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ORIGINAL

Hyperuricemia and shift work: A systematic review and meta-analysis

Hiperuricemia y trabajo por turnos: Una revisión sistemática y metanálisis

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Abstract

Objective. Update the available scientific evidence on the association between shift work and the appearance of hyperuricemia in workers.

Methods: The PICOS strategy was used to conduct a systematic review and meta-analysis of studies found in Pubmed, Web of Science, EBSCOhost, Scopus, and Cochrane Library databases which were published between January 2009 and September 2019 in English or Spanish. We used the CASPe and PRISMA-P 2015 systematic review analysis tools. Study quality was assessed using the STROBE and CONSORT statements. The GRADE-Pro tool was used to evaluate the evidence and the quantitative synthesis was produced with RevMan.

Results: Eight articles were used for the review and five for the meta-analysis. The average difference in uric acid between shift work and non-shift work was not significant. The meta-analysis showed an overall mean difference of -0.04 95% CI (-0.11, 0.04) p=0.32. The heterogeneity of the analysis was low (I2= 40%) p=0.15.

Conclusions: Evidence from the results shows that shift work is not associated with hyperuricemia. However, more research with greater control of bias is needed to support the results found.

Key words: Hyperuricemia; shift work schedule; uric acid; workers; systematic review; meta-analysis.

Resumen

Objetivo: Actualizar la evidencia científica disponible sobre la asociación entre el trabajo por turnos y la aparición de hiperuricemia en trabjadores.

Métodos: La estrategia PICOS se utilizó para realizar una revisión sistemática y un metanálisis de los estudios que se encuentran en las bases de datos Pubmed, Web of Science, EBSCOhost, Scopus y Cochrane Library que se publicaron entre enero de 2009 y septiembre de 2019 en inglés o español. Se utilizaron las herramientas de análisis de revisión sistemática CASPe y PRISMA-P 2015. La calidad del estudio se evaluó mediante las declaraciones STROBE y CONSORT. Se utilizó la herramienta GRADE-Pro para evaluar la evidencia y la síntesis cuantitativa se realizó con RevMan.

Resultados: Se utilizaron ocho artículos para la revisión y cinco para el metanálisis. La diferencia promedio en el ácido úrico entre el trabajo por turnos y el trabajo sin turnos no fue significativa. El metanálisis mostró una diferencia media global de -0,04 IC del 95 % (-0,11; 0,04) p=0,32. La heterogeneidad del análisis fue baja (I2= 40%) p=0,15.

Conclusiones: La evidencia de los resultados muestra que el trabajo por turnos no está asociado con la hiperuricemia. Sin embargo, se necesita más investigaciones con mayor control de sesgos para respaldar los resultados encontrados.

Palabras clave: Hiperuricemia; trabajo a turnos; ácido úrico; trabajadores; revisión sistemática; metanálisis.

Introduction

According to the International Labour Office (ILO), working in shifts is "a method of organization of working time in which workers succeed one another at the workplace so that the establishment can operate longer than the hours of work of individual workers at different daily and night hours"[1]. This way of working is increasing. In Spain in 2017, 12.5% of the workers worked shifts, in 2018 this number increased to 13.2%. Among sectors, the chemical, along with the metal, health and social sectors cover 40% of these[2,3].

Shift work negatively influences not only a person's physical and mental health but also their social, work and family life[4]. In shift workers there is a higher prevalence of risk factors such as smoking, dyslipemia and obesity, and the risk of cardiovascular disease is increased[5-7].

However, due to the multitude of factors affecting shift work, it has not been possible to decide which are relevant. Moreover, in the literature, there is not consensus in the findings of variably designed studies conducted to date. There are studies which confirm the relationship between shift work and higher cholesterol, triglycerides, and glucose[8,9], which either totally or partially contradict other similar studies[10,11], in which this relationship is not evident.

One of the markers that has been assessed as an independent marker of cardiovascular diseases and has been proposed as a possible risk factor is uric acid[12-14].

There are few studies on the relationship between this marker and shift work. It has recently been reported that shift work acts as a protective factor against hyperuricemia[15], but this theory cannot be taken as conclusive since other authors have either found no such link[10] or have found one, but with serious limitations[16,17].

It is, therefore, necessary to evaluate studies that relate shift work and the occurrence of hyperuricemia in the workplace. Our aim was to know if shift workers have higher uric acid levels than non-shift workers.

Materials and methods

Protocol

In September 2019, a systematic review of the literature was performed according to the PRISMA-P 2015 methodology[18]. Two external reviewers evaluated the protocol separately. The review procedure was recorded in the PROSPERO systematic review database (reference number CRD42020180188).

Databases and Search Strategy

The PICOS strategy was used to identify studies on the presence of hyperuricemia in shift workers compared to non-shift workers to test the claim that shift workers have higher uric acid levels (Population: Workers; Intervention: Shift work; Comparator: Shif workers comparated to non-shift workers; Outcome: Hyperuricemia). An independent search was conducted by two of the authors (DPJ, MRS) in the following databases and platforms: Pubmed, Web of Science, EBSCOhost, Scopus and Cochrane, including all types (study type) of full-text documents published over the last ten years (January 2009 to September 2019), in English and Spanish. In addition, the search was also carried out in the grey literature. Searches were performed in the System for Information on Grey Literature in Europe (OpenGrey) and the Grey Literature Report (all types of documents).

The search strategy was based on identifying the terms to be searched according to three categories. The first group of terms was connected to the independent MeSH variable "shift work schedule" and the free terms "shift work", "rotating shifts", "night work", "rotative work", "shift work disorder" and "shift worker". The second group of terms to the dependent MeSH variables "hyperuricemia" and "uric acid". The third group related to the population, with the MeSH term "workers". The combinations of terms for the three categories in the fields "Title", "Abstract" and "Keywords" determined the searches to be carried out. **Table I** shows these combinations and the number of studies selected.

Eligibility criteria

The criteria for selecting the items were: workers aged 18 and over who were subjected to any form of shift work where uric acid was measured. Those studies whose original language was not Spanish or English; which were more than 10 years old; or where shift work was not directly or indirectly related to uric acid were excluded, as well as opinion articles, editorials, or other non-scientific forms of communication. Eligibility was ensured by applying both inclusion and exclusion criteria.

