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Association between dietary flavonoids intake and prostate cancer risk: A case-control study in Sicily

Giulio Reale[a], Giorgio I. Russo[a,*], Marina Di Mauro[a], Federica Regis[a], Daniele Campisi[a], Arturo Lo Giudice[a], Marina Marranzano[b], Rosalia Ragusa[c], Tommaso Castelli[a], Sebastiano Cimino[a], Giuseppe Morgia[a]

[a] Urology section – University of Catania, Catania, Italy
[b] Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Section of Hygiene and Preventive Medicine, University of Catania, Catania, Italy
[c] Health Direction of A.O.U.-VE, Azienda Ospedaliera Universitaria Policlinico "Vittorio Emanuale", Catania, Italy

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ABSTRACT

Objectives: The aim of this study is to test the association between dietary flavonoids intake and prostate cancer (PCa) in a sample of southern Italian individuals.
Design: A population-based case–control study on the association between PCa and dietary factors was conducted from January 2015 to December 2016, in a single institution.
Setting: Patients with elevated PSA (Prostate Specific Antigen) and/or suspicion of PCa underwent transperineal prostate biopsy (≥12 cores). A total of 118 histopathological-verified PCa cases were collected and matched with controls, which were selected from a sample of 2044 individuals randomly recruited among the same reference population. Finally, a total of 222 controls were selected.
Main outcome measures: Prevalence of PCa.
Results: Consumption of certain groups of flavonoids significantly differed between controls and cases, in particular: flavonols (63.36 vs 37.14 mg/d, P < 0.001), flavanols (107.61 vs. 74.24 mg/d, P = .016), flavanones (40.92 vs. 81.32 mg/d, P < 0.001), catechins (63.36 vs. 36.18 mg/d, P = .006). In the multivariate model, flavanols and flavones were associated with reduced risk of PCa, despite not in the highest quartile of intake. Higher flavonol and catechin intake was consistently associated with reduced risk of PCa (Odds Ratio (OR) = 0.19, 95% CI: 0.06–0.56 and OR = 0.12, 95% CI: 0.04–0.36). In contrast, the highest intake of flavanones was positively associated with PCa.
Conclusion: Flavonols and catechins have proved to be the most promising molecules for a potential protective role against PCa. Nevertheless, further research on flavanones is needed to better establish whether they are associated with PCa.

1. Introduction

Prostate cancer (PCa) is the most common cancer in men with incidental diagnosis.[1] Current statistics predicted that in the USA new cases of PCa will be more than 150,000 per annum over the next few years [2]. Although major efforts have been paid to prevent this cancer, including identification of risk factors (racial/ethnic background and family history) [3], there are aspects of etiopathogenesis still not clarified. Identifying causal factors of PCa would lead to new prevention methods. Also for PCa, as for benign prostatic hyperplasia, it has been hypothesized the possibility that the etiopathogenesis of the disorder is linked to chronic inflammation: the main pathway proposed suggests that the presence of oxidative stress associated to chronic inflammation in the cellular environment causes an increase of pro-inflammatory cytokines and growth factors, which in turn may determine an increase of the speed of cell replication, and therefore the possibility of incurring mutations [4,5]. If there is a correlation between prostate diseases, oxidative stress and chronic inflammation, the role of compounds with antioxidant action could play an important role in the prevention of PCa.

Current evidence suggests that adherence to plant-based dietary patterns, such as the Mediterranean diet, may reduce risk of PCa [6–8]. Moreover, patients exhibiting greater adherence to the Mediterranean diet after diagnosis of non-metastatic PCa were associated with lower

* Corresponding author.
E-mail address: giorgioivan.russo@unict.it (G.I. Russo).

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overall mortality [9]. Interestingly, pure vegetarian dietary patterns did not show the same inverse association with risk of PCa [10], suggesting that the retrieved associations are related to beneficial compounds rather than only reduction of unhealthy ones (i.e., trans-fatty acids). Among the others, important components of the Mediterranean diet that have been hypothesized to be responsible for its potential beneficial effects are polyphenols [11]. These compounds occur naturally in plant-derived foods, such as fruits and vegetables, nuts, whole-grains, olive oil, coffee and tea. Based on their biochemical structures, they are divided into different subclasses of which, the most representative, are flavonoids [12]. In turn, the six principal subclass of flavonoids are flavonols, flavones, flavanones, flavanols, and anthocyanidins [13]. The interest on studying flavonoids as anti-cancer substances depends on a variety of properties and potential mechanisms of action that may affect the risk of cancer [14–17]. In example, flavonoids were shown to modulate several molecular pathways implicated in PCa carcinogenesis process; in particular, by targeting important transcription factors, such as NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) and AP-1 (activator protein-1), implicated in regulation of inflammatory response. Results on the association between dietary flavonoid intake and human health are promising, but research in relation to cancer is still ongoing and rather incomplete [18]. Some studies investigated the relation between dietary flavonoids and PCa [19,20]: however, the relation between PCa and flavonoid subclasses remains unclear. Thus, the aim of this article is to test the association between dietary flavonoids, including all major subclasses, and PCa in a sample of southern Italian individuals.

2. Material and methods

2.1. Study population

A population-based case–control study on the association between PCa and dietary factors was conducted from January 2015 to December 2016 in a single institution of the municipality of Catania, southern Italy. Patients with elevated PSA and/or suspicious PCa underwent transperineal prostate biopsy (≥12 cores). A total of 118 histopathological-verified PCa cases were collected.

Controls were selected from a sample of 2044 individuals included in a cohort study [21]: individuals were randomly selected among the same reference population of the cases, and matched by age, BMI, and smoking status with cases. A total of 222 controls were selected.

All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and participants provided written informed consent after accepting to participate. The study protocol was approved by the ethic committee of the referent health authority (Policlinico Hospital of Catania, Registration number: 41/2015).

2.2. Data collection

Demographics (including age, and educational level) and lifestyle characteristics (including physical activity, smoking and drinking habits) were collected. Educational level was categorized as (i) low (primary/secondary), (ii) medium (high school), and (iii) high (university). Physical activity level was evaluated through the International Physical Activity Questionnaires (IPAQ) [22] which comprised a set of questionnaires (5 domains) investigating the time spent being physically active in the last 7 days: based on the IPAQ guidelines, final scores allows to categorized physical activity level as (i) low, (ii) moderate, and (iii) high. Smoking status was categorized as (i) non-smoker, (ii) ex-smoker, and (iii) current smoker. Alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1–12 g/d) and (iii) regular drinker (> 12 g/d).

2.3. Dietary assessment

Dietary data was collected by using two food frequency questionnaires (FFQs) specifically developed and validated for the Sicilian population[23,24]. The long-version FFQ consisted of 110 food and drink items. Patients were specifically asked whether they changed their diet due to course of the disease and to answer to the questionnaire referring to their habitual diet before the disease. Participants were asked how often, on average, they had consumed foods and drinks included in the FFQ, with nine responses ranging from “never” to “4-5 times per day”. Intake of food items characterized by seasonality referred to consumption during the period in which the food was available and then adjusted by its proportional intake in one year.

2.4. Estimation of flavonoid intake

The methodology used to retrieve dietary flavonoids has been widely used in literature and largely described elsewhere [25]. Briefly, data on the polyphenol content in foods was obtained from the Phenol-Explorer database (www.phenol-explorer.eu). A new module of the Phenol-Explorer database containing information on the effects of cooking and food processing on polyphenol contents was used whenever possible in order to apply polyphenol-specific retention factors [26]. A total of 75 items were searched in the database after exclusion of foods that contained no polyphenols. Following the standard portion sizes used in the study, food items were converted in g or ml and then proportioned to 24-h intake. Next, a search was carried out in the Phenol-Explorer database to retrieve mean content values for flavonoid (total and major subclasses) contained in the foods obtained and their intake was then calculated by multiplying the flavonoid content by the daily consumption of each food. Finally, intake of flavonoids was adjusted for total energy intake (kcal/d) using the residual method.

2.5. Statistical analysis

Categorical variables are presented as frequency and percentage, continuous variables are presented as mean and standard deviation. Differences of frequency between groups were calculated by Chi-square test. Total flavonoid intake distribution was tested for normality distribution with the Kolmogorov-Smirnov test and it followed a slightly asymmetric normal distribution due to extreme values of the upper side. Mann-Whitney *U* test and Kruskall-Wallis test were used to compare differences in intakes between groups, as appropriate. Association between dietary intake of total and subclasses of flavonoid and PCa was calculated through logistic regression analysis adjusted for age (years, continuous), energy intake (kcal/d, continuous), weight status (normal, overweight, obese), smoking status (smokers, non-smokers), alcohol consumption (< 12 g/d, ≥12 g/d), physical activity level (low, medium, high), family history of PCa. All reported *P* values were based on two-sided tests and compared to a significance level of 5%. SPSS 17 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical calculations.

3. Results

Table 1 lists the baseline characteristics of cases and controls. Besides the characteristics for which controls were matched with cases, most of other variables had different distribution between groups: specifically, among cases there was a higher prevalence of low education, low physical activity level, higher alcohol consumption and family history of PCa than controls, despite mean BMI levels were lower in the former than in the latter.

No significant differences between cases and controls have been found concerning total dietary flavonoids (Table 2). However, regarding flavonoid subclasses, differences between intake of some compounds were statistically significant: flavonols (63.36 vs. 37.14,

Table 1
Baseline characteristics of cases and controls.

	Cases (n = 118)	Controls (n = 222)	P-value
Age (y), mean (SD)	69.13 (6.60)	68.09 (8.18)	0.238
BMI, mean (SD)	26.49 (3.34)	27.49 (3.28)	< 0.001
Weight status, n (%)			0.220
Normal	42 (35.6	59 (26.6)	
Overweight	60 (50.8)	127 (57.2)	
Obese	16 (13.6)	36 (16.2)	
Smoking status, n (%)			0.220
Non-smoker	68 (57.6)	143 (64.4)	
Current smoker	50 (42.4)	79 (35.6)	
Alcohol intake, n (%)			< 0.001
< 12 g/d	55 (46.6)	153 (68.9)	
≥12 g/d	63 (53.4)	69 (31.1)	
Education, n (%)			< 0.001
Primary	96 (81.4)	49 (22.1)	
Secondary	22 (18.6)	173 (77.9)	
Physical activity level, n (%)			< 0.001
Low	38 (32.2)	49 (26.2)	
Medium	64 (54.2)	67 (35.8)	
High	16 (13.6)	71 (38.0)	
Family history of prostatic cancer, n (%)	43 (36.44)	9 (4.05)	< 0.001

Table 2
Mean differences of total and subclasses of flavonoid intake between cases and controls.

	Cases (n = 118)	Controls (n = 222)	P-value
Flavonoids, mean (SD)	268.68 (166.87)	286.04 (207.38)	0.434
Anthocyanins, mean (SD)	59.82 (51.55)	59.09 (55.57)	0.903
Flavonols, mean (SD)	37.14 (29.23)	63.36 (46.85)	< 0.001
Flavanols, mean (SD)	74.24 (71.42)	107.61 (139.97)	0.016
Flavanones, mean (SD)	81.32 (76.94)	40.92 (40.38)	< 0.001
Flavones, mean (SD)	9.86 (13.84)	8.50 (8.70)	0.266
Catechins, mean (SD)	36.18 (46.43)	63.36 (100.11)	0.006

P < 0.001), flavanols (107.61 vs. 74.24, P = 0.016), flavanones (40.92 vs. 81.32 P < 0.001), and catechins (63.36 vs. 36.18, P = 0.006). There was no statistical significant difference in the subclasses of flavones and anthocyanins between PCa group when compared to controls.

The univariate logistic regression analysis showed that intake of various compounds was associated with PCa (Table 3). When analysis was adjusted for potential confounding factors (including age, energy intake, weight status, smoking status, alcohol consumption, physical activity level, family history of prostatic cancer), only the highest intake of flavonol and catechin intake was consistently associated with less likelihood of having PCa (OR = 0.19, 95%CI: 0.07–0.50 and OR = 0.12, 95%CI: 0.04–0.36, respectively). Moreover, flavanol and flavone intake was also associated with PCa, despite the significant association was relative to third quartile of intake, while the highest showed no significant results (Table 3). In contrast, the highest quartile of flavanone intake was directly associated with higher likelihood of having PCa compared to the lowest (Table 3). No significant association between total flavonoid intake and PCa was found.

4. Discussion

In this study, we tested the association between dietary flavonoid intake and PCa in a sample of individuals living in the Mediterranean area. Although results were not consistently significant for all the various compounds tested, higher intake of nearly all flavonoids was inversely associated with PCa compared to lower intake.

Published data on flavonoid intake and risk of PCa is somehow contrasting. Some individual studies and recent meta-analyses showed

Table 3
Association between quartiles of total and subclasses of flavonoid intake and prostate cancer.

	Q1	Q2	Q3	Q4
Flavonoids				
No. of cases	30	35	19	36
OR (95% CI)[a]	Ref.	0.93 (0.49–1.76)	0.48 (0.24–0.97)	0.75 (0.39–1.45)
OR (95% CI)[b]	Ref.	1.44 (0.57–3.63)	0.51 (0.18–1.42)	1.10 (0.40–2.99)
Anthocyanins				
No. of cases	28	31	32	27
OR (95% CI)[a]	Ref.	1.09 (0.57–2.09)	0.98 (0.51–1.85)	0.62 (0.31–1.25)
OR (95% CI)[b]	Ref.	0.58 (0.23–1.45)	0.51 (0.20–1.31)	0.36 (0.12–1.06)
Flavonols				
No. of cases	64	28	15	11
OR (95% CI)[a]	Ref.	0.44 (0.24–0.79)	0.21 (0.10–0.42)	0.11 (0.53–0.26)
OR (95% CI)[b]	Ref.	0.44 (0.18–1.04)	0.19 (0.07–0.50)	0.19 (0.06–0.56)
Flavanols				
No. of cases	106	9	2	1
OR (95% CI)[a]	Ref.	0.71 (0.29–1.72)	0.03 (0.003–0.33)	0.35 (0.04–3.04)
OR (95% CI)[b]	Ref.	0.76 (0.22–2.58)	0.02 (0.002–0.31)	1.84 (0.17–19.4)
Flavanones				
No. of cases	18	10	19	71
OR (95% CI)[a]	Ref.	0.51 (0.21–1.21)	0.96 (0.45–2.06)	3.03 (1.56–5.87)
OR (95% CI)[b]	Ref.	0.26 (0.07–0.90)	1.59 (0.50–5.02)	5.76 (2.06–16.09)
Flavones				
No. of cases	37	32	10	39
OR (95% CI)[a]	Ref.	0.82 (0.44–1.51)	0.24 (0.11–0.55)	0.84 (0.46–1.54)
OR (95% CI)[b]	Ref.	0.61 (0.25–1.45)	0.33 (0.12–0.91)	0.87 (0.34–2.21)
Catechins				
No. of cases	50	22	31	15
OR (95% CI)[a]	Ref.	0.39 (0.21–0.75)	0.49 (0.27–0.89)	0.20 (0.097–0.41)
OR (95% CI)[b]	Ref.	0.21 (0.08–0.55)	0.35 (0.14–0.90)	0.12 (0.04–0.36)

[a] OR adjusted for energy intake (kcal/d, continuous).

[b] OR adjusted for age (years, continuous), energy intake (kcal/d, continuous), weight status (normal, overweight, obese), smoking status (smokers, non-smokers), alcohol consumption (< 12 g/d, ≥12 g/d), physical activity level (low, medium, high), family history of prostatic cancer.

that a direct association between specific classes of flavonoids (i.e., flavanones and anthocyanins) and likelihood of having PCa may exist, while results on other classes are largely inconsistent [19,20,27]. Thus, our findings are only partially in line with existing literature, as we found a potential protective association for certain classes, while we also reported direct association between flavanone intake and PCa.

