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ANEMIA AND INSOMNIA: A CROSS-SECTIONAL STUDY AND META-ANALYSIS

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ABSTRACT

The association between iron deficiency anemia and the prevalence of insomnia has been studied in the pediatric population, but not well understood in adults. We examined whether adults with anemia had higher odds of having insomnia relative to those without anemia in a cross-sectional study and a meta-analysis. The cross-sectional study included 12,614 Chinese adults who participated in an ongoing cohort, the Kailuan Study. Anemia was defined as hemoglobin levels below 12 g/dL in women and 13 g/dL in men. Insomnia was assessed using the Chinese version of Athens Insomnia Scale (AIS). A total AIS score ≥6 was considered insomnia. The association between anemia and insomnia was assessed using a logistic regression model, adjusting for potential confounders such as age, sex, chronic disease status, and plasma C-reactive protein (CRP) concentrations. A meta-analysis was conducted using a random-effect model to pool results from our study and three previously published cross-sectional studies on this topic in adult populations. All of these studies used a cross-sectional study design. Prevalence was 4.5% and 10.6% for anemia and insomnia, respectively. Individuals with anemia had greater odds of having insomnia (adjusted OR, 1.32; 95% CI, 1.03 to 1.70) compared to individuals without anemia. Significant association persisted after we excluded individuals with chronic inflammation, as suggested by C-reactive protein levels <1mg/L (adjusted OR, 1.68; 95% CI, 1.22 to 2.32). The meta-analysis results, including 22,134 participants, also identified a positive association between anemia and insomnia (pooled OR, 1.65; 95% CI, 1.29 to 2.11). Presence of anemia was significantly associated with a higher likelihood of having insomnia.

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Chapter 1

Introduction and Literature Review

Introduction

Insomnia affects approximately one-third of the population, with 50% of those patients classified as chronic (1,2). It is defined as subjective reports of difficulty falling or staying asleep and nonrestorative sleep (1,2). Insomnia has been linked to psychosocial, psychiatric, and medical disorders and poorer quality of life (3,4). It can impair daytime functioning and decrease memory performance (3,5). Patients with insomnia have been more likely to report headaches, muscle, back, or neck pain, engage in a poorer quality of life, and are more likely to be depressed (3,4). Although insomnia remains one of the most prevalent health concerns in the population, physicians are reluctant to address patient concerns due to idiopathic causes and unfamiliarity with therapy and pharmacologic interventions (6). It is thus of clinical significance to grasp a better understanding of insomnia pathogenesis and identify risk factors for insomnia.

Definition of Insomnia

According to the *International Classification of Sleep Disorders, Second Edition*, general insomnia disorder is defined as "a report of difficulty initiating sleep, difficulty maintaining sleep, or waking too early or sleep that is chronically non-restorative or poor in quality" (7). It is important to note that another characteristic is the difficulty of sleep persists despite opportunity for sleep. Although

nonrestorative sleep and sleep deprivation may be symptoms of insomnia, they are clinically different diagnoses encompassing different epidemiological and functional factors (6). The final clinical evaluation of insomnia is reports of at least one of the following daytime impairments resulting from nighttime sleep difficulty: fatigue or malaise, attention, concentration, or memory impairment, social or vocational dysfunction or poor school performance, mood disturbance or irritability, daytime sleepiness, motivation, energy, or initiative reduction, proneness for errors or accidents at work or while driving, tension, headaches, or gastrointestinal symptoms in response to sleep loss, and concerns or worries about sleep (7). Insomnia may involve altered perceptions of sleep, as identified by comparison of patient reports to polysomnographic data. Many patients reporting insomnia symptoms overestimated sleep latency and wakefulness throughout the night while also underestimating sleep duration (6).

Insomnia has often been classified as a psychological disorder because many early studies were unable to find physiological differences in insomnia patients compared to control patients. However, recent studies have disproved this (8,9). Increased physiological activation such as increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions have been identified in insomniacs 30 minutes before and throughout sleep compared to controls (9). Studies of sleep-onset insomniacs have shown increased frontalis and mentalis electromyograph (EMG), increased heart rate, increased finger temperature, and more beta and less alpha frequencies on their electroencephalogram (EEG) before sleep-onset and normalized during sleep-onset (except EEG changes, which were also seen again during stage 1 of sleep and during REM) (10,11). Along with some changes in EEG studies, functional neuroimaging studies have shown declining brain activity from waking to sleep states in the brainstem thalamus, and prefrontal cortex (12). There are also metabolic reductions in the thalamus, frontal cortex, and parietal cortex after sleep deprivation, contributing to daytime impaired cognition and increased daytime fatigue (13). It has also been shown that poor sleepers have an increased secretion of corticosteroids and adrenaline (14–16), evidencing that insomnia is associated with hyperarousal during sleep (6).

Insomnia is often characterized by subtypes describing the most predominant symptom. The most prevalent subtype in epidemiological studies is 50-70% reporting sleep maintenance symptoms, followed by 35-60% reporting difficulty initiating sleep, and 20-25% reporting nonrestorative sleep (17). Although one symptom characterizes a subtype, many cases of insomnia report multiple sleep symptoms, which is more common than any other single symptom (18). Insomnia can also be diagnosed as primary or secondary, determined by whether insomnia is being caused by another factor (medical or mental condition, or pharmacological or substance use). This is often difficult to discern because many causes of insomnia are currently unknown, and also insomnia is a risk factor for many other disorders (6). These risk factors include heart disease and depression, and anemia, which is what is explored in this research (19,20). Because of these risk factors, the term *comorbid insomnia* is used as a preferred substitute to *secondary insomnia* (21).