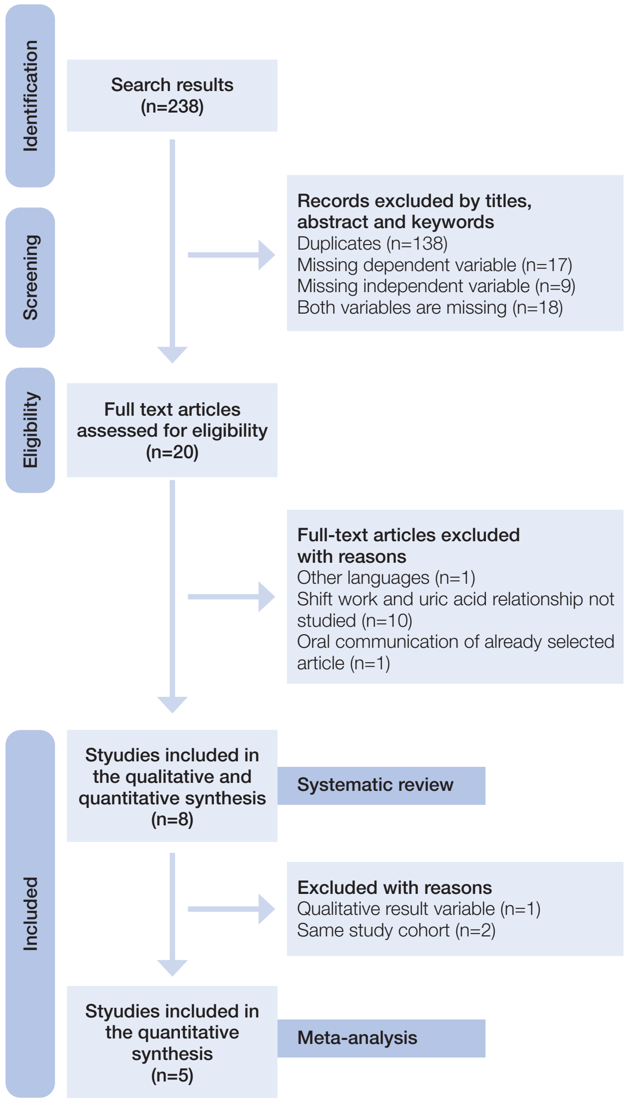
Studies Selection

Two authors (M.R.S. and D.D.P.J.) separately examined the 238 records obtained from the searches for duplicates. Afterwards, three researchers (R.J.M., A.M.M. and R.M.L.) read the titles and abstracts separately to match the eligibility criteria, eliminating those in which one of the variables was missing in these fields. The gray literature search did not retrieve any new studies. After the full-text review of the 20 selected articles, 10 were removed because, although shift work and uric acid were mentioned in the title, abstract or keywords, they were not relevant. One was not deemed relevant because although the selection had been filtered to only include articles in English or Spanish, it appeared in another language (Japanese). Another was eliminated because it was the transcribed oral communication of a previously selected article. Finally, eight articles remained for the qualitative synthesis (systematic review). Of these, five were left for quantitative analysis (meta-analysis), one was excluded because the outcome variable is qualitative and two because they were based on the same cohort as another study (**Figure 1**).

Table I: Search keywords used for the different databases.

Database	Keywords	Result	Pre-selected	Selected	Pre-selected total	Selected total
Pubmed	"shift work Schedule" AND ("uric acid" OR hyperuricemia)	5	5	3	16	3
	"shift work" AND ("uric acid" OR hyperuricemia)	8	8	0		
	"night work" AND ("uric acid" OR hyperuricemia)	2	2	0		
	"rotative work" AND ("uric acid" OR hyperuricemia)	0	0	0		
	"rotating shifts" AND ("uric acid" OR hyperuricemia)	0	0	0		
	"shift work disorder" AND hyperuricemia	1	1	0		
	"shift work disorder" AND "uric acid"	4	0	0		
Web of Science	"shift work schedule" AND "uric acid"	8	8	1	40	2
	"shift work Schedule" AND hyperuricemia	1	1	0		
	"shift work" AND "uric acid"	10	10	1		
	"shift work" AND hyperuricemia	3	3	0		
	"rotating shifts" AND "uric acid"	1	1	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"night work" AND "uric acid"	1	1	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"shift work disorder" AND hyperuricemia	5	0	0		
	"shift work disorder" AND "uric acid"	10	7	0		
	"shift worker" AND "uric acid"	14	8	0		
	"shift worker" AND hyperuricemia	1	1	0		
EBSCOhost	"shift work schedule" AND "uric acid"	4	4	0	35	0
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND "uric acid"	10	10	0		
	"shift work" AND hyperuricemia	3	3	0		
	"night work" AND "uric acid"	3	3	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"rotating shifts" AND "uric acid"	0	0	0		
	"shift work disorder" AND "uric acid"	10	7	0		
	"shift work disorder" and hyperuricemia	0	0	0		
	"shift worker" AND "uric acid"	10	7	0		
	"shift worker" AND hyperuricemia	2	1	0		
Scopus	"shift work schedule" AND "uric acid"	0	0	0	111	3
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND hyperuricemia	3	3	0		
	"shift work" AND "uric acid"	11	11	1		
	"night work" AND "uric acid"	37	37	2		
	"night work" AND hyperuricemia	4	4	0		
	"rotating shifts" AND hyperuricemia	6	6	0		
	"rotating shifts" AND "uric acid"	29	29	0		
	"rotative work" AND "uric acid"	0	0	0		
	"rotative work" AND hyperuricemia	0	0	0		
	"shift work disorder" AND "uric acid"	8	6	0		
	"shift work disorder" AND hyperuricemia	0	0	0		
	"shift worker" AND hyperuricemia	2	2	0		
	"shift worker" AND "uric acid"	22	13	0		
Cochrane	"shift work schedule" AND "uric acid"	0	0	0	0	0
	"shift work schedule" AND hyperuricemia	0	0	0		
	"shift work" AND "uric acid"	0	0	0		
	"shift work" AND hyperuricemia	0	0	0		
	"night work" AND "uric acid"	0	0	0		
	"night work" AND hyperuricemia	0	0	0		
	"rotating shifts" AND "uric acid"	0	0	0		
	"rotating shifts" AND hyperuricemia	0	0	0		
	"shift work disorder" AND "uric acid"	0	0	0		
	"shift worker" AND uric acid	0	0	0		
	"shift work disorder" AND hyperuricemia	0	0	0		
	"shift worker" AND hyperuricemia	0	0	0		
	"rotative shift" AND hyperuricemia	0	0	0		
	"rotative shift" AND "uric acid"	0	0	0		

Figure 1: Flow chart of study selection.