Regarding the potential detrimental effects, it has been hypothesized that excessive antioxidants consumption may actually increase risk of cancer [28]. Despite not relative to flavanones, there is evidence that certain antioxidant vitamins, including ascorbic acid, may have detrimental effects on reactive oxygen species production processes related to PCa [29–31]; it is noteworthy that major source of ascorbic acid coincide with those of flavanones (i.e., citrus fruits), thus potentially leading to collinearity and confusing the interpretation of results on this flavonoid class.

Regarding the potential protective effects of flavonoids, there is evidence of general beneficial effects of dietary flavonoids on metabolic health [32,33] and metabolic status has been shown in a recent meta-analysis to be a mediating factor for PCa risk [34]. Flavonoids may act as activator of the transcription factor NF-kB that regulate a variety of cellular activities that include inflammation, immune response, cell growth and death, therefore resulting in a cascade of events that may lead to carcinogenesis [33]. Overexpression of NF-kB leads to the activation of several signalling pathways, among which also the activation of COX-2 (cyclooxygenase-2), which increases levels of pro-inflammatory cytokines, a perfect scenario for developing PCa cells. It has been shown, that synthetized analogs of flavanols are promising category of compounds that can inhibit cell growth and interfere with the components of the androgen receptor and PSA proteins in human-derived PCa cell line [35] or directly compromise the PCa cell vitality of several prostate cancer cell lines, including: 22Rv1, TRAMP C2, PC-3

and LNCaP [36] Moreover, flavonols may expression of several genes, such as MMP-1 (matrix metalloproteinase-1), MMP-9 (matrix metalloproteinase-9), MMP-14 (matrix metalloproteinase-14), c-Fos (proto-oncogene), c-Jun (a subunit of the transcription factor), and VEGF (vascular endothelial growth factor), that have been previously shown to be associated with PCa [36] and in particular in changing the ratio Bcl-2 (B-cell lymphoma 2)/Bax (apoptosis regulator) mRNA, which directly determines neoplastic cell sensitization for the apoptotic pathway [37,38].

Among individual compounds, higher intake of flavonols and, specifically, catechins was found to be significantly inversely associated with having PCa. Catechins are typically contained in tea, one of the most widely consumed beverage in the world [39]. The tea plant (*Camellia sinensis*) produced in Asia, China, Japan, and Thailand has been traditionally used in natural medicine[40]. The most represented individual compounds contained in tea, such as epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC), and epigallocatechin-3-gallate (EGCG), have been studied in relation to PCa[41]. Among the main mechanisms of action, these molecules may play a role in the prevention of etiopathogeneiss of PCa by inducing cell growth arrest and apoptosis primarily via p53-dependent pathway or inhibiting COX-2 (inducible enzymatic isoform, rapidly induced by growth factors, tumor promoters, oncogenes, and carcinogens) without affecting COX-1 (cyclooxygenase-1), at both the mRNA and protein levels [15,40], Besides these biological properties, previous data found no association between PCa risk and green tea intake [42–44]. However, a recent meta-analysis showed that green tea intake might reduce the incidence of PCa with a linear dose–response effect and decrease PCa risk significantly with daily intake of over 7 cups/day [45]. There is still only limited evidence from randomized clinical trials investigating the association of green tea catechins with the risk of PCa, however showing that green tea catechins had a significant effect on the reduction of PCa risk compared to placebo [46,47].

Some limitations of the present analysis have to be addressed for a better interpretation of the results. First, the observational nature of study does not permit to assess causal relationships, rather only associations. Second, the variety of flavonoid composition is complex and use of FFQs may lead to measurement errors. Third, our sample was based on patients with no previous biopsy and PCa diagnosis could have been underestimated. In contrast, controls were selected from the general population, thus we are unaware whether undiagnosed PCa cases existed.

5. Conclusion

In conclusions, flavonoids may have different levels of protection against PCa. Among the compounds tested in our study, flavonols and catechins have proved to be the most interesting molecules for a protective value. Future randomized clinical trials are needed to strengthen the findings obtained in this study and provide adequate evidence of the potential protective effects of flavonoids toward PCa risk.

Compliance with ethical standards

All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and participants provided written informed consent after accepting to participate. The study protocol was approved by the ethic committee of the referent health authority (Policlinico Hospital of Catania, Registration number: 41/2015).

Conflict of interest

Each author declares no conflict of interest.

Author's contribution

G.R.: Manuscript writing
G.I.R.: Protocol/project development, data management, manuscript editing
F.R.: Data Collection
M.D.: Data Collection
D.C.: Data Collection
A.L.: Data Collection
M.M.: Supervision
R.R.: Supervision
V.F.: Supervision
S.C.: Supervision
G.M.: Supervision

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Adiposity at different periods of life and risk of adult glioma in a cohort of postmenopausal women

Geoffrey C. Kabat*, Thomas E. Rohan

Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, United States

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ABSTRACT

Background: Little is known about risk factors for adult glioma. Adiposity has received some attention as a possible risk factor.

Methods: We examined the association of body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR), measured at enrollment, as well as self-reported weight earlier in life, with risk of glioma in a large cohort of postmenopausal women. Over 18 years of follow-up, 217 glioma cases were ascertained, including 164 glioblastomas. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals.

Results: There was a modest, non-significant trend toward increasing risk of glioma and glioblastoma with increasing measured BMI and WHR. No trend was seen for WC. Self-reported BMI earlier in life showed no association with risk.

Conclusions: Our weak findings regarding the association of adiposity measures with risk of glioma are in agreement the results of several large cohort studies. In view of the available evidence, adiposity is unlikely to represent an important risk factor for glioma.

1. Introduction

Gliomas are the most common primary intracranial cancer and the most fatal type of brain tumor [1]. Little is known about risk factors for gliomas [2]. Established risk factors include several rare, inherited genetic syndromes and exposure to ionizing radiation [2]; however, these account for only a small proportion of gliomas.

Adiposity has received attention as a possible risk factor for glioma [3–10]. Such an association might be mediated by circulating insulin levels, since hyperinsulinemia is common among obese and sedentary individuals, and insulin has pro-mitotic properties [4,5]. Insulin crosses the blood-brain barrier, and insulin's actions within the CNS are mediated by two canonical pathways involved in carcinogenesis [11]. However, most studies have found little evidence of an association with adiposity. Of two meta-analyses of the association of adult body mass index (BMI) and glioma, one found no association in men or women [9], whereas the other reported a significant association in women but not in men [8]. Two other studies [4,5] showed positive associations of BMI at age 18 and 21, respectively, with glioma risk, raising the possibility of an etiologic role of obesity earlier in life.

We examined the association of BMI, waist circumference (WC), and waist-to-hip ratio (WHR) measured at enrollment with risk of glioma in a large cohort of postmenopausal women. Additionally, we assessed the association of BMI at age 18, 35, and 50 with risk of glioma in a subset of the study population.

2. Methods

The Women's Health Initiative is a large, multicenter study designed to advance understanding of the determinants of major chronic diseases in postmenopausal women. It is composed of a clinical trial component (CT, n = 68,132) and an observational study component (OS, n = 93,676) [12]. Women between the ages of 50 and 79 and representing the major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998.

At study entry, self-administered questionnaires were used to collect information on demographics, medical, reproductive, and family history, and lifestyle factors, including smoking history, alcohol consumption, diet, and recreational physical activity. All participants had their weight and height measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Body mass index was computed as weight in kilograms divided by the square of height in meters. Waist circumference and waist-to-hip ratio

* Corresponding author at: Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, United States.
E-mail address: Geoffrey.kabat@einstein.yu.edu (G.C. Kabat).

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Table 1
Association of baseline anthropometric measures with risk of glioma and glioblastoma in the Women's Health Initiative (n = 161,119[a]).

	Glioma (n cases = 217)				Glioblastoma (n cases = 164)			
BMI (kg/m^2)[b]	N cases	N non-cases	HR[d]	95% CI	N cases	N non-cases	HR[d]	95% CI
18.5– < 25.0	70	54,827	1.00	Ref.	53	54,827	1.00	Ref.
25.0– < 30.0	74	55,571	1.06	0.76–1.47	54	55,571	1.04	0.71–1.53
30.0– < 35.0	43	29,684	1.21	0.81–1.79	33	29,684	1.25	0.79–1.97
≥35.0	25	18,582	1.30	0.81–2.08	20	18,582	1.46	0.86–2.50
Missing	5	106			4	106		
P for linear trend			*0.32*				*0.18*	
Waist circumference (cm)								
< 76.0	50	40,525	1.00	Ref.	33	40,525	1.00	Ref.
76.0- < 84.5	60	40,226	1.18	0.80–1.73	48	40,226	1.44	0.92–2.25
84.5- < 95.0	57	39,395	1.24	0.84–1.83	42	39,395	1.38	0.86–2.20
≥95.0	50	40,756	1.11	0.74–1.68	41	40,756	1.41	0.87–2.29
P for linear trend			*0.66*				*0.25*	
WHR[c]								
< 0.76	47	39,855	1.00	Ref.	33	39,855	1.00	Ref.
0.76- < 0.80	59	39,846	1.22	0.83–1.80	44	39,846	1.28	0.81–2.01
0.80- < 0.86	53	40,044	1.22	0.82–1.81	41	40,044	1.30	0.82–2.06
≥0.86	56	39,725	1.34	0.90–2.00	44	39,725	1.45	0.92–2.30
Missing	2	694			2	694		
P for linear trend			*0.17*				*0.09*	

Abbreviations: HR–hazard ratio; 95% CI–95% confidence interval; BMI–body mass index; WHR–waist-to-hip ratio.
[a] Women with anthropometric measurements.
[b] 2,132 women with BMI < 18.5 or BMI missing.
[c] 740 women missing WHR measurement.
[d] Adjusted for age, smoking status, alcohol intake, physical activity, hormone therapy, years of education, ethnicity, and treatment status.

were also measured. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. A variable "current total leisure-time physical activity" (MET-hours/week) was computed by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent (MET) value of the activity and summing over all types of activities [13].

BMI, which reflects overall adiposity, was categorized according to the WHO classification: 18.5- < 25.0 kg/m^2 – normal weight, 25.0- < 30.0 kg/m^2 – overweight, and ≥30.0 kg/m^2 – obese. Waist circumference (WC), a measure of central adiposity, and waist-to-hip ratio (WHR), a measure of the ratio of central to lower extremity adiposity, were categorized into quartiles based on the distribution among non-cases. Information on weight at earlier ages was available only for participants in the Observational Study (n = 92,557) and was used to compute BMI at ages 18, 35, and 50. For this analysis, owing to the reduced sample size, we created tertiles based on the distribution in non-cases.

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of malignancy, including gliomas, were verified by central review of medical records and pathology reports by trained physician adjudicators [14]. Among 161,119 WHI participants with anthropometric measurements, 217 cases of glioma were ascertained over a median of 17.8 years of follow-up. Of these, 164 had glioblastoma. Other gliomas included: mixed glioma, ependymoma NOS, well-differentiated low-grade astrocytoma, anaplastic astrocytoma, and oligodendroglioma.

2.1. Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of anthropometric factors with risk of glioma and glioblastoma, using days to event as the timescale. Participants who had not developed glioma by the end of follow-up, who had died, or who withdrew from the study before the end of follow-up were censored. Cases contributed person-time to the study from their date of enrollment until the date of diagnosis, and non-cases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up, date of death, or date of withdrawal from the study, whichever came first. Hazard ratios were computed by quartile of measured anthropometric variables and by tertiles of self-reported body weight at earlier ages. Covariates were selected for inclusion in the final model if their inclusion changed the parameter estimate by > 10%. Pack-years of smoking and use of hormone therapy did not improve the model and were excluded. The final model included age (continuous), smoking status (never, former, current), alcohol intake (servings/week – continuous), physical activity (metabolic equivalent tasks [MET]-hrs/wk continuous, years of education (less than high school, high school graduate/some college, college graduate, post-college), ethnicity (white, black, other), and allocation in the clinical trial arms or observational study. A test for linear trend over quantiles of anthropometric variables was performed by assigning the median value to each category and modeling this variable as a continuous variable. In order to account for women with a prevalent cancer at the time of enrollment, we carried out a sensitivity analysis in which we excluded women who reported a history of cancer at entry into the study. We tested the proportional hazards assumption using PROC LIFETEST (SAS Institute). The formal test for non-proportional hazards was not significant and the log-log survival plots did not indicate any marked deviation from normality. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). All P-values are 2-sided.

3. Results

Glioma cases did not differ from non-glioma cases in terms of mean age, smoking status, mean pack-years of smoking, alcohol intake, hormone therapy, or physical activity. The proportion of whites was higher among cases than among non-cases (93.5 vs. 82.7 percent, p = 0.0002).

In multivariable-adjusted analyses, HRs for glioma and, particularly glioblastoma were somewhat elevated for the highest quartiles of the anthropometric measures of interest (Table 1). There was a suggestion of a non-significant trend, particularly for the association of BMI with

Table 2
Association of self-reported weight at different ages with risk of glioma in the Observational Study component of the Women's Health Initiative (n = 91,150[a]).

	Glioma (n cases = 115)				Glioblastoma (n cases = 86)			
			HR[b]	95% CI			HR[b]	95% CI
BMI (kg/m^2) at age 18								
< 19.4	31	30,465	1.00	Ref.	25	30,465	1.00	Ref.
19.4 –21.3	45	30,822	1.28	0.81–2.03	33	30,822	1.11	0.71–1.72
≥21.3	39	29,731	1.28	0.80–2.04	28	29,731	1.01	0.63–1.61
P for linear trend			*0.33*				*0.97*	
BMI (kg/m^2) at age 35								
< 20.8	37	30,352	1.00	Ref.	28	30,352	1.00	Ref.
20.8– < 22.9	43	30,122	1.14	0.73–1.77	31	30,122	1.11	0.71–1.72
≥22.9	35	30,472	1.04	0.65-1.66	27	30,472	1.01	0.63–1.61
P for linear trend			*0.92*				*0.99*	
BMI (kg/m^2) at age 50								
< 22.1	39	30,254	1.00	Ref.	30	30,254	1.00	Ref.
22.1– < 25.1	47	30,328	1.21	0.79–1.86	35	30,328	1.17	0.72–1.92
≥25.1	28	30,454	0.84	0.51–1.39	21	30,454	0.87	0.49–1.56
P for linear trend			*0.46*				*0.60*	

Abbreviations: HR – hazard ratio; 95% CI – 95% confidence interval; BMI – body mass index.
[a] Women with self-reported weight earlier in life.
[b] Adjusted for age, smoking status, alcohol intake, physical activity, years of education, and ethnicity.

glioblastoma and for WHR with glioma and glioblastoma. WC showed no association with glioma, and HRs for glioblastoma were similar for quartiles 2 to 4, showing no trend. None of the point estimates was statistically significant, and none of the linear trends over quartiles was significant. Associations with self-reported body weight at earlier points in life (ages 18, 35, and 50), available on a subset of the population (WHI observational study), showed no suggestion of an increasing trend with either glioma or glioblastoma (Table 2). When measured BMI, WC, and WHR were reanalyzed in this subgroup, no suggestive associations or trends were seen for glioma or glioblastoma.

In the sensitivity analysis excluding women with prevalent cancer, the associations with measured BMI, WC, and WHR with glioma and glioblastoma were either unchanged or slightly attenuated (data not shown). In particular, the monotonic trend for WHR with glioblastoma was weakened (HR for 2nd to 4th quartiles: 1.32, 95% CI 0.82-2.14, 1.27, 95% CI 0.77-2.07, 1.35, 95% CI 0.82-2.23, respectively; p for linear trend 0.30).

