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Association between sleep duration and executive function differs between diabetic and non-diabetic middle-aged and older adults

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ABSTRACT

Executive function is defined as a set of cognitive skills that are necessary to plan, monitor, and execute a sequence of goal-directed complex actions. Executive function is influenced by a variety of factors, including habitual sleep duration and diabetes. In the present study, we investigated in 18,769 Swedish adults (mean age: 61 y) the association between executive function, diabetes, and self-reported sleep duration. We observed a significant interaction between diabetes and sleep duration for the Trail Making Test (TMT) ratio ($P < 0.01$). This ratio is a measure of executive function where higher values indicate worse performance. Among diabetic participants (n = 1,523), long (defined as ≥9 h per day) vs. normal sleep duration (defined as 7–8 hours per day) was associated with a higher TMT ratio ($P < 0.05$). Similar significant results were observed in diabetic individuals without pharmacological treatment for diabetes (n = 1,062). Among non-diabetic participants (n = 17,246), no association between long sleep duration and the TMT ratio was observed ($P > 0.05$). Instead, short (defined as < 7 h per day) vs. normal sleep duration was linked to a higher TMT ratio ($P < 0.05$). These findings suggest that the association between sleep duration and executive function differs between diabetic and non-diabetic middle-aged and older adults. Based on the cross-sectional design of the study, no firm conclusions can be drawn on the causality of the relations.

1. Introduction

Epidemiological studies have demonstrated that diabetes and its acute and chronic complications are associated with worse cognitive performance. This includes deficits in attention, learning, and executive function (Benedict et al., 2012; Gregg et al., 2000; Hassing et al., 2004; Manschot et al., 2006; Palta et al., 2017). Moreover, evidence suggests that subjects with diabetes may exhibit accelerated cognitive decline and have a higher risk of dementia, compared with non-diabetic subjects (Gregg et al., 2000; Kanaya et al., 2004; Ott et al., 1999).

Similar to diabetes, impaired sleep patterns, including those characterized by habitual short sleep duration, have been associated with poorer cognitive performance and accelerated cognitive aging (Ferrie et al., 2011; Kronholm et al., 2009; Lim and Dinges, 2010; Williams et al., 2017; Yaffe et al., 2014). Chronic poor sleep also increases the risk to develop dementia (Benedict et al., 2015; Cedernaes et al., 2017; Hahn et al., 2014). For example, in a population-based sample of 214 Swedish older adults who were dementia-free at baseline, reduced sleep was associated with a 75% increased all-cause dementia risk during a follow-up period between 6 and 9 years (Hahn et al., 2014). Noteworthy, evidence also suggests that habitual long sleep duration is associated with poorer cognitive performance and increased risk of dementia (van Oostrom et al., 2018; Westwood et al., 2017).

The results from epidemiological and clinical studies indicate that chronic sleep restriction could also play a significant role in the etiology of diabetes (Gangwisch et al., 2007; Mallon et al., 2005; Tuomilehto et al., 2009; Broussard et al., 2012; Cedernaes et al., 2018; Donga et al., 2010; Herzog et al., 2013; Spiegel et al., 1999). For instance, experimental sleep restriction over several consecutive days has been shown to result in a 30% reduction in the ability of adipocytes to be stimulated

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by insulin (Broussard et al., 2012). Reduced insulin-stimulated glucose disposal is considered as an early key defect in the pathogenesis of type 2 diabetes. The results from a meta-analysis of prospective studies including 482,502 participants with follow-up periods ranging from 2.5 to 16 years suggest that not only short but also long sleep duration may increase the risk of type 2 diabetes. Compared with 7-h sleep duration per day, the pooled relative risks for type 2 diabetes were 1.09 for each 1-h shorter sleep duration among individuals who slept < 7 h per day and 1.14 for each 1-h increment of sleep duration among individuals with longer sleep duration (Shan et al., 2015). Finally, sleep problems, including habitual short and long sleep duration, may not only represent an important risk factor for the development of type 2 diabetes but also contribute to its progression and complications (Tan et al., 2018a,b).

To the best of our knowledge, no large-scale study to date has, however, investigated the association between executive function, diabetes, and self-reported sleep duration. Executive function is defined as a set of cognitive skills that are necessary to plan, monitor, and execute a sequence of goal-directed complex actions (Coppin et al., 2006). In the present study, executive function was measured by the trail making test (TMT) and habitual sleep duration was assessed by a questionnaire, in both participants with and without diabetes.