Quality Assessment

The Spanish critical reading skills program analysis tool, CASPe, was used[19-21]. For the quality analysis, recommendations from the STROBE statement (maximum 22 points for observational studies)[22] and the CONSORT statement (maximum 25 points for randomised cross-over trials) were followed[23]. The sub-sections of each item in the declarations were assessed independently, and if any of the sub-sections did not reflect the recommendation, it was considered not to comply.

Moreover, the GRADE-Pro tool was used to create the evidence profile, and summary of findings. The risk of bias was evaluated using the Cochrane and Revman 5.3 tool, which included the selection bias, performance bias, attrition bias, reporting bias and other biases.

Data Extraction

From each article, one reviewer (D.D.P.J.) was in charge of extracting the data, which was subsequently verified by another reviewer (C.V.E.). The following data was gathered: author and year, country, study design, number of participants, occupation, ages, minimum time worked, sociodemographic variables, life factors and anthropometric measurements, forms of data collection, the definition of hyperuricemia, description of the shift, characteristics of the shift (the type and frequency of rotation, working hours per shift, number of days per month), main type of statistical analysis, main findings/conclusions and limitations. The main characteristics of the studies analysed are shown in **table II**. As no discrepancies were found between the two authors who carried out the searches (kappa index = 1), it was not deemed necessary for a third author to intervene.

Statistical analysis

For the meta-analysis, three authors (D.D.P.J, MRS and RML) used the Cochrane Review Manager software (RevMan 5.3) to perform the statistical analyses and create the forest and funnel plot figures. Due to the effect size variation in the different studies, a meta-analysis was carried out using the Mantel-Haenszel random-effects method and the DerSimonian and Laird model. The difference between the means (mg/dL), with a 95% confidence interval, was used to assess the effect size of shift work on uricemia. Heterogeneity was assessed using the Chi-square test and the inconsistency index (I2). According to the Cochrane Collaboration tool, heterogeneity is classified as: unimportant (0-40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%). A sensitivity analysis was performed for the results of the meta-analysis, in which more than two studies were included, to determine the effect of each trial on the results obtained.

Results

Qualitative Synthesis

In relation to the geographical scope, six of the articles reviewed were Asian (China, Korea and, Japan) and two were European (Netherlands and Austria). According to their design, three had a cross-sectional design, one was a prospective randomised cross-over trial, and the rest were cohort studies. Moreover, three studies came from the same cohort, where 6,886 or 7,104 workers participated, so the total number of workers studied between these and the rest of the studies ranged from 14,863 to 15,081 workers.

The workers were from the energy, automobile, and steel industries and the health services. One study did not detail this aspect; it only referred to shift workers from a cohort study funded by the Dutch National Institute of Public Health and Environment. The ages ranged from 18 to 60 and time spent in the role varied from 1 to 13.9 years (on average).

Several sociodemographic variables, anthropometric measurements and biological samples were taken in all the studies (**Table II**). Some of the less commonly studied variables included chronotype and time spent awake and asleep, all of which appeared in only one study.

Table II: Summary of the studies included in the review and quantitative synthesis: 2009-2019 (N=8).

Author and year	Country	Study design	No of workers	Worksite	Ages	Minimum time in the workplace	Variables (socio-demographic, life factors and anthropometric measurements	Data collection procedure	Definition of hyperuricemia	Shift description	Shift characteristics (type of rotation, rotation speed, working hours per shift, number of days per month	Main type of statistical analysis	Main findings or conclusions	Limitations
Shen et al. (2019) *	China	Cross-sectional	4180	Employees of 23 different workplaces belonging to an electric power industry above 2600 m of altitude	18-60	2 years	Age, sex, educational level, occupation. Smoking, alcohol consumption, fruit and vegetable intake and dietary pattern. Weight and height, BMI, blood pressure Cholesterol, triglycerides, uric acid, glucose.	Self-administered questionnaire (measurements by trained health care professionals in hospital).	≥ 416 μmol/L (7 mg/dl) in men, 357 μmol/L (6 mg/dl) in women	Daytime work/ Shift work	Not collected	Multilevel logistic regression model and restricted cubic spline	Shift workers had a higher prevalence of hyperuricemia in men, not women. After multivariate regression, hyperuricemia was negatively associated with shift work in men (protective factor).	No specific data related to intake were collected (only reporting whether or not they ate little fruit or vegetables). No drug treatments were also collected. No kidney function was measured.
Hulsegge et al. (2019)*	Netherlands	Cohort	1061 workers form the first period (1987-91).	Not detailed	20-59	1 year	Cardiometabolic risk factors (anthropometry, blood pressure, lipids, non-fasting glucose, diabetes, gamma-glutamyltransferase, C-reactive protein, uric acid, cystatin C, creatine and estimated glomerular filtration rate). Education, lifestyle, use of antihypertensive and cholesterol medication, smoking, drinking, leisure time physical activity and occupational physical activity.	Questionnaire, anthropometric measurements and biological samples	>7.0 mg/dl in men, >6 mg/dl in women	Worked evening shifts (i.e. shifts ending before midnight), night shifts (i.e. shifts that continued or started after midnight), sleep shifts and rotating shifts	The year of the beginning and end of the shift work , number of years and months in total. The frequency was classified as: shifts without nights, 1 to 4 nights per month and >=5 nights per month. Compare between day and shift work >= ten years or <10 years.	Linear mixed models	No relation was found.	No details were given on types of work, nor on the direction and speed of rotations
Oh et al. (2014)*	Korea	Cross-sectional	1029 men, 753 shift workers	Steel Company workers	Less than 20 to over 50, but not in detail	In shifts 13.9 years on average	Smoking status, alcohol consumption, physical activity, and others; medical history of hypertension, diabetes mellitus, hyperlipidemia, and current medications. Glucose, total cholesterol, triglycerides, HDL cholesterol, AST, ALT,γ-GTP, blood urea nitrogen, creatinine, and serum uric.	Self-administered questionnaires, anthropometric measurements and biological samples.	≥7.0 mg/dl	Daytime work/ Shift work	Daytime from 9 to 17, other hours are considered shifts. No further specification is given.	Logistic regression	After regression, an association was found between shift work and hyperuricemia. Daytime workers were more active.	Auto-questionnaires, lack of data on shift work. Dietary patterns were not monitored.
Rauchen-zauner et al. (2009)*	Austria	Prospective randomized cross-over trial between 2005 and 2006.	30	Departments of Internal Medicine, Neurology, and Otorhinolaryn-gology at the Medical University Innsbruck	33,5 (31-36)	76 months (58 -106)	Sleep and wake time, number of awakenings, time to wake up, Glucose, urea, creatinine, total cholesterol, triglycerides, HDL, C-reactive protein, IL-6 and TNF-α, urine parameters for adrenalin and noradrenalin, 24 hours ECG. (Uric acid is not detailed).	Self-administered questionnaires and biological samples.	Not detailed	24 h on-call duty and 8 h not on-call duty.	On-call duty: 8 to 16,30 + 16 h. Not on-call duty: 8 to 16,30. 4 on-call duty per month.	Wilcoxon´s signed Rank test and Spearman´s correlation coefficient.	Decreased uric acid values during 24-hour shifts. Higher concentrations after 24-hour shifts compared to non-shifts	Low sample size. Variable shift duration.
Kawada and Otsuka. (2014)**	Japan	Prospective cohort study between 2008 and 2011	1677. Daytime work 868, 2-shift workers 686, 3-shift workers 99, and others, 23.	Car manufacturing company	Daytime work 44.4 (5.5), 2-shift work 44.3 (5.8) and 3-shift work 44.5. (5.2)	Not detailed	HDL, triglyceride, glucose, uric acid, serum insulin. Smoking, alcohol intake, habitual exercise, blood pressure, waist circumference.	Self-administered questionnaires, anthropometric measurements and biological samples.	Not detailed	Daytime from 8 to 17. 2-shifts started at 6,30 or 15 h. 3-shifts started at 6,30, 14,30 and 22,30 h.	8 hours per shift.	Logistic regression	Uric acid and morning/evening shift work contributed to the development of metabolic syndrome. After regression as well.	Self-administered questionnaires, lack of data on shift work (no direction of rotation, years in shifts, changes between shifts) No direct uric acid/ shift relationship.
Uetani et al. (2011)**	Japan	Prospective cohort study between 1991 and 2005***	6886, 4079 daytime workers, 2807 shift workers	Steel company	Not detailed	Not detailed	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed	Daytime work/ Shift work. Irregular shift work such as 24 h and fixed night work were excluded.	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the start of the study, those who were overweight on day shifts had more uric acid than those on rotating shifts (no regression study).	Exercise measured as regular or non-exercise. No variables related to living, working or dietary intake or socioeconomic situation. There were no further conclusions between shift work and uric acid using logistic regression.

