 0.86), p=0.75	-0.04 (-0.77, 0.68), p=0.90	N/A
Body fat percentage	-1.53 (-3.41, 0.34), p=0.11	-1.74 (-3.6, 0.13), p=0.07	N/A
Fat free mass	-0.65 (-2.42, 1.12), p=0.47	-0.7 (-2.47, 1.08), p=0.44	N/A
Total cholesterol ‡	-0.07 (-0.3, 0.16), p=0.56	-0.08 (-0.31, 0.15), p=0.51	-0.08 (-0.31, 0.15), p=0.51
HDL cholesterol ‡	0.01 (-0.09, 0.1), p=0.86	0.01 (-0.08, 0.1), p=0.84	0 (-0.09, 0.09), p=0.93
LDL cholesterol ‡	-0.05 (-0.26, 0.16), p=0.65	-0.06 (-0.27, 0.15), p=0.60	-0.05 (-0.26, 0.16), p=0.63
Triglycerides ‡	-0.05 (-0.17, 0.06), p=0.39	-0.05 (-0.17, 0.06), p=0.37	-0.05 (-0.16, 0.07), p=0.42
log(hs-cTnI)	0.06 (-0.03, 0.15), p=0.18	0.07 (-0.02, 0.16), p=0.12	0.07 (-0.02, 0.16), p=0.13
log(NT-proBNP)	0.06 (-0.01, 0.14), p=0.09	0.06 (-0.01, 0.14), p=0.10	0.06 (-0.01, 0.14), p=0.10
eGFR	2.52 (-0.07, 5.1), p=0.06	**2.65 (0.06, 5.25), p=0.045**	**2.63 (0.06, 5.2), p=0.045**
Systolic BP †	0.21 (-3.78, 4.2), p=0.92	-0.47 (-4.46, 3.51), p=0.82	-0.43 (-4.35, 3.49), p=0.83
Diastolic BP †	-0.06 (-2.52, 2.39), p=0.96	-0.45 (-2.9, 2), p=0.72	-0.41 (-2.73, 1.92), p=0.73
cfPWV †	0.29 (-0.55, 1.12), p=0.50	0.19 (-0.64, 1.02), p=0.66	0.21 (-0.62, 1.05), p=0.61
Stiffness index Beta †	-0.35 (-1.25, 0.54), p=0.44	-0.39 (-1.29, 0.51), p=0.39	-0.44 (-1.34, 0.45), p=0.33
Glucose *	**-0.27 (-0.4, -0.15), p<0.001**	**-0.29 (-0.41, -0.17), p<0.001**	**-0.29 (-0.41, -0.17), p<0.001**
log(Insulin) *	-0.03 (-0.1, 0.03), p=0.30	-0.05 (-0.11, 0.02), p=0.15	-0.05 (-0.11, 0.01), p=0.12
log(HOMA-IR) *	-0.06 (-0.12, 0.01), p=0.11	**-0.07 (-0.14, 0), p=0.045**	**-0.07 (-0.13, -0.01), p=0.028**
Increase in time spent in MVPA and a proportional decrease in the remaining physical behaviours			
Body mass index	**-2.23 (-2.85, -1.62), p<0.001**	**-2.12 (-2.72, -1.51), p<0.001**	N/A
Body fat percentage	**-4.90 (-6.43, -3.37), p<0.001**	**-4.85 (-6.37, -3.34), p<0.001**	N/A
Fat free mass	**-1.58 (-3.03, -0.13), p=0.032**	**-1.54 (-2.99, -0.09), p=0.037**	N/A
Total cholesterol ‡	0.09 (-0.11, 0.29), p=0.36	0.07 (-0.12, 0.27), p=0.48	0.07 (-0.13, 0.27), p=0.50
HDL cholesterol ‡	**0.22 (0.14, 0.30), p<0.001**	**0.21 (0.13, 0.29), p<0.001**	**0.14 (0.07, 0.22), p<0.001**
LDL cholesterol ‡	-0.09 (-0.26, 0.09), p=0.33	-0.11 (-0.29, 0.07), p=0.22	-0.06 (-0.24, 0.12), p=0.51
Triglycerides ‡	**-0.18 (-0.28, -0.08), p<0.001**	**-0.18 (-0.27, -0.08), p<0.001**	**-0.10 (-0.20, -0.01), p=0.037**
log(hs-cTnI)	-0.01 (-0.09, 0.06), p=0.75	-0.01 (-0.09, 0.06), p=0.72	-0.03 (-0.10, 0.05), p=0.48

log(NT-proBNP)	**-0.08 (-0.14, -0.02), p=0.010**	**-0.08 (-0.14, -0.02), p=0.014**	**-0.09 (-0.16, -0.03), p=0.003**
eGFR	**3.45 (1.29, 5.62), p=0.002**	**3.50 (1.33, 5.67), p=0.002**	**2.53 (0.33, 4.74), p=0.024**
Systolic BP †	1.31 (-2.03, 4.65), p=0.44	1.43 (-1.90, 4.77), p=0.40	**3.63 (0.28, 6.98), p=0.034**
Diastolic BP †	-1.12 (-3.18, 0.93), p=0.28	-0.97 (-3.01, 1.08), p=0.36	1.33 (-0.66, 3.32), p=0.19
cfPWV †	-0.12 (-0.82, 0.59), p=0.74	-0.06 (-0.76, 0.65), p=0.88	-0.16 (-0.87, 0.56), p=0.67
Stiffness index Beta †	-0.26 (-1.01, 0.50), p=0.50	-0.30 (-1.06, 0.46), p=0.44	-0.12 (-0.89, 0.65), p=0.77
Glucose *	-0.08 (-0.18, 0.03), p=0.15	-0.07 (-0.17, 0.04), p=0.20	-0.01 (-0.12, 0.09), p=0.79
log(Insulin) *	**-0.19 (-0.25, -0.14), p<0.001**	**-0.18 (-0.24, -0.13), p<0.001**	**-0.11 (-0.16, -0.06), p<0.001**
log(HOMA-IR) *	**-0.20 (-0.26, -0.14), p<0.001**	**-0.19 (-0.25, -0.13), p<0.001**	**-0.11 (-0.16, -0.05), p<0.001**

