Sleep measures and cardiovascular disease in type 2 diabetes mellitus

Authors: Caroline J Magri, A Sara Xuereb, B Rachel-Anne Xuereb, B Robert G Xuereb, A Stephen Fava C and Joseph Galea D

Objective
The objective of this study was to assess whether poor sleep is independently associated with cardiovascular disease in people with type 2 diabetes mellitus (T2DM).

Methods
A cross-sectional study was performed in subjects with T2DM aged between 40 and 80 years. Sleep assessment was achieved by actigraphy and Pittsburgh Sleep Quality Index (PSQI) score.

Results
The study population comprised 108 subjects with T2DM. The mean age was 64.9 years, the median diabetes duration was 6 years and 73.1% were men. No association was shown between sleep parameters as assessed by actigraphy and T2DM-associated micro- and macrovascular complications. However, sleep quality as assessed by PSQI was significantly associated with macrovascular disease in univariate analysis. Multivariate logistic regression analysis showed red blood cell distribution width (RDW) (odds ratio (OR) 1.79, \( p = 0.018 \)) and good sleep quality (OR 0.35, \( p = 0.017 \)) to be independently associated. Binary logistic regression analysis revealed that body mass index (BMI) (OR 1.11, \( p = 0.024 \)), RDW (OR 1.95, \( p = 0.007 \)) and Center for Epidemiologic Studies Depression score (OR 1.06, \( p = 0.012 \)) were independently associated with abnormal carotid intima-media thickness (CIMT).

Conclusions
Poor sleep quality and higher RDW levels are associated with macrovascular disease in a T2DM population. Increased BMI as well as depression also appear to have an independent role in subclinical atherosclerosis, as assessed by CIMT.

KEYWORDS: sleep, actigraphy, cardiovascular disease, type 2 diabetes mellitus

DOI: 10.7861/clinmed.2022-0442

Authors: A consultant cardiologist, Mater Dei Hospital, Malta; B higher specialist trainee in cardiology, Mater Dei Hospital, Malta; C full professor, University of Malta, Malta, and consultant endocrinologist, Mater Dei Hospital, Malta; D associate professor, University of Malta, Malta, and consultant cardiac surgeon, Mater Dei Hospital, Malta

Introduction
Several studies and meta-analyses have reported a link between sleep duration and quality with increased cardiovascular endpoints and all-cause mortality in the general population. \(^1,2\) Many studies have shown a U-shaped relationship between sleep duration and mortality, \(^1,3,4\) coronary artery disease, \(^5\) stroke \(^6,5\) and carotid intima-media thickness (CIMT). \(^6\)

Although numerous studies have shown an association between sleep deprivation and risk of type 2 diabetes mellitus (T2DM), \(^7,8\) there are currently no data on the effect of sleep duration or quality on cardiovascular outcomes in patients with T2DM. The postulated mechanisms linking sleep deprivation with adverse cardiovascular outcomes include inflammation, \(^9\) endothelial dysfunction, \(^10\) consumption of an energy-rich diet \(^11\) and decreased insulin sensitivity. \(^12\) Diabetes can modify all these relationships.

Therefore, the objective of the study was to assess whether poor sleep quality is independently associated with T2DM-associated complications, mainly cardiovascular disease, albuminuria, left ventricular impairment and peripheral neuropathy.

Methodology
Study population
The study was cross-sectional in nature. Inclusion criteria were T2DM (as defined by the World Health Organization Criteria), namely fasting plasma glucose \( \geq 7.0 \) mmol/L or 2-h plasma glucose \( \geq 11.1 \) mmol/l. \(^13\) Patients also had to be taking, and be stable on, antiglycaemic treatment (no change in treatment for \( \geq 1 \) year). Exclusion criteria included dementia or mental illnesses with the consequent inability to give informed consent, recent admission to hospital (ie within the previous 3 months) with consequent disruption of sleep pattern, and subjects with resting tremor, because this could interfere with interpretation of the parameters derived from wrist actigraphy.

