Sleep and cardiometabolic health in children and adults: examining sleep as a component of the 24-hour day

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What is already known on this subject?

Sleep is important for health and well-being. Studies that have examined the association between sleep duration and cardiometabolic health have largely neglected to account for the compositional nature of time-use. Since sleep duration forms part of the 24-hour day, together with sedentary time and physical activity, two other well-recognised predictors of cardiometabolic health, it has recently been suggested that these activity behaviours be examined as a composition of the 24-hour day, rather than separately. To date, few studies have applied compositional data analysis (CoDA) to examine the association between sleep, as a component of the 24-hour day, and cardiometabolic health in children and adults.

What this study adds

This is the first study to examine the association between 24-hour activity profile and cardiometabolic health in a large sample of children and adults, using device-measured activity behaviours and sleep characteristics. We identified an association between 24-hour use of time and all cardiometabolic health outcomes. Higher levels of sleep and moderate to vigorous physical activity (MVPA) were associated with favourable cardiometabolic health. Replacing sleep with sedentary time was associated with unfavorable cardiometabolic health. Replacing any activity behaviour, including sleep, with MVPA was associated with more favourable cardiometabolic health.

Highlights

- We apply compositional data analysis (CoDA), a novel statistical approach that has gained popularity for examining the association between 24-hour use of time and health outcomes.
- Activity behaviours are strongly associated with cardiometabolic health in both children and adults.
- Replacing sleep with sedentary time is associated with less favourable cardiometabolic health.
- Replacing sleep, sedentary time or light physical activity with moderate-vigorous physical activity is associated with more favourable cardiometabolic health.

Abstract:

Study objectives: Sleep, physical activity and sedentary time are all known to play a role in cardiometabolic health. Compositional data analysis (CoDA) enables us to examine associations between 24-hour use of time and health outcomes.

Methods: Data were collected in the Child Health CheckPoint study, a one-off national population-cohort study conducted between February 2015 and March 2016. Wrist-worn actigraphy monitors (GENEActiv Original, Cambs, UK) were used to measure activity behaviours (sleep, physical activity and sedentary time) and sleep characteristics (sleep variability, midsleep, efficiency). CoDA was applied to determine the association between 24-hour use of time and cardiometabolic risk markers (blood pressure; body mass index; apolipoprotein B/A1; glycoprotein acetyls; and composite metabolic syndrome score). Substitution modelling (one-for-remaining and one-for-one) examined the associations of reallocating sleep time with other activity behaviours

Results: Data were available for 1073 Australian children aged 11-12 years (50% male) and 1337 adults (13% male). Strong association was found between 24-hour use of time and all cardiometabolic health outcomes. Longer sleep was associated with more favourable cardiovascular health. Sleep characteristics other than duration (efficiency, timing, variability) were weakly and inconsistently associated with outcomes. Reallocating time from sleep to moderate-vigorous physical activity (MVPA) had favourable associations with cardiometabolic health, but reallocating from sleep to sedentary time was associated with less favourable cardiometabolic health.

Conclusion: The 24-hour activity composition is strongly associated with cardiometabolic health in children and adults. Days with more sleep and MVPA are associated with improved cardiometabolic health.

Disclosure Statement

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1. Introduction:

Sleep is increasingly recognised as important for cardiometabolic health and has been associated with adiposity, hypertension, hyperglycaemia, inflammation and dyslipidemia.[1-6] To date, most studies have examined the relationship between sleep duration and body mass index (BMI).[1,7] In children, short sleep duration has been consistently associated with increased BMI,[4] while some,[8,9] but not all[10-12] studies in adults suggest a U-shaped association, whereby both long and short sleep durations are associated with increased BMI. Relatively few studies have examined the role of sleep duration on cardiometabolic phenotypes, particularly in children. However, available studies tend to suggest short sleep duration is associated with higher blood pressures,[5,6] dyslipidemia[4,6] and metabolic risk[2] in both children and adults.

While lifestyle behaviours are widely recognised as important modifiable risk factors for the prevention and management of cardiometabolic health,[1] guidelines[13,14] have largely overlooked sleep, and focus on advocating regular physical activity, a healthy diet, smoking cessation and reduced alcohol intake for the prevention and management of hypertension, cardiovascular disease and obesity. Perry[15] argues that sleep needs to be considered "as critical to health as diet and physical activity" while Heffron[16] suggests that "sleep is one of the three pillars (diet, exercise and sleep) of a healthy lifestyle". In line with these suggestions, international guidelines are increasingly noting the importance of sleep.[17]

Time-use epidemiologists suggest time spent in activity behaviors (i.e. sleep, physical activity, sedentary behaviors) should be considered as an ensemble of the 24-hour day, rather than separately.[18] Activity behaviors are mutually exclusive and all-inclusive parts of the 24-hour day, and consequently if the time devoted to one behavior changes, there must be an equal and opposite

change in the other behaviors collectively.[19] Accordingly, contemporary time-use epidemiology frameworks suggest a shift from traditional methods of exploring the relationship between just one activity behavior (e.g. sleep) and a given health outcome, to exploring how activity patterns (called *activity compositions*) are associated with health outcomes. Considering time use in this way has become increasingly widespread, and 24-hour activity guidelines have been incorporated into recent guidelines from Canada[20], Australia[21], New Zealand[22], Finland[23] and Croatia[24]. This paradigm shift has implications for measurement (the need to capture the entire 24-hour day), conceptualising mechanisms linking exposures to outcomes (understanding the net effect of time-use changes on health), and intervention design (intervening to achieve the best possible reallocations of time from one domain to another).

Activity behaviours are perfectly multicollinear (always summing to 24 hours) and so standard statistical regression techniques cannot be used.[18] Compositional Data Analysis (CoDA) has gained popularity as a feasible method for the statistical analysis of 24-hour time use.[7,18] CoDA overcomes the problem of multicollinearity by expressing activity behaviors as a set of ratios that can then be used as variables in traditional statistical models to examine relative compensatory change.[18] CoDA allows us to model the effects of reallocating time from one activity behavior to others, for example increasing sleep by one hour and reducing sedentary behavior by the same amount.[18] Rather than exploring the health associations of changing to just one activity, CoDA allows us to explore the associations of reallocating time between activities. This reflects the real-world situation, because the 24-hour daily window means that as one activity increases, other activities must decrease to compensate. That is, time must be reallocated between activities.

