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ORIGINAL ARTICLE

Association of proton pump inhibitor and histamine H_2-receptor antagonists with restless legs syndrome

Eric J. Earley[1,*], Maria Didriksen[2], Bryan R. Spencer[3,4], Joseph E. Kiss[5,6], Christian Erikstrup[7], Ole B. Pedersen[8], Erik Sørensen[2], Kristoffer S. Burgdorf[2], Steven H. Kleinman[9], Alan E. Mast[10,11], Michael P. Busch[12,13], Henrik Ullum[2] and Grier P. Page[14] on behalf of the NHLBI Recipient Epidemiology Donor Evaluation Study (REDS)-III Program and the Danish Blood Donor Study

[1]RTI International, Research Triangle Park, NC, [2]Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [3]Department of Laboratory Medicine, Yale University, New Haven, CT, [4]American Red Cross Scientific Affairs, Boston, MA, [5]Department of Medicine, University of Pittsburgh, PA, [6]Vitalant Northeast Division, Pittsburgh, PA, [7]Department of Clinical Immunology, Aarhus University Hospital, Skejby, Aarhus, Denmark, [8]Department of Clinical Immunology, Naestved Hospital, Naestved, Denmark, [9]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada, [10]Blood Research Institute, Versiti, Milwaukee, WI, [11]Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, WI, [12]Department of Laboratory Medicine, University of California San Francisco, CA, [13]Vitalant Research Institute, San Francisco, CA and [14]RTI International, Atlanta, GA

*Corresponding author. Eric J Earley, RTI International, 3040 E. Cornwallis Rd., P.O. Box 12194, Research Triangle Park, NC 27709-2194, USA. Email: eearley@rti.org.

Abstract

Restless legs syndrome (RLS) is a common sensorimotor disorder, which can disrupt sleep and is thought to be caused in part by low cellular iron stores. Proton pump inhibitors (PPI) and histamine H_2-receptor antagonists (H_2A) are among the most commonly used drugs worldwide and show evidence of causing iron deficiency. We conducted a case/non-case observational study of blood donors in the United States (N = 13,403; REDS-III) and Denmark (N = 50,323; Danish Blood Donor Study, DBDS), both of which had complete blood count measures and a completed RLS assessment via the Cambridge–Hopkins RLS questionnaire. After adjusting for age, sex, race, BMI, blood donation frequency, smoking, hormone use, and iron supplement use, PPI/H_2A use was associated with RLS (odds ratio [OR] = 1.41; 95% confidence interval [CI], 1.13–1.76; p = 0.002) in REDS-III for both PPI (OR = 1.43; CI, 1.03–1.95; p = 0.03) and H_2A (OR = 1.56; CI, 1.10–2.16; p = 0.01). DBDS exhibited a similar association with PPIs/H_2As (OR = 1.29; CI, 1.20–1.40; $p < 0.001$), and for PPIs alone (OR = 1.27; CI, 1.17–1.38; $p < 0.001$), but not H_2As alone (OR = 1.18; CI, 0.92–1.53; p = 0.2). We found no evidence of blood iron stores mediating this association. The association of PPI, and possibly H_2A, consumption with RLS independent of blood iron status and other factors which contribute to RLS risk suggest the need to re-evaluate use of PPI/H_2A in populations at particular risk for RLS.

Statement of Significance

Restless legs syndrome (RLS) afflicts up to 15% of adults in the Western Hemisphere and although its causes are not fully understood, low cellular iron stores appears to be a major contributor. Common antacid medications, proton pump inhibitors, and histamine H_2-receptor antagonists appear to cause iron deficiency and are among the most consumed drugs worldwide. To date, no link between consumption of these drugs and RLS has been found. In this study, we sought to measure the association between antacid use and the risk of having RLS. Evidence of these drugs contributing to RLS risk could suggest a need to re-evaluate the use of antacids in those at higher risk for developing RLS.

Key words: restless legs syndrome; RLS; iron deficiency; blood donors; ferritin

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Introduction

Restless legs syndrome (RLS; Willis–Ekbom disease) is a sensorimotor condition affecting between roughly 4% and 15% of adults in the Western Hemisphere [1]. It is characterized by a compulsion to move one's legs during inactive periods due to discomfort in the legs that is relieved while moving. Symptoms occur predominantly at night and impact sleep and quality of life [2, 3]. RLS is linked to chronic conditions such as insomnia and depression [4, 5].