Coefficients indicate change in cardiometabolic risk factor per 1 unit increase of the ilr coordinate. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, level of education, employment status, alcohol consumption, smoking behaviour, and cardiometabolic medication use. Sensitivity analyses: model 2 + adjustment for body mass index. ‡Participants with hypercholesterolaemia excluded and not adjusted for cholesterol-lowering medication. †Not adjusted for antihypertensive medication. *Participants with diabetes excluded and not adjusted for antidiabetic medication. Bold-print indicates significant estimates and *p*-values. BP: blood pressure, cfPWV: carotid-femoral pulse wave velocity, CI: confidence interval, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, hs-cTnI: high-sensitivity cardiac troponin I, HOMA-IR: homeostasis model assessment of insulin resistance, LDL: low-density lipoprotein, LIPA: light-intensity physical activity, MVPA: moderate-to-vigorous physical activity, N/A: not applicable, and NT-proBNP: amino-terminal pro-B-type-natriuretic peptide.

Supplementary Table S2.

Supplementary Table S2. Participant characteristics of the total sample and by subgroup with versus without body composition measurement.

	Total sample	**Body composition measured**	**Body composition not measured**	***p*-value**
	N=1,041	N=671	N=370	
Age, years	64 (11)	65 (11)	62 (11)	<0.001
Female sex	411 (39.5)	262 (39.0)	149 (40.3)	0.74
Level of education				0.29
Low-to-intermediate	483 (46.4)	308 (45.9)	175 (47.3)	
High	558 (53.6)	363 (54.1)	195 (52.7)	
Employed	539 (51.8)	306 (45.6)	233 (63.0)	<0.001
Alcohol consumption, glasses/week	4 [1, 8]	4 [1, 8]	4 [1, 7]	0.30
Smoking behaviour				0.23
Current smoker	49 (4.7)	32 (4.8)	17 (4.6)	
Former smoker	435 (41.8)	293 (43.7)	142 (38.4)	
Never smoked	557 (53.5)	346 (51.6)	211 (57.0)	
Medical history				
Obesity	65 (6.2)	44 (6.6)	21 (5.7)	0.69
Myocardial infarction †	49 (4.7)	27 (4.0)	22 (6.0)	0.17
Heart failure ‡	34 (3.3)	22 (3.3)	12 (3.3)	>0.99
Stroke ˣ	46 (4.5)	33 (5.0)	13 (3.5)	0.35
Thrombosis ˆ	26 (2.5)	16 (2.4)	10 (2.7)	0.84
Kidney disease *	17 (1.6)	15 (2.2)	2 (0.6)	0.042
Hypercholesterolaemia ˜	209 (20.4)	150 (22.7)	59 (16.3)	0.019
Hypertension *	240 (23.3)	168 (25.2)	72 (19.8)	0.054
Diabetes mellitus *	46 (4.5)	36 (5.4)	10 (2.7)	0.06
Medication use				
Cholesterol-lowering	156 (15.0)	124 (18.5)	32 (8.6)	<0.001
Antihypertensive	215 (20.7)	165 (24.6)	50 (13.5)	<0.001
Antidiabetic	28 (2.7)	26 (3.9)	2 (0.5)	0.001
Sedentary time, hours/day	9.2	9.2	9.1	
LIPA, hours/day	4.6	4.7	4.5	
MVPA, hours/day	1.7	1.7	1.8	
Sleep time, hours/day	8.5	8.4	8.6	
Step count, steps/day	13,867 (4,772)	13,726 (4,742)	14,123 (4,822)	0.20

Results are presented as mean (standard deviation), median [first quartile, third quartile], number (percentage), or geometric mean for physical behaviours. Variables marked with symbols describe †N=1,036, ‡N=1,032, ˣN=1,033, ˆN=1,029, *N=1,031, ˜N=1,024 participants. LIPA: light-intensity physical activity, MVPA: moderate-to-vigorous physical activity.

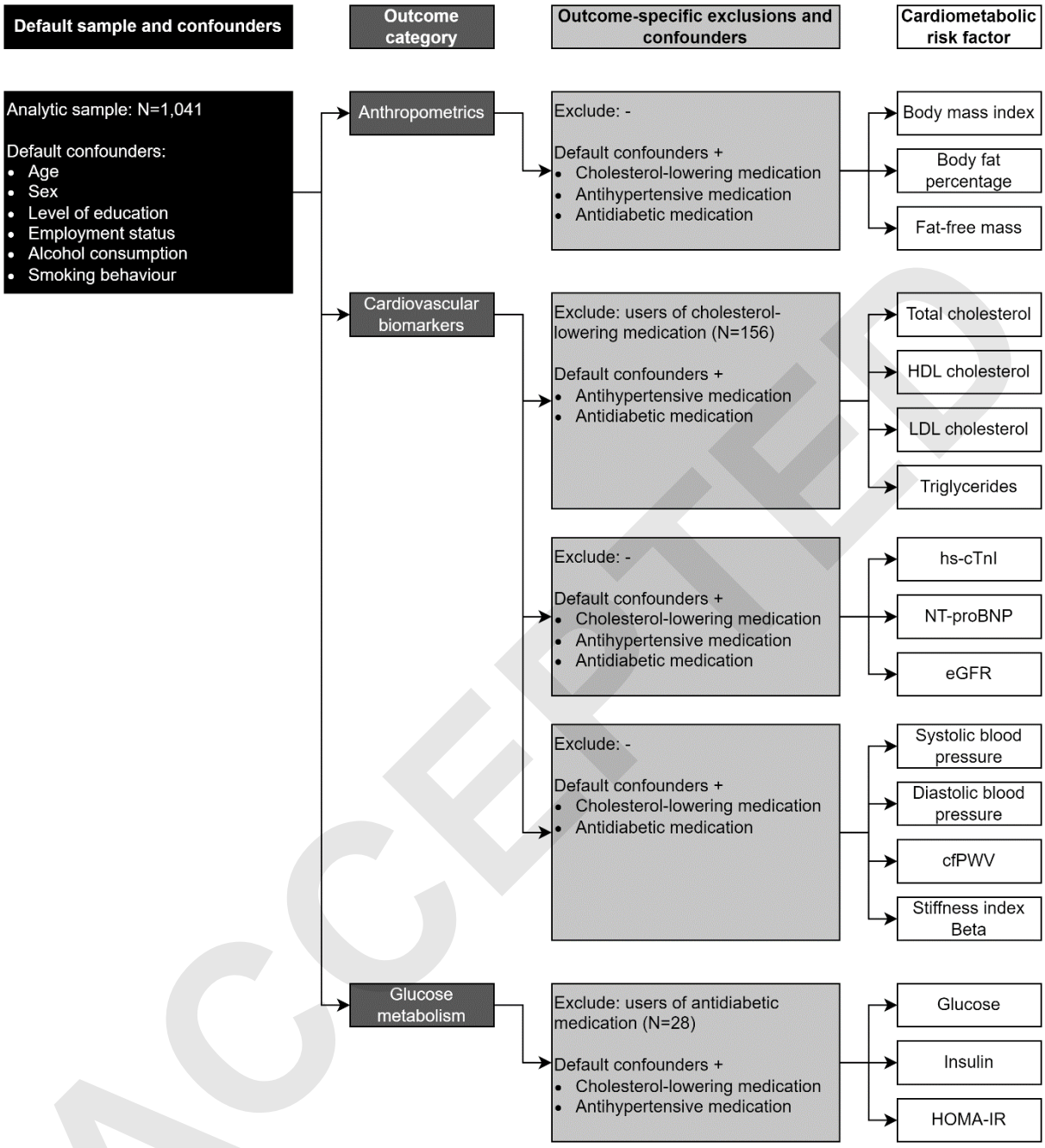
Supplementary Table S3.