4. Discussion

In this large prospective study of postmenopausal women, there was a suggestion of a modest and non-significant positive association of measured BMI and WHR, but not WC, with risk of glioma and glioblastoma. Self-reported BMI earlier in life showed no association with risk of adult glioma or glioblastoma.

Previous studies have found little evidence of an association of adiposity with glioma. A meta-analysis [9] of 5 studies (4 cohort, 1 case-control) with a total of 2,725 cases of glioma, showed that BMI was not associated with glioma: the summary relative risk (RR) for overweight vs. normal weight was 1.06 (95% CI 0.94-1.20) and RR for obesity was 1.11 (95% CI 0.98-1.27). The second meta-analysis [8], which included only 3 studies (2 cohort and 1 case-control) with 2,418 cases of glioma, reported a positive summary association of BMI in females (odds ratio/relative risk 1.17, 95% CI 1.03-1.32), but not in males. However, this result appears to stem from two errors, which appear in Fig. 5 of the publication [8]. First, the meta-analysis included results for "BMI at age 21," rather than "BMI in recent past" from the Little et al. study [5]. BMI at age 21 showed a borderline significant positive association, whereas BMI in recent past showed no association (see Table 2, p. 1029 [5]). It is BMI in midlife that is the focus of the meta-analyses. Second, the authors included data from an analysis of the Nurses' Health Study I by Holick et al. [15]. However, this paper presented data on intake of fruits, vegetables, and carotenoids, but not on BMI, in relation to glioma risk. (GCK contacted both the first and second authors on the paper, and they both confirmed that their data on BMI and glioma risk were not published). Therefore, the source of the data for the two entries from the Holick et al. study ("Holick – NHS I, females, 2007, 25.0-29.9" and "Holick – NHS I, females, 2007, ≥30.0") is unclear.

Since publication of the meta-analyses, results from a large Norwegian cohort study [10] with 4,382 cases of glioma showed no association of overweight or obesity with glioblastoma or any other glioma subgroup; however, information on socioeconomic status and other covariates was not available in this study.

Fewer studies have examined BMI in adolescence in relation to risk of adult glioma [4,5]. The large relative risk for obesity relative to normal BMI reported by Moore et al. [4] was based on 11 glioma cases, and there was no suggestion of an elevated risk in the overweight category. In the case-control study by Little et al. [5], none of the odds ratios for the 25-29.9 or ≥30 kg/m^2 categories was statistically significant in males or females, although the trend per unit increase in BMI was statistically significant in females but not in males.

In the present study, there was a suggestion of increased risk, particularly for glioblastoma in association with BMI and WHR, although the associations were not statistically significant due to small numbers. There was no evidence of an increasing trend for the association of WC with glioma or glioblastoma, in spite of the fact that measured WC is a reliable indicator of central adiposity [16]. When we used self-reported body weight at earlier time points, available on roughly half the study population, there were no clear trends with glioma or glioblastoma. This was also true when associations of measured BMI, WC, and WHR were examined in this subgroup. However, women in the observational study tended to have lower BMI compared to women in the clinical trials, and this could have obscured a positive association.

It should also be mentioned that gliomas are a heterogeneous group of tumors of different histopathologic types and different grades (1). Our results are driven by the results for glioblastoma, the largest single subgroup. However, the numbers of other types of glioma (diffuse astrocytomas, analplastic astrocytomas, pilocytic astrocytomas, and oligodendrogliomas), were too small to analyze separately.

Strengths of the present study include the prospective nature of the study, central adjudication of all malignancies, standardized measurement of anthropometric factors at enrollment, and the availability of self-reported weight at earlier periods of life. Limitations include the

relatively small number of cases and the fact that, due to restriction of the study to postmenopausal women, glioma cases occurring in women below age 50 were not captured.

In conclusion, we found a suggestion of a modest positive association of measured BMI and WHR, but not WC, with risk of glioma and glioblastoma. Self-reported BMI earlier in life showed no association with increased risk. Based on available evidence, it is unlikely that adiposity represents an important risk factor for glioma.

Author's contributions

Conceived the study: Geoffrey Kabat, Thomas Rohan.
Designed the study: Geoffrey Kabat, Thomas Rohan.
Acquired the data: Geoffrey Kabat.
Analyzed the data: Geoffrey Kabat.
Wrote the first draft of the manuscript: Geoffrey Kabat.
Commented on and contributed additional ideas: Thomas Rohan.
Approved the final manuscript and conclusions: Geoffrey Kabat, Thomas Rohan.

Declaration of conflicting interests/disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Impact of nurse-led cardiac rehabilitation on patient's behavioral and physiological parameters after a coronary intervention: A pilot randomized controlled trial

Sriram Premkumar, Lakshmi Ramamoorthy, Ajith A. Pillai[1]

Department of Medical Surgical Nursing, College of Nursing, Jawaharlal Institute of Post Graduate Medical Education and Research, [1]Department of Cardiology, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India

Address for correspondence:
Dr. Lakshmi Ramamoorthy, College of Nursing, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: laxmi_ramamoorthy@yahoo.com

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Abstract:

BACKGROUND: Coronary artery disease, one of the leading causes of mortality and morbidity globally, is a major burden on healthcare resources. Cardiovascular rehabilitation is highly recommended for the early recovery of patients with Ischemic heart disease by improving the functional capacity and decreasing disease progression. A randomized controlled trial was conducted to assess the effect of nurse-led cardiac rehabilitation (CR) on behavioural parameters.

MATERIALS AND METHODS: Sixty-two adult patients who underwent percutaneous coronary intervention (PCI) were randomised to two groups to assess the effect of nurse-led cardiac rehabilitation (CR) on behavioural parameters, including adherence to drugs, cardiac diet, lifestyle changes, and selected physiological parameters. The intervention group had nurse-led individualized discharge counseling and clinical follow-up by telephone, whereas the control group received usual care. The comparisons between the control and intervention groups were made using independent Student's *t*-test or Mann–Whitney U test as appropriate. Pre-test and post-test scores were compared using paired *t*-test; all tests performed at 5% significance level.

RESULTS: Participants in the intervention group presented with moderate to good smoking cessation, improved adherence to drugs ($P < 0.0001$), physically active lifestyle in 90.3 versus 45.2% ($P < 0.0001$), adherence to dietary changes, and improved healthcare satisfaction ($P < 0.0001$). There was also a significant reduction in triglycerides level in the intervention group at 62.51 versus 20.12 mg/dl in the control arm with ($P < 0.05$), and better controlled physiological indices, including a reduction in systolic blood pressure of 1.54 vs-7.12 mmHg ($P = 0.003$), bodyweight reduction of 2.48 kg versus-0.09 kg ($P < 0.0001$) and body mass index of 0.9 versus-0.05 ($P < 0.0001$).

CONCLUSION: Personalised, nurse-led CR significantly improved the participants adherence to healthy lifestyle behaviors and decreased the cardiac risk factors in patients with coronary artery disease.

Keywords:

Cardiac rehabilitation, coranary artery disease, coronary heart disease, coronary intervention, myocardial infarction, nurse-led rehabilitation

Introduction

Coronary artery disease (CAD), the most common type of heart disease, has assumed epidemic proportions worldwide, and the burden of CAD is significant for

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patients as well as healthcare delivery systems. In India, a tenfold increase in the prevalence of coronary heart disease has been seen in urban populations and less than 1% to 4%–6% has been observed in rural populations.[1,2] In spite of evidence-based interventions, CAD remains a leading cause of global mortality.[3,4] Rehabilitation programs with a focus on counseling and health education are vital components of the holistic approach in the treatment of CAD as studies signify that there is a dependent association between behavioral and physiological risk factors in the incidence and progression of CAD.[5,6]

Secondary prevention strategies are vital to the care of the patient with cardiovascular disease (CVD). The term cardiac rehabilitation (CR) denotes coordinated, comprehensive interventions planned to improve a cardiac patient's physical, social and psychological functioning, in addition to slowing or reversing any further development of the underlying atherosclerotic processes, thereby decreasing morbidity and mortality.[7] A supervised CR program can affect the health-related behavior and modify the cardiovascular risk factor profile leading to better clinical outcomes. However, the rather diverse parameters make secondary prevention after a coronary intervention a formidable task,[5,6] a unique challenge for the treating physician.[8]

Published evidence claims that 18% of acute myocardial infarction (AMI) patients are affected with a second CVD event in the 1st year, and approximately half of these readmissions happen after discharge from hospital following an acute coronary syndrome (ACS).[5] Although CR programs reduce morbidity and mortality rates in adults with ischemic heart disease, heart failure, or cardiac surgery, they are not well utilised, since only a few eligible patients participate in them.[9,10] Novel strategies in CR delivery are urgently needed to improve participation. One potential strategy is nurse-led CR to enhance and encourage patients to meet the goals of improved physical activity, good adherence to antiplatelets and other prescribed medications, improved dietary habits, smoking cessation, and optimal psychosocial well-being, and thereby help to reduce their risk of future CVD events. Various studies have shown that nurse-led CR strategies have reduced secondary events and improved the participants' therapeutic lifestyle modification following an AMI.[7,11,12]

Public hospitals with a limited number of specialists attend to a large number of patients, which makes the maintenance of proper controls of the quality of healthcare a challenge. Assent to secondary prevention strategies as vital to treatment after ACSs is unanimous. The core components are well defined, and current guidelines recommend a multidisciplinary approach to a total CVD risk reduction.[13,14] An individual, patient-tailored risk reduction program is supported, and studies have indicated that it is more efficient and cost-effective.[15-17] Hence, we planned to study the effect of nurse-led specific CR programs on patients with CAD who have had elective percutaneous coronary interventions (PCIs), in comparison with routine care, on patients' Behavioural and Bio physiological parameters at 12-week intervals.

Materials and Methods

A nonblinded randomized control trial was designed to assess the effect of a nurse-led CR program on behavioural, physiological and biochemical parameters control at 12 weeks intervals of the patients with CAD who had undergone elective coronary angioplasty at a tertiary care centre in South India. Ethical approval was obtained from the Institutional Review Board vide Letter No. JIP/IEC/SC/2016/29/925 dated 15/07/2016 and informed written consent was taken from all participants. The trial was registered in the Clinical Trial Registry of India (CTRI) Reg. No: CTRI/2017/03/008022. The sample size was calculated by comparing the mean difference of total cholesterol (TC) between the Intervention group and control group as −0.50 (0.47) versus −0.17 (0.47) at 3-months' intervals of the group who had nurse-led CR and routine care, with the power of the study as 80% and at 5% level of significance. The sample for this study consisted of 62 participants with CAD who had undergone elective PCI, 31 of whom belonged to the experimental group and 31 in the control group.[3]

Patients aged more than 18 years with CAD who had undergone elective PCI for chronic stable angina or ACS with left ventricular ejection fraction (EF)[3] 50% and above were eligible for enrolment. We excluded patients with cardiac failure or other debilitating illnesses such as chronic kidney disease, chronic liver disease, and physical disabilities that prevented them from adhering to prespecified rehabilitation protocol, i.e., those who could not perform physical activities, patients with significant visual or hearing impairment, and those with depression or other major psychiatric disorders and any who had earlier participated in any kind of CR program. In this study, a smoker refers to someone who smokes any tobacco product, either daily or occasionally. Alcoholism refers to a person who has the desire or physical need to consume alcohol.

The consecutive sampling technique was used to select the study participants and a simple randomization technique using a computer-generated random number table was employed for random allocation of participants to the control and intervention groups. The random allocation sequence was prepared by a statistician who was not involved in the study. The study participants

were randomized to intervention and control groups after obtaining informed consent. The investigator obtained a socio-demographic and lifestyle history from the enrolled patients when they were stable after the PCI procedure. Information on clinical parameters including body weight, body mass index (BMI) blood pressure (BP) was measured on the day of discharge. Fasting lipid profile blood sample was collected on the day of the coronary intervention procedure. In this study, the following operational definitions were used, i.e., nonvegetarian refers to someone who consumes meat. Lifestyle changes or behavioral parameters refer to adherence to prescribed treatment regime, adherence to a physically active lifestyle (minimum of 30 min of walk/day), following cardiac healthy diet advice, cessation of smoking and alcoholism. Physiological parameters include changes in BMI and BP in both groups, biochemical parameters refer to changes in lipid profile values following intervention. Family history of CAD refers to the presence of myocardial infarction, angina, or coronary revascularization in anyfirst-degree relatives of the family.

The participants in the intervention group were counselled one-on-one by a nurse trained in cardiology nursing. The research nurse was trained on CR with American Heart Association (AHA) guidelines by the faculty from medical and nursing discipline. Personalized discharge counseling was given to all patients in the Intervention Group at a minimum of two to three sessions per patient, with standard audio-visual aids on CR aspects as per AHA guidelines including the importance of adherence to antiplatelets and other drugs, regular physical activity, quitting smoking, and adherence to a cardiac diet. This was given when patient was stabilized following the procedure and before the discharge and all their questions were answered. After the hospital discharge, weekly telephone interviews were made and an assessment of compliance to a healthy lifestyle and medication adherence done with a checklist. Patients were advised to maintain a diary of the physical activity, medication adherence, 24 h food recall, which was checked by the investigator during the monthly follow-ups for 3 months. Personal follow-up and follow-up counseling sessions were conducted in the cardiac outpatient department (OPD) at the end of every month to reassure the patient. Outcome measurement including physiological parameters (BP), biochemical parameters (lipid profile), and behavioral outcome (smoking cessation, drug adherence, cardiac diet adherence, and adherence to physical activity) were taken at the end of 3 months for all patients, their satisfaction with the personalized counseling were assessed and the outcome assessment by the research nurse done. No blinding was used in this study for outcome assessment.

The control group was given a standard discharge procedure, (with discharge summary including treatment plans), that was followed in the department where the decision to discharge was made by the treating physician. The unit nurses discharged the patient based on discharge summary guidelines given by the physician. Patients in both groups were treated equally apart from the issue of comorbidity-specific drugs. Both group patients were advised to come to the cardiology OPD for clinical follow-up and for medication refill.

The participants were administered a questionnaire to assess their baseline compliance to prescribed medications, physical activity, dietary adherence, and smoking cessation. Compliance with medications (drug adherence) was assessed by 8 points on Morisky's scale. This self-report Morisky scale contains 7 items with yes or no answers and 1 item with a 5-point Likert scale. The scores range from 0 to 8. A score below 6 specifies low adherence, a score between 6 < 8 medium adherence and a score of 8 indicates high adherence with content validity score of Cronbach alpha as 0.83 and reliability as 0.8. Exercise pattern was assessed by Dijon's activity scale with a total of 27 scores where <17 was considered as sedentary lifestyle and a score of >17 considered as active lifestyle.[18,19] Cardiac diet adherence, smoking cessation, and patient satisfaction were assessed by using a self-developed structured questionnaire, and content validity established with Cronbach alpha of 0.87, and reliability as $r = 0.9$ by test and re-test method.

All data were analyzed using IBM SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Continuous data were summarized using the mean and standard deviation or median and interquartile range, as appropriate. Categorical data were summarized using frequency and percentage. Chi-square or Fisher's exact test was applied for the comparison of categorical data. A comparison of the impact of counseling between control and intervention groups was done using independent Student's *t*-test or the alternative nonparametric tests like Mann–Whitney U test. A comparison between the pretest and posttest scores was made using paired *t*-test or the alternative nonparametric tests. Independent student *t*-test, analysis of variance, and difference in difference (DiD) were used to evaluate the effectiveness of counseling on CR. All the tests were carried out at a 5% level of significance.