To date, few studies have examined the association between sleep duration and cardiometabolic health in this way. Chastin and colleagues[19] first examined the association between 24-hour activity behaviours and cardiometabolic health markers (BMI, waist circumference, triglycerides, plasma glucose, plasma insulin, systolic and diastolic blood pressure, HDL and LDL). In 1,937 adults they found the strongest associations were when sedentary time was ~~exchanged for~~ reallocated to moderate-vigorous physical activity (MVPA). Similar findings were reported in a non-CoDA isotemporal substitution study by Buman and colleagues[25] who examined the association between cardiometabolic risks and the reallocation of time spent sleeping in a sample of 2,185 adults. In 434 10-13 year-olds, Talarico and Jannsen[26] found that 24-hour activity composition was associated with obesity for reallocations of time to and from MVPA and light physical activity (LPA), but not for other reallocations. In another study on children, Carson and colleagues[27], examined the association between the 24-hour activity composition (consisting of subjectively measured sleep duration and objectively-measured physical activity and sedentary time) and a range of cardiometabolic health markers (i.e. body mass index, waist circumference, blood pressure, aerobic fitness, lipid levels). In this study of 4169 Canadian children aged 6-17 years, ~~found replacing~~ reallocating time from MVPA or sleep to any other movement behaviour had a negative association with health, although replacing MVPA had the largest associations.

The aim of this study was to further build on our understanding of sleep, as a component of time, and cardiometabolic health in both children and adults. Specifically, we aimed to:

1. Determine the association between device-measured sleep, as a component of the 24-hour time-use composition, and cardiometabolic health in children and adults

2. Determine the association between device-measured sleep characteristics (timing, quality and variability) and cardiometabolic health, when sleep is considered a component of the 24-hour time use composition.

3. Examine the associations of reallocating time in sleep to and from MVPA, sedentary time and LPA.

2. Methods:

2.1 Participant/design: Data examined in this study were collected between February 2015 and March 2016 as part of the Child Health CheckPoint (CheckPoint) study. The CheckPoint study was a one-off, comprehensive physical health and biomarker cross-sectional study nested between waves 6 and 7 of the Longitudinal Study of Australian Children (LSAC). Data were collected on 1874 child-parent dyads. LSAC commenced in 2004 with the recruitment of two cohorts (B and K – the latter not relevant to this paper), which have since been followed biennially [28]. Further details of LSAC study design and recruitment are outlined elsewhere.[29,30]

The CheckPoint Study is a national population-cohort study and has been described in detail elsewhere[31,32]. Briefly, during the Wave 6 LSAC home visit, B-cohort families were introduced to the upcoming Child Health CheckPoint and asked to consent to their contact details being shared with the CheckPoint team. Of the families agreeing to receive information about the CheckPoint study, 1874 families took part (53% of eligible participants, 42% of Wave 6 cohort and 37% of original cohort). Each participating child, with one parent or caregiver (usually the biological mother), were invited to attend a 3.5 hour visit at one of the main assessment centre (MAC), most of which were Australian capital cities (Perth, Adelaide, Melbourne, Canberra, Sydney and Brisbane).

If participants were unable to attend a MAC, the option to attend a 2.75 hour visit at a mini-assessment centre (mAC) in eight smaller regional centres (Darwin, Cairns, Townsville, Mackay, Bundaberg, Hobart, Launceston and Bunbury) was provides.[33] Those families (n=378) who could not arrange a visit, were offered a 1.5 hour home visit. Trained research assistants were involved in undertaking a wide range of measures ~~relevant to non-communicable diseases~~ (including anthropometric measures, blood pressure readings and blood samples used to derive the cardiometabolic markers in the current study) and fitted participants with a GENEActiv monitor (which were advised to be worn continuously for a week following application) at the MAC, mAC and home visits.

2.2 Ethics and Consent: The CheckPoint study protocol was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and the Australian Institute of Family Studies Ethics Committee (14-26). The attending parent/caregiver provided written informed consent for themselves and their child to participate in the study.

2.3 Measures:

Activity behaviours

Activity behaviours were quantified using tri-axial GENEActiv accelerometers (Activinsights, Cambs, UK) worn on participants' non-dominant wrist for eight days. The GENEActiv monitor has been used in previous studies to examine sleep of adults[34] and children[35,36], and also physical activity[37] and sedentary time[38]. The GENEActiv monitor has been shown valid and reliable in measuring sleep[34], physical activity [39,40] and sedentary time [41,42].

Participants were asked to complete a self-report record (Activity Monitor Card) marking their bedtimes and wake-times, as well as any times that they removed the accelerometer and the reasons for removal. Activity monitor cards were then used to identify children's bed and wake times, as well as device removals (non-wear). Given that self-reported bedtimes may not accurately reflect sleep onset, children's sleep times were corrected by visual inspection of the activity trace. Visual inspection was also undertaken in cases where sleep times were not reported. Reasons for non-wear were also examined. In case the reason for removal was "sport", and the corresponding non-wear period was four hours or less, the removal period was replaced with MVPA

The van Hees[34] sleep algorithm was used to detect sleep and wake between self-reported bedtime and wake times, and collapsed into 1-min epochs. Each minute was classified as sleep or wake if it contained a majority of sleep or wake 5-s epochs, respectively. Minutes containing equal numbers of sleep and wake 5-s epochs were classified as sleep. Sleep onset was defined as the start of the first three consecutive minutes scored as sleep. Sleep offset was defined as the end of the last five consecutive minutes scored as sleep. Sedentary time and time spent in moderate-to-vigorous levels of physical activity (MVPA), used cut-points defined by Phillips et al.[40] for children and Esliger et al. [39] for adults. Further details of data processing have been reported elsewhere.[43-45]

Participants were included for analysis if they had at least four nights of sleep data recorded, an average sleep time >200 min and at least one non-school night (Fri-Sat) of sleep data. Sleep data for the first night were excluded, as recordings started at 2300.

Sleep characteristics examined in this study included sleep period (the difference between sleep onset and offset), sleep timing (the midpoint between sleep onset and offset), day-to-day sleep variability

(the coefficient of variation of sleep period) and sleep efficiency (the percent of minutes scored as sleep between onset and offset).

Cardiometabolic health

Cardiometabolic health was considered in terms of anthropometric measures, blood pressure, plasma lipids and inflammatory markers, and a composite metabolic syndrome score (MetSS), as defined by Eisenmann[46].