Evidence suggests a link between iron deficiency in the brain and RLS [6, 7]. Multiple genome-wide association studies found associations between variants in the genes *BTBD9* and *MEIS1* and RLS [8–10], which both appear to be involved in iron homeostasis [11, 12], as well as dopamine regulation and lower limb development [13–15]. Supplemental iron has been an effective treatment for some forms of RLS in clinical trials [16–19], and RLS is also seen more often in scenarios where iron deficiency is common, particularly in pregnant women [20], older people [21], and frequent blood donors [22]. However, the etiology of RLS is multifactorial and association with low peripheral iron stores is absent in some populations [23–25]. Interestingly, some medications have been linked to RLS including antidepressants [26, 27] and dopamine antagonists [28].

A growing body of evidence has shown a link between consumption of proton pump inhibitors (PPI) and H_2-receptor antagonists (H_2A) and reduced iron [29–33]. These drugs enzymatically block gastric hydrochloric acid production, and the subsequent increase in gut pH appears to reduce absorption of non-heme dietary iron [34]. At a population level, PPI/H_2A use is linked to an increased risk of iron deficiency [31, 32]. These drugs are some of the most widely used in the United States [35, 36], with use at roughly 8% among the general population and 22% among those older than 65 years [35]. Widespread use of these drugs may be contributing to the prevalence of RLS.

Given the potential connection through body iron stores, the aim of this study was to investigate the association between PPI/H_2A medication use and RLS risk in two groups of blood donors, one from the United States and another from Denmark.

Methods

Study populations

The National Heart Lung and Blood Institute's Recipient Epidemiology Donors Study-III (REDS-III) RBC-Omics study [37] enrolled participants from four blood centers: American Red Cross (Farmington, CT), Institute for Transfusion Medicine (Pittsburgh, PA), BloodCenter of Wisconsin (Milwaukee, WI), and the Blood Centers of the Pacific (San Francisco, CA). Self-reported race, gender, and age, along with other data, were collected by self-administered questionnaire [38] which included questions on use of supplemental iron, PPI/H_2A medications, supplemental hormones, menstrual status, and pregnancy history. Participants also completed the Cambridge–Hopkins RLS questionnaire (CH-RLSq). Other demographic information including the prior 2 years donation history was linked from blood centers' databases.

Parallel analysis (n = 50,232) was performed on a subset of participants from the Danish Blood Donor Study (DBDS) who had completed the CH-RLSq. The DBDS is an ongoing national cohort study comprising more than 115,000 Danish blood donors. Details of this cohort have been described elsewhere [39, 40]. Briefly, blood donors were asked to participate if they had previously donated at least twice in a Danish blood bank and upon inclusion participants completed a comprehensive health questionnaire and provided a whole blood sample for testing. Participants also provided consent for researchers to link their unique civil registration number to information in health-related registries [41].

Serum ferritin and complete blood counts were collected in both cohorts, including hemoglobin, red blood cell (RBC) count, hematocrit, and mean corpuscular volume (MCV).

Ethics statement

Written informed consent was obtained from all participants before enrollment. REDS-III RBC-Omics recruitment materials and protocols were approved by each participating site's Institutional Review Board (IRB). The DBDS was approved by The Scientific Ethical Committee of the Central Denmark Region (M-20090237). The research database was approved by the Danish Data Protection Agency (2007-58-0015).

RLS diagnosis

RLS was diagnosed using the CH-RLSq. This tool has been validated as an effective means of RLS diagnosis (diagnostic sensitivity 87.2% and specificity 94%) [42, 43], and it includes questions on the four essential characteristics of RLS (uncomfortable feelings in the legs causing an urge to move them, symptoms are worse at night, symptoms begin at rest, and symptoms are relieved with movement) as well as questions designed to rule out non-RLS mimics. The CH-RLSq survey was translated from English to Danish using the back-translation method [3].

Because RLS patients experience a range of discomfort preceding the compulsion to move their legs often described as "an urge" or "irritating" instead of "uncomfortable" [44], we classified participants with RLS if they answered "yes" to either the first question ("…recurrent uncomfortable feelings…") or the second question ("…recurrent need or urge to move your legs…") and met the remainder of the CH-RLSq criteria. The Supplementary Appendix contains a detailed description of diagnosis criteria.