Results

The study consisted of 62 patients with 31 in each group. The majority of the study participants were aged between 50 and 65 years, with a male preponderance. Smokers constituted 67.7% in the control group as against

48% in the intervention group; 71% versus 48% of the participants had a history of alcoholism and almost all in both groups were nonvegetarian. The participants in the intervention and control groups were homogenous at baseline as regards the reason for percutaneous transluminal coronary angioplasty (PTCA), BMI, and family history of CAD [Table 1].

The baseline mean values of lipoprotein fractions, i.e., low-density lipoprotein (LDL), triglycerides (TG), and very-low-density lipoprotein (VLDL) ($P < 0.031$, 0.004, 0.001 respectively) was not homogenous at baseline, hence the difference in DiD was calculated for further interpretation. The difference in serum TC levels was significant at the end of 3 months in the intervention group ($P = 0.014$). Although the LDL levels were reduced significantly for both groups, the increased reduction was more evident in the intervention group ($P < 0.051$). The TG and VLDL values were not different ($P = 0.48$ and 0.14 respectively). The DiD analysis revealed an increased reduction in the levels of TG and VLDL cholesterol ($P = 0.04$ and 0.01 respectively) by the 3rd month of follow-up in the intervention group [Tables 2 and 3]. The systolic BP, body weight, and BMI showed a change in the intervention arm at 3 months on Pearson Chi-square analysis of DiD ($P = 0.03$, <0.0001, <0.0001 respectively). The DiD analysis is shown in table [Table 4].

Table 1: Demographic characteristics and baseline behavioral characteristics of patients

Characteristics	Control group (*n*=31) *N* (%)	Intervention group (*n*=31) *N* (%)	*P-value**
Age in years			
25-50	12 (38.7)	9 (29.0)	0.595
50-65	14 (45.1)	18 (58.0)	
>65	5 (16.1)	4 (12.9)	
Gender			0.053
Male	30 (96.8)	22 (70.9)	
Female	1 (3.2)	9 (29.0)	
Education			
Illiterate	4 (12.9)	7 (22.6)	0.680
Primary	21 (67.7)	20 (64.5)	
Higher secondary	4 (12.9)	2 (6.5)	
Graduate	2 (6.5)	2 (6.5)	
Body weight (kg)	65.9±11.1	66.03±11.5	0.964
BMI#	23.9±3.6	24.5±3.6	0.533#
BP#			
SBP	122.3±18.0	129.5±18.8	0.130#
DBP	75.8±12.3	80.5±13.9	0.165#
Reason for PTCA			
Chronic stable angina	6 (19.3)	5 (16.1)	0.72
Unstable angina	6 (19.3)	7 (22.5)	
STEMI	12 (38.7)	13 (41.9)	
NSTEMI	79 (22.5)	6 (19.3)	
History of smoking	21 (67.7)	15 (48.4)	0.123
History of alcoholism	22 (71)	15 (48.4)	0.070
Dietary pattern			
Nonvegetarian	30 (96.8)	29 (93.5)	0.554
Family history of CAD			
Present	10 (32.3)	7 (22.6)	0.393

*Pearson Chi-square, #Student's *t*-test, PTCA: Percutaneous transluminal coronary angioplasty, STEMI: ST elevated myocardial infarction, NTEMI: Non-STEMI, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP, BMI: Body mass index, CAD: Coronary artery disease

The participants in the intervention group were more adherent to medications than those in the control group with a $P < 0.0001$ [Table 5]. The participants in the intervention groups had an active lifestyle and adhered more strictly to the healthy dietary pattern ($P \leq 0.0001$) [Table 4]. Moderate-to-good smoking cessation was noted in the intervention group. Twenty-nine (93.5%) patients were very satisfied with the CR program.

Discussion

We obtained very interesting and encouraging results from this randomized trial of the effect of rehabilitation following PCI. Developing economies like India and middle-income South East Asian countries are facing an epidemic of CAD.[2,4] Public hospitals often have to deal with the burden of a large number of patients with CAD.[1] This raises the issue of the importance of sub-optimal care delivery. Behavioral education for better lifestyle practices and proper drug counseling, which are integral to secondary prevention of CVD are never given the necessary significance.[8] Furthermore, ensuring drug compliance is a major challenge as many patients do not understand the significance of secondary prevention drugs after myocardial infarction. There is very little data on the impact of CR programs in India,

Table 2: Lipid profile values at baseline and at 3 months after intervention (*n*=62)

Name of the variables	At baseline		*P-value*	After 3 months		*P-value**
	Control group (*n*=31) Mean±SD	Intervention group (*n*=31) Mean±SD		Control group (*n*=31) Mean±SD	Intervention group (*n*=31) Mean±SD	
TC	150.3±31.8	148.5±30.4	0.823	152.4±40.1	137.5±39.8	0.014*
HDL	33.8±8.1	34.2±8.5	0.843	39.8±8.4	35.7±6.4	0.039*
LDL	89.5±31.0	73.7±24.9	0.031*	88.6±35.3	72.8±26.5	0.051*
TG	140±69.7	195.2±77.1	0.004*	119.8±71.4	132.7±71.0	0.481
VLDL	27.1±12.5	38.5±13.8	0.001**	21.4±7.5	25.1±11.5	0.144

*P<0.05, **P<0.001, #Student's *t*-test. TC: Total cholesterol, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, VLDL: Very LDL

Table 3: Changes in biochemical parameters following nurse-led cardiac rehabilitation

Name of the variables	Control group (*n*=31)		Mean difference	Intervention group (*n*=31)		Mean difference	*P*-value
	Pre-intervention Mean±SD	Post-intervention Mean±SD		Pre-intervention Mean±SD	Post-intervention Mean±SD		
TC	150.3±31.8	152.4±40.1	−2.09	148.5±30.4	137.5±39.8	11.0	0.143
HDL	33.8±8.1	39.8±8.4	−5.96	34.2±8.5	35.7±6.4	−1.5	0.042*
LDL	89.5±31.0	88.6±35.3	0.90	73.7±24.9	72.8±26.5	0.9	0.997
TG	140±69.7	119.8±71.4	20.1	195.2±77.1	132.7±71.0	62.5	0.056*
VLDL	27.1±12.5	21.4±7.5	5.7	38.5±13.8	25.1±11.5	13.4	0.015*

**P*<0.05-ANOVA. TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low density lipoproteins, TG: Triglyceride, VLDL: Very LDL, SD: Standard deviation

Table 4: Changes in physiological indices following nurse-led cardiac rehabilitation

Name of the variables	Control group		Mean difference	Intervention group		Mean difference	*P*-value
	At baseline Mean±SD	After 3 months Mean±SD		At baseline Mean±SD	After 3 months Mean±SD		
SBP	122.3±18.0	129.5±13.5	−7.1	129.5±18.8	128±0.10.6	1.5	0.003*
DBP	75.8±12.3	79.8±6.9	−3.9	80.54±13.9	79.6±6.7	0.9	0.064
BMI	23.97±3.6	24±3.5	−0.05	24.55±3.6	23.6±3.3	0.9	<0.0001*
Weight	65.90±11.14	66±10.7	−0.09	66.03±11.5	63.5±11.1	2.4	<0.0001*

*Student *t*-test. SBP=Systolic blood pressure, DBP=Diastolic blood pressure, BMI=Body mass index, SD: Standard deviation

Table 5: Effect of nurse-led cardiac rehabilitation on drug adherence and other behavioral parameters (*n*=62)

Name of the variables	Control group (*n*=31) *N* (%)	Intervention group (*n*=31) *N* (%)	*P*-value
Drug adherence			
Low adherence (<6)	24 (77.4)	7 (22.6)	<0.0001*
Moderately adherent (6-7)	5 (16.1)	19 (61.3)	
Highly adherent (8)	2 (6.4)	5 (16.1)	
Physical activity score			
Active (score >17)	14 (45.2)	28 (90.3)	<0.0001
Sedentary (score <17)	17 (54.8)	3 (9.7)	
Dietary pattern adherence score:			
Highly adherent (5-6)	4 (12.9)	12 (61.3)	<0.0001
Moderately adherent (of 3-4)	21 (67.7)	19 (38.7)	
Low adherence (score of 0-2)	6 (19.4)	0	
Smoking cessation (*n*=15 in intervention group and *n*=21 in control group)			
Low (score of "0")	6 (28.5)	2 (13.3)	<0.01*
Moderate (1-2)	12 (57.1)	8 (53.3)	
Good (score of 3)	3 (14.2)	5 (33.3)	
Patient's satisfaction with cardiac rehabilitation			
Yes	-	29 (93.5)	

*Pearson Chi-square

especially after elective coronary intervention. This study reveals the strength of the impact of specific counseling focused rehabilitation program on lifestyle, behavioral changes and drug compliance.

However, though CR should be part of the normal care for patients with cardiovascular disease, few continue in the modified lifestyle strategy following an acute event. The literature advocates that instead of the traditional advice-giving, programs which are patient-centred may have better outcomes by improving the reduction of the risk factors. Nurse-led rehabilitation clinics have been established to provide patients and families with knowledge and skills for symptom management and support, adjust medication and provide the patients with referral for investigations.[9,12-14] Previous studies have shown the effects of the nurse-led rehabilitation clinic on the reduction of hospital readmission, and its positive effects on clinical endpoints such as the improved control of the patients' BP and drug adherence. Our results are similar to the accumulated evidence of the efficacy of nurse-led clinics on clinical outcomes.[19,20]

There was a significant change in the lipid profile parameters as serum TC, TG, and VLDL were found to be significantly reduced in the intervention group at 3 months' follow-up. HDL in this study was increased in

both groups after 3 months and increased significantly in the control group. The lipids level reduction in this study might be credited basically to the medication effect raised by medication adherence as well as cardiac diet adherence of rehabilitation participants.[21] This argument is supported by the demonstration of significantly better adherence to a healthy diet and medication in the intervention group. Similar results were noted in previous studies which showed a successful reduction in TG, TC, and LDL at 3 months ($P < 0.01$) and 6 months ($P < 0.05$).[21,22] In another study also, it was noticed that Median total and LDL cholesterol levels were decreased in the intervention arm, and the relative change in LDL cholesterol levels at 6 months was significant in the intervention arm than in the standard care arm (–36% reduction vs.–26% reduction, p 0.025).[23,24]

The majority of coronary patients have unhealthy lifestyles in terms of sedentary behavior, smoking, and diet, which adversely affects their clinical outcome.[25] Studies that evaluated the effectiveness of nonpharmacological CAD prevention strategies have shown that individual counseling (IC) had a significant impact on the control of BP ($P < 0.05$).[10-13] Similarly, in the present study, by analyzing the difference of the mean scores between the groups, the systolic BP was better controlled (–7.1 mmHg vs. 1.5 mm Hg) in the intervention arm than the control arm ($P < 0.05$). This we believe is the result of the combined effect of counseling on lifestyle changes and improved drug adherence as shown previously.[26,27]

The study also revealed a positive effect of the intervention on the BMI. This is contradictory to the previous studies that showed the effect of counseling on body weight as neutral.[28,29] At 3 months, the rehabilitation group participants had gained 0.06 kg. But by 6 months, the intervention group participants had demonstrated a 0.16 kg weight loss compared to a 0.39 kg weight gain in the control participants ($P < 0.05$), the BMI was slightly lower in the intervention group ($P = 0.05$).

Similar to the previously published studies on CR programs, the cardiac risk factors were considerably modified proving the importance of improved drug adherence, smoking cessation, and adherence to the modified dietary and exercise pattern in the intervention arm for cardiovascular secondary prevention.[28,30-33] We found superior drug compliance in the rehabilitation group. This is crucial, as drug default, especially premature stoppage of antiplatelet drugs is an important cause of sub-acute and late stent thrombosis. We consider this novel concept as successful in most of the parameters we analyzed since it showed the positive impact of the intervention. We plan to do a larger study involving more participants.

The study limitations include single-centre data. Small sample size but the positive impact has made us follow the specified intervention on all of our patients in a similar manner. Only specific predefined parameters were assessed for the effect of an intervention. The major limitation is the rather brief 3-month follow-up. A longer duration would have been of greater value as the intervention effects shown could be transitory.

Conclusion

The study results show a strong favorable impact of a specific CR program on the risk parameters studied. There was an improvement in drug adherence, lifestyle changes such as diet, physical activity, and smoking cessation in addition to improved patient satisfaction on the delivery of care after the rehabilitation program. Biochemical risk factors like blood lipoprotein fractions showed an improving trend with the improved adherence to drugs and the possible effect of adoption of healthy dietary habits. We propose that a dedicated rehabilitation program involving patient-centric counseling and periodic reassurance may prove useful if integrated into secondary prevention programs after elective coronary interventions.

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Conflicts of interest

There are no conflicts of interest.

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Exogenous melatonin as a treatment for secondary sleep disorders: A systematic review and meta-analysis

Tian Li[a,b,1], Shuai Jiang[c,1], Mengzhen Han[a], Zhi Yang[b], Jianjun Lv[b], Chao Deng[d], Russel J. Reiter[e,*], Yang Yang[a,b,*]

[a] Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education, Faculty of Life Sciences, Northwest University, 229 Taibai North Road, Xi'an 710069, China
[b] Department of Biomedical Engineering, The Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China
[c] Department of Aerospace Medicine, The Fourth Military Medical University, 169 Changle West Road, Xi'an 710032, China
[d] Department of Cardiovascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, Shaanxi, China
[e] Department of Cellular and Structural Biology, UT Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA

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ABSTRACT

Melatonin is a physiological indoleamine involved in circadian rhythm regulation and it is currently used for secondary sleep disorders supported by empirical evidence. A small amount of evidence and some controversial results have been obtained in some randomized controlled trials (RCT). The objective of this meta-analysis is to determine the efficacy of exogenous melatonin versus placebo in managing secondary sleep disorders. Literature retrieval of eligible RCT was performed in 5 databases (PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Web of Science). In total, 7 studies of 205 patients were included. Pooled data demonstrate that exogenous melatonin lowers sleep onset latency and increases total sleep time, whereas it has little if any effect on sleep efficiency. Although, the efficacy of melatonin still requires further confirmation, this meta-analysis clearly supports the use of melatonin as a management for patients with secondary sleep disorders.

1. Introduction

Sleep disorders, or somnipathy, are serious public health problems that cause a prominent economic burden worldwide. More than 10% individuals in Western societies have sleep disorders (Auld et al., 2017; Gervais et al., 2017). Conventional drugs usually have a short half-life and a hangover effect that might contribute to a poor compliance (Walters and Lader, 1971). Implementation of non-pharmacotherapy such as cognitive and relaxation therapy is usually a complex process influenced by multiple factors. Thus, an exogenously-administered agent that mimics the actions of an endogenous molecule might serve to cure or improve sleep disorders.

Melatonin, discovered by Aaron Lerner, is an chronobiotic that modulates circadian rhythms (Suhner et al., 2001; Keijzer et al., 2014) and has a wide variety of other functions (Carrier et al., 2017; Reiter et al., 2017, 2014; Yang et al., 2014; Yu et al., 2018). In humans, melatonin enhances darkness-related behavior and induces soporific effects. For example, melatonin has been tested in secondary sleep disorders (namely secondary insomnia) caused by sleep restriction (e.g., shiftwork, jet lag) without organic diseases (Buscemi et al., 2006; Liira et al., 2014). Previous studies have demonstrated that melatonin has a hypnotic action on secondary sleep disorders (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002) with no known adverse effects (Suhner et al., 2001; van Geijlswijk et al., 2010).