2. Materials and methods

2.1. Study population

The present study was based on data from the EpiHealth cohort study. The primary objective of EpiHealth is to study how interactions between genotypes and lifestyle factors contribute to the development of common disorders in humans, such as cardiovascular diseases, cancer, and dementia. Inclusion criteria were age between 45 and 75 years; a permanent address in Sweden; and a Swedish civic registration number. An invitation letter was sent to a random sample of participants who were residents in the Swedish municipalities of Malmö and Uppsala. Subjects who agreed to participate in the study filled out an internet-based questionnaire, as well as visited one of two Swedish test centers for physical examination (located in Malmö or Uppsala, Sweden). A detailed description of the study protocol can be found elsewhere (Lind et al., 2013). From the initial sample size (n = 20,534), 257 individuals were excluded because of missing data on either the TMT-a or TMT-b subtest. A detailed description of the TMT procedure can be found below. Furthermore, extreme outliers regarding the performance on these subtests were excluded (n = 489; absolute Z scores > 3.29 from the population mean). We additionally excluded 403 individuals for the analysis because of missing covariates, and 39 did not provide information on sleep duration. Another 306 subjects could not be considered for analysis, as they had missing data on either fasting glucose concentration or BMI. Lastly, 271 subjects were not included in the final sample because of a history of stroke. Following these exclusions, data from 18,769 subjects (91.4% of the initial sample size) were available for the analysis.

2.2. Physical parameters

Blood pressure was recorded twice in the sitting position by trained personnel with an automatic device (Omron, Kyoto, Japan). Weight and height were measured to calculate the body mass index (BMI; kg/m^2). Fasting plasma glucose concentration was quantified by an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). Hypertension was defined as present when participants' systolic blood pressure was ≥140 and/or diastolic blood pressure was ≥90 mmHg (Hall et al., 2012). Participants were also classified as suffering from hypertension when treated with antihypertensive drugs.

Diabetes was defined as present if any of the following criteria were met: fasting glucose concentration ≥7.0 mmol/L (Alberti and Zimmet, 1998); and/or participant reported to be pharmacologically treated for diabetes; and/or the surveyed participant reported a previous diagnosis of diabetes. The duration of diabetes, type of diabetes, and type of pharmacological treatment for diabetes were not surveyed. Thus, we could not discriminate between cases of type 1 diabetes and type 2 diabetes.

2.3. Sleep assessment

Participants were asked to indicate how many hours per day they habitually sleep ("4 h or less", "5 h", "6 h", "7 h", "8 h", "9 h", "10 h or more" and "don't know/don't want to answer"). The answer "don't know/don't want to answer" was treated as a missing value. Based on findings of a previous meta-analysis showing the lowest type 2 diabetes risk at 7–8 h per day of sleep duration (Shan et al., 2015), sleep duration was divided into three levels: short sleep, ≤ 6 h of sleep per day; normal sleep, 7–8 hours of sleep per day; and long sleep, ≥ 9 h of sleep per day.

2.4. Trail making test (TMT)

A computerized version of the TMT was applied when participants visited one of two test centers. This neuropsychological test consists of two parts, TMT-a and TMT-b. As described elsewhere (Titova et al., 2016), participants were provided computer-based instructions on how to perform the TMT before the start of this test (including short test trials). This was done to ensure that participants would understand the task procedure. The TMT-a determines cognitive processing speed. The TMT-b measures executive functions (Bowie and Harvey, 2006). During the TMT-a subtest, participants must connect circles labeled with numbers 1–25 in ascending order using a computer mouse. During the TMT-b subtest, participants must alternate between numbers (1–13) and letters (A–L) in ascending order (i.e. 1-A-2-B, etc.). The instruction was to complete these subtests as quickly as possible. An erroneously chosen path (e.g., 1–2-4 for the TMT-a and 1-A-2-B-3-D for the TMT-b respectively) was immediately indicated by changing its color to red. The total time needed to connect correctly all symbols during each subtest was measured, which included the time to correct erroneously chosen paths. The scores on the subtests were then utilized to calculate the TMT-b to TMT-a ratio (named TMT ratio in the following). The TMT ratio has been suggested to be a more accurate measure of executive function (Hester et al., 2005), as it accounts for baseline features of performance on the trails such as motor speed (Lezak, 2012). A lower TMT ratio indicates better executive function, and vice versa.

