



Association of Subjective and Objective Sleep Duration as well as Sleep Quality with Non-Invasive Markers of Sub-Clinical Cardiovascular Disease (CVD): A Systematic Review

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Aim: Abnormal daily sleep duration and quality have been linked to hypertension, diabetes, stroke, and overall cardiovascular disease (CVD) morbidity & mortality. However, the relationship between daily sleep duration and quality with subclinical measures of CVD remain less well studied. This systematic review evaluated how daily sleep duration and quality affect burden of subclinical CVD in subjects free of symptomatic CVD.

Methods: Literature search was done via MEDLINE, EMBASE, Web of Science until June 2016 and 32 studies met the inclusion criteria. Sleep duration and quality were measured either via subjective methods, as self-reported questionnaires or Pittsburgh Sleep Quality Index (PSQI) or via objective methods, as actigraphy or polysomnography or by both. Among subclinical CVD measures, coronary artery calcium (CAC) was measured by electron beam computed tomography, Carotid intima-media thickness (CIMT) measured by high-resolution B-mode ultrasound on carotid arteries, endothelial/microvascular function measured by flow mediated dilation (FMD) or peripheral arterial tone (PAT) or iontophoresis or nailfold capillaroscopy, and arterial stiffness measured by pulse wave velocity (PWV) or ankle brachial index (ABI).

Results: Subjective short sleep duration was associated with CAC and CIMT, but variably associated with endothelial dysfunction (ED) and arterial stiffness; however, subjective long sleep duration was associated with CAC, CIMT and arterial stiffness, but variably associated with ED. Objective short sleep duration was positively associated with CIMT and variably with CAC but not associated with ED. Objective long sleep duration was variably associated with CAC and CIMT but not associated with ED. Poor subjective sleep quality was significantly associated with ED and arterial stiffness but variably associated with CAC and CIMT. Poor objective sleep quality was significantly associated with CIMT, and ED but variably associated with CAC.

Conclusions: Overall, our review provided mixed results, which is generally in line with published literature, with most of the studies showing a significant relationship with subclinical CVD, but only some studies failed to demonstrate such an association. Although such mechanistic relationship needs further evaluation in order to determine appropriate screening strategies in vulnerable populations, this review strongly suggested the existence of a relationship between abnormal sleep duration and quality with increased subclinical CVD burden.

Key words: Sleep duration, Sleep quality, Subclinical cardiovascular disease, Coronary Artery Calcium (CAC), Carotid intima media thickness (CIMT), Endothelial function, Flow Mediated Dilation (FMD), Arterial stiffness, Pulse Wave Velocity (PWV)

Introduction

A good hygienic sleep is an essential part of everyday life. It is estimated that humans spend one third of their lifetime sleeping. An estimated 50–70 million Americans suffer from sleep disorders, yet only 20% report it to their physicians¹. Poor sleep may be a risk factor for cardiovascular disease (CVD) and has serious biological consequences². A growing body of literature suggests a relationship of sleep parameters (sleep duration and sleep quality) with CVD, stroke, and all-cause morbidity & mortality³. A recent review of 23 studies determined that both short and long sleep is related to increased risk for all-cause mortality among both men and women, compared to individuals who report a medium amount of daily sleep (7–8 hours)⁴, however, some studies have shown that the sleep disturbances may be associated with CVD mortality with weaker evidence for women⁵. Additionally, acute and chronic sleep deprivation can lead to weight gain, impaired glucose tolerance, activate pro-inflammatory pathways, increased sympathetic activity and higher cortisol levels in healthy subjects⁶.

The epidemiological data suggests strong association of subjectively and/or objectively measured sleep parameters with classical CVD risk factors like hypertension, insulin resistance, hypercholesterolemia, type 2 diabetes and increase in the inflammatory markers leading to subclinical and clinical CVD^{7–10}. The traditional risk stratification has relied mainly on scoring systems such as the Framingham risk score to determine the CVD risks¹¹. However, newer non-invasive techniques that assess coronary artery calcium (CAC), carotid intima-media thickness (CIMT), flow-mediated dilation (FMD), Ankle Brachial Index (ABI) and pulse wave velocity (PWV) provide refined assessment of early atherosclerosis process, endothelial dysfunction and arterial stiffness potentially leading to clinical CVD events. The extent of CAC and CIMT correlates with plaque burden and atherosclerosis, decreased FMD correlates with endothelial dysfunction, decreased ABI but increased PWV measure increasing arterial stiffness^{12–15}. There are some studies that show relationship of these non-invasive subclinical CVD markers with disturbed sleep parameters^{16, 17} and signify the importance of regular sleep habits but such relationships between the sleep parameters and subclinical

CVD markers need to be studied in more detail. As early recognition of subclinical CVD in people with sleep disturbances may impact risk stratification and early treatment of subclinical CVD before the development of clinical CVD events.

The purpose of this systematic review is to evaluate the following: First the relationship between self-reported or/and objectively assessed sleep duration with markers of subclinical CVD. Second, the relationship between self-reported or/and objectively assessed sleep quality with markers of subclinical CVD. Third, the effect of acute and chronic sleep deprivation on subclinical CVD risks. Such association of sleep parameters with subclinical CVD would provide the importance of regular sleep habits and would provide evidence to the stakeholders to consider sleep disturbances as important risk factors for determination of future risk of CVD events. This systematic review may also highlight the role of noninvasive cardiovascular diagnostic procedures in those with sleep disturbances.

Methods

An electronic systematic literature search was performed using the EMBASE (via Emtree) and Medline database (National Library of Medicine, Bethesda, MD via PubMed) for relevant literature up to March 2016 (**Fig. 1**). We used both MeSH and Emtree terms and relevant free text terms. The following search terms (synonyms and combinations) were used: “sleep duration” and/or “sleep quality”. These terms were combined with “sub clinical cardiovascular disease risks”, “coronary artery calcium (CAC)”, “carotid intima-media thickness (CIMT)”, “endothelial function and/or microvascular function via flow mediated dilation (FMD) and/or peripheral arterial tone (PAT) and/or iontophoresis and/or nailfold capillaroscopy”, and “arterial stiffness via pulse wave velocity (PWV)”, and/or ankle brachial index (ABI)”.

The search results were manually scanned for relevant articles by three independent reviewers. References of obtained articles were used for additional articles. The search was limited to original research studies on human subjects published in English language. We included (1) original research articles, AND (2) studies that reported subjective and/or objective sleep duration AND/OR (3) studies that reported subjective and/or objective sleep quality, AND (4) studies that reported PSQI good vs PSQI bad sleep quality and/or insomnia vs. non-insomnia and/or shift vs. non-shift work and/or arousal index and/or sleep efficiency (%) and/or sleep Fragmentation index and/or REM/Non-REM sleep, AND (5) studies that reported an assessment of Non-Invasive Subclinical

