Safety and Health at Work 12 (2021) 390–395

Contents lists available at ScienceDirect

Safety and Health at Work

journal homepage: www.e-shaw.net

Original Article

The Relationship Between Night Shift Work and the Risk of Abnormal Thyroid-Stimulating Hormone: A Hospital-Based Nine-Year Follow-up Retrospective Cohort Study in Taiwan

Hsin-Hao Chen [1,2,3], Hsiao-Hui Chiu [4], Tzu-Lin Yeh [1,5], Chi-Min Lin [1], Hsin-Yi Huang [6], Shang-Liang Wu [6,*]

[1] Department of Family Medicine, Hsinchu MacKay Memorial Hospital, Hsinchu City, Taiwan
[2] MacKay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan
[3] Department of Medicine, MacKay Medical College, New Taipei City, Taiwan
[4] Department Nursing, Taipei Veterans General Hospital, Taipei City, Taiwan
[5] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei City, Taiwan
[6] Laboratory of Epidemiology and Biostatics, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 28 August 2020
Received in revised form
7 April 2021
Accepted 25 May 2021
Available online 1 June 2021

Keywords:
Cohort study
Health personnel
Shift work schedule
Hypothyroidism
Thyroid

ABSTRACT

Background: Health-care providers typically undergo shift work and are subjected to increased stress. Night shift work may induce disturbed sleep cycles and circadian rhythm. The objective of this study was to explore if night shift workers (NSWs) show an increased risk of abnormal thyroid-stimulating hormone (TSH).

Methods: We conducted a retrospective cohort study of 574 employees without thyroid disease and abnormal TSH at baseline who underwent annual check-ups between 2007 and 2016 in a medical center. NSWs were defined as those with working time schedules other than daytime hours. We calculated the incidence rate and estimated the adjusted hazard ratio (HR) for incident abnormal TSH and subclinical hypothyroidism compared with non-NSWs using a Cox regression model.

Results: A total of 56 incident abnormal TSH cases and 39 subclinical hypothyroidism cases in NSWs were identified during 3000 person-years of follow-up. In models adjusted for age, sex, obesity, and working departments, we found no increased relative risk for incident abnormal TSH (HR: 0.72, 95% confidence interval: 0.33–1.60) or subclinical hypothyroidism (HR: 0.52, 95% confidence interval: 0.19–1.45) when comparing NSWs to non-NSWs; nor were incidence rates significantly different among exclusively medical employees after excluding administrative staff.

Conclusion: In this hospital-based nine-year follow-up retrospective cohort study, NSWs were not associated with increased relative risk of incident abnormal TSH and subclinical hypothyroidism, in contrast to previous cross-sectional studies.

1. Introduction

Shift workers are defined as people with working time schedules other than traditional daytime hours; this includes fixed evening or night shifts, as well as three rotating shifts. In the United States, 29% of the fulltime workforce are shift workers, while in Europe and Taiwan they comprise around 20% [1–3]. Shift workers usually have a disrupted normal sleep-wake cycle, resulting in shorter sleep and excessive fatigue [4]. A previous review has suggested that shift workers show adverse long-term health and safety prognoses with elevated risk of obesity, type 2 diabetes, coronary heart disease, and even breast and colorectal cancer [5]. The adverse effect on shift workers' health is mainly attributed to interference with their circadian rhythm [6].

Serum thyroid-stimulating hormone (TSH), commonly used as a screening tool for thyroid dysfunction, shows some physiological variations: higher values at night than during the day, highest values in the early morning and lowest in the afternoon [7–9]. Most people

* Corresponding author. Department of Medical Research, Taipei Veterans General Hospital, No. 201, Section 2, Shipai Road, Beitou District, Taipei City, 11217, Taiwan.
E-mail address: leowsl5@gmail.com (S.-L. Wu).