2.5. Potential confounders

Age, sex, and the use of medication for diabetes and hypertension were recorded when participants visited the test center. Participants' educational attainment, leisure-time physical activity (PA), alcohol consumption frequency, and current smoking status were assessed by an internet-based questionnaire. Participants' educational attainment was defined as primary and elementary school (up to 9 y of formal schooling), upper secondary school (up to 12 y of formal schooling), university, or other (e.g., further training). PA during leisure time was measured on an eight-point scale. A low level of PA was defined as spending most leisure time sedentary or having light PA about 2–4 h per week (e.g. walking, gardening, and light housework). A medium level of PA was defined as moderate PA at least 1–2 times a week (e.g. jogging, swimming, and heavy gardening), light PA for more than 4 h per week, or taking care of all the housework, both light and heavier. A high PA level was defined as more strenuous PA at least 3 times a week (e.g. playing tennis, swimming, and running). Alcohol consumption frequency during the last 12 months was categorized as "never", "≤ 1 time/week", "2-3 times/week", and "≥4 times/week", yielding a 4-level ordinal variable. Regarding self-rated general health status,

participants were asked to choose a point on a subjective rating scale ranging from 0 (the worst possible health status) to 10 (the best possible health status).

2.6. Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, IL). Descriptive data are presented as means (SD) for continuous variables and percentages for categorical variables, respectively. The Pearson chi-square test was used to analyze group differences for categorical variables. Numerical data were analyzed with the Mann-Whitney-U test. Generalized Linear Models (GLMs) with log link function and gamma distribution were used for the main analyses. In the basic model, we adjusted for participants' age (expressed in years), sex, and educational attainment. The (advanced) multivariable model further included BMI, hypertension status, leisure-time PA level, current smoking status, and alcohol consumption frequency. Potential confounders were selected based on our a priori assumptions on the relationships between potential confounders, intermediate variables, exposure, and outcome variables, as well as based on existing information on risk factors for impaired sleep and cognitive performance (Ancoli-Israel, 2009; Baumgart et al., 2015; Titova et al., 2018) using the method of directed acyclic graphs (DAGs) (Textor et al., 2011). This method is widely used to depict graphically assumed causal relationships between predictor, outcome, and confounder variables.

The proportion of missing data in the present study (after exclusions of participants with extreme Z-scores on TMT-a or TMT-b, and history of stroke) was approximately 5%. A sensitivity analysis was conducted to further assess if exclusions of subjects because of missing values could have affected the associations between sleep duration and cognitive performance. We performed multiple imputations (Hayati Rezvan et al., 2015) with the assumption that data were missing at random (Pedersen et al., 2017). Incomplete variables were imputed under fully conditional specification (van Buuren, 2007). The imputation procedure resulted in five imputation data sets.

3. Results

3.1. Study population

Of the 18,769 participants considered eligible for the main analysis, 8.1% met the criteria for diabetes. Compared with those without diabetes, individuals with diabetes were generally older, less educated, had lower PA, higher BMI, higher fasting plasma glucose concentration, and had more often hypertension. Besides, diabetic participants were more often male, reported more often short and long sleep duration, and required more time to complete the TMT-a and TMT-b. For more details, see Table 1.

3.2. Association between sleep duration and performance on the TMT

In both the basic and multivariable models, we found a significant multiplicative interaction between sleep duration and diabetes status for the TMT ratio ($P < 0.01$). Thus, analyses, stratified by diabetes status, were performed to investigate possible associations between self-reported sleep duration and performance on the TMT. These analyses revealed that participants with diabetes reporting habitual long sleep duration exhibited a higher TMT ratio (indicating worse executive function) than those with diabetes and reports of normal sleep duration ($P \leq 0.001$ in both statistical models; Table 2). No such association between long sleep duration and TMT ratio was found among non-diabetic participants. Instead, a significantly higher TMT ratio was observed in non-diabetic subjects reporting short sleep duration, compared with those who habitually slept between 7–8 hours per day, yet this difference was rather small ($P < 0.01$ in both models; Table 2). In the subgroup of individuals with diabetes, participants reporting long sleep duration were generally older, had a higher alcohol consumption frequency (i.e., ≥4 times/week), and indicated worse general health status compared to those reporting either normal or short sleep duration (Table 3). Note that additional adjustments for self-reported health status did not alter the association between long sleep duration and TMT ratio in diabetic subjects (data not shown). Overall, no interactions between sex/age (in years) and sleep duration categories regarding the TMT ratio were found ($P > 0.05$).