Plasma biomarkers were derived from semi-fasted venous blood samples taken from consenting children and adults. In some cases, participants declined to provide venous samples but provided capillary blood samples instead. Trained researchers or phlebotomists collected venous blood samples within assessment centres. Samples were processed within 2 h on-site and stored at −80°C prior to shipping in dry ice as a single batch to the Melbourne Children's Bioresource Center (Murdoch Children's Research Institute). Further detail of blood collection, storage, and processing has been reported elsewhere.[32,47] Further detail as to how different biomarkers were derived have been reported elsewhere.[31]

Anthropometric measures

Waist circumference was measured with anthropometric measuring tape (Lufkin Executive Diameter W606PM, Maryland) and assessed as the narrowest point between the 10th rib and iliac crest, or midpoint between in the absence of visible narrowing. Two measures were taken, or a third (if the first two values differed by ≥1 cm), and the average was calculated. Height was assessed using a portable rigid stadiometer (Invicta IP0955, Leicester, UK). Two measures were taken, or a third (if the first two values differed by ≥0.5 cm), and the average was calculated. Weight was recorded via

the InBody 230 Bioelectrical Impedance Analyser scales.[48] BMI (kg/m^2) was determined and BMI z-score calculated for children using the US Centers for Disease Control CDC reference dataset[32].

Blood pressure

Blood pressure readings were taken using the SphygmoCor[49] automated blood pressure monitoring device after participants were seated for a minimum of three minutes of quiet rest. Three blood pressure measures were considered: systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP). Mean arterial pressure was determined using the following calculation: MAP = [SBP+(2*DBP)]/3 and was used to calculate a metabolic syndrome score.

Blood lipids

We measured plasma Apolipoprotein B/A1 (ApoB/A1). Apolipoproteins are structural and functional proteins of lipoprotein particles (e.g. LDL, HDL, vLDL) that have an important role in lipid metabolism.[50-52] ApoB/A1 reflects the ratio of apolipoprotein B (the largest structural component of LDL and responsible for circulating cholesterol transport) and, apolipoprotein A (the largest structural component of HDL and responsible for reverse cholesterol transport) and has been suggested to more accurately reflect cholesterol balance and potential athrogenic and anti-athrogenic particles.[50,52-55] Higher ApoB/A1 values are suggestive of worse cardiovascular health.

Inflammation

We measured glycoprotein acetyls (GlycA). GlycA a novel composite nuclear magnetic resonance (NMR) inflammatory biomarker, which is suggested to better reflect chronic inflammation than acute phase reactants such as high sensitivity C-reactive protein (hsCRP), especially in children.[31,56 57] Higher GlycA levels are a strong predictor of future cardiovascular events,[58,59] incident type 2

diabetes mellitus,[60] and overall mortality,[59] beyond traditional measures of inflammation, such as hsCRP.[61]

Metabolic syndrome severity score

A metabolic syndrome severity score (MetSS) was calculated to reflect metabolic syndrome severity. In line with Eisenmann's recommendations,[46] we used the sum of the z-scores of MAP, triglycerides, glucose, waist circumference, and HDL. Since HDL is inversely related to metabolic risk, it was subtracted. A higher score indicates a less favorable cardiometabolic profile.

Covariates

Analyses were adjusted for a-priori identified potential confounders of socioeconomic position (SEP), sex, parental age (for adult analyses) and pubertal stage (for children's analyses), sleep characteristics and season of data collection. We used pubertal stage rather than age in child analyses because we expected variation in sexual maturity to be the main driver of any potential confounding, given that the children were of similar age (mean 12 years, SD 0.4 years). SEP was operationalised using a composite measure consisting of self-reported parental income, education and occupation, which was derived from Wave 6 of the LSAC dataset.[62,63] Using this scale, higher scores represent higher socio-economic position. Puberty was self-assessed using the Puberty Development Scale, a validated questionnaire that requires participants to answer five questions, using a four-point scale, with higher overall score representing advanced pubertal development.[64,65] Sleep characteristics included as covariates were sleep timing, variability and sleep efficiency, as defined above.

2.4 Statistical Analysis:

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Compositional data analyses (CoDA) were performed in R (http://cran.r-project.org) using "compositions" and "zCompositions" packages. Separate analyses were performed for children and adults. The 24-hour day composition was considered in terms of sleep, sedentary time, light physical activity (LPA) and MVPA. Measures of sleep duration, sedentary time, MVPA and LPA were averaged using a 5:2 weighting for a weeknight (Sunday–Thursday) and weekend (Friday–Saturday). The geometric mean of each activity behavior was linearly adjusted so that all parts summed to a total of 1440 (minutes in a 24-hour period). Following the procedure in Chastin et al[19], the composition was expressed as four sets of three isometric log ratios (ilr) co-ordinates. The first ilr of each set of ilr coordinates represented one activity behavior, relative to the remaining behaviours.

Four multiple linear regression models (one for each set of ilrs) were used to determine the association between 24-hour activity behavior and markers of cardiometabolic health for both children (z-score of BMI, GlycA, ApoB/A1, SBP, DBP, MetSS) and adults (BMI, GlycA, ApoB/A1, SBP, DBP, MetSS). Analyses were adjusted for sociodemographic covariates (sex, parent age, child's puberty stage, SEP), season of data collection and sleep characteristics (timing, variability and efficiency). The regression beta for the first ilr coordinate of each model was examined for associations between outcomes and increasing one activity, relative to remaining activities. The regression beta estimates for the sleep characteristics were examined to determine associations with each sleep characteristic. The multiple linear regression models were checked for linearity and normality. Since many comparisons were undertaken, Holm Sequential Bonferroni correction was performed to address the risk of capitalisation on chance.

Isotemporal substitution modelling was performed to examine the associations of reallocating time in sleep for MVPA, sedentary time and LPA. Time reallocations were examined in two ways: *one-for-*

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remaining and *one-for-one*. The one-for-remaining simulations reallocated time to one domain by drawing on each of the other domains according to the size of those domains. One-for-one substitutions modeled the associations of direct swaps of time between two domains. One-for-one reallocations and their 95% CIs were plotted using the R package "deltacomp"[66] (see Supplementary files).