PPI/H_2A medication usage assessment

REDS-III participants were asked about regular or occasional use of 10 commercial medication products comprising 9 unique compounds spanning PPIs (Pantoprazole, Omeprazole, Esomeprazole, Rabeprazole, and Lansoprazole) and H_2As (Cimetidine, Nizatidine, Ranitidine, and Famotidine) classes. Prevalence of use was measured as the number of compounds selected from this list. We could not distinguish between concurrent versus serial use for participants who selected multiple compounds.

Using Danish civil registration numbers unique to all permanent Danish residents, DBDS participants were linked to their filled prescription drug information in the Danish National Prescription Registry, containing records from all Danish outpatient pharmacies [45].

Statistical analysis

In the REDS-III and DBDS cohorts, multivariate logistic regression was used to assess the association of RLS risk with antacid use as a binary (Y/N) variable. In REDS-III models were adjusted for sex (M/F), age, race (white/not-white), supplemental iron use (Y/N previous 30 days), hormone use (Y/N, 30 days), donation frequency in previous 2 years, BMI, and smoking status (Y/N, 30 days). DBDS used similar models but did not adjust for supplemental iron use nor hormone use.

The relationship between RLS and antacid use modeled the exposure in several ways: (1) Any PPI or H_2A drug use, (2) Exclusive use of PPI or H_2A classes, (3) Compound-specific testing (omitting nizatidine and rabeprazole due to low power, $N < 30$) with all nine compounds included as independent additive covariates.

Associations between PPI/H_2A use and measures of ln(ferritin), HGB, MCV, and RBC were assessed using linear regression models adjusted for the same covariates as described above. CBC was performed on a subset of participants within a month of completing the RLS assessment.

REDS-III analyses were performed in R version 3.5.0 (2018-04-23). DBDS analyses were performed in Stata/SE v15 (Stata Corp., College Station, TX).

Results

Study populations

The REDS-III study consented 13,770 participants, and 367 were excluded due to informed consent issues, duplicate enrollment, failure to obtain sample for analyses, non-sufficient donation quantity, diversion to double RBC donation, or positive test for infectious disease marker. This resulted in 13,403 participants ages 18 and older (Supplementary Figure S1) with 6,745 women and 6,658 men. There were 558 cases (4.2%) of RLS (Table 1).

The DBDS cohort contains 115,000 blood donors, and 53,175 donors were assessed for RLS using the CH-RLSq instrument. A total of 2,716 were excluded for not completing the entire CH-RLSq, and 227 more were excluded due to missing BMI or smoking status, resulting in a final total of 50,323 participants ≥18 (Supplementary Figure S1) with 24,441 women and 25,791 men. There were 3,540 cases (7.1%) of RLS (Table 1). A subset of 17,865 who had completed the RLS assessment also had CBC measures.

PPI/H_2A medication use was associated with RLS

Medication use was associated with RLS in multivariate logistic models in the REDS-III cohort after adjusting for sex, age, race, supplemental iron use, hormone use, donation frequency in previous 2 years, BMI, and smoking status (odds ratio [OR] = 1.41; CI, 1.13–1.76, $p = 0.002$), and this association was seen for both classes independently (PPI: OR = 1.43; CI, 1.03–1.95, $p = 0.03$; H_2A: OR = 1.56, CI, 1.10–2.16, $p = 0.01$). This association was also seen in DBDS after adjusting for sex, age, ethnicity, donation frequency in previous 2 years, BMI, and smoking status (OR = 1.29, CI, 1.20–1.40, $p < 0.001$). The association of PPIs was also observed in DBDS (OR = 1.27, CI, 1.17–1.38, $p < 0.001$). We did not find association with H_2As for all DBDS participants ≥18 y (OR = 1.18; CI, 0.92–1.53; $p = 0.2$); however, there was evidence of association for DBDS participants <40 y (OR = 1.66; CI, 1.06–2.62; $p = 0.03$; Figure 1).

REDS-III participants using multiple medications exhibited increased rates of RLS compared with participants using one ($p < 0.001$). From a baseline of 3.8% (zero; $n = 11,447$), RLS increased to 6.4% when using one compound ($n = 1,623$), and 8.7% for two or more different compounds of either class ($n = 230$). A similar trend was observed in the DBDS cohort ($p < 0.001$): 6.5% RLS rate for zero drugs ($n = 38,859$), 8.6% for one ($n = 7,965$) and 10.2% for two or more compounds of either class ($n = 3,408$). This trend was also observed both for those taking PPIs exclusively and taking H_2As exclusively (PPI, $p < 0.001$; H_2A, $p = 0.014$; Figure 2).