Risk Factors, Outcomes, and Diagnosis of Insomnia

Risk factors for insomnia include depression, female sex, older age, lower socioeconomic status, concurrent medical and mental disorders, divorced/separated individuals, and individuals of African American race (22). Outcomes and consequences of insomnia include reduced productivity, increased absenteeism, increased health care costs, greater risk for mental disorders, metabolic syndrome, hypertension, and coronary heart disease, and worse treatment outcomes for patients with depression and alcoholism. (23–26).

Diagnosis of insomnia involves review and evaluation of a patient's clinical history and relevant comorbidities. Predisposing, precipitating, and perpetuating are known as the 3-P model to assess insomnia (27). Predisposing factors, such as a family history of insomnia and a lifelong inclination for poor sleep, increases the risk of developing insomnia. Precipitating factors, such as medical, environmental, or psychosocial stressors, constitute a pattern of poor sleep. Perpetuating factors are

behaviors that continue poor sleep, such as spending more time in bed and stressing more about loss of sleep. Other characteristics include maladaptive behaviors, thoughts, and beliefs regarding sleep (28,29). Tools such as sleep-wake diaries that detail timing and variability of sleep episodes can be an important aid in helping clinicians assess insomnia (30).

Treatment of Insomnia

Treatment goals for insomnia include improvements in qualitative and quantitative reports in sleep, reduction in stress and anxiety related to poor sleep, and improvements in daytime functioning (31). Insomnia treatment falls under two categories: cognitive-behavioral treatment and medication treatment. Non-clinical interventions include patients utilizing self-help methods, such as reading, relaxation, sleep hygiene education, alcohol, antihistamines, and herbal remedies (17).

The most prevalent nondrug treatment used is cognitive behavioral therapy for insomnia (CBT-I). Practices include the use of sleep diaries, patient investment in changing behaviors, and voluntary waking behaviors to enhance sleep (6). In meta-analysis studies, 6-10 weeks over CBT-I has been comparable or superior to the treatment effects of hypnotic medications and maintained for up to 3 years (32).

US Food and Drug Administration (FDA) approved hypnotic agents include benzodiazepine receptor agonists (BzRAs), antihistamine drugs such as hydroxyzine and diphenhydramine, a tricyclic drug known as doxepin, and a melatonin receptor agonist known as ramelteon (6). BzRA drugs, such as temazepam, triazolam, zolpidem, zaleplon, and eszopiclone, act by binding to a recognition site on y-aminobutyric acid type A (GABA-A) receptors. Depending on the specific binding site, the BzRA drugs produce sedative, amnestic, anxiolytic, myorelaxant, and anticonvulsant effects (33). Adverse effects for BzRA drugs include morning sedation, anterograde amnesia, anxiety, impaired balance, increased falls, sleepwalking, and sleep-related eating, driving, and sexual behavior (34). Doxepin is used for clinical depression at doses of 100 to 200 mg, and it is also used for insomnia at doses of 3 to 6 mg.

Larger doses affect multiple central nervous system neurotransmitters while small doses only affect histamine 1 receptors, which can induce fatigue (6). Ramelteon is a melatonin 1 and 2 receptor antagonist and acts like melatonin to induce sedation (35).

Other FDA-approved drugs like barbiturates, ethchlorvynol, and chloral hydrate have potential toxicity and are not normally recommended (6,17). Drugs such as anxiolytic benzodiazepines, sedating antidepressants, sedating antipsychotics, and anticonvulsants are also prescribed to patients, however, these drugs do not have an FDA indication for insomnia (36). Treatment of insomnia by primary physicians is appropriate due to its prevalence in the population. Referral to sleep specialists may prove favorable when patients present symptoms of narcolepsy, apnea, sleep-related breathing disorders, circadian rhythm sleep disorder, parasomnia, or patients looking for CBT-I that are not responsive to hypnotics (6).

Iron-deficiency and Insomnia in Genetics

Interestingly, a recent genome-wide association study (GWAS) found that MEIS1, a gene associated with restless legs syndrome (RLS) and iron-deficiency anemia, also exhibits pleiotropy for insomnia (37). The study used 113,006 individuals to identify risk factors for insomnia complaints. Three loci and seven genes were found to be associated with insomnia complaints, with MEIS1 being the gene most strongly associated. A similar significant association between MEIS1 and insomnia was observed in another recent GWAS involving 1,331,010 individuals (38).

Iron-deficiency and Insomnia in Children

Consistently, anemia, particularly iron deficiency anemia (IDA), has been found to be associated with sleep alterations in infancy and children (39–42). Iron deficiency refers to the decrease in iron stores