3. Results:

Of the 1,874 parent-child CheckPoint participants, 1,073 children and 1,378 adults had complete 24-hour activity behaviour data and were examined in this study (Figure 1). Table 1 presents descriptive data for participants included for analysis. Differences in participants included and excluded for analysis (from the Checkpoint study) have been reported elsewhere[45]. In general, children included for analysis were younger, had less advanced pubertal status, were of higher SEP and lower BMI compared to CheckPoint participants excluded from analysis due to incomplete activity data. Similar differences were observed for adults, except, those included for analysis were older than those excluded.

Table 1: Sample characteristics

Characteristics *(arithmetic mean, unless stated otherwise)*	Children	Parents
	n=1073	n=1378
Demographic		
Age in years, mean (SD)	12.0 (0.4)	44.0 (5.1)
Sex (% males)	50	13
SEP, mean (SD)	0.23 (1.02)	0.21 (0.99)
Not born in Australia (%)	0.8	19.7
Language other than English at home (%)	7.6	9.3
Parent is of Indigenous background (%)	0.8	0.8
Puberty stage (%)		
Prepubertal	9.9	
Early puberty	26.1	
Mid-puberty	51.4	
Late Puberty	12.3	
Post Puberty	0.3	
Sleep characteristics		
Duration (min)	544 (43)	498 (56)
Midsleep (min*)	155 (48)	172(53)
Efficiency (%)	86 (4.7)	86 (6.8)
Variability (%)	10.4 (5.3)	10.3 (7.7)
Cardiometabolic Health		
BMI (kg/m^2)	19 (3.1)	27 (5.9)
MetSS	0.09 (2.8)	-0.001 (3.3)
SBP (mmHg)	108 (8)	119(12.5)
DBP (mmHg)	62(6)	73 (8.4)
GlycA (mmol/L)	0.98 (0.13)	1.03 (0.17)
ApoB/A1 (g/L)	0.47 (0.1)	0.52 (0.14)
Activity behaviours (compositional mean)		
Sleep duration	571	508
MVPA	23	113
LPA	159	267
Sedentary time	688	553

*minutes from mid-night

SEP=Socioeconomic position; BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; ApoB/A1= apolipoprotein B/A1; LPA= Light physical activity; MVPA= Moderate-vigorous physical activity

CoDA results for children and adults are presented in Tables 2 and 3, respectively, using three models: (1) unadjusted; (2) adjusted for demographic variables; and (3) additionally adjusted for sleep characteristics of efficiency, timing and variability. The overall 24-hour activity profile was strongly associated with all cardiometabolic health outcomes in all models for both children and adults, except for the adjusted models for SBP in children. Additional adjustment for sleep characteristics (Model 2 vs Model 3) made no difference to the association between composition and outcomes in any analysis. Longer sleep duration was strongly associated with lower BMI and lower MetSS in all models in children and with lower SBP in adults. Longer sleep duration was also positively associated with GlyCA in the unadjusted model in adults. Among other movement behaviours, higher MVPA was significantly associated with lower cardiometabolic risk for all cardiometabolic health indicators except for SBP in adults. Greater sedentary time was consistently associated with higher child BMI, DBP, MetSS and ApoB/A1 and higher adult BMI, SBP, and MetSS. Higher LPA was associated with *higher* BMI in children.

Table 4 presents the regression beta estimates for each of the sleep characteristics. As shown, the only statistically significant association for children was between sleep timing and DBP. In contrast, sleep efficiency was significantly associated with higher adult BMI, GlycA and MetSS. Delayed sleep timing and higher sleep variability were significantly associated with higher adult SBP and ApoB/A1, respectively.

Sleep reallocation methods represent different ways people may choose to reallocate their time to and from sleep. Figures 2 and 3 illustrate the differences in outcomes associated with reallocating time from one movement behaviour to sleep (one-for-one reallocation) and reallocating time from all remaining behaviours collectively to sleep (one-for-remaining reallocations) in children and adults,

respectively. In general, reallocations to sleep from remaining behaviours, sedentary behaviour or LPA were associated with improved outcomes (downward-sloping lines) or no change (flat lines), whereas reallocating time to sleep from MVPA was associated with poorer outcomes (upward-sloping lines). The associations for one-for-remaining sleep reallocations were generally smaller than one-for-one reallocations, since some of the reallocated time was drawn from MVPA.

Associations varied according to whether activity behaviours were examined in terms of *one-for-remaining* (Supplement 1) or *one-for-one* (Supplement 2) time reallocation methods. In general, decreasing sedentary time, increasing LPA and increasing MVPA (at the expense of all other behaviours) were associated with improvements for all outcomes in both children and adults (Supplement 1). As shown in Supplement 2, any reallocation to MVPA was associated with improved outcomes, while any reallocation to sedentary time was associated with poorer outcomes. Reallocating MVPA to LPA was associated with poorer outcomes, whereas reallocating sleep or sedentary time to LPA was associated with no change or minor improvements.

Table 2: CoDA analysis examining the association between 24-hour activity behaviours in children and cardiometabolic health outcome measures (z-scores)

		Sleep duration		Sedentary time		LPA		MVPA		Overall composition		
		β[a]	P-value	β[a]	P-value	β[a]	P-value	β[a]	P-value	SumSq	F	P-value
BMI n=959	Model 1	-0.93	**<0.001**	0.77	**<0.001**	0.30	0.02	-0.14	**<0.001**	27	9	**<0.001**
	Model 2	-0.87	**<0.001**	0.64	0.01	0.34	0.01	-0.12	**<0.001**	18	7	**<0.001**
	Model 3	-0.93	**<0.001**	0.69	0.01	0.36	0.01	-0.12	**<0.001**	18	7	**<0.001**
SBP n=908	Model 1	-0.17	0.56	0.32	0.22	-0.04	0.75	-0.10	0.01	12	4	0.01
	Model 2	-0.10	0.74	0.20	0.42	-0.05	0.70	-0.05	0.19	4	1	0.23
	Model 3	-0.18	0.58	0.29	0.28	-0.06	0.67	-0.06	0.17	5	2	0.14
DBP n=908	Model 1	-0.25	0.41	0.46	0.07	-0.06	0.65	-0.16	**<0.001**	29	10	**<0.001**
	Model 2	-0.29	0.33	0.53	0.04	-0.10	0.46	-0.14	**<0.001**	26	9	**<0.001**
	Model 3	-0.26	0.42	0.55	0.04	-0.15	0.28	-0.15	**<0.001**	29	10	**<0.001**
MetSS n=605	Model 1	-1.26	**<0.001**	1.18	**<0.001**	0.31	0.06	-0.23	**<0.001**	41	15	**<0.001**
	Model 2	-1.18	**<0.001**	1.10	**<0.001**	0.28	0.08	-0.20	**<0.001**	29	11	**<0.001**
	Model 3	-1.22	**<0.001**	1.12	**<0.001**	0.30	0.08	-0.20	**<0.001**	28	10	**<0.001**
GlycA n=644	Model 1	-0.22	0.54	0.26	0.41	0.11	0.5	-0.15	**<0.001**	12	4	0.01
	Model 2	-0.42	0.25	0.47	0.13	0.09	0.59	-0.14	0.01	13	4	0.01
	Model 3	-0.46	0.24	0.47	0.16	0.13	0.45	-0.14	0.01	11	4	0.01
ApoB/A1 n=644	Model 1	-0.50	0.16	0.66	0.03	0.06	0.73	-0.22	**<0.001**	34	12	**<0.001**
	Model 2	-0.53	0.14	0.69	0.03	0.01	0.96	-0.17	**<0.001**	22	8	**<0.001**
	Model 3	-0.42	0.28	0.58	0.08	0	0.99	-0.17	**<0.001**	19	7	**<0.001**

