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Sleep duration and risk of diabetes: Observational and Mendelian randomization studies

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ABSTRACT

Inadequate sleep could contribute to type 2 diabetes, but observational studies are inconsistent and open to biases, particularly from confounding. We used Mendelian randomization (MR) to obtain an unconfounded estimate of the effect of sleep duration on diabetes, fasting glucose (FG) and hemoglobin A1c (HbA1c), and an observation study to assess differences by sex.

Using MR, we assessed the effects of genetically instrumented sleep on diabetes, based on 68 single nucleotide polymorphisms (SNPs), applied to the DIAbetes Genetics Replication and meta-analysis case (n = 26,676)-control (n = 132,532) study and on FG and HbA1c, based on 55 SNPs, applied to the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) study of FG (n = 122,743) and HbA1c (n = 123,665). In the population-representative Hong Kong Chinese "Children of 1997" birth cohort we assessed whether associations of sleep duration at ~17.5 years with FG and HbA1c differed by sex.

Using inverse variance weighting with multiplicative random effects, sleep duration was not associated with diabetes (odds ratio (OR) 0.85 per hour of sleep, 95% confidence interval (CI) 0.64 to 1.13), FG (−0.032 mmol/l per hour of sleep, 95% CI −0.126 to 0.063) or HbA1c (−0.022% per hour of sleep, 95% CI −0.069 to 0.024). In "Children of 1997", the associations of sleep duration with FG differed by sex (p for interaction 0.05) but not with HbA1c.

Overall sleep duration does not appear to be related to diabetes, FG or HbA1c, but the possibility of sex differences merits investigation.

1. Introduction

Diabetes mellitus describes a group of metabolic disorders characterized by poor glucose metabolism. People living with diabetes have a higher risk of mortality and morbidity (Forouzanfar et al., 2016). The prevalence of diabetes in adults was 415 million and global health expenditure due to diabetes was estimated at 673 billion US dollars in 2015 (Ogurtsova et al., 2017). Physical activity, diet and weight management are very well-established diabetes prevention strategies, but have not yet contained the diabetes epidemic. It is imperative to identify other modifiable lifestyle factors to prevent diabetes. Sleep is gaining recognition as an another important lifestyle factor relevant to the prevention of chronic diseases, including diabetes (Anujuo et al., 2015; McNeil et al., 2013).

Several meta-analyses of observational studies have found shorter sleep duration associated with higher risk of type 2 diabetes (Cappuccio et al., 2010; Lee et al., 2017; Shan et al., 2015). Lack of sleep has profound consequences, i.e., setting up "fight or flee" responses, such as increasing cortisol, (Chopra et al., 2017; Oster et al., 2017) and reducing reproductive potential (Leproult and Van Cauter, 2011; Tufik et al., 2009), all of which may affect glucose metabolism, (Grossmann et al., 2015; Manson et al., 2013; McNeil et al., 2013) possibly in a sex-specific manner (Andersen et al., 2011; Reynolds et al., 2012). As such, sleep duration could be an important potential target of public health

Abbreviations: FG, fasting plasma glucose; HbA1c, hemoglobin A1c; RCTs, randomized controlled trials; CI, confidence interval; GWAS, genome-wide association studies; MR, Mendelian randomization; MCHCs, Maternal and Child Health Centers; OR, odds ratio; SNPs, single nucleotide polymorphisms; BMI, body mass index

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intervention for diabetes prevention. However, observational studies are open to biases, particularly from confounding, as disadvantage may be associated with both disturbed sleep conditions and poor health. Observationally it is also difficult to distinguish the possibility that poor sleep causes diabetes and its risk factors from the possibility that poor health results in both shorter sleep and diabetes.