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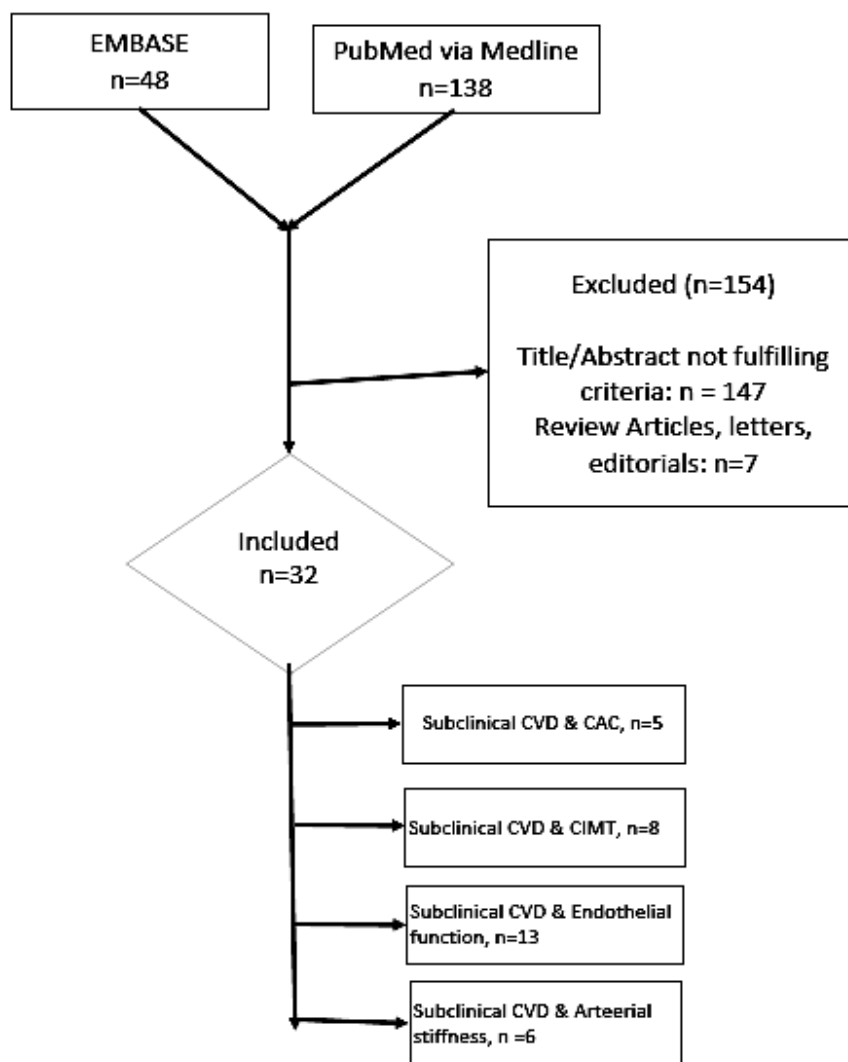


Fig. 1. Literature Search Strategy

CVD: Cardiovascular disease, CAC: Coronary artery calcium, CIMT: Carotid intima-media thickness.

CVD assessment tools as Coronary Artery Calcium (CAC) and/or Carotid Intima Media Thickness (CIMT) and/or Endothelia function and/or Arterial stiffness. The aim of this review was to summarize the evidence of regular daily sleep duration and sleep quality with subclinical CVD, so we excluded any study that discussed the association of sleep disorders and clinical cardiovascular and cerebrovascular diseases. Many research studies have shown that sleep disorders like obstructive sleep apnea has been previously shown to be strongly associated with subclinical CVD¹⁸⁾. In our exclusion criteria, we excluded (1) the letters, editorials (2) the studies on subjects with sleep disorders [obstructive sleep apnea (OSA), parasomnias, and narcolepsy] (3) the studies that discussed clinical CVDs

(angina, myocardial infarction and heart failure) and cerebrovascular diseases (stroke) (4) the studies that have discussed the effect of mental disorders on sleep duration and sleep quality (5) the studies in which participants used any kind of sleeping pills. Thirty-two studies met the inclusion criteria for final review from an initial search result of 186 articles (**Fig. 1** for search algorithm). The authors stated that no financial support was given and that no off-label or investigational use of a drug or device was performed as part of this research.

Sleep duration typically defines as “the total amount of sleep obtained, either during the nocturnal sleep episode or across the 24-hour period”¹⁹⁾. In the studies discussed in this review, the sleep duration was

Table 1. Baseline characteristics of studies used in systematic review.

First Author, Publication Year,	Country	Study Design	Study Population N (age;% female)	Sleep Measurement (Subjective/Self-reported)	Sleep Measurement (Objective)	Non-invasive CVD measurement
King <i>et al.</i> (33), 2008	United States	Cohort	495 (40 ± 4; 59%)	Self-Report (PSQI)	Actigraphy	CAC (Agatston score)-electron beam CT
Matthews <i>et al.</i> (31), 2011	United States	Cross-sectional	195 (60; 50%)	Self-Report (PSQI)	Actigraphy and PSG	CAC (Agatston score)-electron beam CT
Matthews <i>et al.</i> (32), 2013	United States	Cross-sectional	512 (50 ± 3; 100%)	Self-Report (PSQI)	NR	CAC (Agatston score)-electron beam CT
Lutsey <i>et al.</i> (34), 2015	United States	Cross-sectional	1465 (68; 54%)	NR	Actigraphy and PSG	CAC (Agatston score)-electron beam CT
Kim <i>et al.</i> , 2015 (17)	Korea	Cross-sectional	29203 (41.8 ± 7.3; 18.6%)	Self-Report (PSQI)	NR	CAC (Agatston score)-electron beam CT
Wolff <i>et al.</i> (35), 2008	Germany	Cross-sectional	2383 (45–81; 51%)	Self-Report	NR	CIMT (mm)- B-mode ultrasound
Abe <i>et al.</i> (36), 2011	Japan	Cross-Sectional	2214 (64 ± 10; 52%)	Self-Report questionnaire	NR	CIMT (mm)- B-mode ultrasound
Nakazaki <i>et al.</i> (38), 2012	Japan	Cross-Sectional	86 (74 ± 5; 71%)	Self-Report (PSQI),	Actigraphy	CIMT (mm)- B-mode ultrasound
Sands <i>et al.</i> (39), 2012	United States	Cohort	617 (37–52; 58%)	NR	Actigraphy	CIMT (mm)- B-mode ultrasound
Nagai <i>et al.</i> (2), 2013	Japan	Cross-Sectional	201 (80 ± 6; 75%)	Self-Report questionnaire	NR	CIMT (mm)- B-mode ultrasound
Ma <i>et al.</i> (37), 2013	United States	Cross- sectional	257 (42 ± 9; 26%)	Self-Report (PSQI)	Actigraphy	CIMT (mm)- B-mode ultrasound
Ramos-Sepulveda <i>et al.</i> (41), 2010	United States	Cross- sectional	1605 (65 ± 8; 60%)	Self-Report (HRSD)	NR	CIMT (mm)- B-mode ultrasound
Schwartz <i>et al.</i> (40) 2102	United States	Cross sectional	126 (55; 89%)	NR	Actigraphy	CIMT (mm)- B-mode ultrasound
Behl <i>et al.</i> (43), 2014	United States	Cohort	684 (48 ± 11; 68%)	Self-Report (PSQI and ESS)		EF-FMD
Cooper <i>et al.</i> (42), 2014	United States	Cross-sectional	100 (36 ± 10; 43%)	Self-Report (PSQI) and PSG		EF-FMD
Calvin <i>et al.</i> (44), 2014	United States	Cross-sectional	16 (18 to 40; 37.5%)	NR	PSG	EF- FMD
Takase <i>et al.</i> , 2004 (45)	Japan	Cross-sectional	30 (21.7 ± 1.1; 0%)	Self-Report	NR	EF-FMD
Wehrens <i>et al.</i> , 2012 (46)	United Kingdom	Cross-sectional	25 (25–45; 0%)	Self-report questionnaire	NR	EF-FMD
Schmidt <i>et al.</i> , 2013 (47)	Germany	Cross-sectional	75 (20–54; 61.3%)	NR	Actigraphy	EF-FMD

(Cont Table 1)