Patients were randomly selected from the list of outpatients attending the Diabetes Clinic of Mater Dei Hospital, under the care of a consultant diabetologist. Every tenth patient on the list was chosen and invited to participate in the study. All participants gave written informed consent. They were reviewed at Mater Dei Hospital over a 4-month period, during which all relevant investigations were performed, as explained in further detail below.
Sleep measures
Objective sleep assessment was achieved by actigraphy. Participants were asked to wear a wrist actigraph on their non-dominant hand for 3 consecutive days and nights using ActiGraph wGT3X-BT accelerometer (ActiGraph LLC, Pensacola, FL, USA) to assess sleep latency, total sleep time, wake after sleep onset, sleep fragmentation index and sleep efficiency. Efficient sleep was defined as >85% sleep efficiency. Patients kept a sleep diary of the days when they were wearing the actigraph.

Study participants also completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire. This is a well-validated self-reported questionnaire that is designed to assess sleep quality throughout the previous month. A total PSQI score ≤5 is associated with good sleep quality, whereas a total score >5 is associated with poor sleep quality.14

Self-reported depression and stress levels
Study participants were asked to complete the Center for Epidemiologic Studies Depression (CES-D) scale to assess for symptoms of depression.15 The Perceived Stress Scale (PSS) was also completed to assess for the level of personal stress over the previous month.16

Clinical and laboratory measurements
Height and weight were measured using a calibrated balance with a stadiometer, with the subjects wearing light clothes and without shoes. Waist circumference was measured to the nearest 0.5 cm in the horizontal plane at the midpoint between the lowest rib and the iliac crest.17 Waist index (WI) was calculated as waist circumference (cm) divided by 94 for men and 80 for women.17 Office blood pressure (BP) was measured in the supine position after 5 min of rest.

All subjects underwent routine blood investigations in the fasting state on the day of the clinical examination. Estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease (MDRD) formula (National Kidney Foundation Calculator for Healthcare Professionals). Haemoglobin A1c (measured using high-performance liquid chromatography) and fructosamine were taken as markers of glycaemic control. Urine albumin was measured by an immunoturbidometric technique (Roche Diagnostics, Mannheim, Germany). Creatinine was measured by a kinetic colorimetric test using the Jaffe reaction (Roche Diagnostics).

Carotid intima-media thickness measurement
CIMT was assessed in both common carotid arteries in each participant using the Esaote MyLab 30 Gold CV ultrasound machine (Esaote SpA, Florence, Italy). The Esaote Quality intima media thickness (QIMT®) was utilised, with the higher value taken as the reference QIMT for each participant. Abnormal CIMT was defined as increased CIMT and/or the presence of carotid plaque.

Assessment of left ventricular function
All study participants underwent transthoracic echocardiography utilising the Philips iE33 echo system (Philips North America Corporation, Andover, MA, USA). Left ventricular ejection fraction and global longitudinal strain were assessed together with medial and lateral E/e’ velocities as markers of diastolic dysfunction.

Assessment of distal peripheral neuropathy
The vibration perception threshold (VPT) was used as marker of distal peripheral neuropathy (DPN). VPT was measured at the first metatarsal-phalangeal joints using a Horwell neurothesiometer (Scientific Laboratory Supplies, Nottingham, UK) with decreasing stimulation starting from 50 V and then with increasing stimulation starting from 0 V. The subjects were asked to report when they stopped or began feeling vibration, respectively. The mean of the two measurements for the least-sensitive foot was used as the reference VPT and utilised for statistical analysis. The presence of peripheral neuropathy was defined as VPT >15 V, with VPT >25 V being considered to be severe neuropathy.18

Clinical definitions
Metabolic syndrome was defined according to the current International Diabetes Federation definition,19 namely central obesity (defined as waist circumference with ethnicity-specific values) plus any two of the following four factors: raised triglycerides ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality; reduced high-density lipoprotein (HDL) cholesterol <40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality; raised systolic BP ≥130 or diastolic (D)BP ≥85 mmHg or treatment of previously diagnosed hypertension; raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed T2DM. Smoking status was classified as non-smoker, ex-smoker (defined as having stopped smoking for >3 months) and current smoker.