Randomized controlled trials (RCTs) to confirm the role of sleep as a target of intervention show sleep restriction (5 hours/night, 7 nights) in 20 young men significantly reduced insulin sensitivity (Buxton et al., 2010). Slow-wave sleep suppression for 3 nights in 9 young men and women decreased insulin sensitivity (Tasali et al., 2008). However, these RCTs are too small and short-term to be definitive. A recent Mendelian randomization (MR) study found sleep duration was not associated with type 2 diabetes, but did not explicitly consider diabetes risk factors, such as fasting glucose (FG) or hemoglobin A1c (HbA1c), or differences by sex (Jansen et al., 2018).

To clarify the role of sleep duration in diabetes, we assessed the association in two complementary ways. First, we used MR to obtain the overall effect of sleep duration on diabetes and glycemic traits. Since genetic make-up is randomly allocated at conception, analogous to the randomization process in RCTs, MR is less susceptible to confounding than observational studies and has the potential to provide unconfounded estimates of causal effects. Second, as the publically available genetic studies on diabetes and glycemic traits are not sex-specific, we used an observational study to assess differences by sex, because even if the observed associations are confounded the confounding should be similar by sex, meaning differences by sex are informative. We took advantage of a large ethnically homogenous, population-representative Hong Kong Chinese birth cohort "Children of 1997", with little social patterning of sleep duration or glucose metabolism, to assess whether the association of sleep duration with FG and HbA1c differed by sex in young people.

2. Method

2.1. Mendelian randomization

We obtained single nucleotide polymorphisms (SNPs) strongly (p-value $< 5 \times 10^{-8}$) associated with sleep duration from the largest and most recent genome-wide association study (GWAS). Linkage disequilibrium between SNPs was identified from the MRBase "clump_data" R package (Hemani et al., 2016). We checked whether the selected SNPs were associated at Bonferroni corrected significance with any potential confounders, such as education, smoking, physical activity and alcohol use, in the UK Biobank GWAS (Benjiamin, update to Apr 2018). We repeated the analysis after removing these SNPs in sensitivity analysis. Known potentially pleiotropic effects (affecting the outcomes other than via sleep) of the chosen SNPs were obtained from comprehensive curated genotype to phenotype cross-references, Ensembl and PhenoScanner (Staley et al., 2016). To check statistically for unknown pleiotropic effects we used MR-Egger and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) test (Verbanck et al., 2018). The genetic instruments were applied to the largest publically available GWAS of diabetes, FG and HbA1c.

2.2. The 'Children of 1997' birth cohort

"Children of 1997" is a population-representative Chinese birth cohort (n = 8,327) that covered 88% of all births in Hong Kong from April 1 to May 31, 1997, described in detail elsewhere (Schooling et al., 2012). The study was initially established to investigate the impact of second-hand smoke exposure on infant health (Lam et al., 2001). Families were recruited at their first postnatal visit to the 49 Maternal and Child Health Centers (MCHCs) in Hong Kong. Parents of all newborns are strongly encouraged to take advantage of the MCHCs to obtain free postnatal care and vaccinations until 5 years of age. Baseline characteristics, including parental education, parental migrant status and birth characteristics (birth-weight, sex, gestational age) were obtained from a self-administered questionnaire at recruitment. Other measures of socio-economic position, such as household income, were also recorded. Active follow-up via direct contact was instituted in 2007, with surveys conducted in 2008/9 (Survey I), 2010/12 (Survey II) and 2011/12 (Survey III), and a Biobank clinical follow-up in 2013–6. The Biobank clinical follow up included a questionnaire, physical assessment and blood taking after an overnight fast. Sleep duration was self-reported in the questionnaire. Fasting glucose (FG) was analyzed by the enzymatic reference method with hexokinase using the Roche Cobas C8000 System, HbA1c level was analyzed by immunoassay using the Roche Cobas INTEGRA 800 analyser.

2.2.1. Exposure – sleep duration

The main exposure was sleep duration (in hours) calculated as the difference between bedtime and wake-up time, reported as the most common evening bedtime and wake-up time in the past month at about 17.5 years. This method of calculating sleep duration has been widely used in previous studies (Chaput et al., 2006; Eisenmann et al., 2006). Calculated sleep duration was also checked for infeasibility, such as wake-up time before bedtime, and a small number of participants were excluded (n = 9).