Supplementary Table S3. Participant characteristics of the total sample and by subgroup with versus without arterial stiffness measurement.

	Total sample	**Arterial stiffness measured**	**Arterial stiffness not measured**	***p*-value**
	N=1,041	N=589	N=452	
Age, years	64 (11)	64.3 (10.9)	63.9 (11.2)	0.52
Female sex	411 (39.5)	231 (39.2)	180 (39.8)	0.85
Level of education				0.89
Low-to-intermediate	483 (46.4)	277 (47.0)	206 (45.6)	
High	558 (53.6)	312 (53.0)	246 (54.4)	
Employed	539 (51.8)	300 (50.9)	239 (52.9)	0.57
Alcohol consumption, glasses/week	4 [1, 8]	4 [1, 8]	4 [1, 8]	0.56
Smoking behaviour				0.10
Current smoker	49 (4.7)	34 (5.8)	15 (3.3)	
Former smoker	435 (41.8)	252 (42.8)	183 (40.5)	
Never smoked	557 (53.5)	303 (51.4)	254 (56.2)	
Medical history				
Obesity	65 (6.2)	29 (4.9)	36 (8.0)	0.052
Myocardial infarction †	49 (4.7)	27 (4.6)	22 (4.9)	0.88
Heart failure ‡	34 (3.3)	19 (3.2)	15 (3.4)	>0.99
Stroke ˣ	46 (4.5)	26 (4.4)	20 (4.5)	>0.99
Thrombosis ˆ	26 (2.5)	17 (2.9)	9 (2.0)	0.43
Kidney disease *	17 (1.6)	11 (1.9)	6 (1.3)	0.63
Hypercholesterolaemia ˜	209 (20.4)	123 (21.3)	86 (19.2)	0.44
Hypertension *	240 (23.3)	148 (25.3)	92 (20.6)	0.09
Diabetes mellitus *	46 (4.5)	24 (4.1)	22 (4.9)	0.55
Medication use				
Cholesterol-lowering	156 (15.0)	96 (16.3)	60 (13.3)	0.19
Antihypertensive	215 (20.7)	134 (22.8)	81 (17.9)	0.06
Antidiabetic	28 (2.7)	15 (2.5)	13 (2.9)	0.85
Sedentary time, hours/day	9.2	9.2	9.2	
LIPA, hours/day	4.6	4.6	4.6	
MVPA, hours/day	1.7	1.7	1.7	
Sleep time, hours/day	8.5	8.5	8.5	
Step count, steps/day	13,867 (4,772)	13,755 (4,623)	14,013 (4,960)	0.39