2093-7911/$ – see front matter
https://doi.org/10.1016/j.shaw.2021.05.006

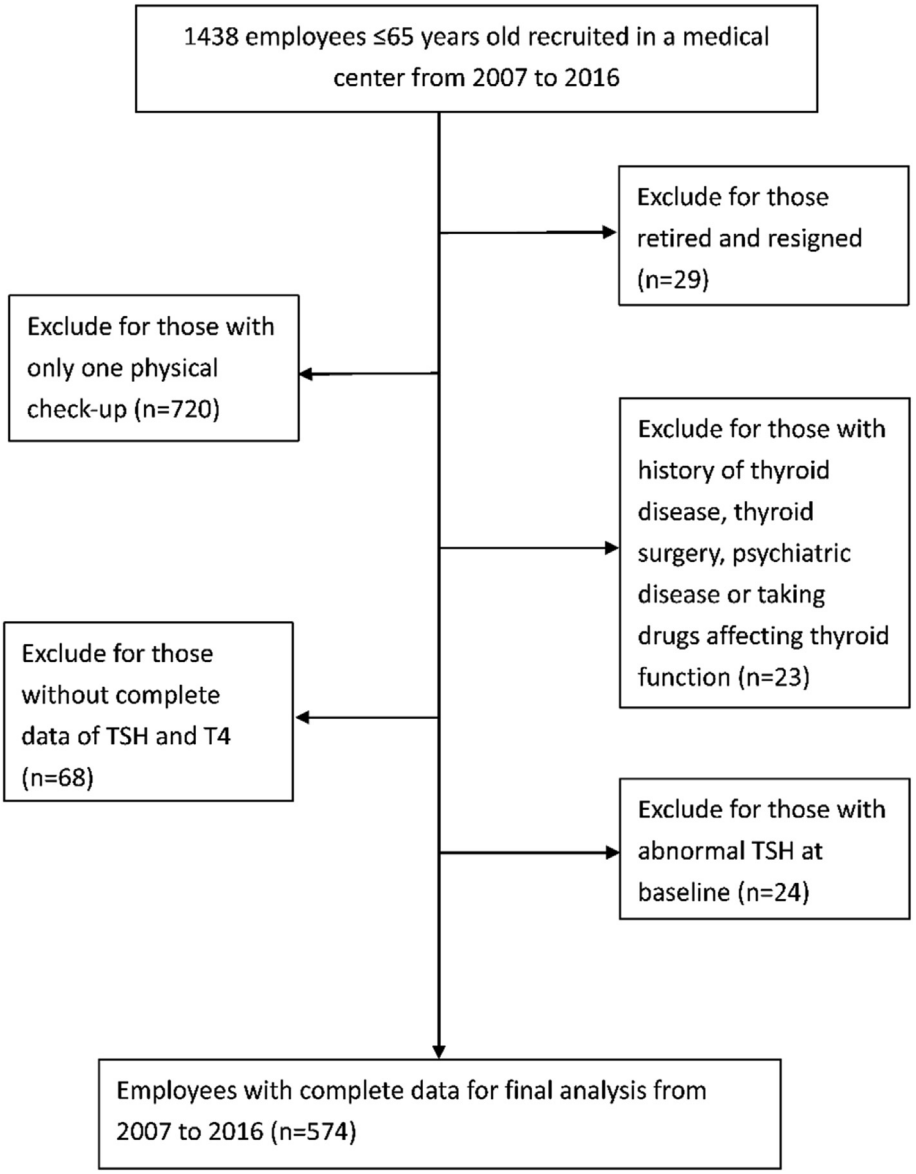

Fig. 1. Diagram showing the selection process of study employees.

with elevated TSH levels have autoimmune thyroid disease and very few have uncommon non-thyroid disorders, such as TSH-producing pituitary tumor. The circadian variation of TSH is affected by body weight change and psychological diseases such as depression and bipolar disorder, even if no thyroid disease is present [10,11]. Night shift work is also associated with delayed circadian thyrotropin rhythm [8], but very few studies have evaluated the relationship between shift work and thyroid function. One meta-analysis conducted in 2020 included only four articles and did not show a significant difference of TSH between day shift and night shift workers (NSWs) [12]. However, the sensitivity analysis by excluding the results reported by Moon et al and showed a significant increase of TSH in NSWs. The study by Moon et al, which included the most of participants, was conducted in a university hospital. They suggested that NSWs showed a higher risk of subclinical hypothyroidism than non-NSWs, but the authors used cross-sectional repeated measures, only included female staff and allowed heterogeneity in the type of night shift [13]. Another systematic review either had no inclusive evidence between shift work and thyroid disease due to poor qualities of included studies [14].