2.2.2. Outcomes – glycemic traits

The outcomes were FG (mmol/l) and HbA1c (%) at ~17.5 years. Fasting glucose and HbA1c reflect different aspects of glucose metabolism. FG is associated with beta cell dysfunction and glucose tolerance (Davies et al., 2000). HbA1c reflects the 2-to-3-month average endogenous exposure to glucose (Selvin et al., 2010), and may represent insulin resistance (Saha and Schwarz, 2017).

2.3. Statistical analyses

The causal associations of sleep (in hours) with diabetes, FG and HbA1c were obtained using two sample instrumental variable analysis. We calculated the F statistic of each SNP, which reflects the magnitude and precision of the genetic effect, to evaluate its strength as an instrument (Li and Martin, 2002; Palmer et al., 2012). We combined Wald estimates (Bowden et al., 2016a) for independent SNPs ($r^2 < 0.01$) (calculated as the estimate for SNP on outcome divided by the estimate for SNP on exposure) using inverse variance weighting (IVW) with multiplicative random effects. Cochran's Q test was used to assess heterogeneity (Cohen et al., 2015). As a sensitivity analysis we repeated the analysis using a weighted median estimator (WM). A WM will produce valid estimate if > 50% of the information comes from valid SNPs. We also repeated the analysis used MR-Egger regression, which may provide correct estimates as long as the instrument strength independent of direct effect assumption is satisfied. A non-zero intercept from MR-Egger indicates that the IVW estimate may be invalid because of potential pleiotropy, i.e., the SNPs affect the outcomes via mechanisms other than sleep. MR-Egger regression can be imprecise if the number of SNPs used as instruments is low or if they all have similar associations with the exposure. Given MR-Egger does not explicitly identify outliers and has stringent assumptions as well as low statistical power (Bowden et al., 2016b), we also used MR-PRESSO to detect and if necessary correct for potentially pleiotropic outliers (Verbanck et al., 2018). We performed 100,000 simulations to calculate the empirical p-value for the MR-PRESSO global test. A p-value > 0.05 on the global test indicates a valid Mendelian randomization estimate. We ensured the same effect allele was used for exposure and outcome based on the effect allele letter for non-palindromic SNPs, and based on all relevant available information for palindromic SNPs, i.e., coded (A/T or C/G), including effect allele frequency and the coding used (forward or reverse).

In the "Children of 1997" birth cohort we used Cohen effect sizes to

compare those with and without information about sleep. Multivariable linear regression was used to assess the adjusted associations of sleep duration (in hours) with glycemic traits. Differences by sex were assessed from the significance of the interaction terms between sleep and sex in a model also including interactions of sex with the confounders. Confounders were selected as likely common causes of sleep duration and glucose metabolism, including body mass index (BMI), parents' place of birth (Hong Kong or other), highest parental occupation (professional, managerial, nonmanual skilled, manual skilled, semi-skilled, unskilled), household income per head (in quintiles), highest parental education level (Grade 9 or below, Grade 10–11, Grade 12 or above) and parent-reported health status of the child (very good, good, average, poor, very poor).

A combination of inverse probability weighting and multiple imputation were used to handle missing data (Seaman et al., 2012). First, we used multiple imputation to predict missing confounders and exposures, based on a flexible additive regression model with predictive mean matching (Schafer, 1999) incorporating data on glycemic traits, sleep duration, confounders, factors potentially related to sleep duration, interaction terms and any confounding interactions. Second, inverse probability weights were then estimated from the model using logistic regression, to recover the representativeness of the sample (Seaman and White, 2013). The model predicting inclusion status was based on factors associated with being excluded, including parents' place of birth, highest parental occupation, household income per head and highest parental education level. Weights were checked to ensure there were the no zero fitted probabilities for the incomplete cases. Third, Rubin's Rules were used to combine each IPW effect estimator and its corresponding sandwich variance estimator.