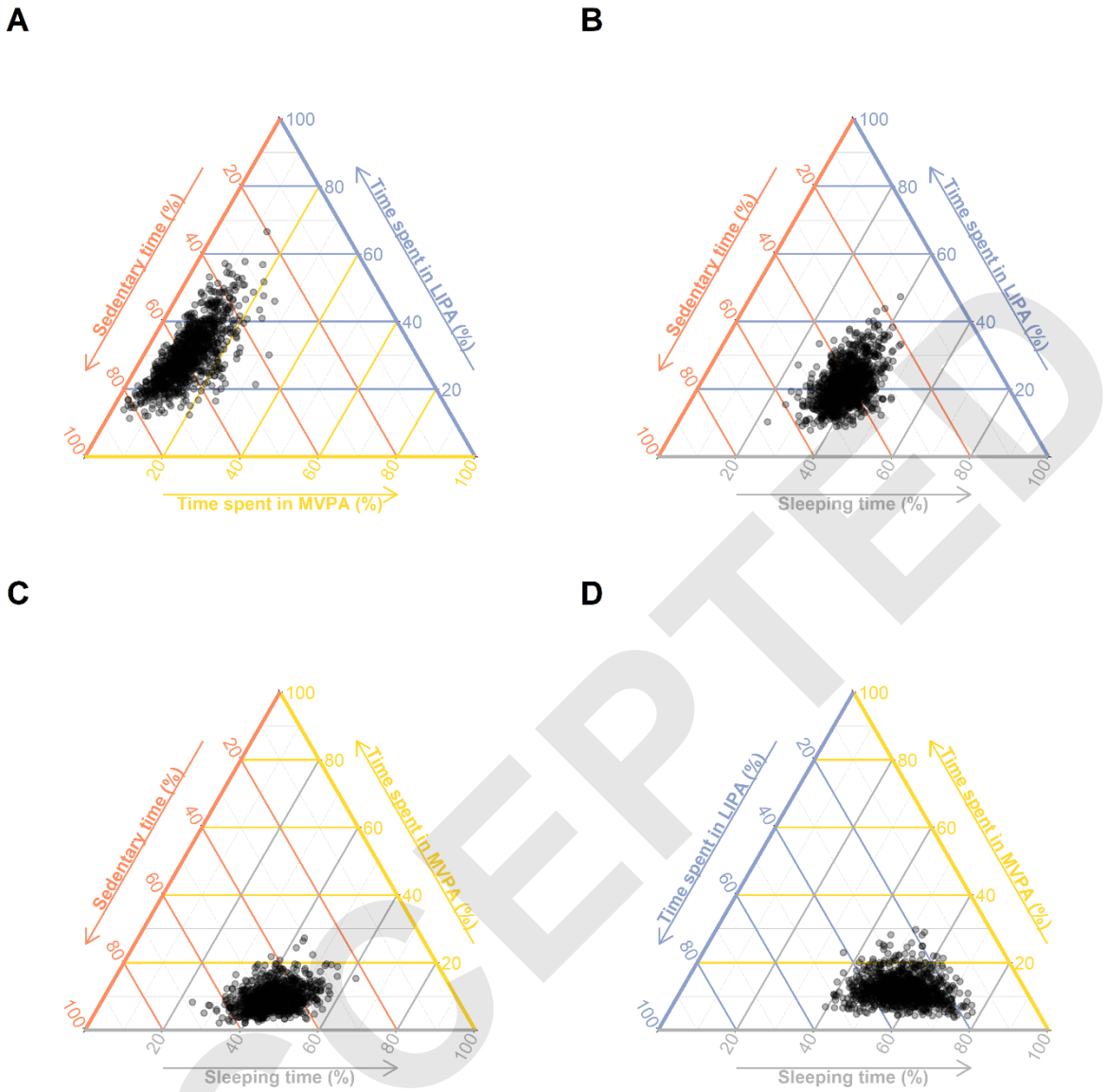
Results are presented as mean (standard deviation), median [first quartile, third quartile], number (percentage), or geometric mean for physical behaviours. Variables marked with symbols describe †N=1,036, ‡N=1,032, ˣN=1,033, ˆN=1,029, *N=1,031, ˜N=1,024 participants. LIPA: light-intensity physical activity, MVPA: moderate-to-vigorous physical activity.

Supplementary Figure S1.



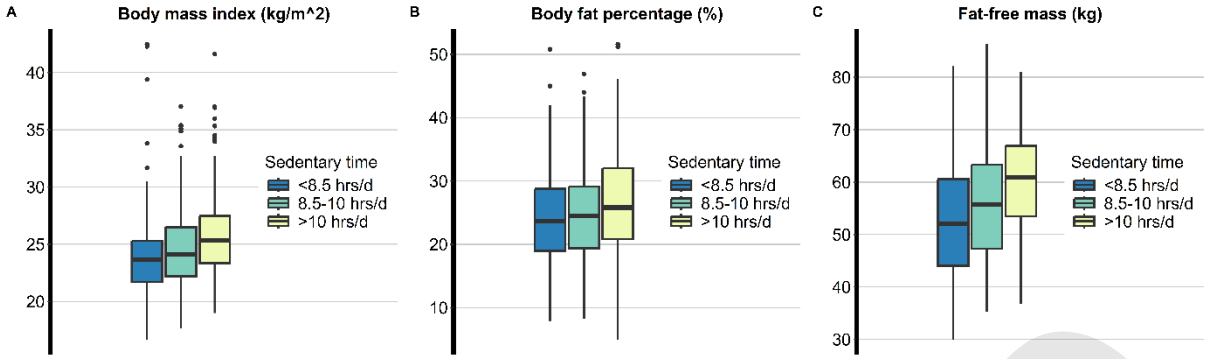
Supplementary Figure S1. Overview of the included participants and set of confounders in the regression models for each cardiometabolic risk factor. cfPWV: carotid-femoral pulse wave velocity, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, hs-cTnI: high-sensitivity cardiac troponin I, LDL: low-density lipoprotein, NT-proBNP: amino-terminal pro-B-type-natriuretic peptide.

Supplementary Figure S2.