Author and year	Country	Study design	No of workers	Worksite	Ages	Minimum time in the workplace	Variables (socio-demographic, life factors and anthropometric measurements	Data collection procedure	Definition of hyperuricemia	Shift description	Shift characteristics (type of rotation, rotation speed, working hours per shift, number of days per month	Main type of statistical analysis	Main findings or conclusions	Limitations
Dochi et al. (2009)**	Japan	Prospective cohort study between 1991 and 2005***	6886, 4079 daytime workers, 2807 shift workers	Steel company	Not detailed.	Not detailed.	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed.	Daytime work/ Shift work	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the beginning of the study, uric acid levels were higher in day workers than in shift workers (no regression study).	Exercise measured as regular or non-exercise. No variables related to living, working, dietary intake or socio-economic situation (although the latter were considered equal between shifts and non-shifts). They did not evaluate the history of shift change. There are no further conclusions between shift work and uric acid with logistic regression.
Suwazono et al. (2009)**	Japan	Prospective cohort study between 1991 and 2005***	7104, 4219 daytime workers, 2885 shift workers	Steel Company. No women in shift work.	Not detailed.	Four groups of 0 years (control), 1-3 years, 4-10 years and over 11 years.	Weight, Height, BMI, age, total cholesterol, creatinine, glycosylated hemoglobin A1c, AST, GGT, uric acid. Smoking and drinking habits, habitual exercise.	Self-questionnaires verified in personal interview during health check-ups, anthropometric measurements and biological samples	Not detailed.	Daytime work/ Shift work	Clockwise rotation. 5 day shifts, 2 rest days, 5 evening shifts, 1 rest day, 5 night shifts, 2 rest days. Every shift started at 7, 15 and 23 h.	Pooled logistic regression	At the beginning of the study, uric acid levels were higher in day workers than in shift workers (no regression study). Shift workers were older, drank daily, smoked and did not exercise regularly, compared to day workers. An inverse relationship was found between uric acid and glycosylated hemoglobin (HbA1c).	Exercise measured as regular or non-exercise. No variables related to living, working, dietary intake or socio-economic situation (although the latter were considered equal between shifts and non-shifts). They did not evaluate the history of shift change. There are no further conclusions between shift work and uric acid with logistic regression.

(*): direct relationship, (**): indirect relationship, (***): different studies from the same cohort

Data collection was carried out using questionnaires and self-administered questionnaires. In three of them, (all from the same cohort) the data collected was later verified in a personal interview. Analytical data was collected in all studies.

Only three studies detailed the values that define hyperuricemia. The study by Oh et al. set the value at ≥7 mg/dL for an exclusively male population; the study by Shen et al., defined hyperuricemia in men at ≥416 μmol/L (7 mg/dL) and 357 μmol/L (6 mg/dL) in women and the study by Hulsegge et al., defined it at >7.0 mg/dL in men and >6 mg/dL in women.

The shift definitions and their characteristics were very heterogeneous. One study described the shift as alternating between daytime and shift work without providing any other characteristics[15]. The studies addressing the same cohort described it as daytime; shift work excluding 24 hours; and the fixed night shift, with the hourly rotation being distributed over five mornings, two rest days, five afternoons, one rest day, five nights, two rest days[25-27]. The study by Hulsegge et al.[10] described the type of shift (afternoon, evening, night but able to sleep and rotating shifts) and collected the total number of years and months of shifts and their frequency (shifts without nights, one to four nights per month and five or more nights per month). Kawada et al. [27] describe daytime shifts as 8 a.m. to 5 p.m. and rotating shifts starting at 6.30 a.m., 2.30 p.m. and 10.30 p.m. Rauchenzauner et al.[28] only differentiate between being on-call for 24 hours and not being on-call (8 a.m. to 4.30 p.m.). They mention a frequency of four 24-hour shifts per month.

The main type of statistical analysis used was logistic regression. One study analysed its data using a linear mixed model and another using the Wilcoxon test and the Spearman correlation coefficient.