All statistical analysis were conducted using Stata version 13.1 (StataCorp LP, College Station, TX), R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria), and the "MendelianRandomization" and "MR-PRESSO" packages. The study in the "Children of 1997" birth cohort obtained ethical approval from the University of Hong Kong–Hospital Authority Hong Kong West Cluster Joint Institutional Review Board. Analysis of publically available summary data that does not require ethical approval.

3. Results

Seventy-eight single nucleotide polymorphisms (SNPs) associated with sleep duration (per hour) at genome-wide significance (p-value $< 5 \times 10^{-8}$) were obtained from the UK Biobank, which included 446,118 individuals of European ancestry mean age 57.3 years (Dashti et al., 2018). Of these 78 SNPs, only 24 SNPs were found in MAGIC, proxy SNPs ($R^2 > 0.9$) were found for 35. Of these total 59 SNPs, rs7616632 and rs2287218 were excluded because of high linkage disequilibrium ($R^2 < 0.01$) and rs17732997 and rs9940646 were excluded because they were palindromic giving 55 independent SNPs. For diabetes, 77 SNPs were found in DIAGRAM and no proxy SNPs were found ($R^2 > 0.9$). rs7115226, rs7616632, rs180769 and rs11614986 were excluded because of high linkage disequilibrium ($R^2 < 0.01$) and rs11643715, rs12791153, rs17732997, rs2079070 and rs9940646 were excluded because they were palindromic. Finally, 68 independent SNPs were used. Fig. 1 shows the selection of SNPs related to sleep duration used as instruments.

Genetic associations with diabetes were obtained from the DIAbetes Genetics Replication and meta-analysis of diabetes (DIAGRAM) diabetes case (n = 26,676)–control (n = 132,532) study of European ancestry (mean age 54.7 years, 44% men) using an additive genetic model including age, sex and principal components (Scott et al., 2017). Genetic associations with FG (mmol/L) and HbA1c (%) were obtained from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). MAGIC gives genetic associations with FG for up to 122,743 adults without diabetes of European descent mean age 52 years (44% men) adjusted for age, sex and study-specific covariates with genomic control (Dupuis et al., 2010). MAGIC gives associations with HbA1c for 123,665 adults without diabetes of European descent, mean age 53 years (48% men) adjusted for age, sex, and other study-specific covariates with genomic control (Soranzo et al., 2010). Appendix Table 2 summarizes the information extracted for each SNP.

Sleep duration was not associated with diabetes, FG, or HbA1c using any method. The MR-Egger intercept suggested no statistical evidence of the genetic variants for sleep acting on glycemic traits and diabetes other than via the sleep duration (directional horizontal pleiotropy) (Table 1). MR-PRESSO detected some outlier SNPs, outlier corrected estimates were also null. Similar null results were found after removing SNPs associated with potential confounders and potentially pleiotropic SNPs (Appendix Table 1).

Of the 8,327 "Children of 1997" participants recruited, 29 had permanently withdrawn before the Biobank Clinical Follow-up, and 414 were not contactable and 1,034 did not respond to the Biobank Clinical Follow-up. Of the 6,850 active follow-up participants in Hong Kong, 3,460 responded and 3,144 provided sleep duration (Appendix Fig. 1). The response rate for Biobank Clinical Follow-up was 50.5%. The participants with and without sleep duration were comparable (Appendix Table 3). A similar confounding structure was found by sex in the "Children of 1997" birth cohort (Appendix Table 4). The average sleep duration was 7.9 h and bedtime after midnight. The mean fasting plasma glucose was 4.64 mmol/l and the mean HbA1c was 5.41%. Table 2 shows higher parental occupation, income and parental education associated with shorter sleep duration but little association of parental socio-economic position with fasting glucose or HbA1c. Sleep duration was inversely associated with HbA1c in both sexes. Similar results were found after adjustment for confounders including BMI. The association of sleep with FG differed by sex (p-value 0.05 in model 3, but not with HbA1c (p-value 0.34). The direction of association of sleep duration with FG was different in boys and girls. Sleep duration tended to be inversely associated with FG only in boys but the confidence intervals included the null value (Table 3). These results were consistent when sleep duration were classified as "≤6", "6–7 h", "7–8 h", "8–9 h" and "≥9 h" (Appendix Table 5).