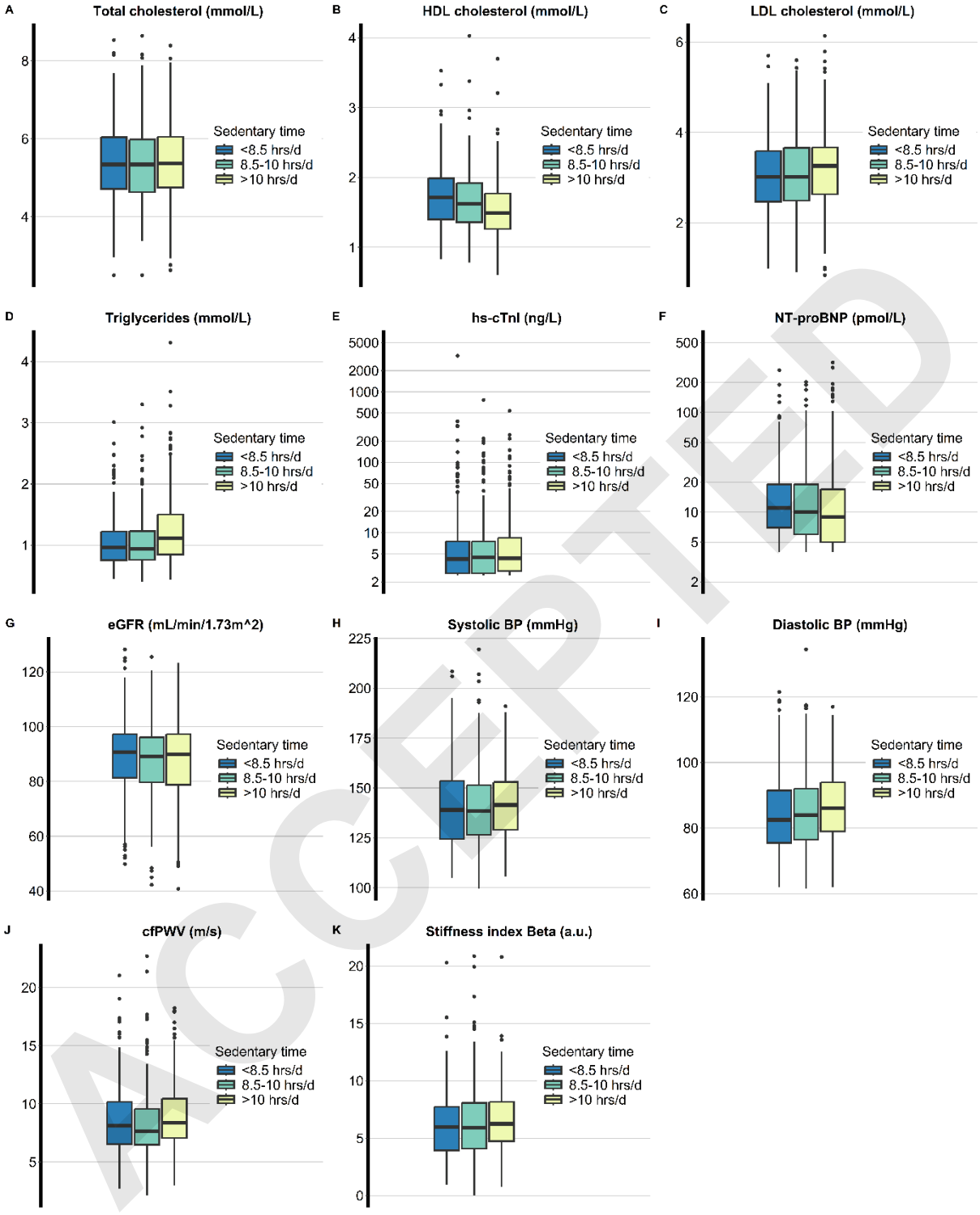
Supplementary Figure S2. Ternary diagrams displaying the proportions of time spent in three physical behaviours: **A**) sedentary time, LIPA, and MVPA; **B**) sedentary time, LIPA, and sleeping; **C**) sedentary time, MVPA, and sleeping; **D**) LIPA, MVPA, and sleeping. Total time differs across panels since the time spent in the physical behaviour that is left out is different for each panel. Each point represents one participant. LIPA: light-intensity physical activity, MVPA: moderate-to-vigorous physical activity.

Supplementary Figure S3.



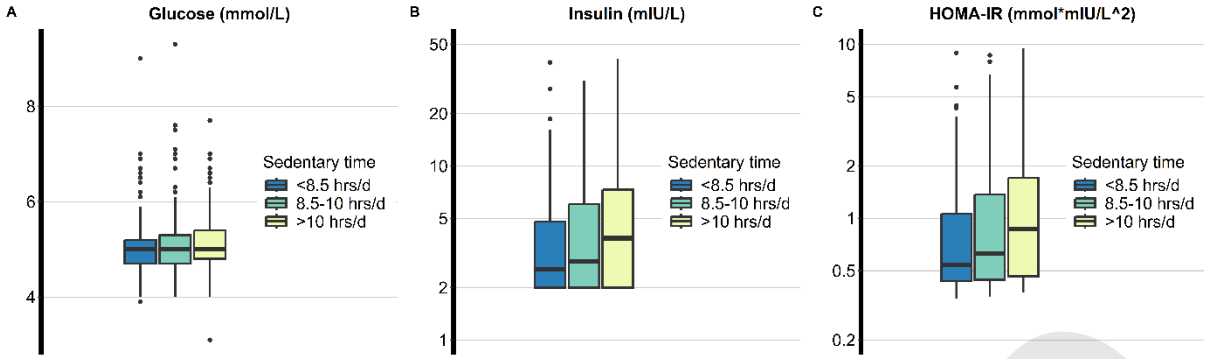
Supplementary Figure S3. Boxplots of **A**) body mass index, **B**) body fat percentage, and **C**) fat-free mass per sedentary time subgroup. The box describes first quartile, median, and third quartile, whiskers extend to 1.5 times the interquartile range, and dots indicate outliers.

Supplementary Figure S4.



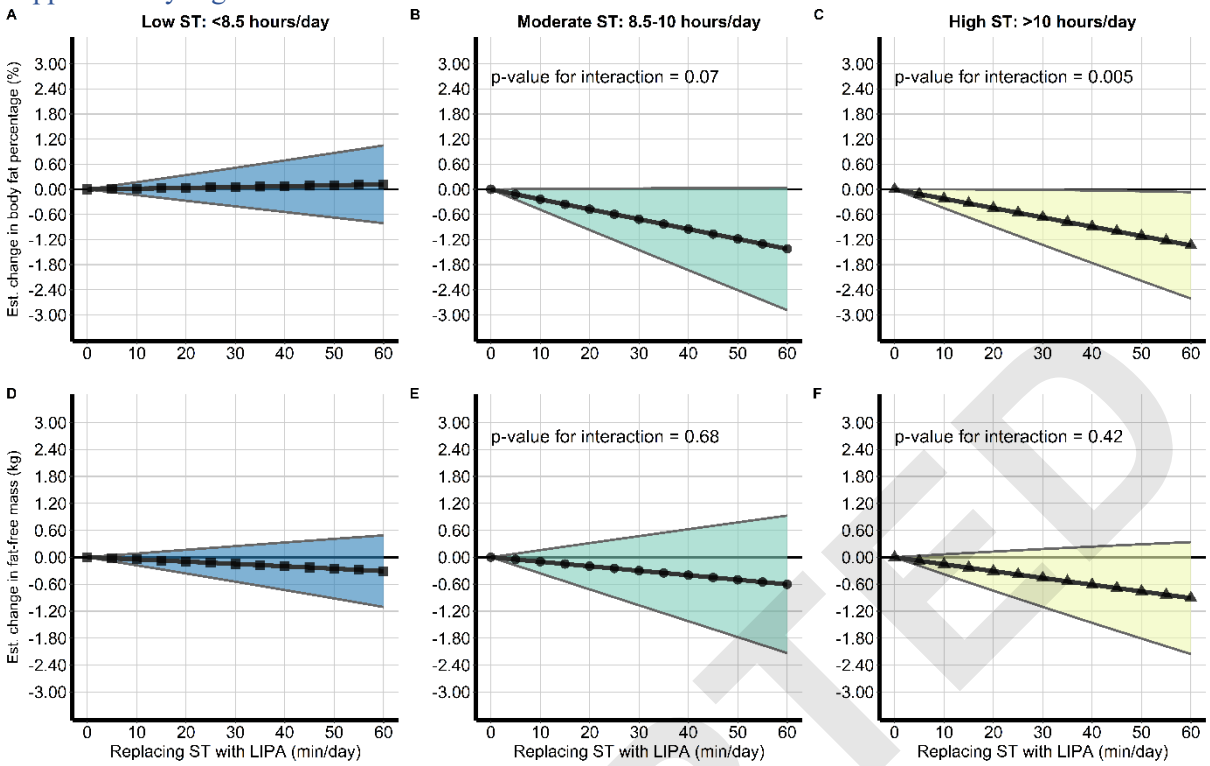
Supplementary Figure S4. Boxplots of **A**) total cholesterol, **B**) HDL cholesterol, **C**) LDL cholesterol, **D**) triglycerides, **E**) hs-cTnI, **F**) NT-proBNP, **G**) eGFR, **H**) systolic BP, **I**) diastolic BP, **J**) cfPWV, and **K**) stiffness index Beta per sedentary time subgroup. The box describes first quartile, median, and third quartile, whiskers extend to 1.5 times the interquartile range, and dots indicate outliers. BP: blood pressure, cfPWV: carotid-femoral pulse wave velocity, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, hs-cTnI: high-sensitivity cardiac troponin I, LDL: low-density lipoprotein, NT-proBNP: amino-terminal pro-B-type-natriuretic peptide.