Ethics statement
The study was approved by the University of Malta Research Ethics Committee.

Statistical analysis
All data were inputted into an Excel sheet and analysed using SPSS version 23.0 for Windows. Results are presented as mean ± standard deviation (SD) or median (interquartile range: IQR). Sample size was determined to achieve 80% statistical power to detect results at $\alpha=0.05$ and $\alpha=0.05$ on multivariate analyses. Continuous variables were checked for normal distribution using Kolmogorov–Smirnov statistics. Comparisons of continuous variables between two groups were made using independent sample t-tests for normally distributed variables. For non-parametric variables, the Mann–Whitney U test was used for comparison of two groups. Categorical variables were compared using the $\chi^2$ test. Pearson and Spearman correlation analyses were used for normally distributed and non-normally distributed variables, respectively.

Univariate followed by logistic regression were performed to identify independent determinants of both the occurrence of macrovascular disease and abnormal CIMT in the study population. Variables were entered into the regression model if their p-value was <0.1 in univariate analysis. Only variables with p<0.05 were kept in the final model.

Results
Characteristics of study population
The participants comprised 108 White European subjects with T2DM. The clinical and anthropometric characteristics are outlined...
Table 1. Demographic and anthropometric characteristics of the study population

<table>
<thead>
<tr>
<th>Patient characteristics (n=108)</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years(^a)</td>
<td>64.9±7.7</td>
</tr>
<tr>
<td>Male gender(^b)</td>
<td>79 (73.1%)</td>
</tr>
<tr>
<td>Diabetes duration, years(^b)</td>
<td>6 (5–8)</td>
</tr>
<tr>
<td>Smoking (non/ex/current)(^b)</td>
<td>52 (48.1%); 40 (37%); 16 (14.8%)</td>
</tr>
<tr>
<td>Hypertension(^b)</td>
<td>71 (65.7%)</td>
</tr>
<tr>
<td>Hyperlipidaemia(^b)</td>
<td>86 (79.6%)</td>
</tr>
<tr>
<td>Metabolic syndrome(^b)</td>
<td>101 (93.5%)</td>
</tr>
<tr>
<td>Known ischaemic heart disease(^b)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Known peripheral arterial disease(^b)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Known cerebrovascular disease(^b)</td>
<td>2 (1.9%)</td>
</tr>
<tr>
<td>Congestive heart failure(^b)</td>
<td>5 (4.6%)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))(^a)</td>
<td>32.02±4.63</td>
</tr>
<tr>
<td>Waist index(^a)</td>
<td>1.19±0.13</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)(^c)</td>
<td>140 (130–150)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)(^c)</td>
<td>80 (70–80)</td>
</tr>
</tbody>
</table>

\(^a\)Data are mean ± standard deviation. \(^b\)Data are number (%) of patients. \(^c\)Data are median (IQR).

in Table 1. The mean body mass index (BMI) was 32 kg/m\(^2\); the mean age was 65 years and the median diabetes duration was 6 years. The study population had multiple health conditions. Thus, metabolic syndrome was highly prevalent (93.5%), hypertension was present in approximately two-thirds of the study population (66%), whereas hyperlipidaemia was present in 80% of subjects. Fourteen subjects (13%) had ischaemic heart disease (IHD), two subjects had sustained a cerebrovascular accident or transient ischaemic attack, whereas one patient had peripheral arterial disease.

Abnormal CIMT was present in 51% of the population (Table 2). Macrovascular disease was present in 56.5%.

DPN was present in 31.5% of the population, with severe neuropathy being present in 18.5%, whereas an increased albumin–creatinine ratio (ACR) was noted in 32.4%. With regards to the latter, only one patient exhibited macroalbuminuria (ie an ACR >300 mg/g); all the other subjects with increased ACR showed microalbuminuria. Likewise, left ventricular systolic and diastolic functions were well preserved, as evidenced by a high median left ventricular ejection fraction (61%) and global longitudinal strain scores (~19), as well as low average E/e\(^’\) values (9.28).