of an individual. If left untreated or becomes severe, iron deficiency can lead to iron deficiency anemia where red blood cells are microcytic and hypochromic. IDA is the leading cause of anemia. Risk factors include insufficient dietary intake, loss of blood, vegetarian eating habits, and malabsorption (43). One study involving infants from Nepal and Zanzibar reported IDA related to increased night waking and reduced total sleep duration, hypothesizing that IDA may reduce dopamine receptor levels and disrupt dopamine regulation and metabolism (39). Dopamine plays an important role in REM sleep quality, quantity, and timing through neuromodulation of the dopamine system (41). Another study found altered sleep spindle patterns in infants with IDA. Reduced spindle index, longer inter-spindle interval, and lower spindle frequency during non-rapid-eye-movement (NREM) sleep stage 2 and slow-wave-sleep (SWS) were observed in IDA infants compared to non-anemic controls, while duration of sleep stages and spindles did not differ between each group. Along with dopamine dysregulation, authors hypothesized that iron has a role in linking the thalamus to the cortex, which regulates sleep spindle patterns. Sleep spindle dysregulation could also be a result of dopamine and other neurotransmitter imbalance (40). Another study found that children with IDA had longer rapid-eye-movement (REM) sleep episodes in the first third and shorter REM sleep episodes in the last third of the night compared to controls. This may be explained by REM sleep rebound effect, which IDA children may experience in the first part of the night due to longer durations of the prior daytime waking episode. It is also hypothesized that due to iron's role in myelination, IDA children may experience disruptions in myelin quantity, quality, composition, and compaction affecting neural signaling in sleep regulation (41).

Iron-deficiency and Insomnia in Adults

However, to the best of our knowledge, only three studies to date have examined the relationship between anemia and insomnia in the adult population and reported a positive association between these two disorders (44–46). A cross-sectional analysis of 2,002 adults from South Korea found a significant

association between anemia and insomnia (OR, 1.28; 95% CI, 1.07 to 1.52) (44). Studying 1,053 adults from the Baltimore Longitudinal Study of Aging, Chen-Edinboro found that individuals with non-iron deficient anemia were at greater risk of occurrence and severity of insomnia (OR, 2.39; 95% CI, 1.40 to 4.07) (45). Another cross-sectional study of 6,465 adults from England found that men with disturbed sleep had higher prevalence of anemia (OR, 1.73; 95% CI, 1.13 to 2.65) as well as disturbed sleep in women was associated with greater likelihood of anemia (OR, 1.59; 95% CI, 1.02 to 2.46) (46). These studies are limited by failure to adjust for some important confounders (e.g., other sleep parameters (44–46) and inflammation status (44,45). Further, the dose-dependent relationship between hemoglobin levels and insomnia were not explored (44–46).

We therefore conducted a large-scale, community-based study of over 10,000 adults to evaluate whether the presence of anemia status was associated with higher likelihood of having insomnia 6 years later. We further conducted a meta-analysis to combine our results with previous population-based studies on this topic.

Chapter 2

Materials and Methods

Participants

The current cross-sectional study was based on a subset of the population from the Kailuan cohort. This ongoing cohort consists of 101,510 Chinese adults (81,110 men and 20,400 women) aged 18-98 years living in Tangshan City, China (47). In 2006-2007 when the cohort was first conducted, all participants completed a baseline questionnaire assessing lifestyle habits, health status, and clinical and laboratory assessments. These assessments were re-evaluated every two years. Sleep parameters such as

insomnia, daytime sleepiness, snoring, and sleep duration were assessed in 2012 among 12,990 participants at the Kailuan General Hospital, as detailed previously (48,49). We excluded 376 participants with incomplete assessment of sleep parameters, hemoglobin levels, and other major covariates (e.g., C-reactive protein and serum creatine) leaving 12,614 participants (10,392 men and 2,222 women) for the current analysis. The study was approved by the Ethics Committee of the Kailuan Medical Group. All participants gave their written informed consent.

Assessment of Anemia (Exposure)

Anemia was assessed using hemoglobin levels measured in 2006. Overnight fasting (8-12 h) blood samples were collected in the 2006 survey. Hemoglobin was assessed using sodium lauryl sulfate-hemoglobin (SLS-Hb) method (SULFOLYSER, SYSMEX medical electronics (Shanghai) co. LTD., Shanghai, China) at the central laboratory of the Kailuan hospital, with a detection range of 0-250 g/L. Laboratory variable coefficients for hemoglobin were ≤1.5%. Anemia was defined as hemoglobin levels below 12 g/dL in women and below 13 g/dL in men (50). To test the dose-dependent relationship, participants were further classified as normal hemoglobin levels (≥ 13 g/dL in men and ≥ 12 g/dL in women), mild anemia (12-12.9 g/dL in men, and 11-11.9 g/dL in women), moderate anemia (9-11.9 g/dL in men, and 8-10.9 g/dL in women), and severe anemia (≤ 9 g/dL in men, and ≤ 8g/dL in women) (51).

Assessment of Insomnia (Outcome)

During the 2012 visit, insomnia was assessed using the Chinese version of the Athens Insomnia Scale (AIS), which was delivered by a trained healthcare professional at the Kailuan General Hospital. The questionnaire includes a total of eight self-reported questions. The first five items of the questionnaire investigate sleep procedure (sleep induction, night awakening, awakening in the early morning, total sleep

duration, and quality of sleep). The last three items of the questionnaire assess decreased sense of well-being, overall functioning, and daytime sleepiness. Each question is scored on a scale of 0-3, with 0 being no problem of the corresponding sleep parameter and 3 being a serious problem (occurrence of greater than 3 times a week in the past month). A total AIS score $\geq$6 was considered insomnia (52). The AIS questionnaire has been validated in China with 83% test-retest readability, 96% sensitivity, and 76% specificity (52).

Assessment of Covariates

Information collected in 2006 via a questionnaire included age, gender, head injury, education level (primary, secondary, or university), income level (<600, 600-1000, >1000 RMB/month), occupation (white collar, blue collar, or coalminer), physical activity status (never, <4 times/week, or $\geq$4 times/week), smoking status (never, past smoker, or current smoker), and alcohol consumption (never, past drinker, or current drinker). History of myocardial infarction, stroke, and cancer were confirmed by review of medical records (49,53).