Primary sleep disorders are rarely markedly improved by exogenous drug treatment, as a result of the existence of protopathy (Zhang et al., 2016). A previous meta-analysis by Buscemi reported that melatonin is ineffective in relieving sleep problems. Buscemi et al. (2006) explored sleep disorders resulting from organic and non-organic factors and concluded that melatonin has no effects, which contradicts the conclusions of some randomized controlled trials (RCT) (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998). Sample sizes of previously published studies were usually small and the results were inconsistent (Beaumont et al., 2004; Folkard et al., 1993; Suhner et al., 2001). However, some of the recent findings published suggest that melatonin is a potent drug candidate for secondary sleep disorders (Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002). Thus, an updated meta-analysis with a different focus is needed

* Corresponding authors at: Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education, Faculty of Life Sciences, Northwest University, 229 Taibai North Road, Xi'an 710069, China (Y. Yang).
E-mail addresses: reiter@uthscsa.edu (R.J. Reiter), yang200214yy@nwu.edu.cn (Y. Yang).
[1] These authors contributed equally to this work.

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to provide the latest evidence for clinical psychiatrists and neurologists. This systematic review summarizes the current data that investigated the roles of exogenous melatonin, versus placebo, in the treatment of secondary sleep disorders.

2. Methods

2.1. Study protocol

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

2.2. Search strategy

A systematic search was performed on PubMed, Embase, Cochrane Register for Systematic Reviews databases, ClinicalTrials.gov, and Web of Science with no language limitations (published between Jan 1, 1950 and Sep 19, 2017). Search terms included "melatonin", or "5-methoxytryptamine", or "ramelteon" in combination with "sleep disorders", or "sleep disturbance", or "sleep dysfunction". For example, the search strategy in PubMed was as follows: "((melatonin[MeSH Terms] OR methoxytryptamine[Text Word])) AND (sleep disorder[MeSH Terms] OR secondary sleep disorder[Text Word] OR sleep dysfunction[Text Word] OR sleep disturbance[Text Word] OR sleep[Text Word])) AND (random allocation[MeSH Terms] OR randomized[Text Word] OR randomly[Text Word] OR placebo[Text Word] OR crossover[Text Word] OR cross-over[Text Word])". Moreover, the references of relevant studies, reviews, editorials, letters, and conference abstracts were also searched. The research work was done independently and in duplicate.

2.3. Eligibility criteria

Studies meeting the following criteria were included: (a) study design is double-blind RCT (crossover or parallel); (b) populations were adult patients with secondary sleep disorders secondary accompanying sleep restriction; (c) intervention comparisons of melatonin versus placebo; (d) outcomes analyzed for nocturnal sleep without diurnal disturbance; (e) enrolled studies report any or all of the following nocturnal sleep outcomes: I. sleep onset latency (the length of time between full wakefulness to sleep onset), II. total sleep time (total time spent asleep in bed), III. sleep efficiency (total sleep time/total time spent in bed). Sleep onset latency was the primary outcome. Total sleep time and sleep efficiency were secondary outcomes.

The exclusion criteria were: (a) articles not peer-reviewed or published; (b) populations that included children (< 18 years); (c) studies that were repeatedly published or had qualitative outcomes; (d) outcomes that analyzed daytime instead of the night sleep. There was no limit on sample size, trial duration, et al. Preliminarily, retrieved results were subjected to a title and abstract screening for inclusion by two independent reviewers (Li & Jiang). Full-text retrieval was performed to determine eligibility using a standardized data abstraction form by the two independent reviewers. Disagreements regarding the inclusion of studies were discussed between the two reviewers (Li & Jiang) and ultimately decided by the third reviewer (Han).

2.4. Data extraction

Two reviewers (Li & Jiang) independently extracted relevant data with a standardized form, including study characteristics and main outcomes. Disagreement was resolved through discussion with a third author (Han). Characteristics of patients such as age, research site, sample size, study design, duration, dosage, and clinical outcomes were collected. Clinical outcomes included continuous variables of sleep onset latency (mean [SD]), total sleep time (mean [SD]), and sleep efficiency (mean [SD]). Two reviewers also independently assessed the risk of bias of enrolled studies using The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). Three types of risk (low risk of bias, unclear risk of bias, and high risk of bias) were identified depending on the following domains: (a) random sequence generation (selection bias), (b) allocation concealment (selection bias), (c) blinding of participants and personnel (performance bias), (d) blinding of outcome assessment (detection bias), (e) incomplete outcome data (attrition bias), (f) selective reporting (reporting bias), (g) other biases. Disagreement was resolved by a third reviewer (Han).

2.5. Statistical analysis

The efficacy of exogenous melatonin versus placebo was evaluated on three continuous outcomes: sleep onset latency (mean [SD]), total sleep time (mean [SD]), and sleep efficiency (mean [SD]). We calculated results for continuous outcomes as mean differences (MD) with 95% confidence intervals (CI), comparing the change from baseline for both melatonin and placebo. All tests were two tailed and a P value of less than 0.05 was deemed statistically significant. Data were analyzed by the latest Cochrane collaboration Review Manager analysis software version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). According to the knowledge from evidence-based medicine and Cochrane Handbook for Systematic Review of Interventions (version 5.1), the weight of enrolled studies depends on the value of mean, [SD], and total sample size. The Z-test determined an overall significance of therapeutic effect versus placebo with values of $P < 0.05$. Heterogeneity was assessed using chi-squared test and I^2 test in accordance with Cochrane collaboration's guidance for assessing heterogeneity in meta-analyses. Data were considered heterogeneous if chi-squared test yielded $P < 0.10$ and $I > 50\%$. Random effects model (REM) was utilized when heterogeneity was absent; otherwise, the fixed effects model (FEM) was chosen. If we identified sufficient trials ($N \geq 10$), a funnel plot was utilized to test potential publication bias.

3. Results

3.1. Study characteristics

The initial search by two reviewers (Li & Jiang) identified 1223 database records and 13 additional records (Fig. 1). 900 records remained after removing 336 duplicates. Then, the title and abstract of remained literature were screened, and 812 records were excluded due to review article, meta-analyses/systematic review, case-control studies, cross sectional studies, or unrelated topics. Thereafter, 88 full-text articles were assessed for eligibility and 81 records were excluded with reasons: children (n = 21), insufficient end points (n = 32), non-randomized studies (n = 10), and irrelevant reports (n = 18). Eventually, 7 RCT (Beaumont et al., 2004; Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998; Yoon and Song, 2002) were included, their characteristics were listed in Table 1.

3.2. Systematic review

These 7 studies of 205 participants were conducted in USA (n = 4) (Beaumont et al., 2004; James et al., 1998; Suhner et al., 2001; Wright et al., 1998), England (n = 1) (Folkard et al., 1993), Republic of Korea (n = 1) (Yoon and Song, 2002), and Iran (n = 1) (Sadeghniiat-Haghighi et al., 2016), published between 1993 and 2016 (Table 1). All studies were double-blind RCT that used standard experimental/control groups (melatonin/placebo). The mean age of participants ranged from 29 (Folkard et al., 1993; James et al., 1998; Yoon and Song, 2002) to 41.3 (Suhner et al., 2001). The sample size ranged from 12 (Yoon and Song, 2002) to 74 (Suhner et al., 2001). Participants include medical staffs (James et al., 1998; Wright et al., 1998; Yoon and Song, 2002), police

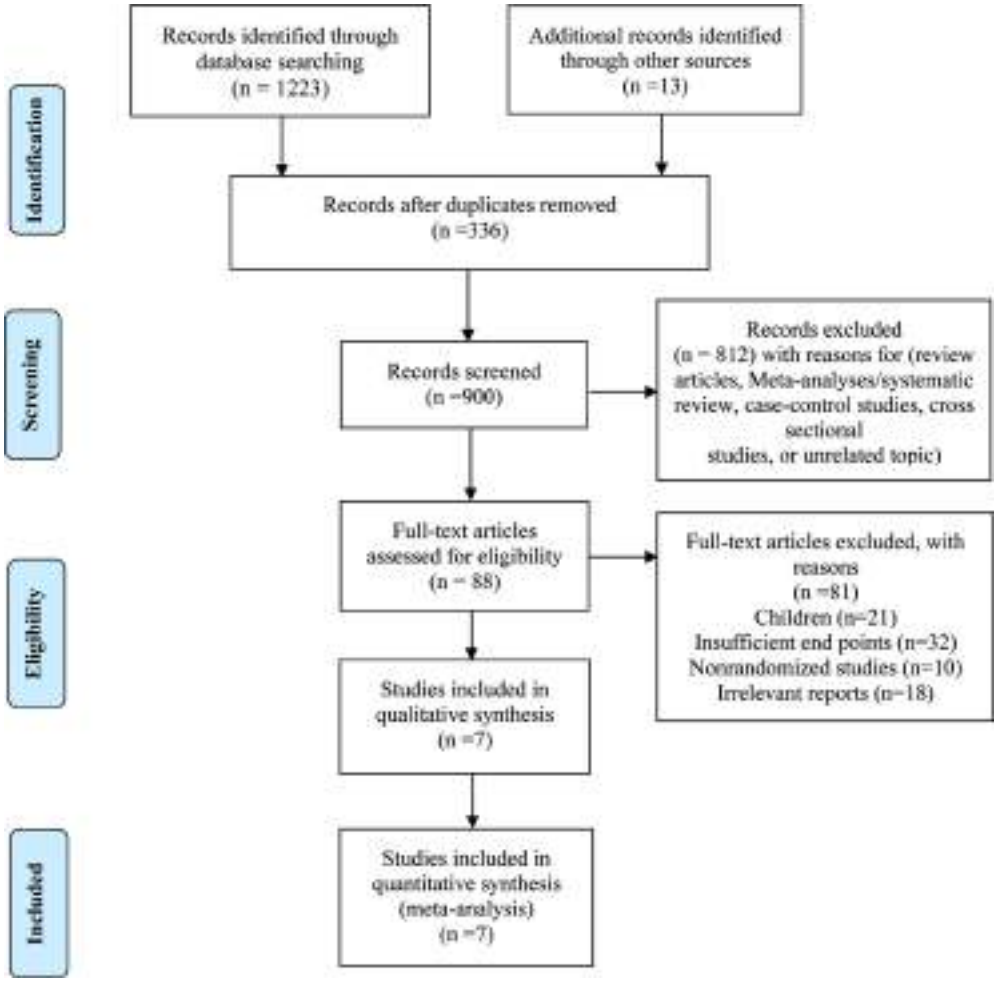

Fig. 1. Flowchart of study screening.

(Folkard et al., 1993), workers (Sadeghniiat-Haghighi et al., 2016) after shift-work, and pilots (Beaumont et al., 2004), travelers (Suhner et al., 2001) after jet lag.

All studies reported the efficacy of melatonin in sleep onset latency. 3 studies reported the efficacy of melatonin in total sleep time (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). 3 studies reported the efficacy of melatonin in sleep efficiency (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). The dosage of melatonin ranged from 3 (Sadeghniiat-Haghighi et al., 2016) to 6 mg (James et al., 1998; Yoon and Song, 2002), among which 5 mg was the most frequently used (Beaumont et al., 2004; Folkard et al., 1993; Suhner et al., 2001; Wright et al., 1998). The duration of treatment ranged from 3 (Sadeghniiat-Haghighi et al., 2016) to 9 days (Beaumont et al., 2004).

3.3. Sleep onset latency

Sleep onset latency is the primary outcome in this meta-analysis. All studies assessed the efficacy of melatonin in sleep onset latency. Pooled analysis of 7 studies (N = 154) demonstrate that exogenous administration of melatonin lowers sleep onset latency (Total mean difference: −2.48 min, 95% CI: −4.56, −0.40, Fig. 2), versus placebo. The overall estimated score of melatonin treatment is significant (Z = 2.33, P = 0.02). No significant heterogeneity was present across these studies (Chi^2 = 7.54, P = 0.27, I^2 = 20%).

3.4. Total sleep time

Total sleep time was the secondary outcome in this meta-analysis. 3 studies reported the efficacy of melatonin in total sleep time (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). Analysis of the 3 studies (N = 71) suggest that exogenous administration of melatonin increases total sleep time (Total mean difference: 29.27 min, 95% CI: 6.68, 51.86, Fig. 3). The overall estimated action of melatonin is significant (Z = 2.54, P = 0.01). No significant heterogeneity was present across the 3 studies (Chi^2 = 2.71, P = 0.26, I^2 = 26%).

3.5. Sleep efficiency

Sleep efficiency was also the secondary outcome in this meta-analysis. 3 studies reported the efficacy of melatonin in sleep efficiency (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002). Analysis of the 3 studies (N = 71) suggested that exogenous melatonin has no meaningful actions on sleep efficiency (Total mean difference: 1.46, 95% CI: −0.43, 3.35, Fig. 4). The Z value of melatonin is 1.52 (P = 0.13). No significant heterogeneity was present across the 3 studies (Chi^2 = 2.03, P = 0.36, I^2 = 1%).

3.6. Risk of bias

Figs. 5 and 6 show the risk of bias across 7 trials. 100% studies have a low risk of bias on random sequence generation, blinding of participants and personnel, and selective reporting. 3 (Beaumont et al., 2004;

Table 1
Characteristic of included studies.

Study	Groups	Participants	Total number	Number (exp)	Age (years)	Research site	Study design	Duration of treatment (day)	Dosage (mg)	Outcomes	Reference
Beaumont et al, 2004	Melatonin/ Placebo	Pilots after a seven-time zone eastbound flight	18	9/9	35.3 ± 8.1 (19–47)	USA	RCT, parallel	9	5	1–3	Beaumont et al. (2004)
Folkard et al, 1993	Melatonin/ Placebo	Police officers after night shift	14	7/7	29 ± 7 (21–48)	England	RCT, parallel	7	5	1	Folkard et al. (1993)
James et al, 1998	Melatonin/ Placebo	Emergency medical staffs after night shift	22	22/22	29 ± 7 (20–41)	USA	RCT, crossover design	4	6	1	James et al. (1998)
Sadeghniiat-Haghighi et al, 2016	Melatonin/ Placebo	Shift workers	50	50/50	32.9 ± 8 (24–52)	Iran	RCT, crossover design	3	3	1–3	Sadeghniiat-Haghighi et al. (2016)
Suhner et al, 2001	Melatonin/ Placebo	Travelers after a jet lag	74	35/39	41.3 (18–68)	USA	RCT, parallel	4	5	1	Suhner et al. (2001)
Wright et al, 1998	Melatonin/ Placebo	Emergency physicians after night-shift work	15	15/15	38.6 (32–45)	USA	RCT, crossover design	4	5	1	Wright et al. (1998)
Yoon et al., 2002	Melatonin/ Placebo	Nurses after night-shift work	12	12/12	29 ± 7 (21–48)	Republic of Korea	RCT, crossover design	4	6	1–3	Yoon and Song (2002)

Suhner et al., 2001; Wright et al., 1998) and 4 (Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Yoon and Song, 2002) studies have a low and unclear risk of bias on allocation concealment, respectively. 1 (Wright et al., 1998) and 6 (Beaumont et al., 2004; Folkard et al., 1993; James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002) studies have a low and unclear risk of bias on blinding of outcome assessment, respectively. As for the incomplete outcome data, 2 (Beaumont et al., 2004; Yoon and Song, 2002), 2 (Folkard et al., 1993; Wright et al., 1998), and 3 (James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001) studies have a low, unclear, and high risk of bias on incomplete outcome data, respectively. 4 (Beaumont et al., 2004; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Yoon and Song, 2002), 2 (Folkard et al., 1993; James et al., 1998), and 1 (Wright et al., 1998) studies have a low, unclear, and high risk of bias on other bias, respectively. Other bias (Higgins et al., 2011) might include the following situations: (1) There was no description of the ingested drug monitoring by physicians, which could result in performance bias. (2) The authors state any important concerns about bias not covered in the other domains in the tool. (3) Bias due to problems not covered elsewhere exists.