First Author, Publication Year,	Country	Study Design	Study Population N (age;% female)	Sleep Measurement (Subjective/Self-reported)	Sleep Measurement (Objective)	Non-invasive CVD measurement
Strand <i>et al.</i> (48), 2012	Norway	Cross-sectional	4739 (50 ± 13; 45.2%)	Self-report questionnaire	NR	EF-FMD
Suessenbacher <i>et al.</i> (49), 2011	Austria	Cross-sectional	48 (43 ± 5; 0%)	Self-report questionnaire	NR	EF- PAT index
Dettoni <i>et al.</i> (50), 2012	Brazil	Cross-sectional	13 (31 ± 2; 0%)	NR	Actigraphy	EF (dorsal hand vein technique)
Sauvet <i>et al.</i> (51), 2009	France	Cross-sectional	12 (29 ± 3; 0%)	Self-report	NR	EF (Iontophoresis of Acetylcholine & Nitroprusside)
Bonsen <i>et al.</i> (52), 2015	Netherlands	Cross-sectional	259 (42; 55%)	Self-report (SWEL)	NR	EF- Nailfold capillaroscopy
Weil <i>et al.</i> (53), 2010	United States	Cross-sectional	80 (56.6 ± 1.2; 39%)	Self-Report	NR	EF- Endothelin (ET)-1 levels
Weil <i>et al.</i> (54) , 2011	United States	Cross-sectional	37 (58 ± 1.5; 41%)	Self-Report	NR	EF- Endothelial progenitor cells (EPCs) functions
Yoshioka <i>et al.</i> (55), 2011	Japan	Cross-sectional	4268 (48 ± 7; 20%)	Self-Report	NR	AS-baPWV
Sunbul <i>et al.</i> (56), 2014	Turkey	Cross-sectional	42 (30 ± 5; 57%)	Self-report questionnaire	NR	AS-baPWV
Tsai <i>et al.</i> (57), 2014	Taiwan	Cross-sectional	3, 508 (age 20–87, 40%)	Self-Report	NR	AS-baPWV
Osonoi <i>et al.</i> , 2015 (68)	Japan	Cross-sectional	724 (57.8 ± 8.6; 37.1%)	Self-Report (PSQI)	NR	AS-baPWV
Yamaki <i>et al.</i> 2015,	Japan	Cross-sectional	101 (70.0 ± 10; 46.5%)	Self-Report (PSQI)	NR	AS-ABI

Abbreviation: NR: Not – reported; SWEL: Sleep Wake Experience List questionnaire

measured either via subjective methods, including self-reported questionnaires and/or Pittsburgh Sleep Quality Index (PSQI) or via objective measures, which include actigraphy and/or polysomnography or by both subjective and objective methods^{20, 21}. The subjective sleep quality is defined as “one’s perception that they fall asleep easily, get sufficient duration so as to wake up feeling rested, and can make it through their day without experiencing excessive daytime sleepiness”²². Using actigraphy to objectively measure sleep quality, the objective sleep quality is defined by sufficient duration (>7 hrs), high efficiency (>85%), and low fragmentation (<25)²³. Using polysomnography (PSG) the sleep architecture is added to the equation,

whereby the objective sleep quality is defined not only by sufficient duration, high efficiency, and low fragmentation, but also by proper staging of sleep (i.e., cycling through non-REM (stages 1–4) and REM)²³. In this review, the sleep quality was measured via subjective methods, including Pittsburgh Sleep Quality Index (PSQI) and/or self-reporting of insomnia vs non-insomnia, shift vs non-shift work, arousal index, or via objective measures, which include actigraphy and/or polysomnography or by both subjective and objective methods^{20, 21}. The Pittsburgh Sleep Quality Index (PSQI) is an effective tool used to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven

Table 2a. Association of Subjective/ Self-reported and Objective Sleep Duration with Coronary Artery Calcium (CAC)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Subclinical CVD assessment tools.	Results	Comments															
Subjective/ Self-reported Sleep Duration																			
King <i>et al.</i> (33), 2008	Self-Report (PSQI)	CAC	Logistic regression of incident CAC [OR (95% CI): Self-reported sleep per hour (Adj ^a): 0.87 (0.67–1.13), <i>p</i> =0.30																
Matthews <i>et al.</i> (31), 2011	Self-Report (PSQI),	CAC	Self-reported Sleep duration (hr) among CAC groups: CAC=0: 6.41 (1.25) CAC=1–99: 6.51 (1.18) CAC=100+ : 6.48 (1.19), <i>p</i> =0.88																
Matthews <i>et al.</i> (32), 2013	Self-Report (PSQI)	CAC	No significant association between longer self-reported sleep duration and increased CAC in linear (<i>p</i> =0.19) or logit models (<i>p</i> =0.06)	Women only sample															
Kim <i>et al.</i> , 2015 (17)	Self-Report (PSQI)	CAC	Sleep duration vs. CAC Score (Adj ^b): OR (95% CI) ≤5 h: 1.50 (1.17–1.93); <i>p</i> : 0.002 6 h: 1.34 (1.10–1.63); <i>p</i> : 0.002 7 h: 1.00 (Reference) 8 h: 1.37 (0.99–1.89); <i>p</i> : ≥0.05 ≥9 h: 1.72 (0.90–3.28); <i>p</i> : 0.002	The association between sleep duration and CAC is “U-shaped”.															
Objective Sleep Duration																			
King <i>et al.</i> (33), 2008	Actigraphy	CAC	Logistic regression of incident CAC [OR (95% CI): Actigraph measured sleep per hour (Adj ^c): 0.66 (0.48–0.92), <i>p</i> =0.01																
Matthews <i>et al.</i> (31), 2011	Actigraphy, Polysomnography	CAC	Objective sleep duration (hr) among CAC groups: <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>Actigraphy:</th> <th>PSG</th> </tr> </thead> <tbody> <tr> <td>CAC=0</td> <td>5.78 (0.98)</td> <td>6.11 (0.91)</td> </tr> <tr> <td>CAC=1-99</td> <td>5.80 (0.82)</td> <td>6.16 (1.00)</td> </tr> <tr> <td>CAC=100+</td> <td>5.92 (0.79)</td> <td>5.90 (1.04)</td> </tr> <tr> <td><i>P</i> value</td> <td><i>p</i>=0.64</td> <td><i>p</i>=0.89</td> </tr> </tbody> </table>		Actigraphy:	PSG	CAC=0	5.78 (0.98)	6.11 (0.91)	CAC=1-99	5.80 (0.82)	6.16 (1.00)	CAC=100+	5.92 (0.79)	5.90 (1.04)	<i>P</i> value	<i>p</i> =0.64	<i>p</i> =0.89	Sleep duration both by Actigraphy and PSG was not significant
	Actigraphy:	PSG																	
CAC=0	5.78 (0.98)	6.11 (0.91)																	
CAC=1-99	5.80 (0.82)	6.16 (1.00)																	
CAC=100+	5.92 (0.79)	5.90 (1.04)																	
<i>P</i> value	<i>p</i> =0.64	<i>p</i> =0.89																	
Lutsey <i>et al.</i> (34), 2015	Polysomnography and actigraphy	CAC	Sleep duration (h) vs CAC ≥400: PR (95% CI): ≤6.65h: 0.75 (0.55–1.03), <i>p</i> =0.08 6.65–7.4 h: Ref ≥7.40h: 0.84 (0.56–1.26), <i>p</i> =0.40	Fully adjusted model is not related to high prevalence of CAC.															

^aAdjusted for race, sex, age, smoking, education, and apnea risk

^bAdjusted for age, sex, study center, year of visit, education, marital status, depression, smoking status, alcohol consumption, physical activity, body mass index, fasting glucose, systolic blood pressure, diastolic blood pressure, height, and heart rate.

^cAdjusted for race, sex, age, smoking, education, apnea risk, BMI, HDL, LDL, BP, DM

sleep components that include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month²⁴. Sleep fragmentation is defined as “an index of restlessness during the sleep period expressed as a percentage”. It is calculated as movement index, a fragmentation index, and total sleep fragmentation Index. The higher

the sleep fragmentation index, the more sleep is disrupted²⁵.