Model 1: Unadjusted, Model 2: adjusted for demographic characteristics (puberty stage, sex, SEP, season); Model 3: adjusted for demographic characteristics (Model 2) and sleep characteristics (sleep midpoint, variability and efficiency) [a]The beta estimated is for the first ilr coordinate representing the activity in the header, relative to remaining activities

BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; APOB/A1= apolipoprotein B/A1; LPA= Light physical activity; MVPA= Moderate-vigorous physical activity
SumSq= Total sum of squares from ANOVA test for set of ilrs
Bolded text: P-values that remained significant following Holm Sequential Bonferroni adjustment have been bolded.

Table 3: CoDA analysis examining the association between 24-hour activity behaviours in adults and cardiometabolic health outcome measures (z-scores)

		Sleep duration		Sedentary time		LPA		MVPA		Overall composition		
		β^a	P-value	β^a	P-value	β^a	P-value	β^a	P-value	SumSq	F	P-value
BMI	Model 1	-0.07	0.69	0.54	**<0.001**	-0.03	0.79	-0.43	**<0.001**	86	31	**<0.001**
n=1324	Model 2	-0.21	0.23	0.69	**<0.001**	-0.07	0.56	-0.40	**<0.001**	96	37	**<0.001**
	Model 3	-0.26	0.15	0.73	**<0.001**	-0.08	0.54	-0.40	**<0.001**	95	37	**<0.001**
SBP	Model 1	-0.48	0.01	0.54	**<0.001**	<0.001	0.99	-0.06	0.4	19	7	**<0.001**
n=1241	Model 2	-0.44	0.02	0.43	**<0.001**	0.10	0.44	-0.09	0.2	14	5	**<0.001**
	Model 3	-0.42	0.03	0.42	**<0.001**	0.09	0.47	-0.10	0.16	13	5	**<0.001**
DBP	Model 1	-0.10	0.61	0.32	0.02	-0.10	0.48	-0.13	0.1	15	5	**<0.001**
n=1241	Model 2	-0.07	0.71	0.21	0.14	0.01	0.94	-0.15	0.04	10	4	0.01
	Model 3	-0.05	0.78	0.21	0.14	0	0.99	-0.16	0.03	11	4	0.01
MetSS	Model 1	-0.23	0.31	0.68	**<0.001**	-0.10	0.53	-0.35	**<0.001**	55	19	**<0.001**
n=911	Model 2	-0.11	0.63	0.53	**<0.001**	-0.02	0.87	-0.4	**<0.001**	49	21	**<0.001**
	Model 3	-0.14	0.52	0.54	**<0.001**	-0.03	0.85	-0.37	**<0.001**	45	19	**<0.001**
GlycA	Model 1	0.49	0.03	-0.03	0.85	-0.12	0.44	-0.34	**<0.001**	27	9	**<0.001**
n=992	Model 2	0.42	0.06	0.01	0.95	-0.07	0.64	-0.36	**<0.001**	28	10	**<0.001**
	Model 3	0.32	0.15	0.08	0.64	-0.08	0.59	-0.32	**<0.001**	24	9	**<0.001**
ApoB/A1	Model 1	-0.05	0.83	0.44	0.01	-0.15	0.33	-0.25	**<0.001**	31	11	**<0.001**
n=992	Model 2	0.08	0.69	0.29	0.07	-0.06	0.69	-0.32	**<0.001**	30	12	**<0.001**
	Model 3	0.06	0.77	0.28	0.09	-0.05	0.74	-0.29	**<0.001**	25	10	**<0.001**

Model 1: Unadjusted, Model 2: adjusted for demographic characteristics (puberty stage, sex, SEP, season); Model 3: adjusted for demographic characteristics (Model 2) and sleep characteristics (sleep midpoint, variability and efficiency) [a]The beta estimated is for the first ilr coordinate representing the activity in the header, relative to remaining activities

BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; APOB/A1= apolipoprotein B/A1; LPA= Light physical activity; MVPA= Moderate-vigorous physical activity
SumSq= Total sum of squares from ANOVA test for set of ilrs

Bolded text: P-values that remained significant following Holm Sequential Bonferroni adjustment have been bolded.