Sixty-one percent of subjects had good sleep quality, as assessed by the PSQI questionnaire. In general, the study population slept less than 7 h, as shown by a mean total sleep time of 6.4 h. The mean total time (±SD) in bed was 452.16 (±78.14) min, whereas the mean (±SD) total sleep time was 384.38 (±71.19) min. Efficient sleep as assessed by actigraphy was noted in 56% of the study population, and the median (interquartile range) sleep efficiency was 86.26% (81.31–90.59).

Table 2. Summary of study findings

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal carotid intima-media thickness(^a)</td>
<td>55 (50.9%)</td>
</tr>
<tr>
<td>Carotid plaques present(^a)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Abnormal CIMT and/or previously documented CVD(^a)</td>
<td>61 (56.5%)</td>
</tr>
<tr>
<td>Abnormal VPT (&gt;15 V)(^a)</td>
<td>34 (31.5%)</td>
</tr>
<tr>
<td>Severe neuropathy (&gt;25 V)(^a)</td>
<td>20 (18.5%)</td>
</tr>
<tr>
<td>Microalbuminuria(^a)</td>
<td>35 (32.4%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %(^b)</td>
<td>61 (58–64)</td>
</tr>
<tr>
<td>Global longitudinal strain(^b)</td>
<td>−18 (−20 to −16)</td>
</tr>
<tr>
<td>Average E/e(^’)</td>
<td>9.28±2.81</td>
</tr>
<tr>
<td>Good sleep quality (PSQI)(^a)</td>
<td>66 (61.1%)</td>
</tr>
<tr>
<td>PSS score(^b)</td>
<td>13 (7–19.75)</td>
</tr>
<tr>
<td>CES-D score(^b)</td>
<td>4 (1–14)</td>
</tr>
</tbody>
</table>

\(^a\)Data are number (%) of patients. \(^b\)Data are median (IQR). \(^c\)Data are mean ± standard deviation. CES-D = Center for Epidemiologic Studies Depression scale; CIMT = carotid intima-media thickness; CVD = cardiovascular disease; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Score; VPT = vibration perception threshold.

Association between sleep measures and diabetes-associated complications

Univariate analysis was performed to assess for a possible relation between measures of sleep quality and diabetes-associated complications. No relation was shown between good sleep quality (as assessed by the PSQI score) or actigraphic measures and DPN, microalbuminuria and left ventricular systolic and diastolic functions. Likewise, no association was demonstrated between actigraphic measures and DPN, and microalbuminuria and left ventricular systolic and diastolic functions. However, a significant association was shown between poor sleep quality derived from PSQI and macrovascular disease (p=0.005).

Associations with macrovascular disease

Macrovascular disease was present in 61 subjects (56.5%). The major factor leading to this relatively high prevalence of macrovascular disease was abnormal CIMT, which was present in 55 subjects (50.9%). Univariate followed by multivariate analysis was performed to identify variables that were independently associated with macrovascular disease in the study population. Variables with p<0.1 in univariate analysis were included in the multivariate model. These included: BMI, red blood cell distribution width (RDW), C-reactive protein (CRP), sleep quality derived from PSQI score, PSS and CES-D scores. Age was not included in the multivariate model because the occurrence of abnormal CIMT (the major factor comprising macrovascular disease) was already adjusted for age. Diastolic blood pressure (DBP) was also not included in the analysis given that neither pulse pressure (PP) nor mean arterial pressure (MAP), which are more relevant parameters, were significant in the univariate analysis.

Consequently, in the multivariate logistic regression analysis, RDW (odds ratio (OR) 1.79; 95% confidence interval (CI) 1.1–2.9; p=0.018) and good sleep quality (OR 0.35; 95% CI 0.14–0.83;
were shown to be independently associated with macrovascular disease.