Supplementary Figure S5.



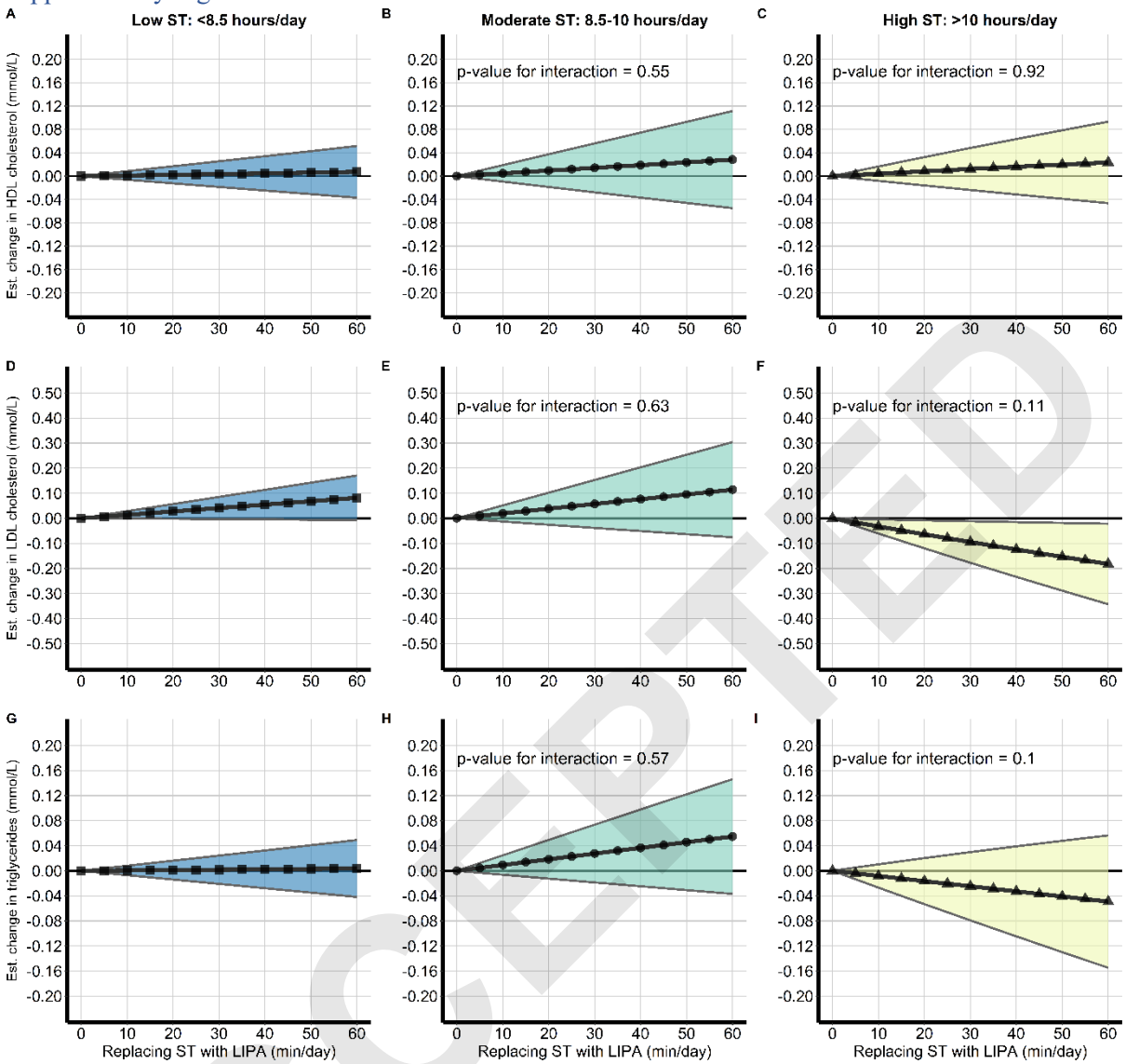
Supplementary Figure S5. Boxplots of **A**) glucose, **B**) insulin, and **C**) HOMA-IR per sedentary time subgroup. The box describes first quartile, median, and third quartile, whiskers extend to 1.5 times the interquartile range, and dots indicate outliers. HOMA-IR: homeostasis model assessment of insulin resistance.

Supplementary Figure S6.