Of the eight articles reviewed, four studied the relationship between shift work and uric acid as the main objective and four did so indirectly. In the first four, different conclusions were obtained. Shen et al.[15] found a higher prevalence of hyperuricemia in men, but after controlling for confounding factors they found shift work to be a protective factor. Oh et al.[16] also found a relationship, whereas Hulsegge et al[10]. Rauchenzauner et al.[28] found that uric acid decreased during 24-hour shifts and then increased, compared to non-shift workers.

One study relates shift work and uric acid to metabolic syndrome, Kawada et al.[27]. Three studies using the same cohort reported higher uric acid levels in daytime workers at the start of the study than shift workers. (Dochi et al. 2009; Suwazono et al. 2009; Uetani et al. 2011)[25-27]. The main limitations were the lack of data linked to food intake and exercise, pharmacological treatments, the measurement of renal function, and, in particular, the lack of information around the shift work characteristics.

Finally, the quality of the studies included in the qualitative synthesis was analyzed according to the STROBE and CONSORT statements. In the STROBE assessment, study quality ranged from 14 to 20 (maximum 22). The lowest scores corresponded to the studies carried out by Kawada et al.[27] and Oh et al.[16] and the highest scores corresponded to Uetani et al.[26] and Shen et al.[15]. The studies' biggest weakness was related to sections 7 (clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.); 13c (Consider the use of a flow diagram); 14b (Indicate the number of participants with missing data for each variable of interest); and 16a (Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision).(**Table III**).

Table III: Assessment of the quality of studies included in the systematic review (STROBE Statement).

	Title/ Abstract		Background/ rationale	Objectives	Study design	Setting	Participants		Variables	Data sources/ measurement	Bias	Study size	Quantitative variables	Statistical methods				
	1		2	3	4	5	6		7	8	9	10	11	12				
	a	b					a	b						a	b	c	d	e
Shen et al. (2019)*	1	1	1	1	1	1	1	na	1	1	1	1	1	1	1	na	na	1
Hulsegge et al. (2019)*	0	1	1	1	1	1	1	na	1	1	0	1	1	1	1	1	na	1
Oh et al. (2014)*	0	1	1	1	0	1	1	na	1	1	0	1	1	1	1	na	na	1
Uetani et al. (2011)**	1	1	1	1	1	1	1	na	0	1	1	1	1	1	1	1	na	1
Dochi et al. (2009)**	1	1	1	1	1	1	1	na	0	1	0	1	1	1	1	1	1	1
Suwazono et al. (2009)**	1	1	1	0	1	1	1	na	0	1	1	1	1	1	1	1	1	1
Kawada and Otsuka. (2014)**	1	1	1	0	0	1	1	na	0	1	1	1	1	1	1	0	1	1

(Continued)

	Participants			Descriptive data			Outcome data	Main results			Other analyses	Key results	Limitations	Interpretation	Generalizability	Funding	Total
	13			14			15	16			17	18	19	20	21	22	
	a	b	c	a	b	c		a	b	c							
Shen et al. (2019)*	1	0	0	0	0	na	1	0	1	na	1	1	1	1	1	0	**18**
Hulsegge et al. (2019)*	1	1	0	1	0	1	1	0	na	na	0	1	1	1	0	1	**15**
Oh et al. (2014)*	1	1	0	0	1	na	1	0	1	na	na	1	1	1	1	0	**14**
Uetani et al. (2011)**	1	1	0	1	1	1	1	0	na	na	1	1	1	1	1	1	**19**
Dochi et al. (2009)**	1	1	0	1	0	1	1	0	na	na	1	1	1	1	1	1	**17**
Suwazono et al.(2009)**	1	1	0	1	0	1	1	0	1	na	1	1	1	1	1	1	**17**
Kawada and Otsuka. (2014)**	1	0	0	1	0	1	1	0	na	na	1	1	1	1	1	1	**14**

1= recommendation included in the study, 0=recommendation not included, na= not applicable. In the items with sub-sections, not complying with it is considered if any of them does not include the recommendation; (*): direct relationship, (**): indirect relationship.

With regard to the CONSORT evaluation, the study by Rauchenzauner et al. [28] was the only one evaluated and it obtained a score of 14 out of a maximum of 25 given by the scale.(**Table IV**).

Quantitative synthesis

Of the eight studies included in the qualitative synthesis, three were excluded for meta-analysis: the studies by Suwazono et al.[25] and Uetani et al.[26] because they used the same worker cohort and sample base as Dochi et al.[24]; and the study by Oh et al.[16], because the outcome variable is qualitative (hyperuricemia >7 mg/dL). Therefore, five studies were finally included in the quantitative synthesis analysis, including a total of 4420 and 9193 shift and non-shift workers respectively. Of these five studies, only Hulsegge et al.[10] showed higher mean hyperuricemia in shift workers, 5.2 mg/dL (SD=1.1), while for the group of non-shift workers, the mean uricemia was 5.0 mg/dL (SD=1.2). The meta-analysis showed an overall mean difference of -0.04 95% CI (-0.11, 0.04) p=0.32 (**Figure 2**). The heterogeneity of the analysis was low (I^2= 40%) p=0.15.

The risk of bias assessment was carried out through the Cochrane RevMan tool (**Figure 3**). The presence of associated biases due to the lack of randomisation in the recruitment of participants has been detected in two studies, Kawada et al.[27] and Shen et al.[15]. On the other hand, four of the five meta-analysed studies are observational: three present a prospective longitudinal analytical design (cohorts) and Shen et al. a cross-sectional design, while Rauchenzauner et al. carried out a randomised clinical trial.

Table IV: Assessment of the quality of studies included in the systematic review (CONSORT Statement).

	Title	Abstract	Background	Objectives	Trial design	Change from protocol	Participants	Settings and location	Interventions	Outcomes	Changes to outcomes	Sample size	Interim analyses and stopping guidelines	Sequence generation (method)	Sequence generation (type)	Allocation concealment mechanism	Implementation	Blinding	Similarity of interventions
	1		2		3		4		5	6		7		8		9	10	11	
	a	b	a	b	a	b	a	b		a	b	a	b	a	b			a	b
Rauchenzauner et al. (2009)	1	0	1	1	0	1	1	1	1	1	1	1	na	1	1	0	1	na	na

(Continued)

Statistical methods	Additional analyses	Participant flow	Losses and exclusions	Recruitment	Trial end	Baseline data	Numbers analysed	Outcomes and estimation	Binary outcomes	Ancillary analyses	Harmst	Limitations	Generalizability	Interpretation	Registration	Protocol	Funding	Total
12		13		14		15	16	17		18	19	20	21	22	23	24	25	
a	b	a	b	a	b			a	b									
1	na	1	0	0	1	1	1	1	na	na	na	1	0	1	0	0	1	**14**

1= recommendation included in the study, 0=recommendation not included, na= not applicable. In the items with sub-sections, not complying with it is considered if any of them does not include the recommendation.