4. Discussion

We found little evidence from MR that overall sleep duration is associated with diabetes, FG or HbA1c. However, at a more granular level, we cannot rule out that the effect of sleep on FG differs by sex.

Our MR findings are consistent with a genetic study that used linkage disequilibrium (LD)-score regression showing little association of sleep duration with diabetes or FG in men and women together (Lane et al., 2017), although LD-score regression uses variants across the whole genome and is a non-directional analysis of exposure on outcome (identifying genetic correlations), whereas MR uses genetic proxies of exposure to provide a directional estimate (Gage et al., 2017). Here, we are considering effects of sleep at the outset of adulthood in the observational study, and causal effects of lifetime sleep patterns in the MR study. Causes are usually expected to act consistently although they may not be relevant in all situations, as such causal effects of sleep at 17.5 years would be expected to have some similarity with lifetime effects of sleep. However, we do acknowledge that the effects of sleep may differ before and after puberty, because sleep may affect sex hormones, whose levels change at puberty. No previous MR study has assessed the effect of sleep duration on HbA1c, nor have any sex-specific MR studies concerning the association of sleep with diabetes or glycemic traits been conducted. Observationally few studies have examined sex differences in the relation of sleep with diabetes or its risk factors. Some studies in adults have found poor sleep associated with higher HbA1c or risk of diabetes in women (Ayas et al., 2003) and in men (Nilsson et al., 2004), however these studies did not formally test for differences by sex (Mallon et al., 2005; Meisinger et al., 2005). RCTs assessing short-term effects of sleep on glucose metabolism have not