Among subclinical cardiovascular disease (CVD) measures, the coronary artery calcium (CAC) was measured by either electron beam computed tomography (EBCT) or multidetector computed tomographic (MDCT) scanner. Increased calcium deposition in coronary arteries is related to the presence of athero-

Table 2b. Association of Subjective/ Self-reported and Objective Sleep Quality with Coronary Artery Calcium (CAC)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Sub-clinical CVD assessment tools.	Results	Comments
Subjective/ Self-reported Sleep Quality				
King <i>et al.</i> (33), 2008	Self-Report (PSQI)	CAC	Logistic regression of incident CAC: (OR; 95%CI): PSQI Score (per SD=2.9 points) (Adj ^d): 1.21 (0.88–1.65), $p=0.24$ Epworth Score (per SD=4.0 points) (Adj ^d): 1.26 (0.96, 1.66), $p=0.10$	
Matthews <i>et al.</i> (31), 2011	Self-Report (PSQI)	CAC	Self-reported sleep quality or efficiency did not differ by CAC groups ($p>0.15$)	Apnea/Hypopnea Index was associated with increased CAC scores ($p=0.04$).
Matthews <i>et al.</i> (32), 2013	Self-Report (PSQI)	CAC	Poor sleep quality was not associated with odds of being in a higher coronary artery calcification (CAC) group.	Women only
Kim <i>et al.</i> , 2015 (17)	Self-Report (PSQI)	CAC	CAC Score by sleep quality: Adj ^b OR (95% CI): Good vs. Poor sleep quality: Men: 1.00 (Reference) vs. 1.10 (0.86–1.42) Women: 1.00 (Reference) vs. 2.46 (1.30–4.65); $p\leq 0.05$	Poor subjective sleep quality was associated with CAC in women only in both crude and adjusted model.
Objective Sleep Quality				
King <i>et al.</i> (33), 2008	Actigraphy	CAC	Logistic regression of incident CAC: (OR; 95%CI) Fragmentation Index (per SD=7.7 points) ^d : 1.07 (0.80, 1.42), $p=0.66$	
Matthews <i>et al.</i> (31), 2011	Actigraphy, Polysomnography	CAC	Sleep quality or efficiency measures did not differ by CAC groups (CAC=0 vs CAC >0); $p>0.05$	
Lutsey <i>et al.</i> (34), 2015	Polysomnography and actigraphy	CAC	Sleep quality vs CAC ≥ 400 : PR (95% CI) Arousal index—1.14 (1.02 to 1.27); $p=0.02$ Arousal index—REM: 1.15 (1.02 to 1.29); $p=0.02$ Arousal index—NREM: 1.14 (1.02 to 1.28); $p=0.03$ Average sleep efficiency%—1.00 (0.89 to 1.13); $p=0.97$ Average sleep WASO—1.03 (0.91 to 1.17); $p=0.62$	

^dAdjusted for race, sex, age, smoking, education, and apnea risk.

^bAdjusted for age, sex, study center, year of visit, education, marital status, depression, smoking status, alcohol consumption, physical activity, body mass index, fasting glucose, systolic blood pressure, diastolic blood pressure, height, and heart rate.

sclerotic process and increased plaque burden¹²). The carotid intima-media thickness (CIMT) was measured using high-resolution B-mode ultrasonography on carotid arteries and increased intima media thickness in carotid artery is related to carotid atherosclerosis and future increased risk of CVD¹³). The endothelial function and/or microvascular function was measured by flow mediated dilation (FMD) and/or peripheral arterial tone (PAT) and/or iontophoresis and/or nail-fold capillaroscopy. The FMD is based on an ultrasound test that measures the changes in the arterial diameter based on their blood flow such as the bra-

chial, radial or femoral arteries. The decrease in the flow mediated dilatation is closely related to endothelial cells dysfunction that leads to increased risk of vessels wall injury causing both the early and late mechanisms of atherosclerosis that include increased leukocyte adherence, platelet activation, and vascular smooth muscle proliferation and decreased production of nitric oxide¹⁴). The PAT is calculated by EndoPAT device (Itamar Medical, Israel) that involves measuring the pulse amplitude in the fingertip at rest and following the induction of reactive hyperemia. The EndoPAT device consists of a fingertip plethysmograph capable

Table 3a. Association of Subjective/ Self-reported and Objective Sleep Duration with Carotid Intima-Media Thickness (CIMT)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Subclinical CVD assessment tools	Results	Comments
Subjective/Self-reported Sleep Duration				
Wolff <i>et al.</i> (35), 2008	Self-Report questionnaire	CIMT	<u>Mean difference (mm) in CIMT across hours of sleep: Adj^c</u> 5h: 0.038 (0.002, 0.074); $p < 0.0$ 6h: 0.007 (-0.012, 0.027); ns 7h: 0.001 (-0.015, 0.018); ns 8h: ref group 9h: 0.022 (0.000, 0.045); ns 10h: 0.043 (0.015, 0.070); $p < 0.01$ > 11h: 0.065 (0.017, 0.113); $p < 0.01$	The association of sleep duration with mean CIMT was J-shaped. The sleep duration group of 7hrs exhibited lowest CIMT, SBP and HbA1c.
Abe <i>et al.</i> (36), 2011	Self-Report questionnaire	CIMT	<u>Odds ratio for presence of IMT ≥ 1.2 mm: Adj^f</u> ≤ 5 h: 1.059 (0.764–1.467), $p = \geq 0.05$ 6h: ref group ≥ 7 h: 1.263 (1.031–1.546), $p = 0.024$	The use of hypnotics like benzodiazepines diminished the association between sleep duration and increased CIMT.
Nakazaki <i>et al.</i> (38), 2012	Self-Report (PSQI)	CIMT	Mean CIMT (mm): < 5h sleep vs. > 7h sleep: (1.3 ± 0.5 vs. 0.9 ± 0.3); $p = 0.009$ Association of sleep duration by PSQI with CIMT ^g : $\beta = 0.22$, $p = 0.05$	Elderly population.
Nagai <i>et al.</i> (2), 2013	Self-Report questionnaire	CIMT	<u>CIMT (mm) among sleep groups:</u> < 6 hr: 1.03 ± 0.29 $\leq 6-9$ hr: 1.01 ± 0.29 ≥ 9 hr: 1.09 ± 0.35 , ($p = 0.26$)	Elderly population.
Ma <i>et al.</i> (37), 2013	Self-Report (PSQI)	CIMT	<u>Self-report sleep duration and Mean CIMT (mm):</u> 3.0–4.9h: 0.657 ± 0.024 5.0–5.9h: 0.615 ± 0.012 6.0–6.9h: 0.624 ± 0.011 7.0–7.9h (Reference): 0.617 ± 0.012 8.0–10: 0.607 ± 0.020 , (p for all = 0.830)	Police officers.

of sensing volume changes in the digit with each arterial pulsation. The volume changes in the fingertip are documented digitally as pulse amplitude that can be tracked over time. The expected response is a post occlusion increase of the PAT signal amplitude and the PAT score is provided automatically by the system's software and is basically the ratio between the post- to pre-occlusion average signal size, corrected for systemic changes and baseline level²⁶. Iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) is a tool used to determine microvascular endothelial function. Two laser-Doppler probes specifically designed with an embedded sponge for skin iontophoresis of agonists are fixed 5 cm apart to the skin with an adhesive patch to measure the endothelium-dependent and endothelium-independent vasodilatation to determine the endothelial function²⁷. The nailfold capillary video microscopy of the dorsal skin of the

third finger is used to determine the endothelial function. The measurements are conducted after at least 30 min of rest and with a minimum hand temperature of 28°C. The microvascular measurements include the duplicate measurements of capillary density at the base of the interphalanx at rest and after 4 min of arterial occlusion²⁸. The arterial stiffness was measured via pulse wave velocity (PWV), and/or ankle brachial index (ABI). The PWV is the time the arterial pressure wave takes to travel a distance between two arterial sites and is measured distance (cm)/time (seconds). Higher value of PWV is directly correlated to the arterial stiffness and when measured over the aorta, it represents an independent risk factor for increased cardiovascular disease¹⁵. There are different methods to measure the PWV that include brachial artery PWV (baPWV), carotid-femoral PWV (cfPWV), heart-femoral PWV (hfPWV) and femoral-ankle PWV