Health-care providers, who are usually exposed to shift work (including night shifts and rotating shifts) and higher stress, are at higher risk of altered immune function [5]. Thyroid hormones are essential in modulating innate and adaptive immune responses [15]. Moreover, subclinical hypothyroidism may be associated with an increased risk of cardiovascular disease, e.g., coronary heart disease and heart failure [16]. In this study, we conducted a nine-year follow-up retrospective cohort study to explore if health care providers working night shifts are subject to increased incidence of abnormal TSH and subclinical hypothyroidism.

2. Materials and methods

The study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guideline.

2.1. Data collection and measures

This study retrospectively explored data from employees whose physical checkups were performed in a medical center in

Northern Taiwan between 2007 and 2016. The physical checkups were mandatory for all subjects annually once the employee entered the hospital due to hospital regulations. We included a total of 1438 employees, including doctors, nurse staff, medical technologists, pharmacists, radiation technologists, and administrative staff. Their working shift status included regular daytime workers (8:00–17:00) and NSWs, including on-call night shift, regular night shift, and day-and-night rotating shift workers who worked rotating shifts composed of morning (8:00–16:00), evening (16:00–24:00), and night (24:00–8:00) shifts. We excluded those who retired and resigned, as their working shift status could not be confirmed. We also excluded employees with only one physical checkup due to any reasons during the nine-year period. The selection process of study employees was shown in Fig. 1.

Employees were required to fast at least 8 hours prior to examination and we followed the rules of health examination center to perform the blood test in the morning 8:00 to 12:00 am. We collected data of TSH and free T4, which were obligate items in routine physical checkups in this medical center. We further excluded employees with any history of thyroid disease, thyroid surgery, psychiatric disease, or took drugs potentially affecting thyroid function (i.e., amiodarone, steroid, sertraline, lithium, tyrosine-kinase inhibitors, et.) [17] and those who had abnormal TSH in their initial health checkup. The normal range was defined as 0.400–4.000 μIU/mL for TSH and 0.80–1.90 ng/dL for free T4. Analysis was carried using an Abbott Architect plus i2000 (Abbott Core Laboratory, Abbott Park, IL, USA).

Demographics, such as sex, age, working department, and past medical history were collected by self-administered questionnaires. Anthropometric measurements such as height, body weight, and body mass index were also collected. We defined obesity as body mass index >27kg/m^2 following the Health Promotion Administration, Ministry of Health and Welfare, Taiwan [18]. Working departments were classified as administration, medical, nursing, radiation, and other medical (laboratory and pharmacy) departments. The study was approved by the institutional review board of Taipei Veterans General Hospital (IRB No: 2017-08-009AC#1).

2.2. Statistical analysis

Demographic data, including sex, age, and working departments were compared between NSWs and non-NSWs. Chi-squared tests and independent Student's t-tests were used for categorical and continuous variables, respectively. We defined abnormal TSH as < 0.400 μIU/mL or >4.000 μIU/mL. We further defined subclinical hypothyroidism as elevated levels of TSH >4.000 μIU/mL with normal free T4 [19]. Follow-up duration for each employee extended from the first year of examination to the year of development of events (abnormal TSH or subclinical hypothyroidism) or the last examination in 2016. We calculated person-years incidence rate as the number of incident cases divided by the total person-years of follow-up.

We estimated the adjusted hazard ratio (HR) with 95% confidence intervals (CI) for incident abnormal TSH or subclinical hypothyroidism between NSWs and non-NSWs, which was adjusted for age, sex, obesity, and working department [10,13]. We further excluded administrative staff due to the nature of the work and compared incidence rate only among medical staff. All statistical analyses were performed using Microsoft Excel 2013 and SPSS for Windows version 22.0 (SPSS Inc, Chicago, IL, USA) software using a p-value < 0.05 to indicate statistical significance.