Table 4: Regression beta estimates (effect sizes) for each of the sleep characteristics

Outcome[*]	Sleep characteristic	Children			Adults		
		β	Std. Error	P-value	β	Std Error	P-value
BMI	Variability	-0.217	0.607	0.72	0.007	0.004	0.10
	Timing	0	0.001	0.97	-0.001	0.001	0.28
	Efficiency	-0.018	0.033	0.58	-0.01	0.004	**0.01**
SBP	Variability	0.029	0.63	0.96	0.01	0.005	**0.03**
	Timing	-0.001	0.001	0.20	-0.001	0.001	0.15
	Efficiency	-0.02	0.034	0.56	-0.002	0.004	0.61
DBP	Variability	0.018	0.637	0.98	0.009	0.005	0.06
	Timing	-0.002	0.001	**0.04**	-0.001	0.001	0.09
	Efficiency	0.026	0.035	0.455	-0.002	0.004	0.62
MetSS	Variability	-0.181	0.742	0.81	0.009	0.005	0.09
	Timing	0	0.001	0.92	0.001	0.001	0.23
	Efficiency	-0.011	0.041	0.80	-0.01	0.005	**0.03**
GlycA	Variability	-0.066	0.758	0.93	0.001	0.005	0.92
	Timing	0.002	0.001	0.10	0.001	0.001	0.19
	Efficiency	-0.031	0.042	0.45	-0.015	0.005	**0.002**
ApoB/A1	Variability	-0.158	0.748	0.83	0.001	0.005	0.82
	Timing	0.001	0.001	0.38	0.002	0.001	**0.01**
	Efficiency	0.031	0.041	0.46	-0.006	0.005	0.22

BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; ApoB/A1= apolipoprotein B/A1

[*]All outcomes were expressed as z-scores

Bolded text: Significant P-values (<0.05)

4. Discussion:

To our knowledge, this is the first study to determine the association between 24-hour time-use composition and cardiometabolic health in both children and adults using CoDA. This is also the first study to explore cardiometabolic associations with actigraphy-derived measures of sleep characteristics (timing, quality and variability) together with *all* activity behaviours (sleep, physical activity and sedentary time).

4.1 Main findings

In this study, 24-hour activity composition was strongly associated with cardiometabolic health outcomes in both children and adults, with short sleep duration strongly associated with higher BMI and MetSS in children and higher SBP in adults. Other characteristics of sleep (efficiency, timing and variability) were weakly and inconsistently associated with outcomes in the most adjusted model. Reallocating time to sleep from sedentary behaviour, LPA or remaining activities generally had weak, but favourable associations with cardiometabolic health, particularly in children.

Consistent with previous studies[18,19,27,67,68], we found replacing sleep with MVPA had the largest associations with cardiometabolic health in both children and adults. While MVPA is a well-known, important predictor of health, one possible reason for these large associations may be that MVPA accounts for such a small proportion of the 24-hour day that just a 20-30 min change results in a larger percent change, compared to other activity behaviours. In this sample, MVPA was higher in adults than children, possibly explaining why adults had smaller effect sizes than children.

Sedentary time was significantly associated with BMI and MetSS in children and BMI, MetSS and SBP in adults. While LPA was not significantly associated with any cardiometabolic health outcome measures, the direction of the association suggested LPA to be generally, but weakly, favourable for cardiometabolic health. While previous studies have identified both sedentary time[69-71] and LPA[72] as "significant independent predictors" of cardiometabolic health outcome markers, analytical approaches have largely neglected to account for the compositional nature of time-use[73]. Consistent with available compositional studies[19], we found that activity compositions with higher amounts of MVPA and sleep were the most favourable.

4.2 Strengths and limitations

To our knowledge, this is the first study to apply compositional data analysis to examine the association between objectively-measured sleep duration, as well as other characteristics of sleep (timing, variability, efficiency), and cardiometabolic health in both children and adults. Strengths of this study include objectively-measured sleep, physical activity and sedentary time, a wide range of standard and novel cardiometabolic health biomarkers collected using standardized protocols, and a large sample of children and adults from a population-derived cohort study.

Despite these strengths, there are methodological issues that also need to be considered. Firstly, although the GENEActiv monitor is valid for measuring sleep when compared to polysomnography in adults,[34] there are no studies that have validated the monitor against polysomnography in children. The van Hees algorithm is based solely on the device's orientation (not the acceleration magnitude). Therefore, it detects changes in position during sleep,

regardless of the age group. Thus, even if children move more or less than adults during sleep, the algorithm detects orientation changes in the same manner for all age groups. This suggests that the algorithm is likely transferrable to children, despite not yet being tested in children. It must also be noted that we applied the Sadeh algorithm to score sleep onset and offset, for both adults and children. While the Sadeh algorithm[74] is generally applied to children's data and the Cole-Kripke algorithm[75] to adult data, Quante and colleagues[11] recently compared the two algorithms (albeit with a different actigraphy monitor) against polysomnography in both adults and children concurrently and found reasonably similar sensitivity, specificity, and accuracy of epoch-by-epoch comparisons with PSG. Given that our sleep estimates are consistent with previous studies,[76,77] it suggests that the algorithm used yields sensible results. Secondly, the narrow age range for children (11-12 years) precludes generalisation to other childhood ages, and 87% of parents were mothers. Thirdly, this study is cross-sectional and hence we are unable to infer causality. Fourthly, this study only examined children and adults in the CheckPoint study who had complete 24-hour activity profile data available and who agreed to have blood samples take, blood pressure assessed and/or body mass index calculated. Lastly, we did not examine parent-child concordance, and future studies are needed to explore the influence of shared, family-based factors.

4.2 Meaning and implications for clinicians and policy makers and areas in need of future research:

The association between sleep duration and cardiometabolic outcomes were markedly stronger in children than in adults. A reallocation of 20 minutes from MVPA to sleep, for example, was associated with an average effect size across the six outcomes of +0.05 in adults; in children the

average effect size was +0.18. Reallocations of 60 min to sleep from LPA, sedentary time or the remaining parts of the composition were associated with effect sizes of –0.04 to 0 in adults, compared to –0.09 to –0.10 in children. Overall, effect sizes were small, even with quite large (60 min) reallocations, which may be unrealistic or unachievable for some.

Our findings are of relevance to sleep extension/restriction studies as they suggest that detrimental effects observed with sleep restriction may reflect an integrated change in use of time. Failure to account for the displacement effects of time reallocation may inflate the independent importance of sleep. It is therefore important where time is taken from. For example, increasing adult sleep by one hour at the expense of MVPA was associated with a 0.2 SD *increase* in BMI (approximately 1.9 kg/m^2), while increasing adult sleep by the same amount, at the expense of sedentary time, was associated with a 0.1 SD *decrease* in BMI (0.6 kg/m^2). It must be acknowledged, however, that it is unlikely that anyone would perfectly reallocate the amount of time from one activity to just one other activity over 24 hours. One-for-remaining reallocations, where time is taken pro rata from the remaining activity domains, may also be modelled. In practice, time reallocations are likely to be complex and variable

Sleep characteristics distinct from duration were rarely associated with cardiometabolic health outcomes in children and inconsistently associated with cardiometabolic health outcomes in adults. In this sample, however, most children and adults slept the recommended amount (average of 9 hr for children and 8.3 hr for adults). Hence the lack of associations may reflect the relatively good sleep habits of this sample.