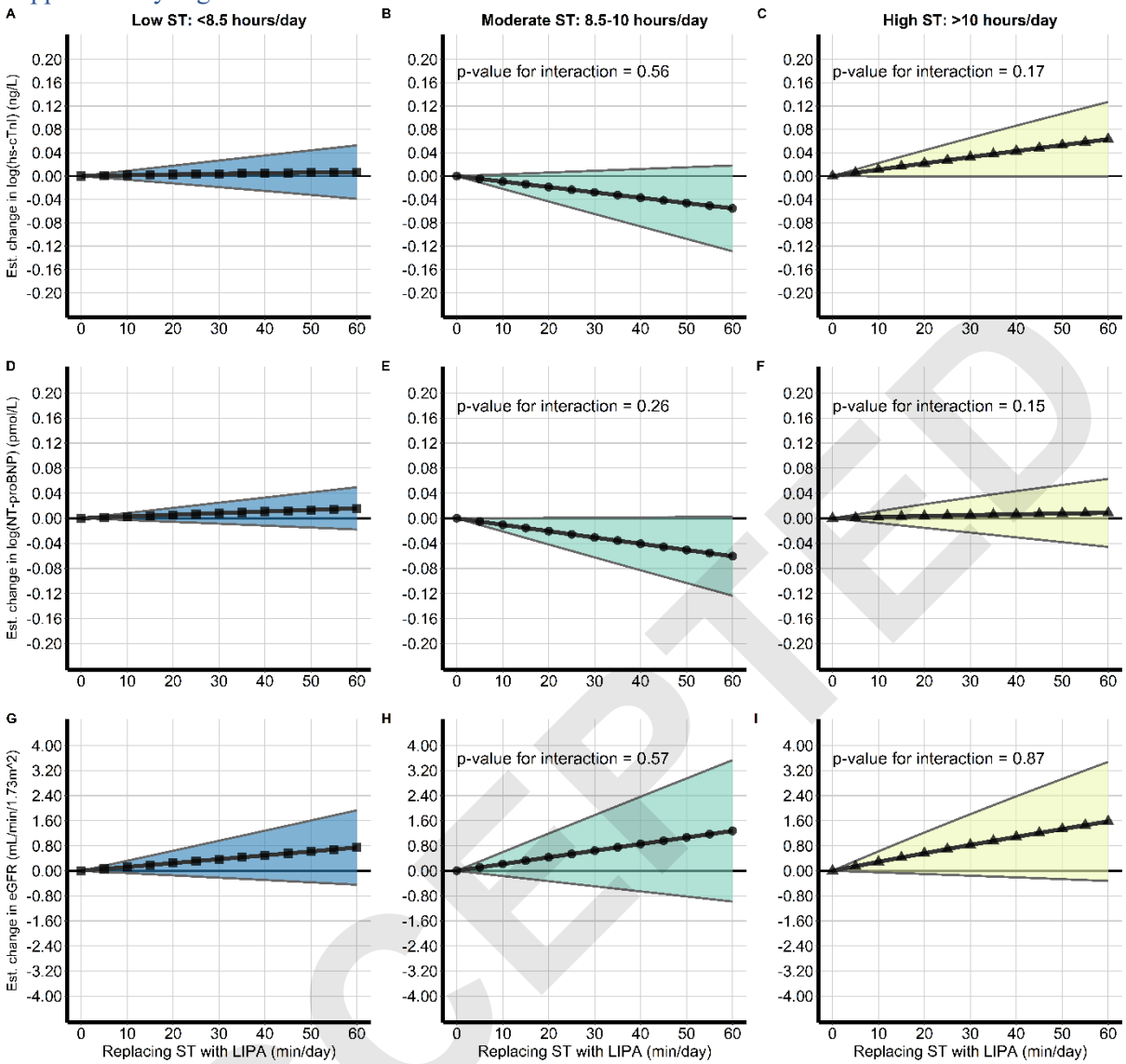
Supplementary Figure S6. Estimated changes in **A-C**) body fat percentage and **D-F**) fat-free mass induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). LIPA: light-intensity physical activity, ST: sedentary time.

Supplementary Figure S7.



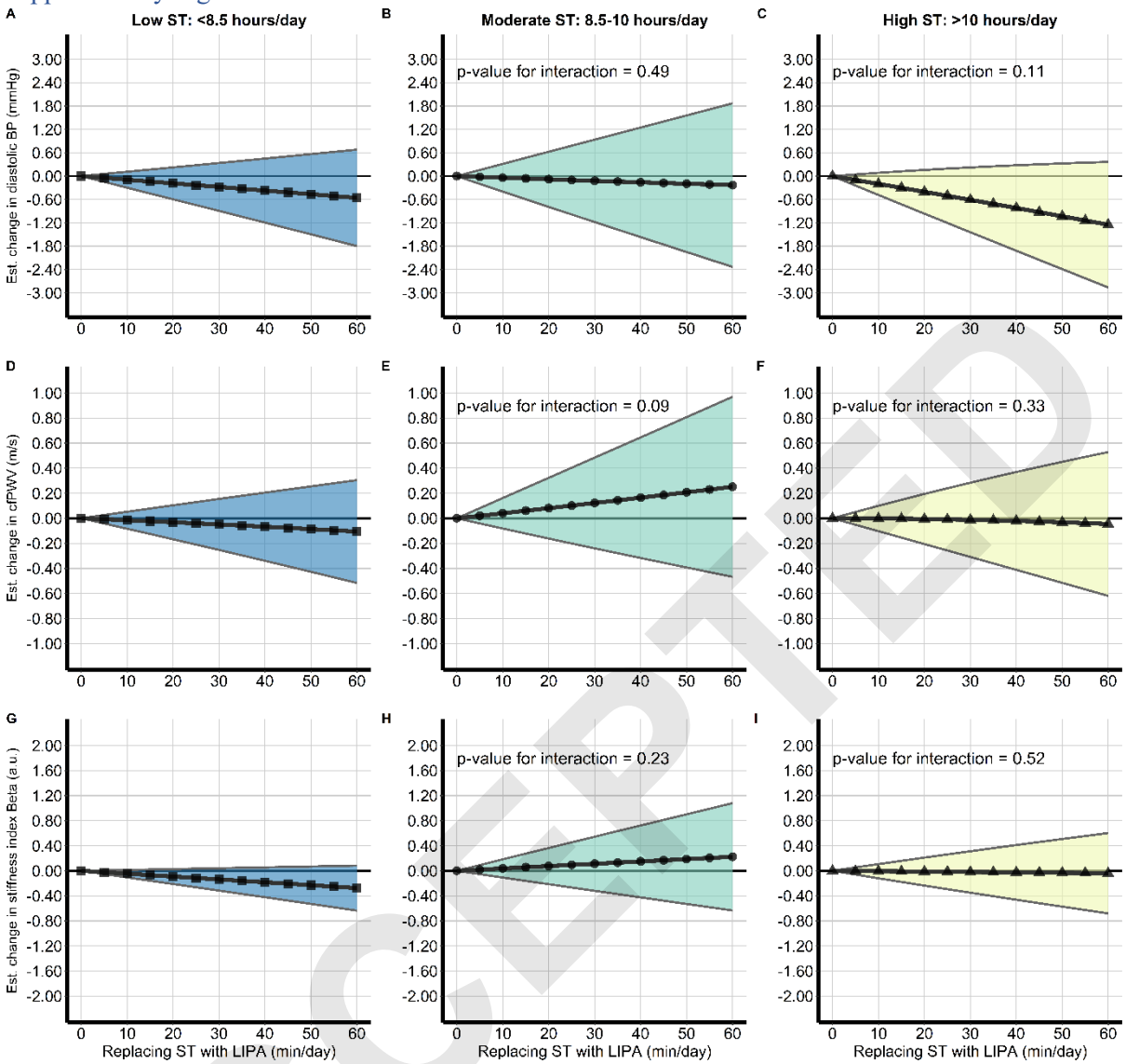
Supplementary Figure S7. Estimated changes in **A-C**) HDL cholesterol, **D-F**) LDL cholesterol, and **G-I**) triglycerides induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). HDL: high-density lipoprotein, LDL: low-density lipoprotein, LIPA: light-intensity physical activity, ST: sedentary time.