Figure 2: Meta-analysis forest plot.

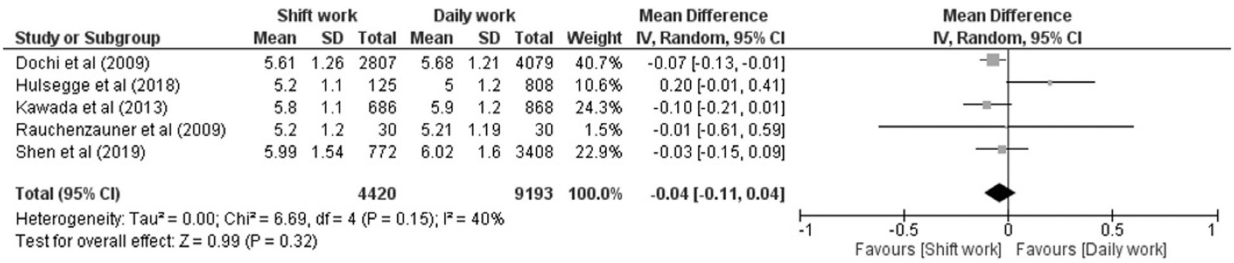
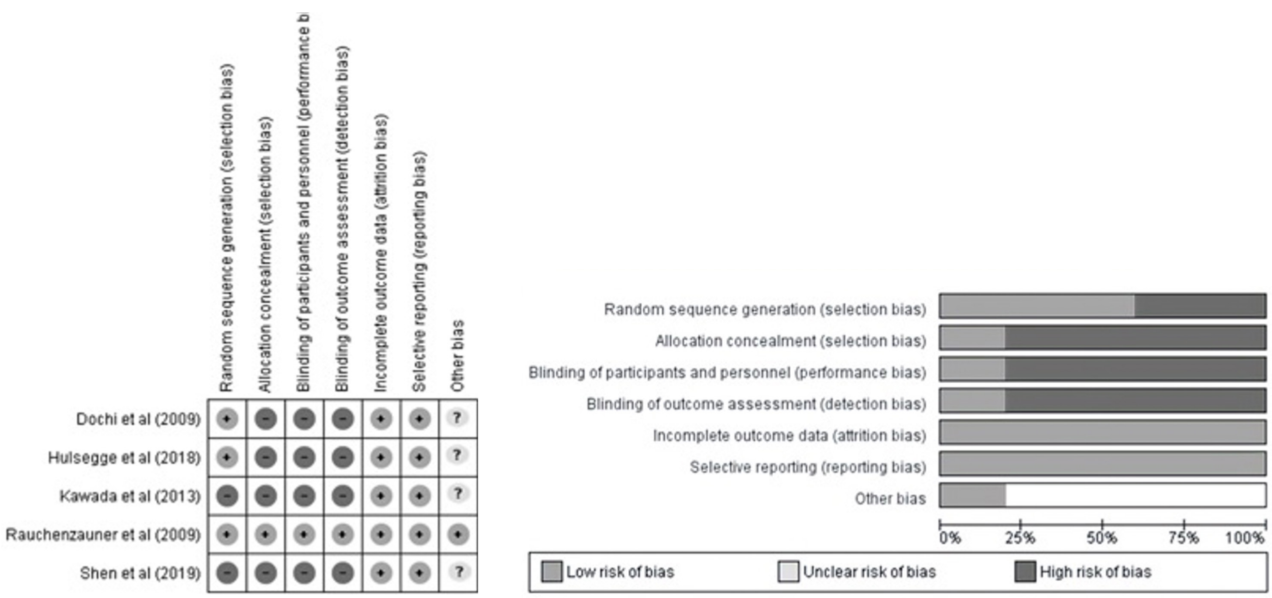


Figure 3: Overall risk of bias (Revman).



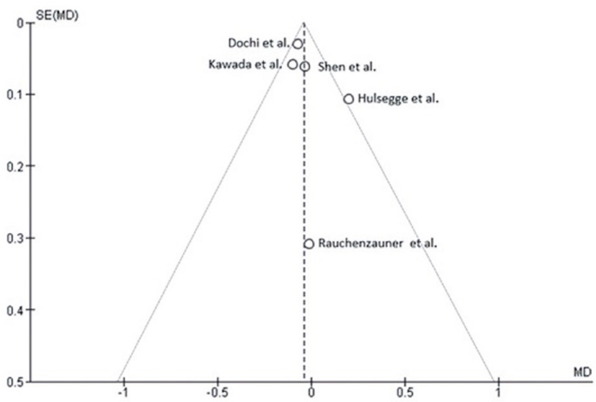
In the latter, there is concealment in the results evaluation but in the others there is only concealment in the allocation and blinding for participants and staff. The evaluation of the degree of evidence and a summary of findings table was produced with the Grade Pro tool, and the overall evidence score is low (**Table V**).

Finally, publication bias was analysed for the five studies included in the meta-analysis through the funnel plot, highlighting their low standard error and their symmetry, which is interpreted as low risk for publication bias. (**Figure 4**).

Table V: Evidence profile (Grade Pro).

Question: Do shift workers have more hyperuricemia than non-shift workers?										
Certainty assessment							No of patients		Effect	Certainty of evidence (GRADE)
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shift Work	Daily Work	Mean Differences (95% CI)	
Average uric acid value (mg/dL) in shift workers and non-shift workers										
5	Observational studies (Cohort study n=3) Observational studies (Cross-sectional study n=1) Experimental study (Randomized clinical trial n=1)	No serious	No serious	No serious	No serious	All possible residual confounding factors could reduce the demonstrated effect	4.420	9.193	-0.04 (-0.11, 0.04)	⊕⊕◯◯ LOW

Figure 4: Publication bias (Funnel plot).



Discussion

This systematic review and meta-analysis has aimed to evaluate studies that relate to shift work and hyperuricemia in order to answer the question: do shift workers have higher uric acid levels than non-shift workers? The available evidence demonstrates independence between shift work and hyperuricemia.