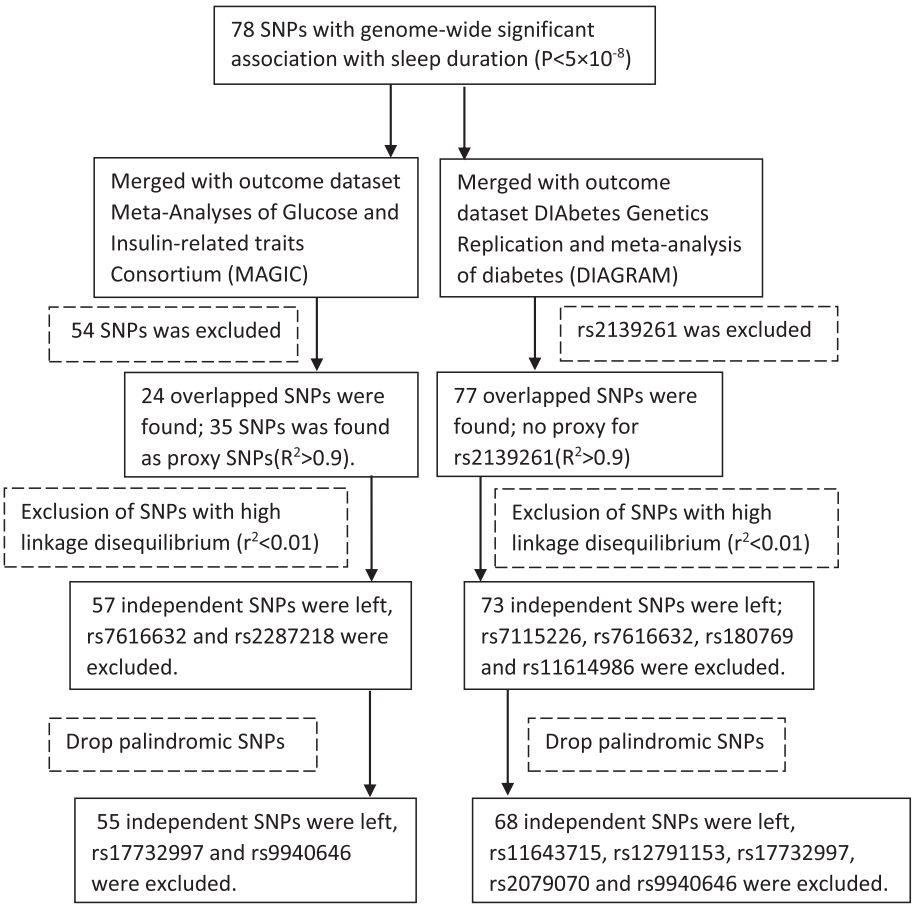

Fig. 1. Selection of SNPs related to sleep duration used as instruments in analysis of effect on risk of diabetes.

Table 1
Mendelian randomization estimates of the effect of sleep duration (per hour) on glycemic traits using the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) and DIAbetes Genetics Replication and meta-analysis (DIAGRAM).

	Mendelian randomization method	SNPs used	β/OR	95% confidence interval	Cochran's Q (p-value)	MR-Egger intercept (p-value)	Outliers from MR-PRESSO
Diabetes	IVW with random-effects	68	0.85	0.64,1.13	126.2 (*0.0001*)	−0.006 (*0.56*)	rs4592416
	WM		0.99	0.71,1.38			rs56372231
	MR Egger		1.16	0.40,3.37			
	Corrected MR-PRESSO		0.86	0.67,1.11			
Fasting plasma glucose (mmol/l)	IVW with random-effects	55	−0.032	−0.126,0.063	103.2 (*0.0001*)	−0.001 (*0.80*)	rs174548
	WM		−0.024	−0.131,0.083			
	MR Egger		0.014	−0.361,0.389			
	Corrected MR-PRESSO		−0.007	−0.085,0.072			
HbA1c (%)	IVW with random-effects	55	−0.022	−0.069,0.024	104.3 (*0.0001*)	0.003 (*0.09*)	rs1263056
	WM		−0.035	−0.087,0.018			rs174548
	MR Egger		−0.176	−0.360,0.007			
	Corrected MR-PRESSO		−0.021	−0.062,0.021			

IVW: inverse variance weighting; WM: weighted median method; MR-PRESSO: Mendelian randomization pleiotropy residual sum and outlier.

been designed to consider differences by sex.

Potential mechanisms by which sleep could affect glucose metabolism differently by sex exist, such as melatonin or hormones. An RCT found long-term prolonged-release melatonin administration had a beneficial effect on HbA1c in both sexes (Garfinkel et al., 2011). Sleep restriction studies in animals and in men have indicated that sleep disturbances resulted in reduced levels of circulating testosterone (Reynolds et al., 2012; Wu et al., 2014). However, less information is available in women concerning the effect of sleep on sex hormones (Lord et al., 2014), such as whether sleep loss affects estrogen (Mong et al., 2011). RCTs show testosterone has beneficial effects on glucose metabolism in men with type 2 diabetes (Cai et al., 2014) and estrogen reduces diabetes (Manson et al., 2013).

We used an MR design to assess the association of sleep duration with diabetes and its risk factors, we then used an observational study to investigate differences by sex. Nevertheless, several considerations and limitations bear discussion. First, MR has stringent assumptions concerning the association of the genetic variants with the exposure, lack of confounding of the genetic variants with the outcome and that the genetic variants should only be associated with the outcome via the exposure. The SNPs used were all genome-wide significant and the *PAX8* locus has been confirmed as associated with sleep across ancestry groups in at least three large GWAS (Gottlieb et al., 2015; Jones et al., 2016; Lane et al., 2017). rs7556815 near *PAX8* is functionally relevant

Table 2
Baseline characteristics from Hong Kong's "Children of 1997" birth cohort (2013-6).