Table 1
Baseline characteristics of employees included in the study, defined by night shift worker status

Characteristics	Night shift				p
	No		Yes		
	Number	%/SD	Number	%/SD	
Sex					0.390
Women	245	58.1%	95	62.5%	
Men	177	41.9%	57	37.5%	
Age (years)	47.8	±8.1	47.6	±7	0.829
Working department					<0.001
Doctor	129	30.6%	110	72.4%	
Nurse	77	18.2%	23	15.1%	
Radiologist	47	11.1%	10	6.6%	
Other medical staff*	23	5.5%	9	5.9%	
Administration staff	146	34.6%	0	0.0%	

SD, standard deviation.
* Including medical technologist and pharmacist.

3. Results

A total of 574 employees fulfilled the inclusion criteria with normal TSH and free T4 at baseline. The mean (standard deviation) age of employees was 47.7 (7.8) years and 234 (40.8%) of them were male workers. Doctors accounted for a majority (41.6%), followed by administrative staff (25.4%), nurses (17.4%), radiation technologist (9.9%), and other medical staff (medical technologist and pharmacist, 5.7%). Among the included hospital employees, 152 (26.5%) workers belonged to the NSWs and almost half (46%) of the doctors were on rotating night shift. About one fourth of the nurses and other medical staff (17.5%–36%) were also NSWs, whereas all administrative staff were non-NSWs.

There was no significant difference in age and sex between non-NSWs and NSWs (Table 1). There was a significant difference in working departments between the two groups: doctors accounted for a majority (72.4%) of NSWs, and around one third (34.6%) of non-NSWs were administrative staff.

During 2897 person-years of follow-up, 56 employees developed abnormal TSH (incidence rate 1.93 per 100 person-years). The median follow-up duration for employees was 5 years (interquartile range 2–9). Although NSWs had a lower incidence of abnormal TSH, there was no significant difference compared with non-NSWs when adjusted for age and sex (adjusted HR: 0.55, 95% CI: 0.27–1.12; Table 2). In addition to age and sex, we further adjusted for working departments and obesity occurrence, because a previous study indicated that obesity was associated with increased TSH levels [10]. However, there was no significant difference in incidence rate of abnormal TSH between the two groups (adjusted HR: 0.72, 95% CI: 0.33–1.60).

A total of 39 employees developed subclinical hypothyroidism (incidence rate 1.30 per 100 person-years) during 3000 person-years of follow-up. The incidence rate of subclinical hypothyroidism in NSWs was still lower than in non-NSWs, but with no significant difference after adjusting for age and sex (adjusted HR: 0.41, 95% CI: 0.16–1.05) or for obesity and working departments (adjusted HR: 0.52, 95% CI: 0.19–1.45; Table 2).

We performed subgroup analysis by excluding administrative staff, all of whom were non-NSWs. Among the 428 medical staff, the incidence rate of abnormal TSH and subclinical hypothyroidism was 1.65 per 100 person-years and 1.15 per 100 person-years, respectively. However, there was no significant difference in incidence rate between NSWs and non-NSWs after adjusting for the same confounders as above (Table 3).

Table 2
The person-years incidence rate and hazard ratio of abnormal TSH and subclinical hypothyroidism of all workers, defined by night shift worker status

Abnormal TSH	Incident cases	Person-years	Incidence rate (per 100 person-years)	Model 1		Model 2		Model 3	
				HR	95% CI	HR	95% CI	HR	95% CI
Night shift(−)	47	2327	2.02	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Night shift(+)	9	570	1.58	0.55	0.27−1.12	0.53	0.26−1.09	0.72	0.33−1.60
Subclinical hypothyroidism									
Night shift(−)	34	2413	1.41	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Night shift(+)	5	587	0.85	0.41	0.16−1.05	0.4	0.15−1.01	0.52	0.19−1.45

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and obesity; model 3: adjusted for age, sex, obesity, and working department.
Abbreviations: CI, confidence interval; HR, hazard ratio; ref, reference; TSH, thyroid stimulating hormone.

4. Discussion

In this hospital-based nine-year follow-up retrospective cohort study, we did not find significant differences in the incidence rate of abnormal TSH and subclinical hypothyroidism in NSWs compared with non-NSWs after adjusting for age, sex, obesity, and working department. These results were similar among exclusively medical employees after excluding administrative staff. To our knowledge, this is the first retrospective cohort study to explore the relationship between TSH and night shift work.