(Cont Table 3a)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Subclinical CVD assessment tools	Results	Comments
Objective Sleep Duration				
Nakazaki <i>et al.</i> (38), 2012	Actigraphy	CIMT	Association of total sleep time by Actigraphy with CIMT ^g : $\beta = -0.32, p = 0.005$ Sleep efficiency (%): Insomnia group vs. non-insomnia group (78.6 ± 11.3 vs. 89.3 ± 7.1); $p < 0.0001$	Elderly population.
Sands <i>et al.</i> (39), 2012	Actigraphy	CIMT	Linear regression for sleep duration (h) on CIMT (mm) Adj ^h : OR (95% CI) Male: $-0.026 (-0.047, -0.005)$; $p = 0.02$ Female: $-0.001 (-0.020, 0.022)$; $p = 0.91$	Model significant in men only.
Ma <i>et al.</i> (37), 2013	Actigraphy	CIMT	Actigraphy measured sleep duration and mean CIMT mm (SE) (Adj ⁱ): 1.7–4.9h: 0.633 ± 0.012 5.0–5.9h: 0.617 ± 0.010 6.0–6.9h: 0.623 ± 0.012 7.0–7.9h (Reference): 0.590 ± 0.019 8.0–10.7: 0.625 ± 0.027 (p for all = 0.692)	Police officers. .
Schwartz <i>et al.</i> (40) 2102	Actigraphy	CIMT	Sleep duration (h) vs. CIMT (mm): β (95% CI) ^j Nighttime sleep duration: $-0.01 (-0.03, 0.01)$; $p \geq 0.05$ Daytime sleep duration: $-0.04 (-0.07, -0.01)$; $p \leq 0.05$	Study was done on elderly Alzheimer Caregivers

^eAdjusted for lifestyle variables include smoking status (number of cigarettes per day), alcohol consumption, physical activity, and shift work; socioeconomic factors include monthly family income, marital status, primary education, vocational status; and biological risk factors include BMI, lipid profile (total cholesterol/HDL cholesterol ratio), diabetes, previous myocardial infarction and hypertension.

^fAdjusted for age, sex, LDL-cholesterol, HDL-cholesterol, triglyceride, fasting plasma glucose, HbA1c, fasting insulin, BMI, alcohol intake (never, monthly, weekly, daily), and current smoking

^gAdjusted for age, gender, BMI, SBP, DBP, PSQI, AHI, lowest SpO₂, sleep efficiency, total sleep time, hypertension, hyperlipidemia, diabetes, sleep apnea syndrome and insomnia.

^hAdjusted for age, race/ethnicity, smoking, education, depression, BMI, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and diabetes

ⁱAdjusted for age, gender, race/ethnicity, abdominal height, systolic blood pressure, anti-hypertensivemedications, glucose, low-density lipoprotein, high-density lipoprotein, lipid lowering medications, sleep quality (Pittsburgh Sleep Quality Index global score after removing sleep duration component), perceived stress score, depressive symptoms score, physical activity index, smoking status, shiftwork, and having a second job.

^jAdjusted for age and gender, education, BMI, physical activity, smoking, hypertension, dyslipidemia, diabetes, history of CVD, Role Overload and depression (CESD-10) scores

(faPWV) and these reflect properties of central, peripheral or mixed properties of both central and peripheral arterial stiffness. All studies used in this review discussed the relationship of sleep parameters with baPWV which is considered as an important parameter of both central and peripheral arterial stiffness²⁹. ABI is a measure reflective of systemic atherosclerosis and predict the stiffness in the vessels. The ABI is the ratio of the systolic blood pressure at the ankle to the average systolic blood pressure at the right arm. The lower the value of ABI below 1.0 correlates with the severity of arterial stiffness³⁰.

Results

Thirty-two studies met the final selection criteria and discussed the relationship of subjective (self-report) and objective (actigraphy and/or polysomnography) sleep duration as well as subjective and objective sleep quality with non-invasive markers of subclinical CVD. Sleep duration and sleep quality are two distinct parameters of sleep, and these are discussed separately along with each non-invasive marker of subclinical CVD in respective tables. Five studies evaluated association of sleep parameters with coronary artery calcium (CAC)^{17, 31-34}, eight evaluated association with carotid intima-media thickness (CIMT)^{2, 35-41}, thirteen evaluated association with endothelial func-

Table 3b. Association of Subjective/ Self-reported and Objective Sleep Quality with Carotid Intima-Media Thickness (CIMT)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Sub-clinical CVD assessment tools.	Results	Comments
Subjective/Self-reported Sleep Quality				
Abe <i>et al.</i> (36), 2011	Self-Report questionnaire	CIMT	Sleep quality was not significantly associated with CIMT ($p \geq 0.05$)	Japanese population.
Nakazaki <i>et al.</i> (38), 2012	Self-Report (PSQI)	CIMT	Association of sleep quality by PSQI with CIMT ^k : $\beta = 0.22$, $p = 0.05$ Mean IMT (mm): Insomnia group vs. non-insomnia group (1.3 ± 0.5 vs. 1.1 ± 0.4); $p = 0.03$	Elderly population only.
Nagai <i>et al.</i> (2), 2013	Self-Report questionnaire	CIMT	Mean IMT (mm): Insomnia group vs. non-insomnia group (1.16 ± 0.37 vs. 1.04 ± 0.30); $p < 0.01$	Elderly patients.
Ma <i>et al.</i> (37), 2013	Self-Report (PSQI)	CIMT	PSQI sleep quality score & CIMT (mm): Pearson correlation coefficient ($r = -0.0762$); $p = 0.235$	Police officers.
Ramos-Sepulveda <i>et al.</i> (41), 2010	Self-Report (HRSD)	CIMT	Association of insomnia with CIMT (mm) Adj ^l : OR (95% CI) 1.08 (0.70–1.66); $\beta = -0.0012$, $p = 0.829$	Multi-ethnic population
Objective Sleep Quality				
Schwartz <i>et al.</i> (40) 2102	Actigraphy	CIMT	Sleep quality vs. CIMT (mm): β (95% CI) ^j Nighttime WASO: 0.04 (0.001, 0.08), $p \leq 0.05$	Study was done on elderly Alzheimer Caregivers

^kAdjusted for age, gender, BMI, SBP, DBP, PSQI, AHI, lowest SpO₂, sleep efficiency, total sleep time, hypertension, hyperlipidemia, diabetes, sleep apnea syndrome and insomnia.

^lAdjusted for age sex, race LDL, HDL BMI hypertension, diabetes, current smoker and any cardiac disease.

^jAdjusted for age and gender, education, BMI, physical activity, smoking, hypertension, dyslipidemia, diabetes, history of CVD, Role Overload and depression (CESD-10) scores.

tion⁴²⁻⁵⁴), and six studies assessed relationship with arterial stiffness^{17, 55-58}). Kim *et al.* 2015 studied both the subjective sleep duration and subjective sleep quality with both CAC as well as PWV in same paper so the results of CAC and PWV outcomes were stated separately in the relevant tables¹⁷. **Table 1** shows the baseline characteristics of all the studies used in this review.

Association of Subjective and Objective Sleep Parameters with Coronary Artery Calcium (CAC)

Table 2a shows the association of subjective and objective sleep duration with CAC. Kim *et al.* showed that association of subjective sleep duration with CAC is “U” shaped with stronger association of short subjective sleep duration with increased CAC. King *et al.* showed that objective longer sleep duration is better predictor of CAC as compared to objective shorter sleep duration with 0.66 times increase in CAC with each hour increase in sleep duration. All other studies did not show any significant association of sleep duration with CAC.

The association of sleep quality with CAC is less

robust with only one study among the total of three showed that poor sleep quality is associated with increased CAC among women only. Objective sleep quality only in the form of arousal index was directly associated with increased CAC as, higher the arousal index, higher the risk of being in a CAC group of CAC ≥ 400 Agatston units (**Table 2b**)

Association of Subjective and Objective Sleep Parameters with Carotid Intima Media Thickness (CIMT)

Table 3a showed that subjective and objective sleep duration were associated with CIMT with stronger evidence present for shorter sleep duration with increased CIMT as compared with reference sleep hours (6–8 hours). The population used in these studies was heterogeneous with mostly elderly and police officers. Among all studies assessing the CIMT, the sleep duration group of average 7 hours exhibited lowest systolic blood pressure and Hemoglobin A1c.