4. Discussion

4.1. Main findings

In this meta-analysis of 7 studies that analyzed exogenous melatonin versus placebo in the treatment of secondary sleep disorders, we found that melatonin reduces sleep onset latency and increases total sleep time (Figs. 2 and 3). However, based on current data, melatonin has no actions on sleep efficiency of patients with secondary sleep disorders (Fig. 4). Overall, these data demonstrate that melatonin improves sleep quality with respect to sleep onset latency and total sleep time, which lends support to melatonin as a potential approach to secondary sleep disorders.

4.2. Interpretation

Secondary sleep disorders, namely secondary insomnia caused by sleep restriction, have caused a huge economic and social burden in the world (Liira et al., 2014). The management of secondary sleep disorders remains a big issue in clinical psychiatry and sleep medicine. So far, there are no effective treatments for secondary sleep disorders. Pharmacotherapies usually have a short half-life and a hangover effect. Non-pharmacotherapies (e.g., cognitive therapy and relaxation therapy) are complex and patients usually have poor compliance with them. Therefore, the low toxicity may facilitate melatonin as a therapeutic candidate for secondary sleep disorders (Jan et al., 2009; Li et al., 2017).

This meta-analysis was conducted under the guidance of PRISMA (Moher et al., 2009). The search strategy of this meta-analysis is thorough and the inclusion criteria are broad. Both MeSH Terms and Text Word were utilized in databases from PubMed, Embase, Cochrane Library, et al., which includes a wide variety of publications from 1950 to 2017 (Robinson, 2005). Enrolled studies were analyzed by two authors (Li & Jiang) independently using unitive criteria and disagreement was solved through discussion with a third author (Han). Based on previous works (Chan et al., 2011; Nathan et al., 2017), this review also provides a general introduction for all enrolled studies in Section Systematic review and has mentioned Buscemi's work in Section Introduction. In Buscemi's work, secondary sleep disorders were clearly distinguished from those accompanying sleep restriction. In this review, secondary sleep disorders are referred to as sleep disorders accompanying sleep restriction (e.g. shift work and jet lag). Compared to Buscemi's work in 2006, this meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

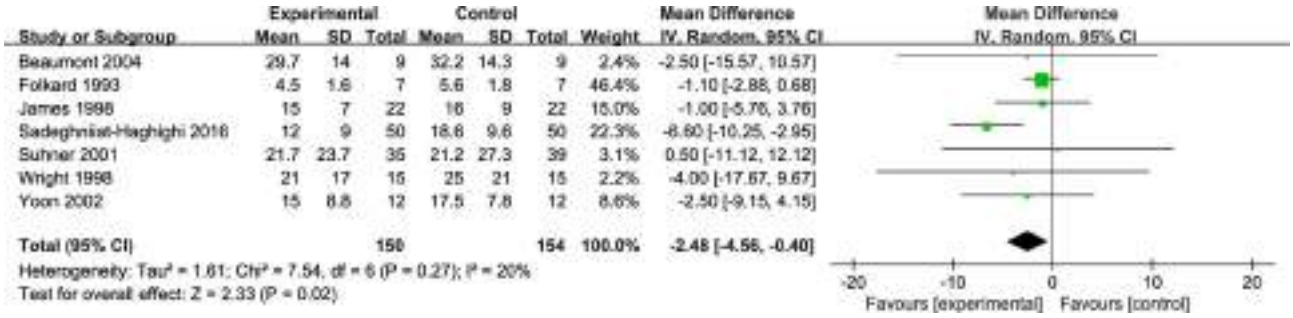

Fig. 2. Effects of melatonin on SOL. This forest plot demonstrates that exogenous administration of melatonin lowers sleep onset latency. SOL, sleep onset latency.

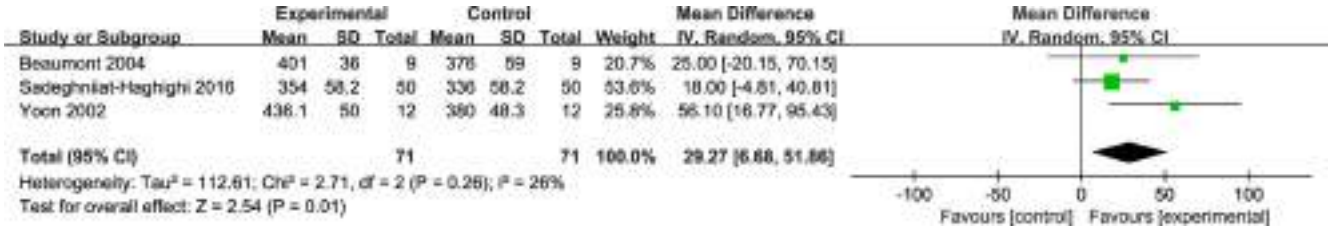

Fig. 3. Effects of melatonin on TST. This forest plot suggests that exogenous administration of melatonin increases total sleep time. TST, total sleep time.

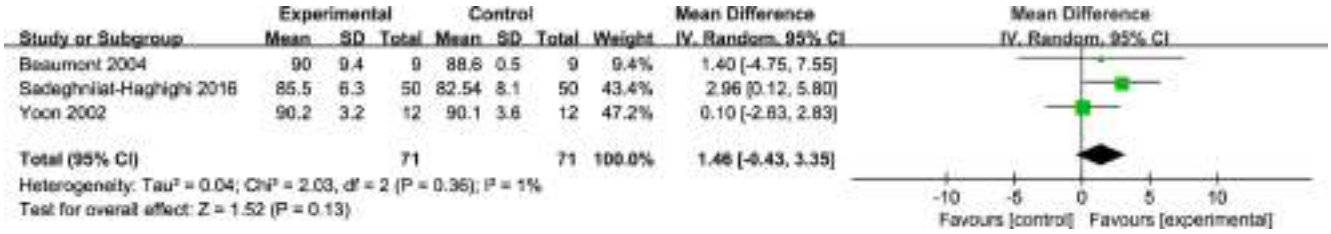

Fig. 4. Effects of melatonin on SE. This forest plot reveals that melatonin has no significant effects on sleep efficiency. SE, sleep efficiency.

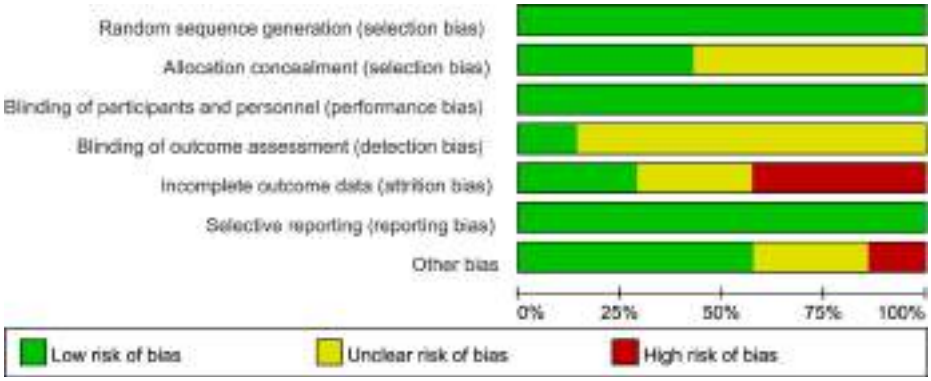

Fig. 5. Risk of bias graph. This figure shows review authors' judgements about each risk of bias item presented as percentages across all included studies.

and aimed to explore the new literature and provide a different emphasis. Thus, there is a difference of included studies between this review and other meta-analysis. So far, the safety issues of melatonin in pediatrics remain a big concern (Kennaway, 2015) and there is a lack of RCTs on long-term usage of melatonin in pediatrics. Thus, children (< 18 y) are excluded in this article, which is in accordance with previous meta-analysis (Brzezinski et al., 2005). Risk of bias of enrolled studies were assessed using The Cochrane Collaboration's tool (Figs. 5 and 6) (Higgins et al., 2011) and the overall risk of bias is low or unclear. Besides, we also searched for unpublished and commercially-sponsored work during searching. These data are excluded due to the absence of peer review and potential interacted interest.

Strikingly, the strong effect of melatonin seems to be opposed to the results of the present study. Based on previous studies and hypothesis, the following explanations may address this question: (1) The studies on the sleep induction effect of melatonin are mainly conducted in animals (Fisher et al., 2008; Fisher and Sugden, 2009), instead of human beings. (2) The meta-analysis articles are based on RCTs, some of which demonstrated that the effects of melatonin are not strong (Folkard et al., 1993; James et al., 1998; Yoon and Song, 2002), (mean difference < 5 min compared to the controls (Wade et al., 2007; Zhdanova et al., 2001)). (3) Different eligibility criteria in those meta-analysis articles contribute to different enrolled population.

As shown in Fig. 2, pooled data reveal that compared to placebo, exogenous melatonin lowers sleep onset latency (Total mean difference: −2.48 min, 95% CI: −4.56, −0.40, I^2 = 20%). The heterogeneity is less than 50% and is not significant, suggesting a good homogeneity among the enrolled studies. Auld's work evaluates the effects of

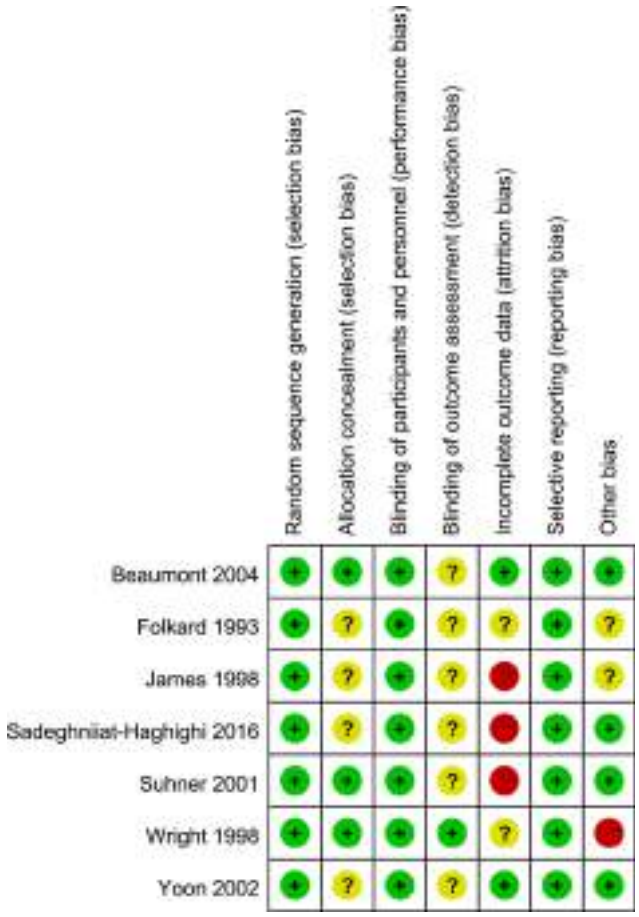

Fig. 6. Risk of bias summary. This figure shows review authors' judgements about each risk of bias item for each included study.

melatonin on primary sleep disorders and concluded a total mean difference of −5.05 min (95% CI: −8.51, −1.59) (Auld et al., 2017). Brzezinski's study assessed the effects of exogenous melatonin on sleep (including primary and secondary outcomes). The total mean difference of sleep onset latency are −4.0 min (95% CI: −2.5, −5.4) (Brzezinski et al., 2005). The result of this meta-analysis is similar to previous results (Auld et al., 2017; Brzezinski et al., 2005). Overall, despite the statistically significant mean differences, 2.48 min for secondary insomnia patients is not clinically relevant, which requires further studies to evaluate its efficacy.

Fig. 3 shows that melatonin increases total sleep time (Total mean difference: 29.27 min, 95% CI: 6.68, 51.56, $I^2 = 26\%$). The heterogeneity is also non-significant among the included studies. Fig. 4 shows that melatonin has no significant actions on sleep efficiency (Total mean difference: 1.46, 95% CI: −0.43, 3.35, $I^2 = 1\%$). It is clear that total sleep time is increased and sleep onset latency is reduced. Notably, the sleep efficiency does not increase. The following explanations may account for the observations reported. On one hand, the enrolled studies of Figs. 2 and 4 are different. Seven studies are included in Fig. 2, whereas three are inlcuded in Fig. 4. Sleep efficiency is not provided by the Folkard's study (Folkard et al., 1993), or in 3 other studies (James et al., 1998; Suhner et al., 2001; Wright et al., 1998). Thus, only 3 studies are included in Fig. 4. This difference might contribute to the insignificance of sleep efficiency. Conversely, the enrolled studies and sample size in Figs. 2 and 4, as well as the total number of individuals is small. Risk of bias of enrolled 7 studies are summarized in Figs. 5 and 6, according to The Cochrane Collaboration's tool (Higgins et al., 2011), which bears a high risk of bias on attrition bias and other biases across the 7 studies. Of note, the researches by James, Sadeghniiat-Haghighi, Suhner, and Wright have a high risk of bias (James et al., 1998; Sadeghniiat-Haghighi et al., 2016; Suhner et al., 2001; Wright et al., 1998), which also contribute to the suspicion of literature quality, which needs further study.

4.3. Limitations

There are some limitations to this review. Firstly, unpublished studies were excluded in this meta-analysis, which may increase the publication bias (Kicinski et al., 2015). Secondly, although data analysis revealed that melatonin reduces sleep onset latency and increases total sleep time, these results need additional support from additional RCT. The reduced time of sleep onset latency is not clinically significant. Third, each study does not adjust for the same confounders, such as duration of administration and dosage, therapeutic period, and gender, which requires further well-designed RCT where these issues are taken into consideration.

4.4. Conclusion

This meta-analysis is dedicated to elucidating the effects of exogenous melatonin, compared to the placebo, on the nocturnal outcomes of secondary sleep disorders. Meta-analysis of the data from a series of studies with small sample size demonstrates that exogenous melatonin improves the sleep quality of secondary sleep disorders. Based on the current advantages of melatonin in the management of secondary sleep disorders, it is hoped that there will be a tremendous growth in the use of melatonin application worldwide. Besides, little evidence is available regarding the adverse effects of long-term use of melatonin (Brzezinski, 1997; Zisapel, 2018). Clinicians should be alert to these shortcomings but also aware of the potential role of melatonin in clinical psychiatry and sleep medicine. Although further studies are needed to establish the optimal approach to this treatment in clinic, this meta-analysis clearly supports the use of melatonin as a management for patients with secondary sleep disorders as a complementary therapy.

5. Authors' contributions

Yang Y designed the study. Li T and Jiang S searched the literature and wrote the manuscript. Li T and Yang Z verified the data and participated in the resolution of disagreements. Han MZ, Lv JJ, and Deng C extracted and analyzed the data. Yang Z draw the picture. Reiter RJ revised the manuscript. All authors read the manuscript with critical revision

6. Disclosures

All authors declare no competing interests. The National Natural Science Foundation of China and China Postdoctoral Science Foundation have no roles in the design, data collection and analysis, writing of the report, or approval of the manuscript.

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Keeping nurses in nursing: a qualitative study of German nurses' perceptions of push and pull factors to leave or stay in the profession

Catharina Roth[1*], Michel Wensing[1], Amanda Breckner[1], Cornelia Mahler[2], Katja Krug[1] and Sarah Berger[3]

Abstract

Background: The increasing nursing shortages worldwide has focused attention on the need to find more effective ways to recruit and retain nurses. The aim of this study was to gain understanding of factors that keep German nurses in nursing and explore their perceptions of factors that contribute to nurses leaving or staying in the profession.