The 24-hour activity composition is significantly associated with cardiometabolic health in children and adults. Increasing sleep will displace some other activity, and the type of activity displaced will be associated with different outcomes. If advocating increased sleep duration, clinicians should stress that the time should not be taken from MVPA, but ideally from sedentary behaviour.

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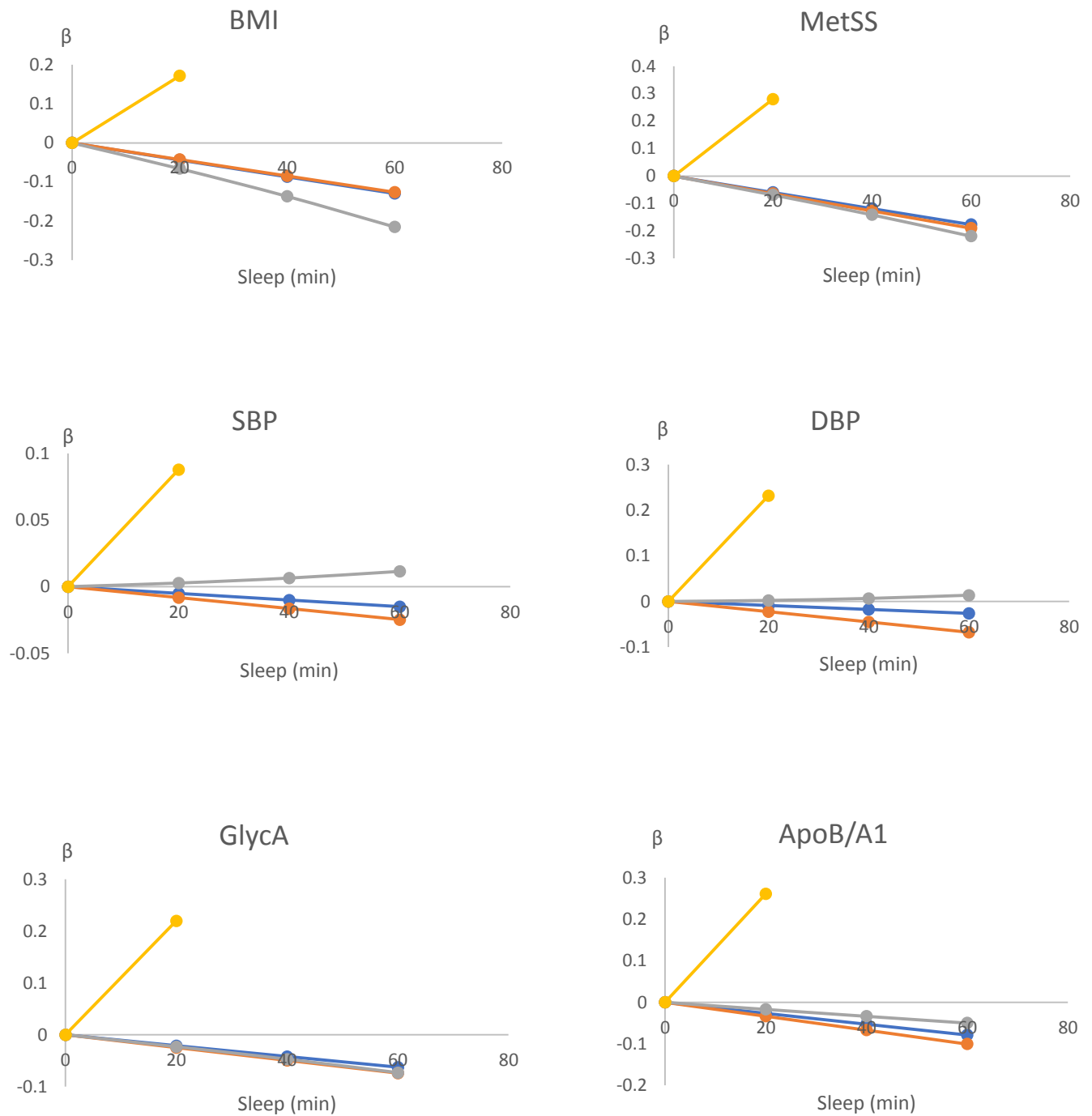
Figure