Table 1. Characteristics of RBC-Omics and DBDS cohorts

	REDS-III			DBDS		
	RLS, N = 558	No RLS, N = 12,845	P	RLS, N = 3,540	No RLS, N = 46,692	P
Age (mean ± SD)	48.0 (±15.2)	45.2 (±16.6)	0.90	42.4 (±12.4)	40.0 (±13.1)	<0.001
Women—no. (%)	373 (67)	6,372 (50)	<0.001	2,132 (60.2)	22,309 (47.8)	<0.001
Race—no. (%)			<0.001			0.020
White	472 (85)	8,687 (68)		3,487 (98.5)	45,751 (98.0)	
Black	32 (5.7)	1,639 (13)		–	–	
Asian	22 (3.9)	1,653 (13)		–	–	
Native American	0	32 (0.25)		–	–	
Hawaiin Pacific	0	20 (0.16)		–	–	
Multiple	4 (0.7)	133 (1.0)		–	–	
Other	18 (3.0)	480 (4.0)		–	–	
Danish immigrants	–	–		9 (0.25)	280 (0.60)	
Descendants of Danish immigrants	–	–		44 (1.24)	658 (1.41)	
Smoking—no. (%)	49 (10.1)	1,051 (9.2)	0.31	512 (14.5)	6,107 (13.1)	0.019
Suppl. iron—no. (%)	256 (46.4)	4,691 (37.2)	0.09	–	–	
Hormones—no. (%)	60 (10.8)	1,247 (9.9)	0.42	–	–	
Donation frequency (mean ± SD)	4.2 (3.9)	3.6 (3.8)	0.05	4.9 (2.6)	5.0 (2.6)	0.829
PPI—no. (%)	62 (12.5)	893 (7.5%)	0.03	954 (26.95)	9,561 (20.48)	<0.001
H_2A—no. (%)	49 (10.1)	702 (6.0)	0.01	189 (5.34)	1,677 (3.59)	<0.001
GERD drugs—no. (%)	124 (22.2)	1,729 (13.6)	0.002	1,029 (29.1)	10,344 (22.2)	<0.001

	REDS-III			DBDS		
	N	OR	95% CI	N	OR	95% CI
Any drug	1,853	1.41	1.13–1.76	12,381	1.29	1.20–1.40
PPI	955	1.43	1.03–1.95	10,515	1.27	1.17–1.38
omeprazole	561	1.36	0.93–1.94	3,526	1.20	1.06–1.36
pantoprazole	100	2.40	1.15–4.49	5,012	1.17	1.05–1.30
lansoprazole	147	0.94	0.42–1.84	4,089	1.17	1.04–1.32
rabeprazole	20	NA	NA	74	2.22	1.23–4.02
esomeprazole	174	1.38	0.70–2.49	1,436	1.04	0.86–1.26
H2A	751	1.56	1.10–2.16	1,866	1.18	0.92–1.53
cimetidine	45	NA	NA	1,118	1.17	0.95–1.43
ranitidine	371	1.45	0.95–2.12	542	1.02	0.76–1.38
famotidine	373	1.73	1.13–2.54	NA	NA	NA
nizatidine	3	NA	NA	354	1.31	0.97–1.89