TSH level is a sensitive measure for initially identifying thyroid disorder. Its magnitude increases with age, independent of the presence of anti-thyroid antibodies [20]. It shows circadian rhythm peaks at night, early morning, and trough in the afternoon and evening [8,9]. A previous survey reported a prevalence of subclinical thyroid disease was 4%−15% [21]. The United States Third National Health and Examination Survey (NHANES III) for 1988−1994 showed that 4.3% of 16,533 people had subclinical hypothyroidism and 0.7% had subclinical hyperthyroidism, with higher TSH levels in females than males [21,22]. However, there is considerable variability and controversy regarding the appropriate upper limit of normal TSH according to age and time of blood sampling. Some studies have suggested that the true upper limit is only 2.5−3 μIU/mL in healthy individuals without thyroid disease [20,23]. One study showed that higher TSH was associated with obesity and that TSH levels fall with weight loss [23].

Few studies have evaluated the relationship between thyroid disorder and NSWs. Most of these applied cross-sectional measures only and yielded conflicting results; further, most included only female workers [13,24,25]. Our results are similar to the meta-analysis conducted in 2020, which against indicated that TSH is significantly higher in NSWs compared to day shift group [12]. Another review stated that a positive association between NSWs and elevated TSH was reported by most of the articles, but the cross-sectional design, poor qualities of the included articles, and heterogeneity in the shift-work scheduling make it difficult to integrate results and conclude definitely [14]. Among these included articles in the two reviews, one cross-sectional study conducted in Poland with 725 nurses and midwives showed no significantly increased risk of thyroid disorder among NSWs compared with other workers [24]. A further two studies conducted in Italy and Korea revealed that subclinical autoimmune hypothyroidism was significantly higher in NSWs than in daytime workers, with an OR of 2.12 and 1.39, respectively [13,25]. The Korean study also demonstrated that TSH levels were higher in NSWs than in non-NSWs. However, that study did not record the time of day of blood sample collection, used only cross-sectional repeated measures for analysis, and only included females that were predominately nurses [13].

Apart from the difference in the study design, our research differed from these other studies by including several kinds of medical and administrative staff employees with no significant difference in sex and age between NSWs and non-NSWs. Both of these factors may be expected to account for the differences among results. The heterogeneity in the average number of night shifts per month, continuous or rotating shift type, and duration of night shift work may also explain some of the conflicting results. Because of the “healthy worker effect”, workers with a generally better health status more easily adapted to night shift work and may work longer under such conditions. Tolerance to night shift work deteriorated with age, which may cause issues when older staff change roles to day shifts only [26].

Previous works showing NSWs associated with elevated TSH may provide possible mechanisms. One study considered that night shift work may induce sleep deprivation and changes to sleep schedules, timing, and quality, resulting in abnormalities or oscillations in the TSH circadian rhythm [13,27]. TSH release into the blood, which is normally inhibited during sleep, continues happen during sleep deprivation. So morning plasma TSH are higher in subjects who had a sleepless night [6,28]. However, according to a previous survey of the thyrotropin circadian rhythm, regular NSWs experienced a shift in sleep period by 8 hours, resulting in a mean shift of the TSH acrophase by 6.5 hours; it thus remained around the time of sleep onset as in daytime workers. Moreover, TSH values in NSWs returned more rapidly to baseline levels, indicating that the TSH acrophase adapted to regular night work. The TSH acrophase in NSWs also shifted by an equivalent amount and there was no significant difference in the mean amplitude of TSH between NSWs and daytime

Table 3
The person-years incidence rate and hazard ratio of abnormal TSH and subclinical hypothyroidism of medical staff only by excluding administrative staff, defined by night shift worker status

Abnormal TSH	Incident cases	Person-years	Incidence rate (per 100 person-years)	Model 1		Model 2		Model 3	
				HR	95% CI	HR	95% CI	HR	95% CI
Night shift(−)	26	1549	1.68	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Night shift(+)	9	570	1.58	0.66	0.31−1.42	0.64	0.30−1.38	0.76	0.34−1.70
Subclinical hypothyroidism									
Night shift(−)	20	1586	1.26	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Night shift(+)	5	587	0.85	0.48	0.18−1.27	0.45	0.17−1.19	0.57	0.20−1.59