Table 3b showed that most of the studies discussed the relationship of subjective sleep duration with CIMT. Only one study discussed association of

Table 4a. Association of Subjective/ Self-reported and Objective Sleep Duration with Endothelial Function (EF)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Subclinical CVD assessment tools.	Results	Comments
Subjective/Self-reported Sleep Duration				
Behl <i>et al.</i> (43), 2014	Self-Report (PSQI)	EF (FMD)	Total PSQI score was unrelated to brachial artery FMD; $p \geq 0.05$	
Bonsen <i>et al.</i> (52), 2015	Self-Report questionnaire	EF (nailfold Capillaroscopy)	Sleep duration & endothelial function: regression coefficient 95% CI Men: $\beta = -0.79$, 95% CI (-7.20 to 5.63), $p = 0.81$ Women: $\beta = -11.17$, 95% CI (-21.80 to -0.55); $p = 0.04$	Significant only in women
Weil <i>et al.</i> (53), 2010	Self-Report questionnaire	EF [Endothelin (ET)-1 levels]	Sleep duration and endothelial function as ET-1-mediated vasoconstrictor tone: (Correlation) $r = -0.32$; $p < 0.01$	Increased ET-1 vasoconstrictor activity positively correlated with CVD risks.
Weil <i>et al.</i> (54), 2011	Self-Report questionnaire	EF [endothelial progenitor cells (EPCs) functions]	There were no significant correlations between sleep duration and any endothelial progenitor cells (EPCs) measure.	Circulating endothelial progenitor cells (EPCs) are vital to endogenous vascular repair processes and cardiovascular health.
Objective Sleep Duration				
Cooper <i>et al.</i> (42), 2014	Polysomnography	EF (FMD)	Total sleep time (TST) was not associated with FMD: (Correlation) $r = 0.03$; $p \geq 0.05$	

the objective sleep quality with CIMT and it was significant ($p \leq 0.05$). Among these studies insomnia was strongly associated with CIMT as compared to non-insomnia. PSQI as a parameter of sleep quality was discussed only in two studies and was significant only in one study ($\beta = 0.22$, $p = 0.05$).

Association of Subjective and Objective Sleep Parameters with Endothelial Functions

Table 4a discussed the subjective and objective sleep duration with endothelial functions. Among total of five studies, only one study discussed the objective sleep duration and endothelial functions and it was not significant. Among the other four studies, only two studies showed the significant association of subjective sleep duration with endothelial dysfunctions.

Table 4b discussed the subjective and objective sleep quality with endothelial functions. Most of the studies showed a significant association of low sleep quality with reduced endothelial functions. The low sleep quality was expressed variably in these studies by PSQI quality scores, acute sleep deprivation, difficulties initiating sleep or maintaining sleep, REM sleep, REM latency, noise level during sleep, chronic stress vs no stress, shift vs. non-shift workers.

Association of Subjective and Objective Sleep Parameters with Arterial Stiffness

Table 5a discussed the association of subjective sleep duration with arterial stiffness. All studies showed that subjective long sleep duration was associated with increased arterial stiffness; however, only one study showed a relationship between subjective short sleep duration and arterial stiffness and other studies failed to demonstrate such association.

In **Table 5b**, all studies that discussed the subjective association of sleep quality with arterial stiffness, showed a strong positive association of bad sleep quality with arterial stiffness in terms of increased brachial artery pulse wave velocity (baPWV) and decreased ankle brachial index (ABI). There was no study in this review that reported the association of objective sleep quality with arterial stiffness.

Discussion

This systematic review investigated the association of subjectively and/or objectively measured sleep duration as well as sleep quality with non-invasive markers of sub-clinical cardiovascular disease (CVD). According to this review, subjective short sleep duration was associated with CAC and CIMT, but variably

Table 4b. Association of Subjective/ Self-reported and Objective Sleep Quality with Endothelial Function (EF)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Sub-clinical CVD assessment tools.	Results	Comments
Subjective/ Self-reported Sleep Quality				
Behl <i>et al.</i> (43), 2014 Cohort study	Self-Report (PSQI)	EF (FMD)	Low PSQI quality component was associated with lower FMD; $p=0.038$ Higher ESS scores were associated with lower FMD; $p=0.026$	
Cooper <i>et al.</i> (42), 2014 Cross-sectional	Self-Report (PSQI)	EF (FMD)	Total PSQI Scores and FMD%: $\beta = -0.22$; $p=0.024$ % REM sleep and FMD%: $\beta = 0.25$; $p=0.022$ REM latency and FMD%: $\beta = -0.2$; $p=0.036$	
Takase <i>et al.</i> , 2004 (45)	Self-report	EF (FMD)	FMD (%): Controls vs. Chronic stress: 7.4 ± 3.0 vs 3.7 ± 2.3 ; $p < 0.05$	Only male sample
Wehrens <i>et al.</i> , 2012 (46)	Self-report questionnaire	EF (FMD)	There were no significant effects of day, time, group, or interactions on %FMD among both shift and non-shift workers.	Only male sample
Strand <i>et al.</i> (48) 2102 Cross-sectional	Self-report questionnaire	EF (FMD)	There was no evidence for an association of having difficulties initiating sleep or maintaining sleep with FMD in both genders.	
Suessenbacher <i>et al.</i> (49), 2011	Self-report questionnaire	EF (PAT index)	PAT index: shift vs non- shift workers: 1.73 ± 0.4 vs 1.94 ± 0.5 ; $p=0.03$	Only male sample
Sauvet <i>et al.</i> (51), 2009	Self-Report	EF (Iontophoresis of Ach & Na-nitroprusside)	The endothelium-dependent and -independent cutaneous vascular conductance were significantly decreased after 29 h of TSD ($P \leq 0.05$).	40 hours of total sleep deprivation.
Bonsen <i>et al.</i> (52), 2015	Self-report (SWEL)	EF (Nailfold capillaroscopy)	Sleep quality& endothelial function: regression coefficient 95% CI Men: $\beta -3.81$, 95% CI (-9.45, 1.83); $p=0.18$ Women: $\beta 2.11$, 95% CI (-3.14, 7.36); $p=0.43$	

associated with endothelial dysfunction (ED) and arterial stiffness, however subjective long sleep duration was associated with CAC, CIMT and arterial stiffness, but variably associated with ED. Objective short sleep duration was positively associated with CIMT, variably with CAC but not associated with ED. Objective long sleep duration was variably associated with CAC and CIMT but not associated with ED. Poor subjective sleep quality was significantly associated with ED & arterial stiffness but variably associated with CAC& CIMT. Poor objective sleep quality was significantly associated with CIMT, and ED but variably associated with CAC (**Table 6**)

There is a growing body of literature linking sleep duration with CVD outcomes. Sabanayagam *et al.* revealed a higher odds of myocardial infarction and stroke in subjects that slept ≤ 5 h and ≥ 9 h⁵⁹). In 2011, Cappuccio *et al.* performed a systematic review show-

ing that both short and long sleep durations were associated with a greater relative risk of coronary heart disease and stroke⁶⁰). Sleep quality as assessed by insomnia and sleep deprivation have also been linked with adverse CVD outcomes. Westerlund *et al.* revealed that insomnia itself was not related to CVD risk, but when considered together with short sleep duration, there was a higher risk of overall cardiovascular events³). The exact mechanism by which compromised sleep quality lead to CVD is not clear, but possible explanations include changes in hormones and inflammatory markers, lipid levels, glucose tolerance/metabolism, sympathetic nervous system and subclinical atherosclerosis⁶¹). Cappuccio *et al.* performed another systematic review and meta-analysis in 2010 of 10 cohort studies showing that sleep $\leq 5-6$ h and $> 8-9$ h were associated with higher relative risk of developing Type 2 DM⁶²). Gangwisch *et al.* showed

(Cont Table 4b)