In the multivariable GLMs, main effects of sleep duration and diabetes status on the TMT-a and TMT-b were found (mean (SEM), TMT-a: short sleep vs normal sleep, 38.87 (0.23) vs 38.72 (0.21) s, $P > 0.05$; long sleep vs normal sleep, 40.33 (0.44) vs 38.72 (0.21) s, $P < 0.001$; diabetes vs no diabetes, 39.74 (0.33) vs 38.86 (0.21) s, $P = 0.002$; TMT-b: short sleep vs normal sleep, 59.38 (0.43) vs 58.30 (0.39) s, $P < 0.001$; long sleep vs normal sleep, 61.99 (0.82) vs 58.30 (0.39) s, $P < 0.001$; diabetes vs no diabetes, 60.64 (0.61) vs 59.11 (0.38) s, $P = 0.003$). In contrast, no interactions between sleep duration and diabetes status for the TMT subtests were noted in the basic model ($P = 0.250$ for TMT-a and $P = 0.055$ for TMT-b, respectively). Associations between sleep duration and performance on the TMT subtests (i.e., TMT-a and TMT-b), stratified by diabetes status, are nonetheless shown in Table 2.

3.3. Sensitivity analyses

A multiple imputation approach was used to investigate whether exclusions because of missing values may have influenced our results. The analysis of the imputed dataset revealed similar results when stratified by diabetes status (data not shown).

In the present study, 602 participants of the diabetes group reported that they were diagnosed with diabetes. Among them, 69.4% (n = 418) had a fasting plasma glucose concentration of ≥7.0 mmol/L. In the entire group of diabetic participants (i.e., either identified by self-report or fasting plasma glucose concentration of ≥7.0 mmol/L; n = 1523), 30% (n = 461) reported that they were pharmacologically treated for diabetes. The type of medication was, however, not specified. A sensitivity analysis performed among those without reports of medication for diabetes (n = 1062) revealed similar results as in the full group of diabetic subjects. Specifically, diabetic long-duration sleepers had a higher TMT ratio, compared with those reporting normal sleep duration (β (95% CI): 0.125[0.041 to 0.210]). No association between short sleep duration and the TMT ratio was observed (β (95% CI): 0.007[-0.030 to 0.045]). Finally, results for the TMT subtests were similar to those in the full group of diabetic subjects (data not shown).

In the present study, 3940 participants reported that they received antihypertensive treatment. When re-running the multivariable analysis with three instead of two hypertension status categories (i.e., normotensive, n = 8369); hypertensive + no medication, n = 6460; and hypertensive + medication, n = 3940), similar results were observed (data not shown).

4. Discussion

Utilizing the trail making test (TMT), a widely-used neuropsychological tool to screen for basic cognitive deficits (Tombaugh, 2004), we demonstrate that the association between sleep duration and executive function differs between diabetic and non-diabetic middle-aged and older adults.

Diabetes combined with long sleep duration (≥9 h per day) was associated with worse executive function (as shown by a higher TMT ratio) when compared with diabetic normal-duration sleepers (7–8 hours per day). These results contrast to those of a cross-sectional study including 162 participants with type 2 diabetes or prediabetes (mean age < 60 years). In this study, no association between sleep duration and global cognitive scores was found (Saetung et al., 2018). Possible explanations for these conflicting results between the present

Table 1
Cohort characteristics.