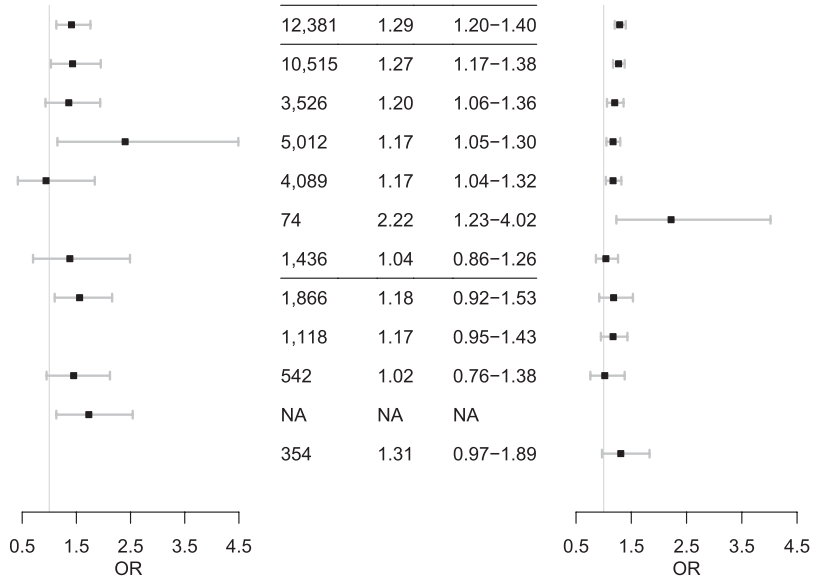

Figure 1. Forest plot of ORs and 95% CIs for the PPI and H_2A medication classes and individual compounds resulting from a multivariate logistic model of RLS rate. REDS-III (left) adjusted for age, sex, race, BMI, blood donation frequency, smoking, hormone use, and supplemental iron use; DBDS (right) adjusted for age, sex, ethnicity, BMI, blood donation frequency, and smoking. Compounds with $N < 30$ were excluded. Famotidine is not available in Denmark. PPI, proton pump inhibitor; H_2A, Histamine H_2-receptor antagonist.

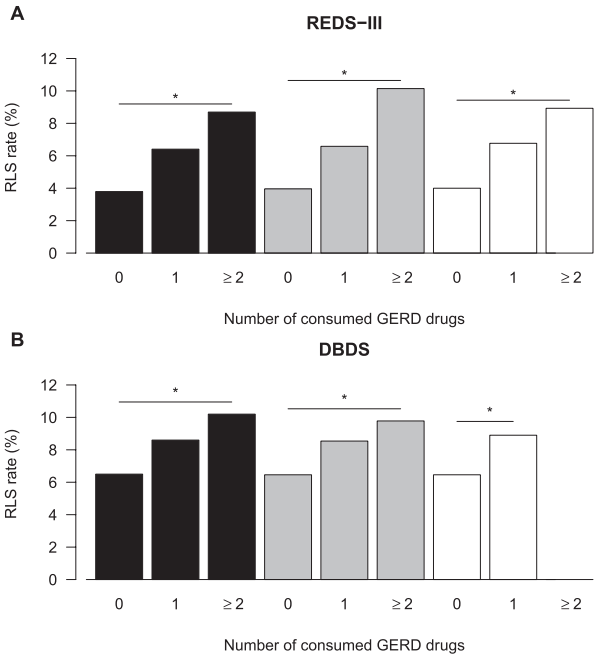

Figure 2. RLS rates versus number of consumed medications by class. Colors represent GERD drug class: any class (black), PPIs (gray), H_2As (white). Horizontal lines and asterisks represent a positive trend across 0, 1, or 2 or more different medications ($p < 0.05$) within that class. (A) RBC-Omics cohort, (B) DBDS cohort. Sample size for ≥2 concurrent H_2A compounds was $N < 30$ and not included in analysis.

Pantoprazole was associated with higher RLS rates in both REDS-III (OR = 2.40; CI, 1.15–4.49; $p = 0.01$) and DBDS (OR = 1.17; CI, 1.05–1.30; $p = 0.004$). Famotidine was associated in REDS-III (OR = 1.73; CI, 1.13–2.54; $p = 0.008$) but not DBDS. Omeprazole (OR = 1.20; CI, 1.06–1.36; $p = 0.004$), lansoprazole (OR = 1.17; CI, 1.04–1.32; $p = 0.008$), and rabeprazole (OR = 2.22; CI, 1.23–4.02; $p = 0.009$) were each associated with RLS in DBDS but not REDS-III (Figure 1).

Use of antidepressants (ATC: N06A), dopaminergic agents (N04B), and gabapentin (N03AX12) have also been linked to increased risk of RLS. We investigated whether previous use of these classes of drugs influenced the association between RLS and consumption of PPI/H_2A. Multivariate logistic models which adjusted for the common confounders as above (i.e. age, race, sex, BMI, smoking, and donation history) as well as previous use of antidepressants, dopaminergic agents, and gabapentin did not alter the observed association between RLS and use of PPI/H_2A (data not shown).

No evidence of blood iron measures mediating this association

In multivariate linear models with REDS-III participants, we observed reduced ferritin (–10.5%; CI, –6.1% to –14.7%; $p < 0.001$), reduced HGB ($\beta = -0.09$; CI, –0.15 to –0.04; $p = 0.001$), and reduced MCV ($\beta = -0.35$; CI, –0.62 to –0.08; $p = 0.01$) among consumers of PPI/H_2A but observed no appreciable difference in RBC count ($p = 0.4$). We found no evidence of reduced ferritin ($p = 0.2$), HGB ($p = 0.4$), MCV ($p = 0.2$), nor RBC ($p = 0.1$) in consumers of PPI/H_2A within the DBDS.