Trained field workers measured height and weight to obtain BMI (kilograms) / height (meters squared). Blood pressure (BP) was measured twice in the seated position using a mercury sphygmomanometer; the average of the two readings was used for analyses. Hypertension was defined as $\geq$140 mmHg systolic and $\geq$90 mmHg diastolic BP readings, or use of antihypertensive medication prior to two weeks. Prehypertension was defined as systolic BP 120-129 mmHg and diastolic BP 80-89 mmHg. Blood concentrations for glucose, triglycerides, HDL cholesterol, LDL cholesterol, and creatinine were measured via an enzymatic method using an autoanalyzer at Kailuan General Hospital. Diabetes was defined as a fasting blood glucose level $\geq$7 mmol/L, or any active insulin-related medication. A fasting blood glucose level of 5.6-6.9 mmol/L was defined as impaired fasting glucose. Estimated glomerular filtration rate (eGFR) was computed using serum creatinine, sex, and age, according to the CKD

Epidemiology Collaboration equation (53). Plasma high sensitive C reactive protein (hs-CRP) concentrations were measured using a high-sensitivity, particle-enhanced immunonephelometric assay (Cias Latex CRP-H, Kanto Chemical Co. Inc.), as detailed previously (54).

Statistical Analyses

Existing data was used and analysis was completed for this study. We used the SAS statistical package (version 9: SAS Institute, Cary, NC) for the cross-sectional analyses, and STATA (version SE15; College Station, TX) for the meta-analysis.

Cross-Sectional Analysis

This study should be considered cross-sectional due to lack of insomnia assessment at baseline in 2006, preventing us from establishing a causality and temporal relationship between anemia and insomnia. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between anemia and insomnia. We adjusted for covariates, which could be associated with both the exposure and the outcome, including age, sex, education level, income level, occupation, physical activity, smoking status, alcohol status, body mass index, history of myocardial infarction history, stroke history, cancer history, hypertension, diabetes (yes/no for each), eGFR and blood concentrations of triglycerides, low-density lipoprotein, and high-density lipoprotein. We used a binary variable of anemia as the primary exposure. In a secondary analysis, we calculated the ORs for insomnia across four hemoglobin categories to explore the potential dose-dependent response relationship.

Because we did not have information on whether the anemia status was defined as iron-deficient or non-iron deficient, we conducted a sensitivity analysis by excluding individuals with chronic inflammation (hs-CRP $\geq$1 mg/L). Because poor kidney function is associated with both reduced

hemoglobin production (55) and increased risk of insomnia (53), we conducted another sensitivity analyses by excluding those participants with severe chronic kidney disease or kidney failure (eGFR <30 mL/min per 1.73 m^2).

We explored potential interactions between anemia status and age (<60y vs ≥60 y) and sex in relation to odds of having insomnia by including multiplicative terms in the logistic regression models with adjustment for aforementioned covariates.

Meta-analysis

As part of this thesis, we identified relevant studies by searching the Medline and the PubMed for all published studies from 1966 through June 2018, using the following search algorithm: (anemia OR iron-deficiency anemia OR hemoglobin) AND (insomnia OR sleep disorder). We also manually searched the reference lists of relevant publications to identify additional studies. The studies that were included in the meta-analysis had to 1) be human studies including at least 40 participants, and 2) be conducted among adult populations (age >18). Three previously published studies were identified (Supplementary Table 1) (44–46). The pooled OR was calculated using the random-effects model because significant heterogeneity across studies was detected by Q statistic (P for heterogeneity =0.005). We also calculated I^2 value, which describes the percentage of variation across the studies due to heterogeneity.

Chapter 3

Results

Cross-Sectional Analysis

Approximately 4.5% of the population was defined to have anemia based on hemoglobin levels and 15.2% of the population reported to have insomnia (Table 1). Basic characteristics of the participants are present in Table 1.

Table 1 The basic characteristics in 2006 according to anemia status

		Anemia	
		No	**Yes**
N		12076	538
Age, year		54.5 ± 11.1	54.2 ± 13.1
Men, %		83.7%	53.4%
Athens Insomnia Scale Score (AIS)	<6	89.4%	84.8%
	≥6	10.6%	15.2%
The Epworth Sleepiness Scale score (ESS)	<10	97.9%	97.6%
	≥10	2.13%	2.42%
Head injure	Yes	2.55%	2.04%
Education level	Primary school	8.90%	8.18%
	High school	81.8%	78.3%
	College	9.32%	13.6%
Income level (RMB/month)	<600	33.3%	31.7%
	600-1000	60.0%	55.1%
	>1000	10.7%	13.3%
Occupation	White collar	7.12%	12.4%
	Blue collar	51.2%	67.4%
	Coalminer	41.7%	20.2%
Physical activity	Never	8.66%	8.63%
(each time more than 20 min)	<4 times/week	77.2%	77.5%
(each time more than 20 min)	≥4 times/week	14.1%	13.9%
Smoking status	Never	47.2%	70.6%