Characteristics	Classification	n	Average sleep duration(hours)	*P-value*	Fasting glucose (mmol/l)	*P-value*	HbA1c (%)	*P-value*
		3144	7.95(1.61)		4.64(0.34)		5.41(0.25)	
Participant & Family Characteristics								
Sex				*0.42*		*0.80*		*0.84*
	Boys	1577	7.97(1.53)		4.69(0.35)		5.41(0.25)	
	Girls	1567	7.92(1.68)		4.60(0.32)		5.41(0.25)	
Parents' birthplace				*< 0.01*		*0.31*		*0.63*
	Both parents migrant	827	8.08(1.60)		4.64(0.36)		5.39(0.26)	
	One parent migrant	682	7.96(1.60)		4.63(0.32)		5.40(0.24)	
	Both parents Hong Kong	1619	7.87(1.62)		4.65(0.34)		5.42(0.25)	
Highest parental occupation				*< 0.01*		*0.34*		*0.34*
	I (professional)	741	7.76(1.54)		4.66(0.35)		5.42(0.26)	
	II (managerial)	412	7.78(1.55)		4.65(0.34)		5.41(0.24)	
	IIINM (nonmanual skilled)	799	7.96(1.58)		4.65(0.33)		5.40(0.24)	
	IIIM (manual skilled)	447	8.21(1.66)		4.63(0.35)		5.41(0.25)	
	IV (semi-skilled)	261	7.98(1.63)		4.62(0.32)		5.39(0.24)	
	V (unskilled)	86	8.39(1.91)		4.59(0.33)		5.36(0.22)	
Household income per head in quintiles				*< 0.01*		*0.74*		*0.46*
	1st quintile (HK$ 1751 ± 413)	504	8.08(1.68)		4.62(0.34)		5.38(0.26)	
	2nd quintile (HK$ 2856 ± 325)	549	8.01(1.64)		4.66(0.36)		5.42(0.25)	
	3rd quintile (HK$ 4362 ± 556)	560	8.04(1.62)		4.65(0.34)		5.40(0.25)	
	4th quintile (HK$ 6822 ± 886)	589	7.87(1.50)		4.62(0.32)		5.41(0.25)	
	5th quintile (HK$ 14850 ± 16050)	597	7.72(1.54)		4.67(0.36)		5.42(0.24)	
Highest parental education level				*< 0.01*		*0.66*		*0.50*
	Grade 9 or below	878	8.14(1.69)		4.64(0.36)		5.40(0.26)	
	Grade 10-11	1352	7.92(1.57)		4.64(0.33)		5.40(0.25)	
	Grade 12 or above	903	7.78(1.56)		4.64(0.34)		5.42(0.25)	
Parental-reported health status				*0.12*		*< 0.01*		*0.21*
	Very good	365	7.85(1.65)		4.62(0.31)		5.40(0.25)	
	Good	1257	7.87(1.63)		4.64(0.34)		5.40(0.27)	
	Average	284	8.13(1.46)		4.62(0.34)		5.41(0.23)	
	Poor	26	8.13(1.58)		4.69(0.35)		5.36(0.24)	
	Very poor	3	7.53(1.31)		4.60(0.14)		5.33(0.21)	