Supplementary Figure S8.



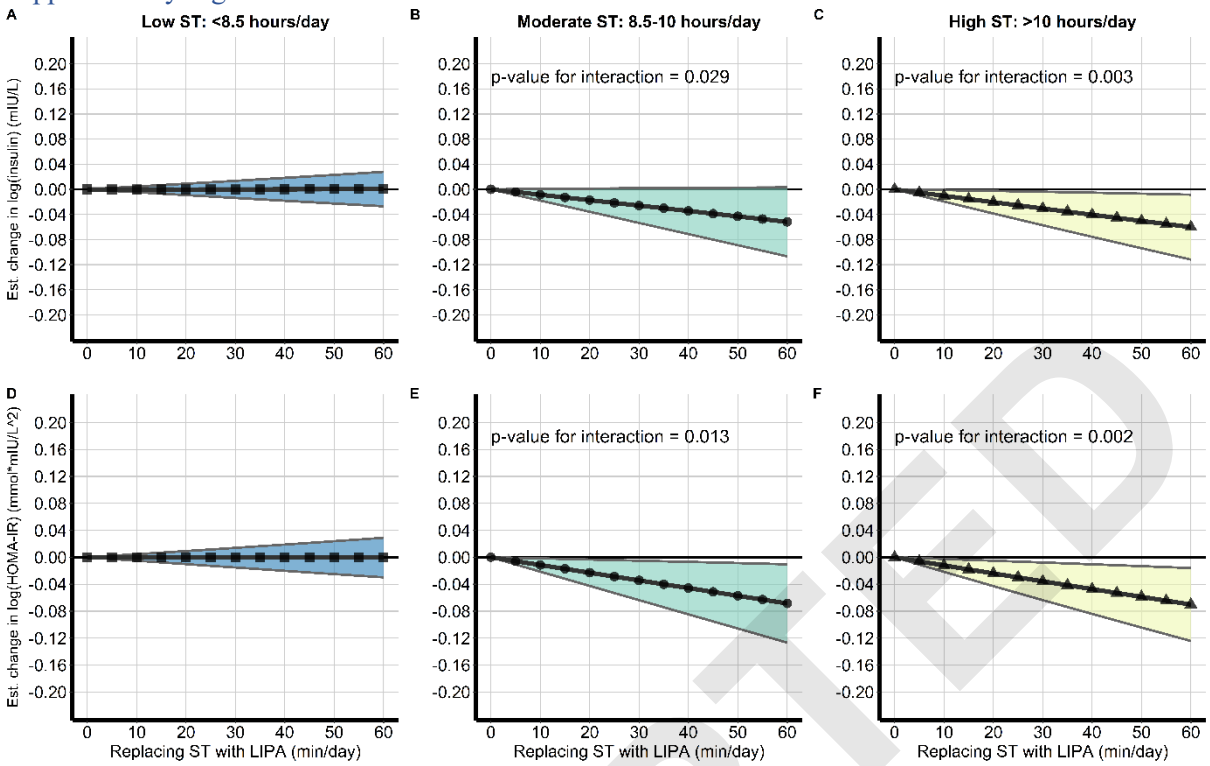
Supplementary Figure S8. Estimated changes in **A-C**) log(hs-cTnI), **D-F**) log(NT-proBNP), and **G-I**) eGFR induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). eGFR: estimated glomerular filtration rate, hs-cTnI: high-sensitivity cardiac troponin I, LIPA: light-intensity physical activity, NT-proBNP: amino-terminal pro-B-type-natriuretic peptide, ST: sedentary time.

Supplementary Figure S9.



Supplementary Figure S9. Estimated changes in **A-C**) diastolic BP, **D-F**) cfPWV, and **G-I**) stiffness index Beta induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). BP: blood pressure, cfPWV: carotid-femoral pulse wave velocity, LIPA: light-intensity physical activity, ST: sedentary time.

Supplementary Figure S10.



Supplementary Figure S10. Estimated changes in **A-C**) log(insulin) and **D-F**) log(HOMA-IR) induced by hypothetically reallocating sedentary time to time spent in light-intensity physical activity stratified by sedentary time subgroup. The thicker line with data points represents the estimates, and the thinner lines and fill indicate the 95% confidence interval. The *p*-values represent the interactions between the first isometric log ratio coordinate and the sedentary time subgroups (reference: low sedentary time). HOMA-IR: homeostasis model assessment of insulin resistance, LIPA: light-intensity physical activity, ST: sedentary time.

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