	Past smoker	6.97%	5.20%
	Current smoker	45.8%	24.2%
Alcohol consumption	Never	43.5%	60.8%
	Past drinker	4.31%	4.09%
	Current drinker	52.2%	35.1%
Myocardial Infarction history	Yes	1.11%	1.87%
Stroke history	Yes	2.85%	2.60%
Cancer	Yes	0.33%	0.37%
Hypertension	Yes	48.5%	35.1%
Diabetes	Yes	12.1%	7.06%
Body Mass index (BMI, kg/m^2)	-	25.2 ± 3.47	24.1 ± 3.63
LDL_C (mmol/L)	-	2.23 ± 0.71	2.01 ± 0.84
HDL_C (mmol/L)	-	1.57 ± 0.39	1.58 ± 0.39
Triglyceride (mmol/L)	-	1.60 ± 1.29	1.21 ± 1.03
eGFR,ml/min/1.73m^2		81.7 ± 21.2	80.5 ± 15.6

Footnotes: eGFR, estimated glomerular filtration rate; LDL_C, low density lipoprotein cholesterol; HDL_C, high-density lipoprotein cholesterol.

Individuals with anemia had a higher prevalence of insomnia, relative to those without anemia (15.2% vs 10.6%). Presence of anemia was associated with 32% increased odds (adjusted OR, 1.32; 95% CI, 1.03 to 1.70) of having insomnia six years later, relative to those without anemia (Table 2), after adjustment for potential confounders. The association became stronger after we excluded those with chronic inflammation, as suggested by hsCRP concentration ≥1 mg/L (Table 2). Excluding individuals with eGFR<30 mL/min/1.73 generated similar results (Table 2). We observed a marginally significant dose-dependent response relationship between anemia severity and odds of having insomnia (P-

trend=0.06) (Table 3). Severe anemia, but not mild and moderate anemia, was significantly associated with higher odds of insomnia (adjusted OR, 1.95; 95% CI, 1.06 to 3.62) (Table 3).

Table 2 The odds ratios (ORs) and 95% confidence intervals (95% CIs) of insomnia according to anemia status (yes/no).

	Anemia		
OR(95%CI)	No	Yes	P-value
Model 1	Ref	1.52 (1.19-1.94)	<0.001
Model 2	Ref	1.32 (1.03-1.70)	0.040
Excluding participants with CRP>1 mg/L [1]	Ref	1.68 (1.22-2.32)	0.002
Excluding participants with eGFR<30 mL/min/1.73 m^2	Ref	1.30(1.01-1.67)	0.045

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, education level (primary, middle, college), income level (<600RMB/month, 600-1000 RMB/month, >1000 RMB/month), occupation (white collar, blue collar, coalminer), physical activity (never, <4 times/week, 4+ times/week), smoking status (never, past smoker, current smoker), alcohol status (never, past drinker, current drinker), myocardial infarction history (no, yes), stroke history (no, yes), cancer history (no, yes), hypertension (no, prehypertension, hypertension), diabetes(no, prediabetes, diabetes), body mass index (<24kg/m2, 24-28kg/m2,≥28kg/m2), triglyceride (<0.82mmol/L, 0.82-1.22mmol/L, 1.22-1.87mmol/L,≥1.87mmol/L), low density lipoprotein (<1.76mmol/L, 1.76-2.12mmol/L, 2.12-2.65mmol/L, ≥2.65mmol/L), C-reactive protein (mg/L) and high-density lipoprotein (<1.31mmol/L, 1.31-1.54mmol/L, 1.54-1.79mmol/L,≥1.79mmol/L).

CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate

Table 3 The odds ratios (ORs) and 95% confidence intervals (95%CIs) of insomnia according to four anemia groups

	Normal	Mild	Moderate	Severe	P-trend
Total population (n/case #)	1278/12076	49/313	19/153	14/72	---
Model 1	Ref	1.29(0.63-1.67)	1.02(0.63-1.67)	2.08 (1.15-3.76)	0.040
Model 2	Ref	1.33(0.97-1.84)	1.04(0.64-1.71)	1.95 (1.06-3.62)	0.060

Normal was defined as the level of hemoglobin more than or equal to 130 (if man,g/L)/120 (if woman,g/L); Mild anemia was defined as the level of hemoglobin more than or equal to 120 and less than 130 (if man,g/L)/more than or equal to 110 and less than 120 (if woman,g/L); Moderate anemia was defined as the level of hemoglobin more than or equal to 90 and less than 120 (if man,g/L)/more than or equal to 80 and less than 110 (if woman,g/L); severe anemia was defined as the level of hemoglobin less than 90 (if man,g/L)/80 (if woman,g/L).

Model 1 adjusted age and sex. Model 2 adjusted for age, sex, education level (primary, middle, college), income level (<600RMB/month, 600-1000 RMB/month, >1000 RMB/month), occupation (white collar, blue collar, coalminer), physical activity (never, <4 times/week, 4+ times/week), smoking status (never, past smoker, current smoker), alcohol status (never, past drinker, current drinker), myocardial infarction history (no, yes), stroke history (no, yes), cancer history (no, yes), hypertension (no, prehypertension, hypertension), diabetes (no, prediabetes, diabetes), hemoglobin, body mass index (<24kg/m2, 24-28kg/m2,≥28kg/m2), triglyceride (<0.82mmol/L, 0.82-1.22mmol/L, 1.22-1.87mmol/L,≥1.87mmol/L), low density lipoprotein (<1.76mmol/L, 1.76-2.12mmol/L, 2.12-2.65mmol/L, ≥2.65mmol/L), and high-density lipoprotein (<1.31mmol/L, 1.31-1.54mmol/L, 1.54-1.79mmol/L,≥1.79mmol/L).