Parameter	Total cohort	Diabetes	No diabetes	P-value
Total participants, n (%)	18,769	1523 (8.1)	17,246 (91.9)	
Age, yr, mean (SD)	60.6 (8.5)	64.0 (7.5)	60.2 (8.5)	< 0.001
Females, n (%)	10,711 (57.1)	567 (37.2)	10,144 (58.8)	< 0.001
Educational attainment, n (%)				
Primary/elementary school	2,809 (15.0)	328 (21.5)	2481 (14.4)	< 0.001
Upper secondary school	4,820 (25.7)	381 (25.0)	4439 (25.7)	
University	9,062 (48.3)	636 (41.8)	8426 (48.9)	
Other	2,078 (11.1)	178 (11.7)	1900 (11.0)	
Leisure-time physical activity level, n (%)				
Low	7,371 (39.3)	807 (53.0)	6564 (38.1)	< 0.001
Moderate	7,904 (42.1)	514 (33.7)	7390 (42.9)	
High	3,494 (18.6)	202 (13.3)	3292 (19.1)	
Current smoking status, n (%)				
Non-smoker	17,379 (92.6)	1405 (92.3)	15,974 (92.6)	0.595
Smoker	1,390 (7.4)	118 (7.7)	1272 (7.4)	
Alcohol consumption frequency, n (%)				
Never	998 (5.3)	87 (5.7)	911 (5.3)	0.768
≤ 1 time/week	9,973 (53.1)	801 (52.6)	9172 (53.2)	
2-3 times/week	6,108 (32.5)	490 (32.2)	5618 (32.6)	
≥4 times/week	1,690 (9.0)	145 (9.5)	1545 (9.0)	
Fasting plasma glucose, mmol/L, mean (SD)	5.95 (0.91)	7.88 (1.89)	5.78 (0.48)	< 0.001
BMI, kg/m^2, mean (SD)	26.2 (4.0)	28.8 (4.5)	25.99 (3.9)	< 0.001
Hypertension status, n (%)				
Normotensive	8369 (44.6)	296 (19.4)	8073 (46.8)	< 0.001
Hypertensive	10,400 (55.4)	1227 (80.6)	9173 (53.2)	
Self-reported habitual sleep duration, n (%)				
≤ 6 h per day	6,065 (32.3)	518 (34.0)	5547 (32.2)	< 0.001
7-8 h per day	12,007 (64.0)	916 (60.1)	11,091 (64.3)	
≥9 h per day	697 (3.7)	89 (5.8)	608 (3.5)	
Time to complete the TMT-a test,[A] sec	37.5 (11.6)	40.6 (11.8)	37.3 (11.5)	< 0.001
Time to complete the TMT-b test,[A] sec	55.3 (21.5)	61.2 (23.6)	54.8 (21.2)	< 0.001

Group comparisons between the subsamples were either performed with the Mann-Whitney U test or the Pearson Chi-square test. [A] longer time to complete the test indicates worse performance. *Abbreviations*: SD, standard deviation; TMT, the trail making test.

and the aforementioned study could relate to differences in the sample size and the method used to assess cognitive function (TMT in the present study vs. Montreal Cognitive Assessment in the other study). In the present study, individuals with diabetes reporting long sleep duration were older, had worse self-reported health status, and reported higher levels of alcohol consumption, compared with diabetic participants reporting either normal or short sleep duration. Further studies are therefore warranted to investigate whether these factors modulate the association between sleep duration and executive function in diabetic patients.

Diabetes has previously been associated with worse cognitive performance, including the cognitive domains learning, attention, and executive function (Gregg et al., 2000; Hassing et al., 2004; Holingue et al., 2018; Manschot et al., 2006). In the present study, we also found a main effect of diabetes on the performance on the TMT in that diabetic participants required more time to complete this test compared with non-diabetic study participants. Of note, several neuroimaging studies have found links between hallmark symptoms of diabetes, such as higher fasting blood glucose levels, and brain pathology, such as incident infarcts, worsening sulcal widening, and worse white matter microstructural integrity (Knopman et al., 2011; Power et al., 2017; Zhang et al., 2014). Hence, it could be speculated that neurodegenerative processes caused by diabetes may additionally affect the structural and functional integrity of brain regions involved in executive functions (e.g. the prefrontal cortex) and regulating arousal (e.g. the reticular formation or the lateral hypothalamus producing the wake-promoting neuropeptide orexin). If proven by future studies, this could explain why diabetes and long sleep duration may coincide with worse executive function, as observed herein. Noteworthy, prolonged sleep duration has been proposed as a marker of early neurodegeneration (Westwood et al., 2017).

In non-diabetic participants, short sleep duration (defined as ≤6 h sleep per day) was linked to a slightly higher TMT ratio. These findings are in line with numerous epidemiological studies that have consistently demonstrated that short sleep duration is associated with deteriorations in a wide range of cognitive functions (Gildner et al., 2014; Kronholm et al., 2009; Lo et al., 2014; Ohayon and Vecchierini, 2005). For example, it was demonstrated in a cohort of older individuals (≥ 60 years) that short (< 6 h per day) but not long sleep duration (≥9.5 h per day) was associated with impaired global cognitive functioning (Ohayon and Vecchierini, 2005). One possible explanation for why short sleep duration may impair executive function in healthy humans could be that brain circuits critically involved in this cognitive domain, such as the prefrontal cortex, are vulnerable to sleep loss. Notably, during rapid-eye movement (REM) sleep, a sleep phase predominantly found during late hours of sleep, frontal lobes rest, as indicated by less activity in comparison with other states of sleep and wakefulness (Braun et al., 1998). Thus, it could be speculated that impaired prefrontal cortex functioning may occur especially when less time is spent asleep in REM sleep, i.e., as found under conditions of habitual short sleep duration. Surprisingly, while short sleep duration was associated with the TMT ratio among non-diabetic subjects, no such association was observed among diabetic subjects. One explanation could be that the negative impact of short sleep duration on executive function was masked by the general adverse impact of diabetes on cognitive performance.