Associations with abnormal carotid intima media thickness

Given that abnormal CIMT (a combination of increased CIMT and carotid plaques) was the major determinant of macrovascular disease, the independent determinants of abnormal CIMT were also assessed. The following variables had p<0.1 in univariate analysis and, thus, were included in the multivariate model: BMI, WI, RDW, good sleep quality (derived from PSQI), PSS and CES-D scores. As previously stated, age was not included in the multivariate model because the occurrence of abnormal CIMT was already age-adjusted.

Binary logistic regression analysis revealed that BMI (OR 1.11; 95% CI 1.01–1.22; p=0.024), RDW (OR 1.95; 95% CI 1.2–3.18; p=0.007) and CES-D score (OR 1.06; 95% CI 1.01–1.11; p=0.012) were independently associated with abnormal CIMT.

Associations with total sleep time

No association was demonstrated between cardiometabolic factors and the following sleep parameters: latency, efficiency, sleep fragmentation index and wake after sleep onset. However, several relevant factors were shown to be associated with total sleep time in univariate analysis. The variables with p<0.1 in univariate analysis (age, BMI, eGFR, low-density lipoprotein (LDL)-cholesterol levels and FPG) were entered in the model and linear regression analysis was performed to assess for independent associations with total sleep time. This revealed age [β=2.96; 95% CI: 1.34–4.59; p<0.001], LDL (β=−25.27; 95% CI: −43 to −7.55; p=0.006) and microalbuminuria (β=−33.87; 95% CI: −60.36 to −7.38; p=0.013) to be independently related to total sleep time. Figs 1 and 2 show the relationship between total sleep time and LDL-cholesterol levels, and between total sleep time and age, respectively.

Discussion

The main findings of this study are that: good sleep quality, as assessed with the PSQI score, was an independently associated with low risk of cardiovascular disease in a T2DM population; increased BMI and CES-D scores were independently associated with subclinical atherosclerosis, as assessed with the use of CIMT; RDW was independently associated with both increased risk of cardiovascular disease and increased CIMT; and low total sleep duration, as detected with actigraphy, was independently associated with higher LDL-cholesterol and microalbuminuria.

Therefore, the results show that poor sleep quality in a T2DM population is associated with adverse cardiovascular outcomes. Poor sleep quality has been reported to be associated with progression of arterial stiffness in the general population as well as with endothelial dysfunction in both healthy controls and in those with type 1 diabetes mellitus. Another possible mechanism is that poor sleep quality results in non-dipping BP. However, the effect of poor sleep quality on nocturnal dipping of heart rate has been inadequately investigated.

The study did not find a U-shaped relationship between sleep duration and cardiovascular outcomes as reported in the general population (with an optimal sleep duration of 7–9 h). This could be because the mean sleep duration in this population was only 384 min with a standard error of 142 min (ie 95% of patients had sleep duration of between 5 and 8.5 h). Therefore, the study cohort might not have included patients with a long enough sleep duration to show a U-shaped relationship.

The results also show that none of the sleep parameters measured by wrist actigraphy were associated with cardiovascular disease, CIMT or microvascular disease. The discrepancy in the results

Fig 1. The relationship between total sleep time and low-density lipoprotein (LDL)-cholesterol levels. Black line indicates line of best fit.
obtained between sleep quality as assessed with wrist actigraphy versus those obtained via the PSQI score could be explained by the fact that data from sleep actigraphy were collected over a 3-day period and, hence, might not have been sufficient to reflect sleep habits. Furthermore, the use of wrist actigraphy could have led to bias, with the participant changing their usual sleep pattern. Such bias was overcome with the use of the PSQI score. Short sleep duration, as assessed with wrist actigraphy, was associated with higher LDL-cholesterol. Gangwisch et al reported short sleep duration to be significantly longitudinally associated with higher total cholesterol in young women. By contrast, in another longitudinal study, Petrov et al found that longer sleep duration was significantly associated with a poorer lipid profile. There are various possible explanations for this discrepancy. There might be a U-shaped relationship between sleep duration and cholesterol profiles. In this regard, the mean sleep duration was shorter in the study by Petrov et al compared with that by Gangwisch et al. There might also be differences in the correlation of sleep duration with other factors in different patient cohorts. There might be some factors that result in positive association between sleep duration and total and LDL-cholesterol, whereas others result in negative association. The balance of these factors might vary in different cohorts. Factors that result in a positive association include the following: higher endogenous cholesterol syntheses with longer sleep duration; longer sleep time acting as a marker of reduced physical activity; and large meals inducing sleep. By contrast, sleep deprivation can stimulate appetite, cause day-time fatigue with consequent low physical activity and induce stress.