The association between anemia and insomnia was modified by sex. It was stronger in men (adjusted OR, 1.70; 95% CI, 1.22 to 2.36), but not significant in women (adjusted OR, 1.03; 95% CI, 0.69 to 1.52) (P-interaction <0.01). In contrast, we did not find a significant interaction between anemia and age in relation to insomnia.

Table 4 The sex-specific odds ratios (ORs) and 95% confidence intervals (95% CIs) of sleep problems according to anemia status

	Anemia		
	No	Yes	p-interaction
Sex			0.040
Men	Ref	1.70 (1.22-2.36)	
Women	Ref	1.03 (0.69-1.52)	

Adjusted for anemia status, age, sex, education level (primary, middle, college), income level (<600RMB/month, 600-1000 RMB/month, >1000 RMB/month), occupation (white collar, blue collar, coalminer), physical activity (never, <4 times/week, 4+ times/week), smoking status (never, past smoker, current smoker), alcohol status (never, past drinker, current drinker), myocardial infarction history (no, yes), stroke history (no, yes), cancer history (no, yes), hypertension (no, prehypertension, hypertension), diabetes (no, prediabetes, diabetes), hemoglobin, body mass index (<24kg/m2, 24-28kg/m2,≥28kg/m2), triglyceride (<0.82mmol/L, 0.82-1.22mmol/L, 1.22-1.87mmol/L,≥1.87mmol/L), low density lipoprotein (<1.76mmol/L, 1.76-2.12mmol/L, 2.12-2.65mmol/L, ≥2.65mmol/L), and high-density lipoprotein (<1.31mmol/L, 1.31-1.54mmol/L, 1.54-1.79mmol/L,≥1.79mmol/L).

Meta-Analysis

In the meta-analysis pooling the current study and three other studies, including 9,520 participants from the United States, South Korea, and England, the overall association was statistically significant in the relationship between anemia and insomnia risk (OR, 1.65; 95% CI, 1.29 to 2.11; I-squared 72.9%) (Figure 1).

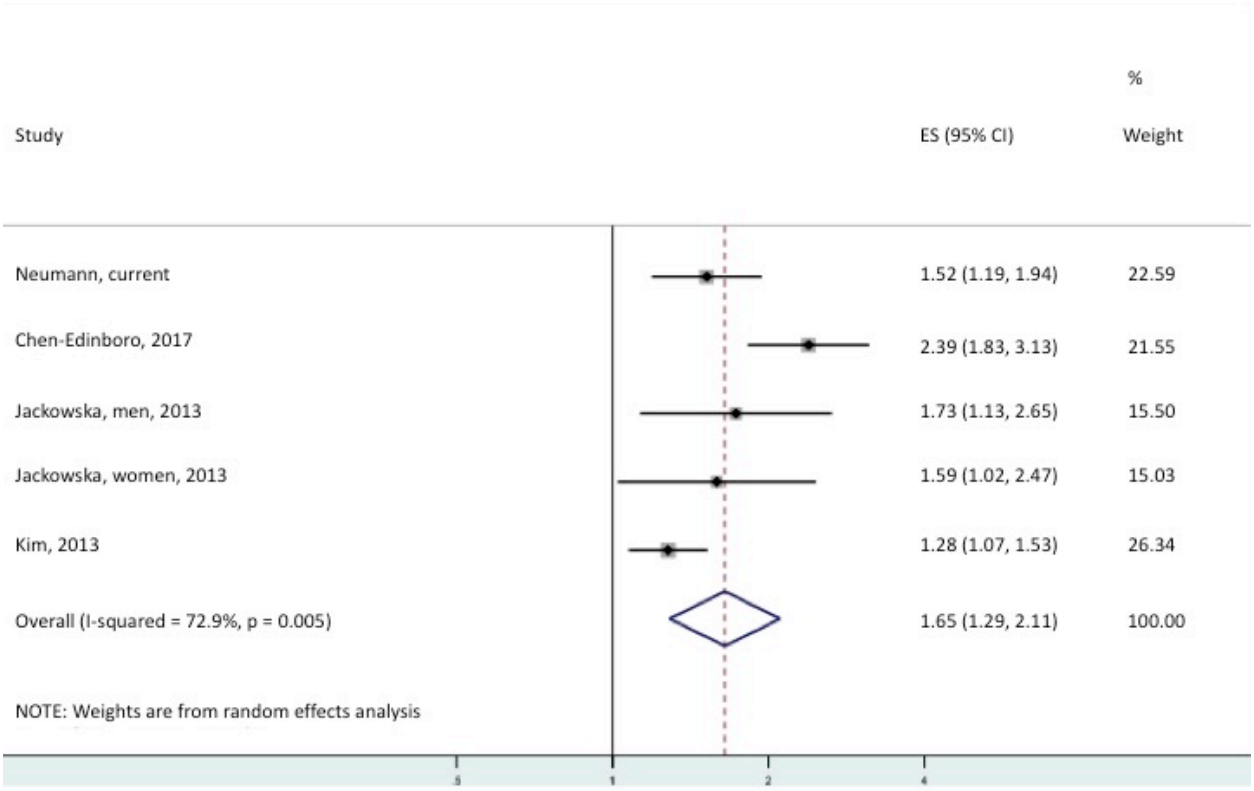

Figure 1 Meta analysis of association between anemia and insomnia

Squares indicate study-specific odds ratios (ORs); error bars indicate 95% confidence intervals (CIs); diamond indicates OR and 95% CIs from pooled analysis. p = 0.005 for heterogeneity test. I-squared = 72.9%

Chapter 4

Discussion

In this large-scale community-based study of over 12,000 participants, we found that anemia was associated with higher odds of having insomnia. This finding was further supported by a subsequent meta-analysis on this topic. A sex difference was also observed; the relationship was substantial in men but no relationship was observed in women. This study has several strengths. To our knowledge, it has

the largest sample size out of all the relevant publications. Further, the meta-analysis contributes a larger pooled sample size, offering greater support for our results. We adjusted for many covariates, including inflammation status, daytime sleepiness, sleep duration, and snoring status, showing that our results were independent from these factors. The study also differentiated between sex, age, and anemia status, and included a validated insomnia questionnaire.