Methods: An explorative qualitative study was undertaken at four different hospitals (two university hospitals and two public hospitals) in Baden-Wuerttemberg, a state in South Germany. Semi-structured face-to-face or telephone interviews were conducted with 21 state-qualified nurses who had graduated from a German nursing program. Each interview was pseudonymized and transcribed. Transcripts were coded according to Qualitative Content Analysis with data structured into themes and subthemes. The study was reported according to the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist for qualitative research.

Results: Two themes emerged from the analysis and each theme had several subthemes: a) PUSH FACTORS i.e. factors that may push nurses to consider leaving the profession included limited career prospects, generational barriers, poor public image of nursing, and workplace pressures; b) PULL FACTORS i.e. factors that nurses wished for and could keep them in the profession included professional pride, improved remuneration, recognition of nursing, professionalisation, and improving the image of nursing as a profession.

Conclusion: The decision to leave or stay in nursing is influenced by a complex range of dynamic push and pull factors. Nurse Managers responsible for stabilizing the workforce and maintaining their health system will continue to have to navigate challenges until working conditions, appropriate wages and career development opportunities are addressed. A key to tackling nursing shortages may be focusing on pull factors and nurse managers listening in particular to the perspectives of junior nurses directly involved in patient care, as giving them opportunity to further develop professionally, reinforcing a strong and supportive workplace relationships, paying an appropriate salary, and improving the public image of nursing profession.

Registration number: The study has been prospectively registered (27 June 2019) at the German Clinical Trial Register (DRKS00017465).

Keywords: Health workforce, Nursing, Workforce management, Germany, Qualitative research

Background

Health systems globally are facing a crisis of workforce shortages [1, 2]. According to the World Health Organisation (WHO), the International Council of Nurses (ICN), and Nursing Now (global campaign run in collaboration

*Correspondence: catharina.roth@med.uni-heidelberg.de
[1] Department of General Practice and Health Services Research, Heidelberg University Hospital, Marsilius Arcades, West Tower, Im Neuenheimer Feld 130, 69120 Heidelberg, Germany
Full list of author information is available at the end of the article

with the International Council of Nurses and the World Health Organization) there is a global nursing shortage of 5.9 million nurses, with the greatest need of qualified nurses in South East Asia and Africa [3, 4]. In the European Region, around 7.3 million nurses and midwives are currently employed, however, this number is not adequate to meet current and future needs [5]. Although Germany has the highest number (13.9 nurses) of nurses per 1000 inhabitants in the European Union (OECD (2021)), it has been struggling also to address the increasing need for qualified nurses [6]. A study by the Prognos AG [7], for example, predicted a nursing shortage of 520,000 full-time nurses in Germany in 2030.

The shortage of nurses can be viewed in terms of real nursing shortage and pseudo-shortage. The latter refers to a sufficient availability of qualified nurses, but low willingness to work under present conditions, which results in the decision to leave practice or the profession [2]. Nursing shortages differ by specialty, country, healthcare sector, healthcare service, and organisation [2]. Primary contributing factors are the increased demand for nurses and decreased supply worldwide. Factors linked to increased demand include an aging population, globalization and a growing private sector, and increased social mobility [2]. Unsatisfactory working conditions (e.g., high workloads, inadequate support staff, work-related stress, and workforce burnout) [8], insufficient remuneration, lack of participation in decision making, lack of leadership support, and changes in health human resources approaches are factors associated with a decreased supply of qualified nurses [2, 9, 10]. The demographic changes, particularly in Europe [11, 12], the high prevalence of chronic diseases [13], the fact that more and more qualified nurses are close to retirement [12, 14], and a decreasing number of student nurses puts an increased pressure on the healthcare system [2, 12]. In addition, the shortage of nurses is exacerbated by an aging nursing workforce [12, 15]. Studies have shown that nursing workforce shortages increase the risk of adverse events, nurse-sensitive outcomes e.g. pneumonia or falls, and mortality [12, 16–18], which all have direct impact on the quality of patients care and patient safety [16].

Internationally, several strategies to address the nursing workforce shortage have been undertaken. This includes measures to improve working conditions, expand the recruitment base, and target qualified nurses who have left the nursing profession to return, recruitment of internationally trained nurses, and improved remuneration [19, 20]. However, previous studies have shown that financial incentives are only one of many drivers of nursing shortage [21]; the underlying causes of the global nursing shortages are complex [22]. Strategies that have been applied to date internationally to tackle the increasing nursing workforce shortage seem to be inadequate. Many countries are not able maintain supply of qualified nurses including Germany [6]. The shortage of qualified nurses has been becoming increasingly acute due to increased demand especially in developed countries with aging populations and an aging workforce. The demand for healthcare will continue to increase, while the supply of qualified healthcare staff to meet those needs is going to be limited [6]. The urgent need for newly qualified nurses and also the retention of experienced nurses [23] requires immediate attention. Measures to address these issues need to be implemented in a concerted manner. Improved understanding of factors that keep nurses in nursing may be a key to improving recruitment and retention. In the light of an aging nursing workforce and fewer student nurses, further evidence is needed to identify what attracts young Germans to enter the nursing profession, and what keeps them nursing.

To date, research on turnover and nursing workforce shortages in Germany have mainly focused on assessing factors that influence intention to leave workplace. Few studies have examined factors that keep nurses in nursing, attract young Germans to entering nursing profession, and what the wish for in order to stay. Gaining a better understanding of perceptions of factors that contribute to nurses leaving or staying in the profession in Germany by qualified nurses directly involved in patient care is key to development of successful strategies for future recruitment and retention.

Study aim

The aim of this study was to advance understanding of factors that keep German nurses in nursing and explore their perceptions of factors that contribute to nurses leaving or staying in the profession.

Methods

Study design

The research presented in this manuscript is part of a larger research project (the *Nurse Migration Project)*, conducted by the Department of General Practice and Health Services Research of the University Hospital Heidelberg, Germany. The main aim of the research project *Nurse Migration* was to explore the integration process of internationally trained nurses into the German nursing workforce from the perspective of German trained nurses (GTN) and internationally trained nurses (ITN). Another aim was to gain more in-depth knowledge regarding the experiences of GTN and ITN in the workplace.

The present study reports the findings from a qualitative interview study with GTN with data collected by semi-structured face to face or telephone interviews.

Study setting

Four German hospitals were invited to participate in this study:

- Centre 1 (University Hospital) has 57 specialized clinical departments with 1.600 beds in total. These services provide high-quality inpatient treatment with best practice medical and nursing standards. Currently, 2601 nurses are employed at Centre 1.
- Centre 2 is (with 310 beds in total) one of the largest lung care clinics in Europe and currently employs more than 200 nurses.
- The Centre 3 works closely with the Centre 1 and has six different departments with around 200 beds in total and employs more than 200 nurses.
- The Centre 4 is a public acute hospital (with 234 beds) which provides basic and standard medical care and currently employs around 280 nurses.

Participants

Nurses were eligible to participate in this interview study if they were at least 18 years old and were employed in one of the involved hospitals. Other healthcare professionals (e.g., physicians, physiotherapies, nurse aides), as well as student nurses and nurses who did not consent to participate were excluded from the present interview study. No minimum employment working hours was set. All nurses gave their written informed consent to participate in the study prior to the start of the interview.

Sampling and recruitment process

The nursing leaders of the four hospitals were initially informed about the purpose of the study and the recruitment process by a member of the research team via email and by phone. All hospitals decided to participate in the research project. Different sampling and recruitment methods were applied at the four remaining hospitals.

At Centre 1, a key contact person was appointed by the Director of Nursing management. The key contact person was responsible for informing the ward managers about the nature and the purpose of this study. At Centre 2, all ward nurse managers were informed during a meeting with a member of the research team, that was organized by the nursing management. At Centre 1 and Centre 2 the ward nurse managers were responsible for the distribution of the study material. Each nurse received an envelope with information resources including an invitation letter to take part in the study, an information leaflet, an informed consent form, and a reply envelope for return in the internal mail system. The information leaflet included contact details of the research team. Nurses who decided to take part were requested to contact the research team directly.

At Centre 3 and Centre 4 nursing management informed ward nurse managers about the study. Ward managers then informed their nursing teams and decided together with their teams who was eligible and was willing to participate. They then informed the research team about the interested nurses. Those nurses also received information resources including an invitation letter to take part in the study, an information leaflet, an informed consent form, and a reply envelope via the internal mail system. Together with the interested nurses, the ward nurse manager and a member of the research team arrange interview appointments.

Four weeks and six weeks after the first distribution of the study material reminders were sent to the nursing management and ward managers of each hospital to increase the respondent's rate. Ward managers were asked to make the survey public at regular team meetings. In addition, nurses who took part in an interview were asked to invite their peers in all four hospitals.

Data collection

Semi-structured individual face-to-face or telephone interviews were conducted between September 2019 to August 2020 by a female health services researcher with a background in nursing and public health (CR). The interview guide was initially developed by CR (female health services researcher with a background in nursing and public health) and discussed in a qualitative research colloquium at the Department of General Practice and Health Services Research, Heidelberg University Hospital. Adjustments were made according to recommendations by the participants of the colloquium. The interview questions were open-ended and based on an extensive literature search. Interview questions addressed experiences and perceptions regarding workplace experiences. The data collection process was interrupted by the SARS-CoV-2 pandemic in 2020 and was therefore prolonged. Face-to-face interviews were conducted in a separate and quiet room on the ward. All interviews were digitally recorded, pseudonymized and transcribed verbatim. Each transcript was reviewed whilst listening to the digital recording to ensure accuracy. Data gathering was finalized when saturation was reached. Information such as sociodemographic data, work experience, and place of work were collected in addition to the interviews. No additional field notes were taken during or after the interview. Interviews were not repeated. Transcripts were not returned to participants for verification or feedback. Only the participants and the researcher were present during the interview.

Data analysis

Data was analysed according to Qualitative Content Analysis [24] to structure collected data into themes and subthemes using an inductive approach. In a first step, two female researchers (CR and AB) familiarised themselves with the whole data set. They coded the first three interviews independently. The results were discussed, and a coding system was developed by consensus. The transcripts were then coded line-by-line by CR (health services researcher with background in nursing) and AB (health services researcher). The coded transcripts were compared against the coding system in further discussions. Disagreements regarding codes were resolved in discussions with CR, AB and SB (health services researcher with background in nursing). All transcripts were analysed using the same method by the two coders. Moreover, the final coding system including themes and subthemes and illustrative quotes were discussed between CR, AB and SB in order to ensure consensus as part of the quality management process for qualitative data analysis. Interview data was analysed using MAXQDA, version 2020.1.0 [25], a computer-assisted qualitative data management software.

Quotations presented in this paper were translated into English and slightly adapted to maintain meaning by CR (fluent in German and English) and checked for accuracy by SB (a native English speaker fluent in German).

Ethical considerations

The study was approved by the Medical Ethics Committee of the Medical Faculty of Heidelberg University (S-367/2019). In addition, the staff council of each hospitals approved the study. Written informed consent was provided prior commitment to interviews by participants. Research conducted in this study was performed in accordance with the Declaration of Helsinki [26]. The study was reported according to the Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist for qualitative research [27].

Management of data quality

Rigorous procedures were implemented to enhance the credibility of findings: (a) using more than one data coder during data analysis, (b) peer debriefing (qualitative research colloquium), (c) consensus discussion between the two coders and if necessary, a senior researcher, and (d) member checking/ respondent validation with a senior researcher. In addition, an audit trail of the research process was developed to document the research process [28].

Results

Twenty-one interviews with German trained nurses were conducted. The majority of nurses were employed at Centre 1. The mean age was 40.4 years (SD 11.4), with the youngest participating nurse being 22 years old and the oldest being 60 years old. More than three-quarters of the total sample identified as female (81.0%). They had work experience of 19.5 years on average. Participants were employed in a variety of different departments. The majority worked on inpatient wards with a small number of nurses from on an intensive care unit (Table 1). Mean interview duration was 17.25 min (range 8.14–23.41).

Two main themes emerged from qualitative content analyses in relation to nursing workforce shortage: a) Push Factors and b) Pull Factors (Table 2). Each theme included subthemes. Exemplar quotations were used to illustrate meaning and themes emerging from the considerable data set that was generated from the study. Exemplar quotes were anonymised to protect the identity of participants.

Table 1 Sociodemographic characteristics of the nurses who participated in this study ($n = 21$)

	German trained nurses $n = 21$ (100%)
Study Centre	**n (%)**
Centre 1	14 (66.7)
Centre 2	2 (9.5)
Centre 3	4 (19.0)
Centre 4	1 (4.8)
Age in years	**mean (SD)**
	40.4 (11.4) Min 22 Max 60
Gender	**n (%)**
Female	17 (81.0)
Male	4 (19.0)
Work experience in years	**mean (SD)**
	19.5 (12.8) Min 0 Max 44
Role	**n (%)**
State-Qualified-Nurse	14 (66.7)
Charge Nurse	7 (33.3)
Department	**n (%)**
Department of Cardiology and Pneumology	3 (14.3)
Pneumology Department	2 (9.5)
Surgical Department	6 (28.6)
Department of Internal Medicine	5 (23.8)
Gastro-Enterology Department	2 (9.5)
Other	3 (14.3)
Ward	**n (%)**
Intensive Care Unit	5 (23.8)
Intermediate Care	1 (4.8)
Inpatient Ward	15 (71.4)

Table 2 Overview of themes and sub-themes

Themes	Definition	Subthemes
Push Factors	This theme included factors that may push nurses to consider leaving the profession as demotivators from the perspective of nurses trained in Germany	• Limited Career Prospects • Generational Barriers • Poor Public Image • Workplace Pressure
Pull Factors	This theme included factors that could keep nurses in the profession or factors that nurses wished for in order to stay as motivators from the perspective of nurses trained in Germany.	• Professional Pride • Improved remuneration • Recognition of Nursing • Professionalisation • Marketing

Theme 1: push factors

This theme included factors that may push nurses to consider leaving the profession as demotivators from the perspective of nurses trained in Germany.

Limited career prospects

Some nurses indicated that a lack of opportunities for professional advancement may be demotivating and thus contribute to nursing shortages in Germany. Participants emphasized the limited opportunities for professional advancement.

> *I think it would be more lucrative. Because then people would also come in and say: "Well, I studied" […] and maybe I can develop a bit more diversely […] to study nursing science or nursing management would perhaps be a bit better, I hope, if you do it for a year longer. (Nurse_26, Age 29)*

However, it was also acknowledged that just the higher qualification alone would not always be enough and that there was no easy answer.

> *It's just difficult to get promoted, although I also have to say: Well, in the past there was no university degree for nursing. As I said, I see it critically. I don't know... I think at the management level it is good, it's okay if someone has a university degree [...] and then maybe also a degree in business administration, but whether or not a ward manager necessarily has to have an advanced training course or a university degree, I honestly don't know. (Nurse_24, Age 48)*

Generational barriers

Some participants described perceived differences between the younger and the older generation of nurses, which involved divergent values and motivations. Some younger nurses highlighted that they wished to have the chance to influence their workplace and have a voice, but they felt their group was too small to initiate change. They had the impression that older nurses have a different mindset and that it was sometimes challenging to find common ground between the two generations, which could be demotivating at work.

> *And that is not in the minds of the nurses, that is mainly a generational problem. It works better with the younger ones [younger nurses], it's easy to get them on board, but my generation or my level of education is not yet in a position to perceive it at all. Very few people are, that's my experience. And I think that... they are... Many of them [older nurses] just want to do their work in peace, […] they want to do their work in the best possible way in the area where they feel comfortable. I think that's the difficulty, to get the generations together a bit. (Nurse_22, Age 40)*

Poor public image

Participants reported that perceptions in German society had of the nursing profession such as the stereotypical picture of nurses given in the media contributed to a poor public image. They highlighted that many people did not realise the range of professional skills nursing required to provide patient care and how demanding the nursing job really was and that this had a demotivating effect.