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Sub-clinical CVD assessment tools.	Results	Comments
Objective Sleep Quality				
Cooper <i>et al.</i> (42), 2014 Cross-sectional	Polysomnography	EF (FMD)	% REM sleep and FMD%: $\beta = 0.25$; $p = 0.022$ REM latency and FMD%: $\beta = -0.2$; $p = 0.036$	
Calvin <i>et al.</i> (44), 2014 Cross-sectional	Polysomnography (PSG)	EF (FMD)	FMD%: Acclimation phase vs. Experimental phase Sleep restriction group: $8.6 \pm 4.6\%$ vs $5.2 \pm 3.4\%$; $p = 0.01$ Control group: $5.0 \pm 3.0\%$ vs $6.73 \pm 2.9\%$; $p = 0.10$ Group differences: -4.40% . 95% CI (-7.00 , -1.81); $p = 0.003$	Smaller sample
Schmidt <i>et al.</i> , 2013 (47)	Actigraphy	EF (FMD)	FMD% among groups: Control: $10.4 \pm 3.8\%$; Noise30 dB: $9.7 \pm 4.1\%$; Noise60 dB: $9.5 \pm 4.3\%$; $p = 0.052$ A monotone dose-dependent effect of noise level on FMD was significant ($p = 0.020$)	There was a priming effect of noise, i.e. the blunting in FMD was particularly evident when subjects were exposed first to 30 and then to 60 noise events ($p = 0.006$).
Dettoni <i>et al.</i> (50), 2012	Wrist actigraphy	EF (dorsal hand vein technique)	Endothelial dependent venodilatation in sleep groups: Control sleep (>7 h): $100 \pm 22\%$ Partial sleep deprivation (<5 h): $41 \pm 20\%$; $p < 0.05$	5 nights of partial sleep deprivation was sufficient to cause significant venous endothelial dysfunction.

that ≤ 5 hours of sleep significantly increased the risk of hypertension⁶³. Dettoni *et al.* showed that five nights of partial sleep deprivation can significantly cause a trigger in the sympathetic activity and venous endothelial dysfunction and this evidence is in alignment with the association between short sleep and increased cardiovascular risk in other epidemiological studies⁵⁰.

Many animal studies have also found sleep deprivation causes an increase in endothelin levels. Endothelin is a potent vasoconstrictor that has been implicated in the pathogenesis of hypertension⁶⁴. Meier-Ewert *et al.* revealed that both total (88 hrs of no sleep) and short-term partial sleep (4.2 hrs of sleep) deprivation resulted in elevated high-sensitivity CRP concentrations, compared to those who slept 8.2 hours⁶⁵. Sauvet *et al.* demonstrated that total sleep deprivation in rats induces a reduction in endothelial-dependent vasodilation independent of blood pressure and sympathetic activity⁶⁴. Carreras *et al.* showed in mice that long-term sleep fragmentation lead to vascular endothelial dysfunction, mild increase in blood pressure, vascular elastic fiber disruption and disorganization, and increased recruitment of inflammatory

cells⁶⁶. According to a review by Elliott *et al.* sleep deprivation can cause death sooner than food deprivation in both *Drosophila* and rats, further favoring importance of regular sleep habits⁶⁷.

Our review provided mixed results in terms of subjective and/or objective short and/or long sleep duration and sleep quality with sub-clinical CVD, with a greater percentage of studies showing a relationship with sub-clinical CVD. However, only some studies in this review failed to demonstrate such an association^{31, 32, 37, 43} and one possible reason for such results could be due to the use of subjective/self-report versus objectively measured sleep parameters to assess the association with subclinical CVD causing biased results. Lauderdale *et al.* found a correlation between self-reported and objectively measured sleep duration of 0.45, which is generally considered as a moderate correlation. In current review, while one study reports a “J-shaped” association³⁵, the other two study reports a “U-shaped” association^{17, 37} between sleep duration and sub-clinical CVD outcomes. Some studies report a positive association of sleep duration with sub-clinical CVD only with short sleep duration; some only with long sleep duration; some studies show a positive asso-

Table 5a. Association of Subjective/ Self-reported and Objective Sleep Duration with Arterial Stiffness.

First Author, Publication Year, Study Type	Sleep Measurement	Non-Invasive Subclinical CVD assessment tools.	Results	Comments
Subjective/Self-reported Sleep Duration				
Yoshioka <i>et al.</i> (55), 2011	Self-Report questionnaire	baPWV	Association of sleep duration and mean baPWV: PRC (95%CI) Adj ^m : ≤ 5h, 6h, 8 h, $p = \geq 0.05$ ≥ 9hr: 44.69 (17.69-71.69); $p < 0.01$	In gender stratified analyses, ≥ 9h sleep duration was associated with increased baPWV in males only ($p < 0.01$).
Tsai <i>et al.</i> (57), 2014	Self-Report questionnaire	baPWV	Relationship of sleep duration with arterial stiffness: Adj ⁿ Males: Short Sleep: 0.98 (0.72–1.35); $p = 0.920$ Long sleep: 1.75 (1.04–2.94); $p = 0.034$ Females: Short Sleep: 0.86 (0.56–1.31); $p = 0.476$ Long Sleep: 1.02 (0.48–2.15); $p = 0.963$	
Kim <i>et al.</i> (17), 2015	Self-Report (PSQI)	baPWV	Sleep duration (h) vs PWV (cm/s) (Adj ^b): OR (95% CI) < 5h: 6.7 (0.75–12.6) 6h: 2.9 (–1.7 to 7.4) 7h: Reference (0.0) 8h: 10.5 (4.5–16.5) 9h: 9.6 (–0.7 to 19.8); $p = 0.019$	The association between sleep duration and baPWV was U-shaped
Objective Sleep Duration				
Not even a single study have described the association of objective sleep duration with Arterial Stiffness.				

^mAdjusted for age, sex, SBP, hypertension, HR, biological risk factors (BMI, TC, log TG, HDL-C, and FBS), lifestyle factors (education, exercise, smoking, and alcohol consumption), and occupational factors (occupation, working hours, shift work, days off, and job strain)

ⁿAdjusted for age, BMI, eGFR, Hypertension, DM, TC/HDL-C, sleep duration, smoking, alcohol drinking, regular exercise, and snoring ≥ 3/week

^bAdjusted for age, sex, study center, year of visit, education, marital status, depression, smoking status, alcohol consumption, physical activity, body mass index, fasting glucose, systolic blood pressure, diastolic blood pressure, height, and heart rate.

ciation with both short and long duration^{33, 38, 39, 57}) but almost all studies favor the duration of the reference sleep (average 6–8 hours of regular daily sleep). To our surprise, some studies have even shown long sleep hours is related to decrease in CAC³³, decrease in CIMT³⁸⁻⁴⁰, decrease in PWV⁵⁶) and one study by Yoshioka *et al.*⁵⁵) even showed that sleep duration of ≤ 6 hours was associated with a significant decrease in PWV and thus produced a great source of heterogeneity in the review. Although most of the studies in the current review demonstrate that sleep parameters are associated with early sub-clinical CVD, there is, as yet, no consensus on the biological pathways linking these processes. It is entirely possible, given the complexity of factors responsible for sleep habits that sleep disturbances may be an epiphenomenon of subclinical and clinical CVD rather than the proximate cause¹). The population used in these studies is highly heterogeneous based on age and gender differences, and thus no consensus can be made about the particular nature

of subclinical CVD burden due to changes in the sleep parameters in specific age groups and gender.

Our systematic review findings need to be considered in light of the following limitations. The meta-analysis for this review is not applicable because the studies included in our review are highly heterogeneous in population, outcome reporting and sleep duration and quality assessment groups, precluding a quantitative or meta-analytical synthesis of evidence. Some studies reported only subjective measures of sleep duration and sleep quality, some only objective measures, and some both. Not all studies used similar/standardized subjective and objectives measures of sleep duration and quality. Some studies used simple questionnaire to measure sleep duration and quality, some used Pittsburgh Sleep Quality Index (PSQI), some used actigraphy and some used polysomnography creating further heterogeneity in assessment of predictor variable. Furthermore, the reference/control sleep duration used in these studies was not a stan-

Table 5b. Association of Subjective/ Self-reported and Objective Sleep Quality with Arterial Stiffness.