Our observation is consistent with previous epidemiological studies on this topic. In a cross-sectional study using the Baltimore Aging Longitudinal Study, Chen-Edinboro *et al.* reported that patients with non-iron deficient anemia were associated with a higher likelihood and greater severity of insomnia compared to non-anemic participants (45). However, in this study, iron-deficient anemia was not examined due to low prevalence (0.9%). Kim *et al.* found a significant association between anemia and insomnia in a South Korean population of 2,002 participants (44). In a cross-sectional study from England, Jackowska *et al.* discovered that anemia was more prevalent among men with disturbed sleep (46).

The exact underlying mechanisms for the observed anemia-insomnia relationship remain unclear. One potential explanation is that iron deficiency could increase insomnia risk through a shared gene. Interestingly, two genome-wide association studies showed that the MEIS1 gene, which is associated with iron status (37,56), was associated with insomnia. Consistent with this notion, we found that the association between anemia and insomnia became stronger after we restricted our analysis to those participants without chronic inflammation. This result also suggests that inflammation, another major cause of anemia, may not be the major contributor for the observed anemia-insomnia relationship. In sleep studies conducted in children, it has been postulated that IDA affects temporal organization during sleep. Pierano *et al.* found that children with IDA present a longer REM sleep episode in the first third of the night and shorter in the last third of the night compared to non-IDA children (42). The dopamine system plays an important role in REM sleep quantity, quality, and timing. In the basal ganglia, high concentrations of iron are highly connected to REM-regulatory structures, and supplementation of iron

may not correct early iron deficiency in this area (42). Further, disruption in iron availability or storage can affect its normal role in myelination, leading to a decreased efficiency in neural signals in sleep organization circuitry (42).

Other pathways could also be involved in the observed association between anemia and insomnia. For example, fatigue as a symptom of anemia (46) may induce sleep problems due to the reduction of physical activity during the day or light exposure variants that may affect the circadian rhythm and sleep patterns. Another potential mechanism of this phenomenon may be explained by altered blood flow in the brain, which was associated with both anemia and insomnia (45). A neuroimaging study found that cerebral blood flow in the frontotemporal region was linked to hemoglobin levels and anemia status (57), and another neuroimaging study found that cortical thinning in the frontotemporal region was linked to shorter sleep duration (58). The overlap of the same brain region linked to both hemoglobin levels and shorter sleep duration may suggest a common pathway in the development of anemia and insomnia. In addition, living with a chronic disease such as anemia may result in large stressors, leading to shorter sleep duration and more disturbed sleep. Further exploration into these hypotheses is required for verification.

We observed a significant sex-difference in the anemia-insomnia relationship and the association was more pronounced in men, relative to women. This potential sex-difference was only examined in one of previous study (46). Consistent of our findings, a stronger association between anemia and disturbed sleep was observed in men (adjusted OR, 1.73; 95% CI, 1.13 to 2.65), relative to women (adjusted OR, 1.59; 95% CI, 1.02 to 2.46) (46). However, the significant level of interaction was not tested in this study. Interestingly, women are generally more likely to have anemia and insomnia than men due to possible biological, psychological, and social factors (59–62). However, in older age, the decrease in production of estrogen may be a protective factor in women for the development of anemia. Yang *et al.* reported high levels of 17B-estradoil (E2), a negative regulator of iron absorption from the liver, and low levels of iron in young women, compared to the low levels of E2 and high levels of iron in post-menopausal women.

They found that E2 inhibits hepcidin, causing an iron decrease in young women, while the opposite happens in older women, causing iron overload (63). This may be a potential explanation for why our study found that the anemia-insomnia relationship in men was more pronounced. Further studies are needed to understand the biological mechanisms underlying this potential sex-difference.

Drawing an association between anemia and insomnia has important clinical implications. If anemia is a risk factor for insomnia, clinical intervention can be focused on the treatment of anemia to relieve both conditions. Healthcare professionals should be mindful of insomnia complaints when caring for patients with anemia. In this context, further prospective studies are warranted to elucidate the temporal relationship between anemia and insomnia.

This study has several limitations. First, although the insomnia questionnaire was validated, it was self-reported. This subjects the data to recall bias and misclassification. Second, we did not measure ferritin level and thus cannot directly classify if the anemia was iron-deficient or non-iron deficient. Third, residual confounding is of concern. For example, we did not assess RLS status. It has been discovered that RLS patients have a high prevalence of iron deficiency and a decreased expression of the MEIS1 gene (64). However, prevalence of RLS in Asian population is low (~1-2%) (65). For example, in a community-based study including 2609 Chinese older adults, only 0.69% of participants were found to have RLS after face-to-face interview (66). Further, the Kailuan study is not a representative population, which limits the generalizability of our findings. However, a subsequent meta-analysis reported similar results. Finally, although we used anemia status in 2006 to predict the likelihood of having insomnia in 2012, our study should be considered as cross-sectional due to lack of insomnia assessment at the baseline (2006), which prevents us from establishing causality and a temporal relationship between anemia and insomnia.