Previous reports suggest that not only short but also long sleep duration is associated with poor cognitive function in the general population. For instance, long sleep duration (defined as > 9 h/night) has been associated with a lower global cognitive score relative to intermediate sleep lengths (defined as 6–9 h/ night) (Gildner et al., 2014). In line with this result, we found that the performance on both TMT-a and TMT-b subtests was worse in non-diabetic subjects reporting long sleep duration, compared with non-diabetic subjects reporting normal sleep

Table 2
Association between habitual sleep duration and performance on the trail making test, stratified by diabetes status.

Habitual sleep duration per day	Basic model		Advanced model	
	EMM (SEM)	β [95% CI]	EMM (SEM)	β (95% CI)
	Subsample with diabetes (N = 1523)			
	TMT ratio			
≤ 6 hours	1.54 (0.02)	0.002 [-0.030 to 0.034]	1.58 (0.03)	0.002 [-0.030 to 0.034]
7-8 hours	1.54 (0.02)	Ref	1.58 (0.03)	Ref
≥ 9 hours	1.71 (0.05)	**0.107 [0.042 to 0.171]**	1.76 (0.06)	**0.105 [0.040 to 0.170]**
	TMT-a			
≤ 6 hours	40.34 (0.47)	−0.009 [-0.037 to 0.018]	40.71 (0.74)	−0.011 [-0.039 to 0.017]
7-8 hours	40.72 (0.38)	Ref	41.16 (0.69)	Ref
≥ 9 hours	40.92 (1.12)	0.005 [-0.051 to 0.061]	41.09 (1.25)	−0.002 [-0.057 to 0.054]
	TMT-b			
≤ 6 hours	60.95 (0.93)	−0.008 [-0.044 to 0.028]	63.35 (1.49)	−0.010 [-0.045 to 0.026]
7-8 hours	61.43 (0.73)	Ref	63.98 (1.38)	Ref
≥ 9 hours	68.44 (2.42)	**0.108 [0.036 to 0.180]**	70.43 (2.77)	**0.096 [0.024 to 0.168]**
	Subsample without diabetes (N = 17,246)			
	TMT ratio			
≤ 6 hours	1.54 (0.01)	**0.015 [0.006 to 0.025]**	1.56 (0.01)	**0.014 [0.005 to 0.023]**
7-8 hours	1.51 (0.00)	Ref	1.54 (0.01)	Ref
≥ 9 hours	1.52 (0.02)	0.005 [-0.018 to 0.028]	1.54 (0.02)	0.004 [-0.020 to 0.027]
	TMT-a			
≤ 6 hours	37.43 (0.14)	0.008 [-0.001 to 0.016]	38.27 (0.21)	0.005 [-0.003 to 0.013]
7-8 hours	37.15 (0.10)	Ref	38.08 (0.18)	Ref
≥ 9 hours	38.97 (0.41)	**0.048 [0.027 to 0.069]**	39.90 (0.45)	**0.046 [0.025 to 0.067]**
	TMT-b			
≤ 6 hours	56.29 (0.25)	**0.026 [0.016 to 0.036]**	58.29 (0.38)	**0.021 [0.011 to 0.031]**
7-8 hours	54.86 (0.19)	Ref	57.08 (0.33)	Ref
≥ 9 hours	58.12 (0.75)	**0.058 [0.032 to 0.084]**	60.30 (0.82)	**0.055 [0.029 to 0.080]**

Results derive from generalized linear models using a gamma distribution with a log link function. Results are presented as estimated marginal means (SEM) and parameter estimates of unstandardized β (95% confidence intervals). If the 95% confidence interval did not pass zero, the test of the statistical hypotheses was considered significant at the 5% level (shown in bold). Note that the interaction between sleep duration and diabetes status only reached significance for the TMT ratio (i.e., performance on the TMT-b divided by the performance on the TMT-a; see results section). *Basic model*: adjusted for sex, age, and educational attainment. *Advanced model*: adjusted for sex, age, educational attainment, BMI, hypertension status, leisure-time physical activity level, current smoking status, and alcohol consumption frequency. *Abbreviations:* TMT, trail making test; CI, confidence interval; BMI, body mass index; EMM, estimated marginal means; Ref, reference group.

duration. However, no association between long sleep duration and TMT ratio was observed in non-diabetic subjects. This pattern could indicate that overall processing speed was impacted in non-diabetic long sleepers, rather than executive set-shifting.