Increased total sleep time was also shown to be independently associated with a lower incidence of microalbuminuria. Microalbuminuria is a known adverse cardiovascular risk factor. This relation between total sleep time and microalbuminuria could be explained by a higher incidence of non-dipping BP status with shorter sleep duration. Unfortunately, it was not possible to perform 24-hour BP monitoring in the study population; this might have elicited interesting information with regards to the underlying pathophysiology.

RDW emerged as being independently associated with cardiovascular disease and with subclinical atherosclerosis following adjustment for known cardiovascular risk factors, such as increased BMI. It has previously been shown that higher RDW is independently associated with increased myocardial scar burden and with diminished left ventricular ejection fraction and with all-cause mortality and major adverse cardiovascular events. The consistency of the findings with regards to the association of high RDW with diverse adverse cardiovascular outcomes in different patient cohorts reinforces the validity of RDW as an adverse prognostic indicator. Importantly RDW is an inexpensive and readily available haematological parameter. There are several possible mechanisms mediating the link between high RDW and adverse cardiovascular outcomes. For example, it has been reported to be associated with decreased red cell deformability and consequent microcirculation blood flow dysfunction, inflammatory markers and increased blood viscosity.

Abnormal CIMT was also shown to be associated with higher scores on the CES-D scale, independent of known adverse cardiovascular factors. This suggests that the known association of depressive symptomatology with sleep disturbance also applies to patients with T2DM. Thus, the mechanisms linking depression with increased CIMT warrant further study.

Limitations of the study
A large proportion of the study population were men, possibly because generally women might be less keen to attend outpatients;
Poor sleep quality (Pittsburgh Sleep Quality Index score) is associated with increased cardiovascular disease (CVD) in people with type 2 diabetes mellitus (T2DM); this could be partly mediated through increased LDL-cholesterol levels as well as microvascular disease, as suggested by the findings derived from wrist actigraphy. In addition, depressive symptomatology might not necessarily be representative of sleep in the preceding years. In addition, it was not possible to keep the wrist actigraph for longer than 3 days; however, many sleep studies have utilised wrist actigraphy for a similar duration.

Conclusion

This study showed a novel association between poor sleep quality and cardiovascular disease in a population with T2DM; this could be partly mediated through increased LDL-cholesterol levels as well as microvascular disease, as suggested by the findings derived from wrist actigraphy. In addition, depressive symptomatology appears to have a role in the occurrence of subclinical atherosclerosis as assessed by CIMT. Finally, increased RDW was shown to be an independent predictor of both subclinical atherosclerosis and macrovascular disease in T2DM; this merits further study to enable a fuller understanding of the underlying pathophysiology linking RDW with cardiovascular disease.

Summary

What is already known on the subject

Sleep duration and quality are associated with increased cardiovascular end-points and all-cause mortality in the general population.

Current research questions

To assess whether poor sleep is independently associated with cardiovascular disease in people with type 2 diabetes mellitus (T2DM).

Main messages

- Poor sleep quality (Pittsburgh Sleep Quality Index score) is associated with macrovascular disease in T2DM.
- Increased red cell distribution width (RDW) is independently associated with macrovascular disease.
- Increased body mass index, RDW and depression are independently associated with increased carotid intima-media thickness (a marker of atherosclerosis) in T2DM.

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Address for correspondence: Professor Stephen Fava MD, 
Diabetes & Endocrine Centre, Mater Dei Hospital, Msida, Malta. 
Email: stephen.fava@um.edu.mt