In conclusion, this large-scale community-based study found that individuals with anemia have greater odds of insomnia. A prospective analysis with objective sleep measures and direct assessment of

iron status is recommended for further verification. If our findings are confirmed, the change of clinical treatment for insomnia may improve the outcome of patients with anemia.

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EDUCATION

The Pennsylvania State University, *University Park, PA* 2015-2019
Schreyer Honors College
General Science: Biological Sciences and Health Professions Option
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Research

Nutritional Sciences Lab, *University Park, PA* 2016-2019
Research Assistant (RA)
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- Examined the association between low-density lipoprotein and the risk of intracerebral hemorrhage, conducted background research. Manuscript is in the process of submission
- Examined the association between dietary nicotine and the risk of Parkinson Disease, edited the manuscript "Nicotine from cigarette smoking and diet and Parkinson Disease: a review" that was published in *Translation Neurodegeneration* in July of 2017
- Examined the association between anemia and the risk of insomnia, currently drafting a manuscript for submission for publication. Poster presented at The Undergraduate Exhibition in April 2018 in University Park, PA. Poster to be presented at The American Society for Nutrition's Annual Conference in June 2018 in Boston, MA

Nutritional Sciences Lab, *University Park, PA* 2016
Research Assistant (RA)
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- Explored how mice are affected by the knockout of interleukin-6 and how the gene relates to gut flora, inflammation, and gastrointestinal disease
- Utilized polymerase chain reactions and western blot technique to analyze knockout gene

Publications

- Ma, C., Gao, X., Liu, Y., Neumann, S. Nicotine from cigarette smoking and diet and Parkinson Disease: a review. Translational Neurodegeneration. 2017: 6(18). Available at https://doi.org/10.1186/s40035-017-0090-8
- Neumann, S., Li, J., Xiaodong, Y., Chen, S., Murray-Kolb, L., Han, J., Wu, S., Gao, X. Anemia and insomnia: a cross-sectional study and a meta-analysis. Poster session presented at: The Undergraduate Exhibition; 2018 April 18; University Park, PA. Poster session presented at: The Health and Human Development Alumni Society Research Poster Competition; 2018 April 6; University Park, PA. To be presented at poster session at The American Society for Nutrition's Annual Conference; 2018 June 9-12; Boston, MA.

Leadership

Healthy Penn State, *University Park, PA* 2016-2019
Wellness Services Leader

- Promote wellness and healthy behaviors within the Penn State student body through community outreach and wellness services
- Lead and organize the wellness services and activities that are available to students at the Health Promotion and Wellness Center

Sigma Delta Tau, *University Park, PA* 2016
Assistant Scholarship Chair

- Provided academic support for members
- Ensured each individual in the chapter was upholding the minimum GPA requirement
- Awarded individuals for good academic standing

Community Service

THON Volunteer, *University Park, PA* 2015-2019
Dancer Relations Committee Member: Emergency Medical Services Chair

- Provide emotional support to THON participants during THON weekend, helping to maintain their wellness and safety
- Educate participants about wellness and safety

Alpha Epsilon Delta Beta Chapter, *University Park, PA* 2015-present
Club Member
- Member of nationally recognized medical honor society and service organization for undergraduate students
- Attend bi-weekly meetings with speakers in the medical field
- Mentor pre-medical underclassmen

The Pimlico Elementary and Middle School, *Baltimore, MD* 2018
Alternative Spring Break Volunteer
- Assisted elementary school teachers at an underserved inner-city school by working one-on-one with students
- Learned first-hand about issues surrounding race, poverty, and access to education

Clinical Experience

Mount Nittany Medical Center, *State College, PA* 2019
- Shadowed a family physician

Hershey Medical Center Penn State Health, *State College, PA* 2019
- Shadowed family physicians

Abington Hospital-Jefferson Health, *Abington, PA* 2019
- Shadowed a pediatrician

Wills Eye Hospital, *Bala Cynwyd, PA* 2018
- Shadowed an anesthesiologist
- Shadowed various ophthalmologists

Abington Hospital-Jefferson Health, *Abington, PA* 2017
Pre-Medical Volunteer
- Selected to participate in program to shadow physicians in the emergency department, surgery department, and department of obstetrics and gynecology
- Attended lectures on topics such as radiology, medical ethics, end-of-life care, and family medicine
- Observed breast reconstructions, uteroscopies, valvulopasties, partial colectomies, abdominal aortic aneurysm repairs

Fox Chase Cancer Center, *Philadelphia, PA* 2015
- Shadowed in the medical oncology, surgical oncology, and radiation oncology departments
- Observed radiation procedures, laparoscopic prostatectomies, and laparoscopic nephrectomies

Work Experience

Morgan Academic Center, *State College, PA* 2018
Peer Tutor
Supervisor: Anna Belpedio
- Tutored peer athletes in chemistry and nutrition

Nutrition 251: Introductory Principles of Nutrition, *University Park, PA* 2017
Learning Assistant
Professor: Lynn Parker Klees, RD, CDE, LDN
- Assisted undergraduate students in understanding basic concepts of nutrition through weekly office hours
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Biology 110: Basic Concepts of Biodiversity, *University Park, PA* 2016
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