The different kinds of shift work and their superficial descriptions are a usual problem[29]. Only four studies differentiated between day and shift work, and of these, only two (from the same cohort) specified the type of rotation, frequency and hours per shift. Of the remaining four, the descriptions were also incomplete as Chastin et al.[30] have also pointed out. To the lack of unanimity in their definition must be added the absence of assessment of aspects that influence shift work, such as the type of shift, the direction and frequency of rotation or the absence of data on intensity measured by years of exposure and number of shifts per month. Factors associated with shift work disorder, defined by the International Classification of Sleep Disorders (ICSD) as the presence of insomnia and/or excessive sleepiness temporarily due to a work schedule that overlaps with usual sleep time (Sateia, 2014), should also be assessed, since the relationship between shift work, night work, and sleep-related problems is well documented[31].

Other factors, directly related to uric acid, such as the lack of assessment of dietary aspects, which are in turn influenced by cultural, demographic and social aspects; pharmacological and even herbal dietary treatments or renal function, should be included in research as their influence on uric acid metabolism has been clearly substantiated and the need to address them in a systematic way is essential if generalisable results are to be achieved. Even in values such as the reference value for considering hyperuricemia, a small but important difference in valuation was detected since some considered the initial value to be high if it was ≥7 mg/dL and others if it was >7 mg/dL, which makes reviewing the intervals and biological reference criteria necessary in order to adequately evaluate the results[32].

Uric acid is a value that is increasingly being recognised as a cardiovascular risk factor[33,34] and is usually included in serological marker assessments associated with this risk. However, the associations between these and shift work are inconclusive [35,36] . This is more evident, as we have shown in this review, if we focus exclusively on uric acid.

Study limitations

Several limitations are the result of the high level of heterogeneity in the analysed studies' conclusions and quality. This is in line with the problems outlined and the results seen in this review. First, the low representation of studies outside Asia makes multi-ethnic comparisons between workers difficult. Second, the scarcity of studies detected limits comparison and discussion between studies, making it difficult to analyse publication bias due to the small sample size. Third, as we have shown, the definitions of shift work were very heterogeneous and the confounding factors and statistical analyses also varied between studies. Fourth, the inclusion of studies with an observational design in the meta-analysis led to the existence of biases derived from non-randomisation in recruitment and non-blinding for participants and researchers, which subtracted evidence from the quantitative analysis. Finally, limiting searches to the last ten years as well as only English and Spanish publications should also be taken into account.

In conclusion, the evidence provided in this review shows independence between shift work and hyperuricemia. Studies related either directly or indirectly to shift work and hyperuricemia in the last ten years have been identified and this has revealed a deficit of updated studies in different populations and work situations. In addition to the shift type and its characteristics (total years of shift work, type of rotation, frequency, hours of work per shift and number of days per shift and month), it would be of particular interest to collect data on dietary, pharmacological and physical activity patterns, the chronotype, sleep time and renal function, among others, as the limitations of the analysed studies have revealed.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. ILO. Conditions of Work and Employment Programme. Shift work. http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---travail/documents/publication/wcms_170713.pdf. Published 2004. Accessed October 10, 2019).

2. Instituto Nacional de Estadistica. Encuesta de Población Activa (EPA). Variables de submuestra 2018. https://www.ine.es/prensa/epa_2018_s.pdf. Published 2019. Accessed October 10, 2019.

3. Remesal AF, Pastor AO, Puente RP, Folgado RR, Pastor CB, Bertomeu JMB et al. Buenas prácticas de la industria química para prevenir riesgos en el trabajo a turnos de los trabajadores mayores. *Biomecánica* 2011; 57: 59-62.

4. Nea FM, Pourshahidi LK, Kearney JM, Livingstone MBE, Bassul C, Corish CA. A qualitative exploration of the shift work experience: the perceived effect on eating habits, lifestyle behaviours and psychosocial wellbeing. *J Public Health (Bangkok)* 2018; 40(4): e482-92. https://doi.org/10.1093/pubmed/fdy047

5. Buchvold HV, Pallesen S, Øyane NMF, Bjorvatn B. Associations between night work and BMI, alcohol, smoking, caffeine and exercise--a cross-sectional study. *BMC Public Health* 2015; 15(1):1112. https://doi.org/10.1186/s12889-015-2470-2

6. Torquati L, Mielke GI, Brown WJ, Alexander TK. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose-response relationship. *Scand J Work Environ Health* 2018; 44(3): 229-38. https://doi.org/10.5271/sjweh.3700

7. Peplonska B, Bukowska A, Sobala W. Association of rotating night shift work with BMI and abdominal obesity among nurses and midwives. *PLoS One* 2015; 10(7): e0133761. https://dx.doi.org/10.1371%2Fjournal.pone.0133761

8. Guo Y, Rong Y, Huang X, Lai H, Luo X, Zhang Z et al. Shift Work and the Relationship with Metabolic Syndrome in Chinese Aged Workers. *PLoS One* 2015; 10(3): e0120632. https://doi.org/10.1371/journal.pone.0120632

9. Morris CJ, Purvis TE, Mistretta J, Scheer FAJL. Effects of the internal circadian system and circadian misalignment on glucose tolerance in chronic shift workers. *J Clin Endocrinol Metab* 2016; 101(3): 1066-74. https://doi.org/10.1210/jc.2015-3924

10. Hulsegge G, Picavet HSJ, Van der Beek AJ, Verschuren WMM, Twisk JW, Proper KI. Shift work, chronotype and the risk of cardiometabolic risk factors. *Eur J Public Health* 2019; 29(1): 128–34. https://doi.org/10.1093/eurpub/cky092

11. Silva-Costa A, Rotenberg L, Coeli CM, Nobre AA, Härter-Griep R. Night work is associated with glycemic levels and anthropometric alterations preceding diabetes: Baseline results from ELSA-Brasil. *Chronobiol Int* 2016; 33(1): 64-72. https://doi.org/10.3109/07420528.2015.1115765

12. Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. *J Adv Res* 2017; 8(5): 537-48. https://dx.doi.org/10.1016%2Fj.jare.2016.11.004

13. Zheng BK, Li N. Association of serum uric acid levels and cardiovascular risk score. *Int J Cardiol* 2018; 258: 297. https://doi.org/10.1016/j.ijcard.2018.01.087

14. Cabrera-Rode E, Parlá Sardiñas J, Olo Ncogo J, Lezcano Rodríguez SE, Rodríguez Acosta J, Echevarría Valdés R et al. Relación del riesgo cardiovascular global con el ácido úrico y algunos componentes del síndrome metabólico. *Rev Cuba endocrinol* 2018; 29(2): 1-16.