Multivariate logistic regression showed that RLS was not associated with reduced ferritin, HGB, MCV, nor RBC in either REDS-III or DBDS. Mediation analysis also found no evidence of blood iron mediating the association between PPI/H_2A and RLS status in either cohort (Supplemental Table S1).

Discussion

PPI/H_2A medication use was associated with increased prevalence of RLS and this appeared not to be mediated by serum

ferritin levels. Blood donors who reported regularly or occasionally using two or more different gastric acid reducing drugs were 1.6–2.2 times more likely to have RLS compared with people who took none. This association was observed in two large blood donor cohorts: REDS-III in the United States representing multiple racial groups, and independently for PPI in DBDS, a predominantly white cohort from Denmark.

Participants in this study were otherwise healthy adults who successfully donated a whole blood unit and reported no history of diabetes or other conditions which would have excluded them from donation. Previous work has shown that blood donation is associated with reduced serum ferritin [46], and repeated donations are associated with iron deficiency [38]. RLS has been associated with iron deficiency anemia [47], and oral or intravenous iron is effective at treating RLS in some cases [48]. However, within blood donor populations the association between levels of serum ferritin and RLS is either weak [24, 49] or non-existent [23].

We hypothesized that blood iron mediated the observed association between PPI/H_2A use and RLS. While REDS-III respondents exhibited reduced ferritin and HGB among consumers of PPI/H_2A, we observed no evidence of either ferritin nor HGB mediating the association between PPI/H_2A use and RLS. No reduction in ferritin nor HGB was observed in DBDS participants who consumed PPI/H_2A medications.

This association of gastric acid suppression with RLS independent of peripheral iron was surprising and suggests some possibilities. The lack of observed peripheral iron depletion as measured by serum ferritin may not necessarily correspond to a similar state in the brain. For example, serum ferritin does not appear to correlate with iron transport across models of the blood–brain barrier [50], and serum ferritin can be an imperfect measure of body iron stores especially in those suffering from inflammatory diseases [51]. On the other hand, the underlying cause for PPI/H_2A use may itself be the contributing factor to RLS risk. For example, GERD or other gastric pathologies unmeasured by either cohort could result in chronic bleeding resulting in subclinical iron deficiency. This study is limited in a few ways. First, since RLS status was measured at a single time point in both REDS-III and DBDS, we were not able to determine whether RLS developed after exposure or was concurrent. Second, exposure in REDS-III was determined by questionnaire which captured both prescription and OTC use and could be affected by recall bias, whereas in DBDS, exposure was determined from filled prescriptions only and could reflect a population that was suffering more from GERD. The lack of association between H_2A drugs and RLS in the DBDS cohort may be due to these medications being available over the counter (OTC) in Denmark, but PPI not being OTC, and thus H_2A use may be undercounted. Third, we do not have indications for PPI/H_2A use and an underlying condition could be promoting RLS risk independently of medication use. Finally, cohorts of blood donors have lower iron stores on average compared with the general population. On the other hand, blood donors are generally healthier than non-donors, and this "healthy donor effect" [49, 52] could skew our estimates of iron levels, RLS risk, or both. However, as RLS was assessed when participants were eligible to donate blood, case status at time of enrollment was likely not affected by other medications or known related diagnoses needing chronic medical treatment, which is a strength of the present study. Finally, as RLS severity is not assessed in the CH-RLSq, it is not clear whether PPI/H_2A use influences the strength or frequency of RLS.

The results from this study show a strong replicated association between PPI use and RLS risk even after controlling for many factors which influence RLS risk and blood iron levels. There is a possible association of H_2A with RLS. Future studies will need to untangle the causality of this association applying longitudinal studies tracking exposure and RLS emergence over time.

Supplementary material

Supplementary material is available at *SLEEP* online.

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- **Hubs:** A.E. Mast, J.L. Gottschall, W. Bialkowski, L. Anderson, J. Miller, A. Hall, Z. Udee, and V. Johnson, BloodCenter of Wisconsin, Milwaukee, WI; D.J. Triulzi, J.E. Kiss, and P.A. D'Andrea, Vitalant Northeast Division, Pittsburgh, PA; E.L. Murphy and A.M. Guiltinan, University of California, San Francisco, San Francisco, CA; R.G. Cable, B.R. Spencer, and S.T. Johnson, American Red Cross Blood Services, Farmington, CT.
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