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and obesity; model 3: adjusted for age, sex, obesity, and working department.
Abbreviations: CI, confidence interval; HR, hazard ratio; ref, reference; TSH, thyroid stimulating hormone.

workers [8]. Some ergonomic studies also provide psychological and medical evidence showing that night workers are a subgroup of shift workers more prone to adjusting their circadian rhythm to a nocturnal work schedule [8,29]. Therefore, higher TSH levels in NSWs may stem from the time point of check-up rather than from persistent high values. Further, these levels may indeed be the normal "time shift" or "phase shift" levels and not a true "abnormality" [28].

In addition, a previous study indicated that recovery sleep following sleep deprivation suppresses TSH levels further than normal sleep [30]. Sleep can inhibit TSH secretion and opposes the circadian influence on this hormone [6,28]. Night shift medical staff also show a more frequent use of sleep aids than the general population [31]. Another study showed that hypnotic facilitation of sleep may limit how strongly the decline of TSH levels is diminished due to abrupt time shifts and accelerated adaptation of circadian rhythmicity [32]. Some authors mentioned that NSWs may experience irregular eating habits and nocturnal eating, which may affect TSH levels. However, similar to our study, the employees included in the Korean study were all required to fast for at least 8 hours. One study even showed that meal intake decreased TSH concentration irrespective of diet [13,33]. Therefore, we do not expect meal intake to greatly affect the TSH levels of NSWs.

To our knowledge, this is the first retrospective cohort study to explore the incidence of abnormal TSH and subclinical hypothyroidism for a follow-up period of comparable duration. Some limitations of our design need to be considered. First, the shift work status in our study, as in the study in Korea, was based on worker status according to the most recent check-up. It is possible that not all daytime employees were consistently working daytime throughout the study period due to the healthy worker effect, especially for the group of nurses and doctors. We neither collected the data with regard to the number of years of shift work nor accurately differentiate the type of night shift work, which included regular night shifts, day and night shifts, and on-call shifts. One previous cross-sectional study showed that NSWs working for $\geq$15 years had an almost two-fold higher relative risk of thyroid disease [24]. Therefore, further studies using night-shift as a time-dependent variable and quantifying night-shifts with a longer follow-up warrant consideration. Second, TSH distribution became progressively higher with age. Some authors consider that the prevalence of subclinical hypothyroidism can be significantly overestimated unless an age-specific range for TSH is used [20]. This suggests that the normal range of TSH levels should be redefined based on age for future research. Third, we cannot totally exclude the employees who took anti-thyroid drug and became normal TSH during the period between two health check-ups even we did the examination annually.

In conclusion, while the above limitations need to be kept in mind, this study constitutes the first retrospective cohort study showing that night shift work was not associated with increased relative risk of incident abnormal TSH and subclinical hypothyroidism, in which finding it differs somewhat from previous cross-sectional studies. The thyroid hormone is essential in neural and endocrine systems and subclinical hypothyroidism may increase the risk of cardiovascular disease. Health care providers are typically confronted with higher job stress and higher frequency of night shifts. More detailed studies regarding the relationship between night shift work and thyroid function are therefore needed to promote occupational health among health care providers.

Funding/support

Nil.

Ethics approval

The study was approved by the institutional review board of Taipei Veterans General Hospital (IRB No: 2017-08-009AC#1) and the requirement for patient consent was waived by the ethics board.

Authors' contributions

All authors made substantial contributions as follows: (1) S.L. Wu, H.H. Chen, and C.M. Lin conceived and designed the study; (2) S.L. Wu, H.H. Chiu, H.Y. Huang and H.H. Chen acquired, analyzed, and interpreted the data; and (3) H.H. Chen drafted the article and T.L. Yeh critically revised it to add important intellectual content.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Acknowledgment

Thanks to the MacKay Memorial Hospital librarian, Pei-jin Li, for examining the references. The authors would like to thank Anthony Abram (www.uni-edit.net) for editing and proofreading this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2021.05.006.

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