First Author, Publication Year	Sleep Measurement	Non-Invasive Sub-clinical CVD assessment tools.	Results	Comments
Subjective/Self-reported Sleep Quality				
Sunbul <i>et al.</i> (56), 2014	Self-Report questionnaire	baPWV	PWV cm/sec.: [Sleep Deprivation (SD) vs Regular Sleep (RS)]: 5.33 ± 0.46 vs 5.15 ± 0.26; $p=0.001$ Augmentation index (AIx) ² : [SD vs RS]: 20.5 ± 11.9 vs 26.0 ± 8.4%; $p=0.008$	Turkish population.
Kim <i>et al.</i> , 2015 (17)	Self-Report (PSQI)	baPWV	PWV cm/sec.: [Good vs. Poor sleep quality] 95% CI Adj ^b : Men: 0.0 (Ref.) vs. 7.6 (1.2 to 13.9) Women: 0.0 (Ref.) vs. 2.7 (- 5.3 to 10.7)	Poor subjective sleep quality was associated with increase in PWV in men only in adjusted model.
Osonoi <i>et al.</i> , 2015 (68)	Self-Report (PSQI)	baPWV	PWV cm/s: [Among sleep quality groups] (95% CI) Adj ^o Good: 1523 (1500, 1547) Average: 1570 (1533, 1606) Poor: 1604 (1547, 1661); $p<0.05$	Poor sleep quality associated with higher PWV
Yamaki <i>et al.</i> 2015	Self-Report (PSQI)	ABI	PSQI sleep quality score and ABI ($\rho = -0.31$); $p<0.005$	Lower the ABI, more the arterial stiffness.

Objective Sleep Quality

Not even a single study have described the association of objective sleep Quality with Arterial Stiffness.

^b Adjusted for age, sex, study center, year of visit, education, marital status, depression, smoking status, alcohol consumption, physical activity, body mass index, fasting glucose, systolic blood pressure, diastolic blood pressure, height, and heart rate.

^o Adjusted for age, gender, BMI, morningness eveningness questionnaire, Beck Depression inventory, energy intake, alcohol intake, current smoking, physical activity, systolic BP, HbA1c, total cholesterol, HDL-cholesterol, triglyceride and sleep duration

standardized duration, some studies used 6 hours as reference sleep duration, some used 7 hours, some used 8 hours and some studies even used 6–8 hours as reference sleep duration. The assessment of subjective and objective sleep quality was also different among the studies used in this review. Some studies used insomnia vs. non-insomnia, some used shift vs non-shift work, some used fragmentation index and/or arousal index and/or REM/Non-REM sleep to assess the sleep quality. A few studies that examined both subjective and objective sleep parameters demonstrated different outcomes depending on the nature of the predictor variable used in their analysis (subjective versus objective).

Some of the studies included in our review are of questionable methodological quality, which may be another source of observation bias. The population discussed in this systematic review ranges from 20 to 87 years and due to heterogeneous nature of these studies we could not conclude what age groups were at more risk of subclinical CVD based on their sleep disturbances, thus more focused studies directed to

specific age group are needed to further clarify this concern. Furthermore, ethnic-specific variations in sleep parameters and association with subclinical CVD have not been discussed and compared in these studies and thus question the need of further studies discussing the comparison of subclinical CVD burden in the multi-ethnic populations. Another concern is that most of the studies used in this review are cross sectional and as a result, causality cannot be determined. Our findings show the need for follow up studies to assess the rapid progression of subclinical CVD with sleep disturbances. This will further clarify the association of sleep parameters with an increased subclinical and clinical CVD burden. Finally, the implications of the associations demonstrated in our review are unclear. Should individuals with sleep disturbances be considered candidates for subclinical CVD screening? Most sleep disturbance treatment focuses on lifestyle modification, which is beneficial for CVD. However, in scenarios where one is found to have these findings, should one be a candidate for aggressive preventive pharmacotherapy such as Statins? What will be the

Table 6. Snapshot of association of “Non-Invasive Subclinical CVD assessment tools” with Sleep Duration and Sleep Quality

Non-Invasive Subclinical CVD assessment tools	Subjective sleep duration Vs Reference Sleep Duration (6-8 hrs)		Objective sleep duration Vs Reference Sleep Duration (6-8 hrs)		Subjective sleep quality	Objective sleep quality
	Short subjective sleep duration	Long subjective sleep duration	Short objective sleep duration	Long objective sleep duration		
CAC	Association present	Association present	Association variable	Association variable	Association variable	Association variable
CIMT	Association present	Association present	Association present	Association variable	Association variable	Association present
Endothelial function	Association variable	Association variable	Lack of association	Lack of association	Association present	Association present
Arterial stiffness	Association variable	Association present	NR	NR	Association present	NR

NR=Not reported.

Association variable: In this review some studies showed positive and some studies showed negative and some studies showed lack of an association between sleep duration and sleep quality with Non-Invasive Subclinical CVD assessment tools.

Association present: In this review most of the studies showed presence of an association between sleep duration and sleep quality with Non-Invasive Subclinical CVD assessment tools.

Lack of association: In this review most of the studies showed lack of an association between sleep duration and sleep quality with Non-Invasive Subclinical CVD assessment tools.

Subjective Sleep Quality: Expressed as PSQI, good vs PSQI bad sleep quality, insomnia vs non-insomnia, shift vs. non-shift work, arousal index, sleep efficiency (%), REM/Non-REM sleep.

most cost effective method for screening? Unfortunately, no consensus exists in this specific area.

Conclusion

In conclusion, based on our systematic review, individuals with sleep disturbances, both quantitative and qualitative, have an accelerated subclinical CVD burden in the form of augmented Coronary Artery Calcium (CAC), increased Carotid Intima Media Thickness (CIMT), impaired endothelial function, and augmented arterial stiffness. **Table 6** provides a snapshot of association of non-Invasive Subclinical CVD assessment tools with sleep duration and sleep quality. These findings suggest that association between sleep disturbances and increased CVD risk is exemplified by early changes in sub-clinical CVD status. Important issues that need further exploration include the public awareness of regular sleep habits, and potential consequences of compromised sleep duration and quality in terms of causing hypertension, high cholesterol and risk of diabetes. There is a need to identify appropriate screening and treatment strategies across different group of populations with sleep disturbances and whether these preventive approaches can slow progression of sub-clinical CVD and reduction in clinical events. Comprehensive studies aimed at answering these key questions can facilitate generation of information to guide preventive efforts in this

population.

Conflict of Interests

M. Aziz, SS. Ali, S. Das, A. Younus, R. Malik, M. Latif, Choudhry H, D. Anugula, G. Abbas, Joseph S, JV Elizondo, E Veledar, and K. Nasir stated that no conflict of interest exists. No financial support was given and that no off-label or investigational use of a drug or device was performed as part of this research.

Author Contributorship

Conception and design: Aziz, M; Veledar, E; Nasir, K. Analysis and interpretation: Aziz, M; Das. S; Ali, SS. Data collection: Latif, M; Malik, R. Table formation: Aziz, M; Younus, A; Choudhry, H; Writing the article: Aziz, M; Das. S; Ali. SS; Salami, J. Critical revision of the article: Elizondo JV; Anugula, D; Younus, A; Final approval of the article: Aziz, M; Abbas, G; Nasir, K. Obtained funding: N/A. Overall responsibility: Aziz, M; Nasir, K

Abbreviations Frequently used in this Review

CAC=Coronary Artery Calcium, CIMT=Carotid Intima Media Thickness, ED=Endothelial dysfunction, AS=Arterial stiffness, baPWV=brachial artery

Pulse Wave Velocity, PSQI=Pittsburgh Sleep Quality Index, PSG=Polysomnography

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