A major strength of our study is that the analysis was based on a relatively large sample. Moreover, to the best of our knowledge, our study is the first that has investigated the interplay between sleep duration and diabetes status with regards to executive function. An additional strength of our study is that a digitalized version of the TMT was used. Cognitive test results can be influenced by the test administrator effect in the range of 2–4 percent of total variation (Overton et al., 2016). Several limitations, however, apply to our observational study. Sleep duration was based on self-reports. As sleep habits can change across the lifespan (Ohayon et al., 2004), it must be kept in mind that participants' reports of sleep duration at the time of the survey may have not been representative for sleep duration patterns in the past. Information on when and which type of diabetes was diagnosed were not available. Other potential confounders, such as sleep-related medication and the use of antidepressants were not included in the present analysis. Finally, most of the participants were of northern European origin which may reduce the generalizability of our results to other ethnic groups.

5. Conclusions

It is well-known that diabetes can lead to several health complications, including cognitive impairment (Moheet et al., 2015). Here, we show that diabetes combined with long sleep duration is associated with worse executive function. Executive functioning is an important cognitive domain that is negatively affected by a number of neurological conditions, such as Alzheimer's disease (Lafleche and Albert, 1995). This suggests that patients with diabetes reporting habitual long sleep duration should be followed-up carefully for cognitive impairment. Whether long sleep duration is a cause or a consequence of impaired executive function among diabetic patients can, however, not be inferred from our study and therefore warrants further investigation in future studies.

Ethics statement

The Ethics Committee at Uppsala University approved the general procedures of the EpiHealth study. All subjects gave written informed

Table 3
Characteristics of participants with diabetes, stratified by sleep duration.

Parameter	*Habitual sleep duration (hours per day)*		P-value
	< 9 h per day	*≥ 9 h per day*	
Total participants with diabetes, n (%)	1434 (94.2)	89 (5.8)	
Age, yr, mean (SD)	63.8 (7.5)	67.0 (6.0)	< 0.001
Females, n (%)	531 (37.0)	36 (40.4)	0.517
Educational status, n (%)			
Primary/elementary school	311 (21.7)	17 (19.1)	0.135
Upper secondary school	365 (25.5)	16 (18.0)	
University	596 (41.6)	40 (44.9)	
Other	162 (11.3)	16 (18.0)	
Leisure-time physical activity level, n (%)			
Low	753 (52.5)	54 (60.7)	0.262
Moderate	487 (34.0)	27 (30.3)	
High	194 (13.5)	8 (9.0)	
Current smoking status, n (%)			
Non-smoker	1,319 (92.0)	86 (96.6)	0.111
Smoker	115 (8.0)	3 (3.4)	
Alcohol consumption frequency, n (%)			
Never	77 (5.4)	10 (11.2)	0.007
≤ 1 time/week	761 (53.1)	40 (44.9)	
2-3 times/week	466 (32.5)	24 (27.0)	
≥4 times/week	130 (9.1)	15 (16.9)	
Fasting plasma glucose, mmol/L, mean (SD)	7.88	7.87	0.672
BMI, kg/m^2, mean (SD)	28.72 (4.45)	29.44 (4.45)	0.125
Hypertension status, n (%)			
Normotensive	283 (19.7)	13 (14.6)	0.235
Hypertensive	1,151 (80.3)	76 (85.4)	
Self-reported health status,[A] mean (SD)	7.45 (1.69)	6.82 (2.18)	0.016

Group comparisons between the subsamples were either performed with the Mann-Whitney U test or Pearson Chi-square test. [A] 10-point scale (higher values indicating better health status). Abbreviations: SD, standard deviation.

consent in accordance with the Declaration of Helsinki. Additional ethical approval for the current data analyses was obtained from the Ethics Committee at Uppsala University.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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