15. Shen Y, Wang Y, Chang C, Li S, Li W, Ni B. Prevalence and risk factors associated with hyperuricemia among working population at high altitudes: a cross-sectional study in Western China. *Clin Rheumatol* 2019; 38(5): 1375-84. https://doi.org/10.1007/s10067-018-4391-9

16. Oh JS, Choi WJ, Lee MK, Han SW, Song SH, Yun JW et al. The association between shift work and hyperuricemia in steelmaking male workers. *Ann Occup Environ Med* 2014; 26(42): 1-7. https://dx.doi.org/10.1186%2Fs40557-014-0042-z

17. Uetani M, Suwazono Y, Kobayashi E, Inaba T, Oishi M, Nogawa K. A longitudinal study of the influence of shift work on serum uric acid levels in workers at a telecommunications company. *Occup Med (Chic Ill)* 2006; 56(2): 83-8. https://doi.org/10.1093/occmed/kqi178

18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ* 2015; 349(January): 1-25. https://doi.org/10.1136/bmj.g7647

19. Cabello J. Plantilla para ayudarte a entender Estudios de Cohortes. Guía CASPe. Lect Crítica la Lit Médica 2005;(II): 23-7.

20. Cabello J. Plantilla para ayudarte a entender una Revisión Sistemática. CASPe Guías CASPe Lect Crítica la Lit Médica 2005;(I): 13-7.

21. Cano Arana A, González Gil T, Cabello López J. Plantilla para ayudarte a entender un estudio cualitativo. CASPe Guías CASPe Lect Crítica la Lit Médica 2010;(III): 3-8.

22. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al. Mejorar la comunicación de estudios observacionales en epidemiología (STROBE): explicación y elaboración. *Gac Sanit* 2009; 23(2): 1-28.

23. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: Extension to randomised crossover trials. *BMJ* 2019;366. https://doi.org/10.1136/bmj.l4378

24. Dochi M, Suwazono Y, Sakata K, Okubo Y, Oishi M, Tanaka K et al. Shift work is a risk factor for increased total cholesterol level: a 14-year prospective cohort study in 6886 male workers. *Occup Environ Med* 2009; 66(9): 592-7. https://doi.org/10.1136/oem.2008.042176

25. Suwazono Y, Dochi M, Oishi M, Tanaka K, Kobayashi E, Sakata K. ShiftWork and Impaired Glucose Metabolism: A 14-Year Cohort Study on 7104 Male Workers. *Chronobiol Int* 2009; 26(5): 926-41. https://doi.org/10.1080/07420520903044422

26. Uetani M, Sakata K, Oishi M, Tanaka K, Nakada S, Nogawa K et al. The influence of being overweight on the relationship between shift work and increased total cholesterol level. *Ann Epidemiol* 2011; 21(5): 327-35. https://doi.org/10.1016/j.annepidem.2011.01.001

27. Kawada T, Otsuka T. Effect of Shift Work on the Development of Metabolic Syndrome After 3 Years in Japanese Male Workers. *Arch Environ Occup Health* 2014 Jan; 69(1): 55-61. https://doi.org/10.1080/19338244.2012.732123

28. Rauchenzauner M, Ernst F, Hintringer F, Ulmer H, Ebenbichler C.F, Kasseroler MT et al. Arrhythmias and increased neuro-endocrine stress response during physicians' night shifts: a randomized cross-over trial. *Eur Heart J* 2009; 30(21):2 606-13. https://doi.org/10.1093/eurheartj/ehp268

29. Proper KI, Van De Langenberg D, Rodenburg W, Vermeulen RCHH, Van Der Beek AJ, Van Steeg H et al. The relationship between shift work and metabolic risk factors: A systematic review of longitudinal studies. *Am J Prev Med* 2016; 50(5): e147-57. https://doi.org/10.1016/j.amepre.2015.11.013

30. Chastin SFM, Palarea-Albaladejo J, Dontje ML, Skelton DA. Combined Effects of Time Spent in Physical Activity, Sedentary Behaviors and Sleep on Obesity and Cardio-Metabolic Health Markers: A Novel Compositional Data Analysis Approach. *PLoS One* 2015; 10(10): e0139984. https://doi.org/10.1371/journal.pone.0139984

31. Vallières A, Azaiez A, Moreau V, LeBlanc M, Morin CM. Insomnia in shift work. *Sleep Med* 2014; 15(12): 1440-8. https://doi.org/10.1016/j.sleep.2014.06.021

32. González de la Presa B, Canalias Reverter F, Esteve Poblador S, Gella Tomás FJ, Izquierdo Álvarez S, López Martínez RM et al. Procedimiento para la transferencia y revisión de intervalos de referencia biológicos. *Rev del Lab Clin* 2017; 10(2): 91-4. http://dx.doi.org/10.1016/j.labcli.2016.11.004

33. Ilundain-González AI, Gimeno-Orna JA, Sáenz-Abad D, Pons-Dolset J, Cebollada-del Hoyo J, Lahoza-Pérez MC. Influencia de los niveles de ácido úrico sobre el riesgo de mortalidad cardiovascular a largo plazo en pacientes con diabetes de tipo 2. *Endocrinol Diabetes y Nutr* 2018; 65(6): 335-41. https://doi.org/10.1016/j.endinu.2018.01.004

34. Serrano N, Ojeda CA, Gamboa-Delgado EM, Mejia CCC, Quintero-Lesmes DC. Ácido úrico y su asociación con los componentes del síndrome metabólico en adolescentes colombianos. *Nutr Hosp* 2019; 36(2): 325-33. http://dx.doi.org/10.20960/nh.2242

35. Loef B, Van Baarle D, Van Der Beek AJ, Beekhof PK, Van Kerkhof LW, Proper KI. The association between exposure to different aspects of shift work and metabolic risk factors in health care workers, and the role of chronotype. *PLoS One* 2019; 14(2). https://doi.org/10.1371/journal.pone.0211557

36. Saulle R, Bernardi M, Chiarini M, Backhaus I, La Torre G. Shift work, overweight and obesity in health professionals: a systematic review and meta-analysis. *Clin Ter* 2018; 169(4): e189-197. https://doi.org/10.7417/t.2018.2077