Figure 1: Flow diagram of participants included for analysis
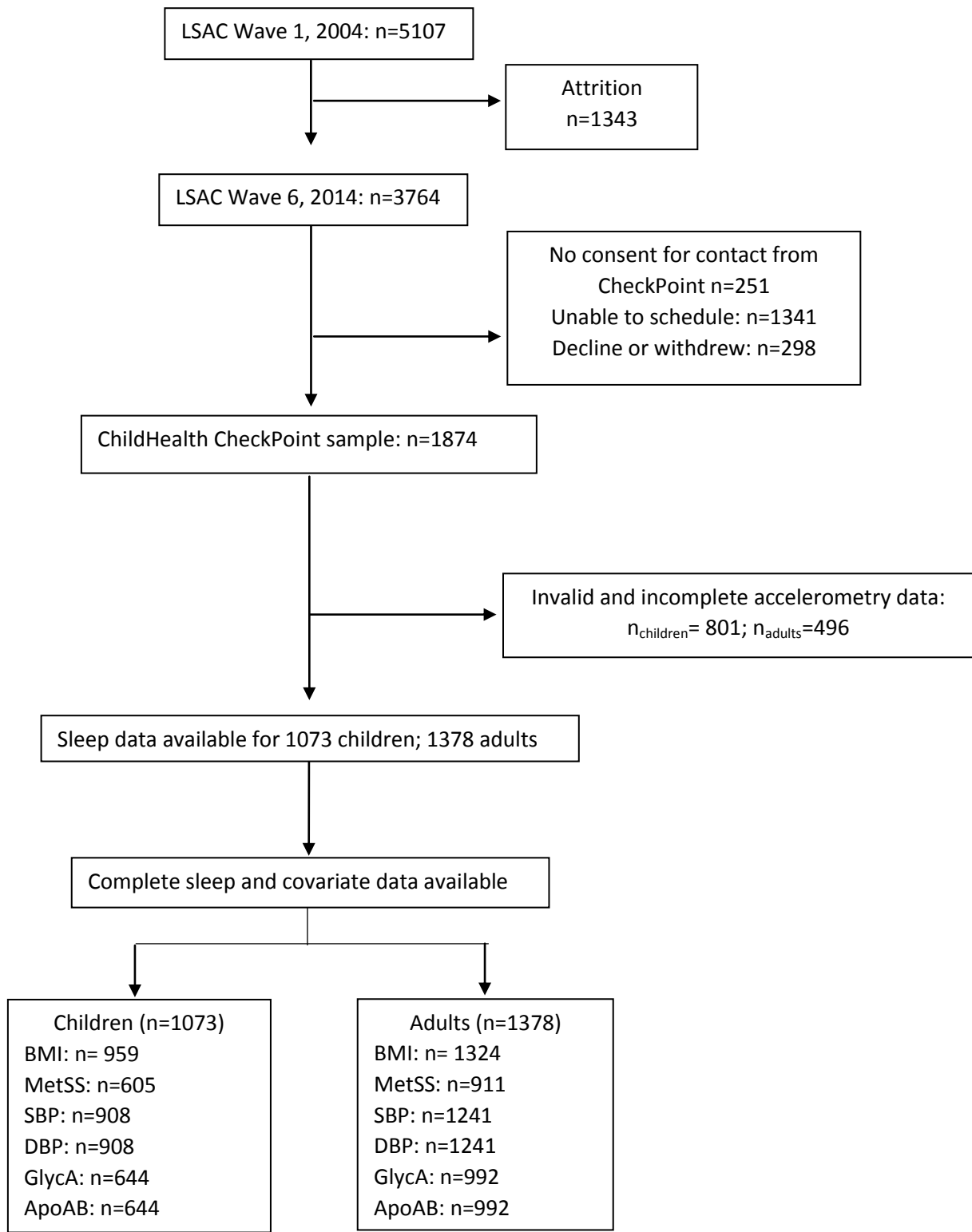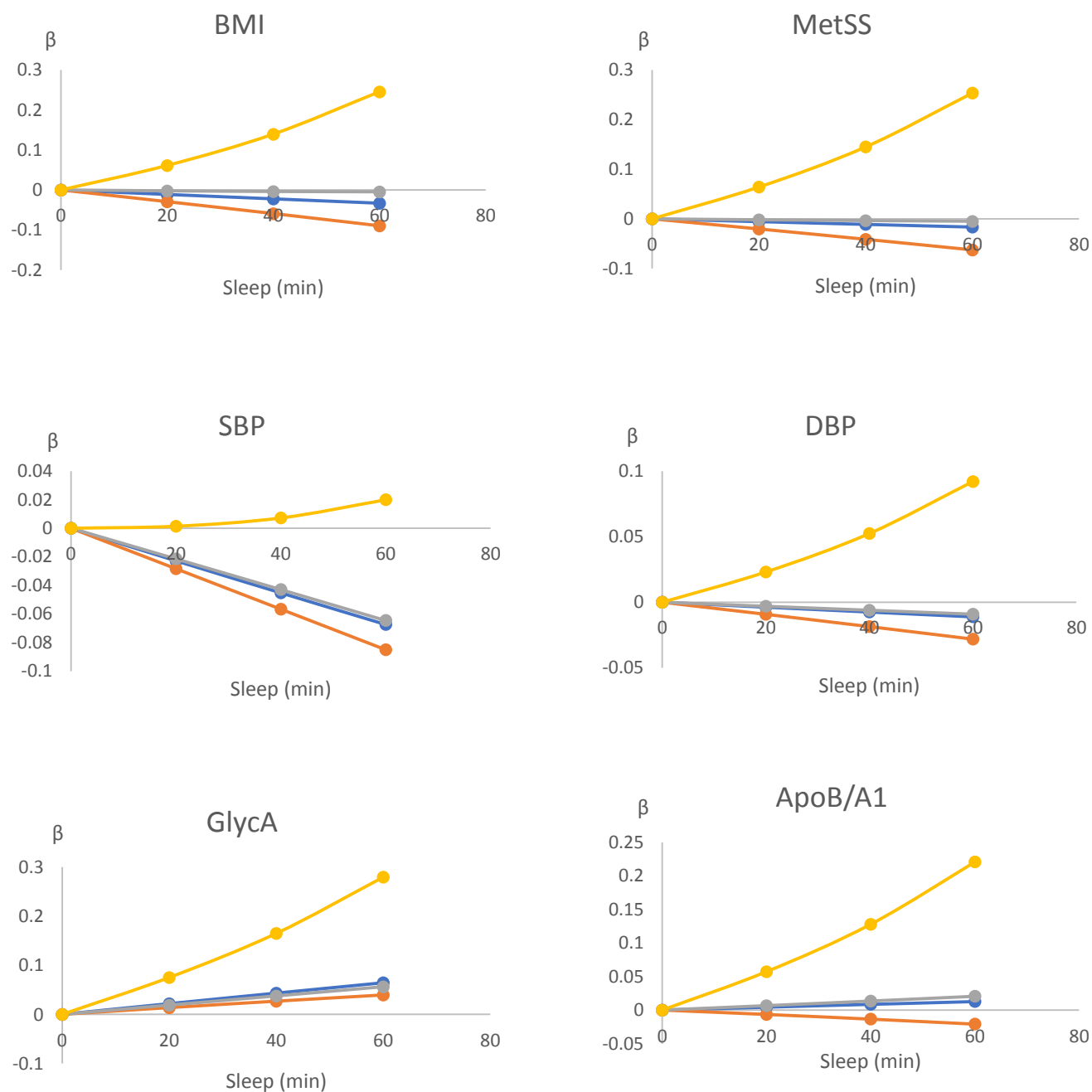
BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; ApoB/A1= apolipoprotein B/A1;

Figure

Figures 2: the differences in outcomes associated with reallocating time from one movement behaviour to sleep (one-for-one reallocation) and reallocating time from remaining behaviours to sleep (one-for-all reallocations) in children

BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; ApoB/A1= apolipoprotein A-1 to apolipoprotein B ratio

Figures 3: the differences in outcomes associated with reallocating time from one movement behaviour to sleep (one-for-one reallocation) and reallocating time from remaining behaviours to sleep (one-for-remaining reallocations) in adults

BMI=body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure; MetSS= Metabolic syndrome severity score; GlycA= glycoprotein acetyls; ApoB/A1= apolipoprotein B/A1