to sleep duration. Population stratification could be a potential confounder, but the underlying studies used genomic control and relate to relatively ethnically homogeneous populations of mainly European ancestry, making such confounding unlikely. Results were similar after removing potentially confounding SNPs. We found no statistical evidence (from MR-Egger) of the genetic variants for sleep acting on diabetes, FG or HbA1c other than via sleep. However, some heterogeneity were evident, but the weighted median and MR-Egger, with different assumptions, produced estimates in keeping with the null IVW estimates. MR-PRESSO did identify some outliers, whose exclusion did not alter the findings. Similar estimates after removing potentially pleiotropic SNPs again gave little indication that the results are due to pleiotropy. Given the use of two samples, sleep duration were not measured in the sample with the outcome so we could not investigate whether non-linear or sex-specific associations of sleep duration with diabetes, FG or HbA1c exist. However, two sample MR provides greater robustness to chance findings because participants from different studies are less likely to share a common confounding data structure (Taylor et al., 2014). Second, sleep duration was self-reported in the MR study and "Children of 1997", which might be less accurate than objective methods, such as actiography or polysomnography. However, acceptable correlations between self-reported sleep duration and that measured by these techniques have been reported (Cespedes et al., 2016). More detailed information for sleep duration was not collected, such as differences between weekdays and the weekend, which may introduce some misclassification and most likely some bias towards the null. Missing data in longitudinal studies is common and inevitable, but we used a combination of inverse probability weighting and multiple imputation to handle missing data, to capitalize on the data available and to increase efficiency. Finally, we were unable to adjust for all factors that might determine sleep duration and FG or HbA1c, such as study workload or parental attitudes. However, residual confounding would be expected to have systematic rather than sex-specific effects. We checked the assumption that confounding is the same for both sexes (Appendix Table 4), so that differences by sex may be informative even in the context of confounding.

Our study has important strengths. By integrating summary statistics from > 100,000 individuals, our MR study was well powered to assess small effect estimates. We took advantage of recent methodological developments to assess thoroughly the possibility of pleiotropy, for which we found little evidence. However, as diabetes is a complex and heterogeneous disease, examining the links between sleep duration and other diabetes traits, such as insulin resistance or insulin deficiency, could be worthwhile. Moreover, future studies should examine the role of more nuanced sleep characteristics, such as architecture and quality, in diabetes.

5. Conclusion

Our novel study found overall sleep duration does not appear to be related to diabetes, FG or HbA1c, but the possibility of differences by sex merits investigation. Further research is warranted to better identify whether lack of sleep could be an endocrine disruptor with corresponding consequences.

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Table 3
Associations of sleep (in hours) at ~17.5 years with glycemic traits in the "Children of 1997 Birth Cohort" (2013–6).

		Model 1[a]		P for interaction by sex	Model 2[b]		P for interaction by sex	Model 3[c]		P for interaction by sex
	Glycemic traits	β	95% CI		β	95% CI		β	95% CI	
Overall	Fasting plasma glucose (mmol/l)	−0.006	−0.013, 0.002	*0.044*	−0.001	−0.009, 0.006	*0.046*	−0.004	−0.012, 0.003	*0.050*
	HbA1c (%)	−0.008	−0.014, −0.003	*0.430*	−0.009	−0.015, −0.004	*0.434*	−0.007	−0.013, −0.002	*0.340*
Boys	Fasting plasma glucose (mmol/l)	−0.014	−0.026, −0.003		−0.009	−0.021, 0.003		−0.013	−0.024, −0.001	
	HbA1c (%)	−0.006	−0.014, 0.002		−0.006	−0.015, 0.002		−0.004	−0.012, 0.004	
Girls	Fasting plasma glucose (mmol/l)	0.001	−0.009, 0.011		0.005	−0.005, 0.015		0.003	−0.007, 0.012	
	HbA1c (%)	−0.010	−0.018, −0.003		−0.012	−0.020, −0.004		−0.010	−0.017, −0.002	

[a] Model 1: adjusted for gender, unadjusted in sex-specific analysis.
[b] Model 2: adjusted for age and gender in overall, adjust only age in sex-specific analysis.
[c] Model 3: adjusted for age, gender, BMI, parents' place of birth, highest parental occupation, household income per head, highest parental education levels and parent-report health status for children.

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Conflict of interest statement

All authors declared no conflict of interest. All authors revised the manuscript critically for important intellectual content; and gave final approval of the version to be submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2018.11.019.

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