> *[...] because the nursing profession has been dragged through the mud and degraded, […] we support and remove natural needs from the human being. That's nothing bad and nothing disgusting in my eyes, but one should just, because that was put in the foreground, yes, just the nurse was degraded to the rear cleaner and that's what society has now and it's just yes: "Give food, a bit of washing and yes and therefore they still get too little money for that." (Nurse_31, Age 36)*

> *Personally speaking, I think it would be much more beneficial for the nursing profession if we showed a certain amount of transparency. It is... I notice that*

in my patients, there are many who have no idea about what we actually do here. All the hospital series like "Grey's Anatomy" and I don't know what else, we have already been asked whether we really have relationships with our physicians. Yes, so you have to listen to things like that. Of course, it is completely misrepresented, even if you watch private channels like SWR or ARD and all the others, that this is not the job or the day of a nurse. There are very few nurses who stand up and say: "No, we do much more than just supporting patients with personal hygiene. We do much more than just prophylaxis." (Nurse_26, Age 29)

Participants described the nursing profession as a highly specialised field that has a wide spectrum of responsibilities and wide range of competencies. Participants stressed that they felt a need to show for society to better understand what nurses do and what they are capable of in order to increase the attractiveness of the profession.

[…] because many people think: "The doctors are always there", but especially at an intensive care unit, the physicians are usually not at patient's bedside, [..] the nursing staff actually do everything, they are responsible for the ventilation of patient and things like that […] You also have a lot of responsibility for it, so I think that's more appealing somehow if people would know that […]. (Nurse_18, Age 30)

Workplace pressure

The workplace pressures linked to inadequate staffing were not going to improve if even gaining entry to nursing training was perceived as a barrier for some. Participants indicated that some nursing schools required a secondary school certificate to be able to enrol in nursing school, which could be a barrier for some otherwise suitable candidates for the nursing profession. Participants described the negative impact on their motivation to work due to inflexible rostering choices. They suggested a more family-friendly roster.

[…] more flexible working hours, more possibilities, everything is still too rigid. (Nurse_22, Age 40)

Participants described workplace pressure that had a demotivating effect included inadequate staffing levels, constant time pressure during patient care, physical stress, inflexible rostering choices, the impact of political decisions, and managing the physical and emotional work.

And this time pressure that we have here because we learn to give everything for our patients during nursing training, this and that, hygiene also needs a certain amount of time, yes, and we also need time for conversations, but it is not possible, because otherwise you simply won't get through and won't get any further, yes, that is very difficult. […] We work with people and very often we forget that, because there is simply pressure from above and that is just a pity, because that is not what we have learned in this profession, […] and at some point, after the time I say: "I can't do any more." Yes, I cannot spend 24 hours here doing what I do. I just have to do the bare minimum and that's not why I'm a nurse. (Nurse_25, Age 30)

Theme 2: pull factors

This theme included factors that could keep nurses in the profession or factors that nurses wished for in order to stay as motivator from the perspective of nurses trained in Germany.

Professional pride

Participants emphasized the importance of a sense of pride for their profession. These nurses described their feelings of pride, and that nursing work was meaningful and contributed to society.

To be proud of what we have learned and what we are doing as nursing profession, […]. (Nurse_24, Age 48)

And that's where I say, "Ok we are nurses, we just have to learn to be happy with it." [...] Of course more money is great; of course, more recognition is great. But […] it just helps me to say: "Hey, I'm proud of my profession it is not just a job, it's a vocation". (Nurse_26, Age 29)

Improved remuneration

Participating nurses discussed factors related to remuneration or salary as a pull factor for staying in the workforce. They highlighted that higher payment could raise the status of the profession. In addition, improved remuneration would show nurses that they were valued and that their work was appreciated.

In order to address the shortage of skilled workers in nursing, I see above all an attractive salary that expresses a certain appreciation for nursing staff and that should definitely become apparent, which will perhaps be a factor for many to return to the nursing profession. (Nurse_10, Age 29)

However, some participants indicated that a better salary alone was not enough to increase the attractiveness of the nursing profession.

I think that more money alone doesn't make it [nursing] more attractive, at least not in the long term. (Nurse_29, Age 42)

Yes, and I mean payment is always quite nice and good, but I think the work has to be fun. Of course, you have to be able to make a living from it, but it also has to be fun [...]. (Nurse_24, Age 48)

Recognition of nursing

Participants stressed that the recognition of nursing started with how they sew themselves but also how other healthcare professionals and society saw them. They indicated that in order to be recognised as a profession they had to show the world what it meant to be a nurse and what the world would be like without nurses. Factors participants thought that positively impacted on the image of nursing were a strong social standing, being proud of being a nurse, and a professional association that worked towards maintaining high status of the nursing profession.

I think that it is a shame and I have a lot of criticism for the society in general, but especially now with nursing, it starts with us, so if someone young were to ask me, a young woman who is perhaps thinking about becoming a nurse, I would advise her to (Nurse_8, Age 56)

Participant were in favour of collaborating with other healthcare professionals to find best practice solutions. They highlighted the desire to improve collaboration and increase recognition of nursing by other professions.

I think it would help if we worked more in an interdisciplinary team, I personally suffer from the hierarchical structures and sometimes I think I've been working as nurse for so long and I'm always here, but I'm just not allowed to have a say in ward decisions [...] I find really bad, and that's also something that probably won't change in the time I'm there, but for the future I hope that there will be more equality [...]. (Nurse_8, Age 56)

Another factor mentioned in relation to g the image or recognition of nursing was how nurses talk about their profession themselves. Some participants were concerned that other nursing colleagues had sometimes discouraged young people to choose nursing as profession and wished that their colleagues acted differently.

It starts with us, so if someone young were to ask me, a young woman who is perhaps thinking of becoming a nurse, I would advise her to do so, well, I would, for example, I've really had good experiences all my life, I've learned a lot for myself, I've managed to raise three children at the same time and I also find that it's always manageable with shift work and with sometimes more and sometimes less work. [...] And besides, I think that there are a lot of people working there who are very open-minded and social, good colleagues and I would advise, but I also find that there are a lot of people who say 'Oh, don't do that, don't do that' because of the shift work, so I don't think it's that bad. (Nurse_8, Age 56)

Professionalisation

The advancement of the profession with transition to university qualification was an important pull factor for sustaining the workforce. The majority of participants perceived the opportunity to get a university degree in nursing as important, nevertheless indicating that it would be important to generate jobs including an adequate salary for nurses with a university degree, not only for academics but also for those in clinical practice.

I also think it is important to build up a mix of qualifications, because I think the professionalisation of nursing is relatively important. In my opinion, this does not have to happen extensively, because perhaps it is not important for everyone, but the possibility of getting a university degree in nursing should exist, and it should then also result in appropriate jobs with appropriate remuneration - that's it. (Nurse_10, Age 29)

[...] That's something, you have to get the two fields together, then I think professionalisation has a better chance. If you could get it closer to practice. Most people are moving away from practice, as far as that's concerned, and.... because there are no fields. That's also the thing with... You have to take fields of activity, for example in the clinic, and that's what's still missing. If you don't manage to do that, then I think the nursing profession will develop into the blue-collar sector and the academic sector, and then we'll have a gap that I don't think is really good. (Nurse_22, Age 40)

Nevertheless, participants stressed that transition to university qualification could not be the only way. They wished that nurses without a university degree also received recognition and appreciation.

And I see that as a huge problem, so you would have

to create something, so professionalisation on the one hand, but on the other hand I would have to create something where I have people who are professionally qualified [without a university degree], where I know they will stay in nursing […]. (Nurse_24, Age 48)

Some participants indicated that professionalisation could enhance the image of the nursing profession and contribute to workforce retention.

I think it has to be about a status. With the new Nursing Reform Act, we are perhaps on the right path towards having clearly defined tasks, reserved tasks and no longer being regarded as an auxiliary profession, but as a profession in its own rigth. Of course, it will take a few more years for this to become established, but I think that this is actually a good way forward, as is this university degree, that we are becoming more professional. What I think is important is that we get a skills-mix on the wards, i.e. students with different qualification [pathways e.g. hospital and university training programs] but also support roles such as healthcare assistant, ward secretary, […] Yes, so that a qualified nurse or also a ward nurse manager can then also pursue their activities accordingly, namely the planning, control and organisation of a patient's care needs and control and is involved. (Nurse_29, Age 42)

Marketing

Finally, participants highlighted the need for effective advertising and marketing campaigns targeting young people, improving the image of the different hospitals, job information day at schools, showing presence at job fairs, and increasing positive media presence as another pull factor to attract young people into the workforce.

Yes, I don't know about job information days at schools or so. I've never actually had nursing anywhere or at these job fairs, yes at Jobs4Future they are, or presentations at the job centre or so, where I used to go nursing was not present, at least I hadn't seen any nurses […], maybe with practical exercises and so, I think you can catch the people. (Nurse_16, Age 22)

Discussion

Key findings highlighted that primary push factors for nurses questioning whether to stay in nursing were workplace pressures and poor public image followed by limited career prospects and generational barriers. Moreover, pull factors such as improved remuneration, professionalisation, professional pride, effective marketing and increased social recognition were all factors that could attract young people into nursing and motivate them to stay in nursing as a satisfying and meaningful profession.

Limited career prospects, not having a voice, and not being able to influence ones working environment have been recognised in other studies [29–33]. Flinkman et al. [29], conducted a qualitative case study with young registered nurses in Finland and explored why they intended to leave the nursing profession. Lack of career advancement and the fear of being stuck at one place without being able to further develop were factors that contributed to their decision to change their career. Clendon et al. [30] found that for young nurses in New Zealand career progression (e.g. completing master's degrees) was important and a factor in retention. Hasselhorn et al. [32] found that nurses in Europe with an intention to leave the profession were usually young, highly qualified and looking for a way to professionally develop. Lynn et al. [33] explored solutions to the nursing shortage from the point of view of nurses working in eight different states in the USA. Career progression and educational opportunities were key motivators to stay in the profession [33]. In addition, studies conducted in the USA suggested that giving nurses a voice to influence their work environment resulted in increased satisfaction and retention [34, 35]. In light of an aging nursing workforce, the loss of highly motivated and qualified (young) nurses due to limited career prospects and lack of new challenges is unacceptable.

Nurses in our study, particularly the younger generation, indicated that the opportunity to obtain a university degree was important to them for realising their professional potential. In addition, limited career prospects were perceived as a push factors for considering leaving the profession. The commitment and wish to gain experience and skills is typical for millennial generation nurses [36]. Shields et al. [37], examined the impact of job satisfaction of British nurses on intention to quit and found that dissatisfaction with promotion and training opportunities are found to have a stronger impact than workload or insufficient remuneration. A study conducted in Ethiopia found that nurses with a bachelor or a master degree scored higher on the motivation score compared to nurses with less education [38]. Watts et al. [39], found that the intention to leave was lower in certified nurses than in non-certified nurses.

Differences between younger generations and the older generations of nurses are also an important consideration. Particularly, the younger generation of nurses participating in our study were enthusiastic and excited about their chosen career. They highlighted their desire

to shape their workplace and further develop professionally but felt held back by those from an older generation. These results reflect the findings by Clendon et al. [30] and Dols et al. [40]. Retention strategies that enabled young nurses to be heard and have an opportunity to advance in their career through for example professional development or project work are necessary. However, these strategies will only be effective in the long term if nurses are paid accordingly and have sufficient time and resources needed to do their work [30].

In our study nurses, described stereotypical portrayals of nurses in the media that contributed to poor public image. They felt that the nursing profession was undervalued by other professions and society in general in Germany. These findings are supported by the work of other researchers [29, 41, 42]. Historically, the nursing profession has been a female profession and has been associated with stereotypical attributes such as being the submissive handmaids of dominant physicians with little responsibility [42–44]. Particularly, young nurses in our study did not identify with this picture. They rather saw themselves as highly skilled and ambitious professionals. This is consistent with findings by Flinkman et al. [29] and Takase et al [41]. .Takase et al. [41], conducted a study investigating the impact of the perceived public image of nursing on nurses' work behaviour in Australia and found that the poor public image can decrease self-esteem and lead to job turnover.

Previous research has already established that workplace demands have a significant impact on the physical and emotional health of nurses and their intention to leave the nursing profession [22]. Findings in our study highlighted that high workplace demands and poor practice environment were reasons for intention to leave, which is consistent with those by Huntington et al. [45], Haywards et al. [46], and Flinkman et al. [29]. In a multinational study with nurses working in New Zealand, Australia, and the United Kingdom high workload, constant pressure, and staff shortages had a negative impact on the job satisfaction of nurses and increased intention to leave [45]. Flinkman et al. [29], also identified workplace pressure as a major driver for young nurses to leave the nursing profession especially those linked to insufficient practice environment and nurse-patient ration. In an Canadian study [46], factors that influenced experienced nurses' decision to leave their profession included increased workload due to a higher number of acutely ill and sicker patients.

Not being able to provide a high standard of patient care and the ensuing moral distress was a reason for some nurses in our study to think about leaving the profession. Nurses experiencing emotional and physical exhaustion due to the inability to provide a reasonable level of care over time leads to moral distress that in turn prompts nurses to consider leaving their profession [29, 45–47]. There are growing demands of the nursing profession as patient acuity increases linked to longer lifespans of people with long-term conditions and multimorbidity. Nurses need to be able to fulfil the requirements of modern patient care by applying evidence-based interventions. However, in order for nurses to be willing to stay in nursing, workplace conditions need to be such that they have the ability to provide patient care without experiencing chronic emotional and physical exhaustion.

Given the challenges face by nurses in contemporary clinical practice, which threaten further losses to an already dwindling workforce, a clear understanding of factors that keep nurses in nursing is essential. In our study positive workplace relationships contributed to a positive feeling and increased job satisfaction, which has also been reported elsewhere [45, 46]. Fair and appropriate remuneration is another strong motivating factor. Nurses in a Swedish study [31] indicated, that an unsatisfactory salary was the main reason for leaving the nursing profession. Flinkman et al. [29] found that nurses thought their salary was not adequate, and that a higher salary would improve attractiveness of nursing [29]. However, improved remuneration alone does not compensate if other factors are unsatisfactory. Cox et al. [48], reported that moral distress and poor interpersonal relations were the primary mediating factor for turnover rather than pay. Improved remuneration alone is not a solution to nursing workforce shortages but are part of a bundle of strategies needed to improve the image of nursing and increase nurse satisfaction, so they stay in nursing.

Similar to findings in our study, Hayward et al. [46], described the lack of respect in their working relationships with physicians contributed to nurses decision to leave their jobs. Rosenstein et al [49], .conducted a survey in the USA investigating the effect of nurse-physician relationship on nurse satisfaction and intention to leave. Disruptive behaviour from physicians increased work-related stress and frustration [49]. This behaviour was not only experienced in physicians-nurse relationships but also in nurses-nurse relationships [49]. Our findings also indicated that the way nurses talk with each other particularly about their own profession may have a negative impact on retention or recruitment. Rosenstein et al. [49] showed that the prevalence of disruptive behaviour resulted in nurses resigning [49]. Nurses seek to be recognized and wish for positive workplace relationships not only with their peers but also other healthcare professionals. Improving collaborative interprofessional teamwork may be another key to improved interprofessional relationships and thus enhance the recognition of the nursing profession. Integration of interprofessional

education into the education of different healthcare professionals may be a strategy to address this issue.

Conclusion

The decision to leave or stay in nursing is influenced by a complex range of dynamic push and pull factors. Nurse Managers responsible for stabilizing the workforce and maintaining their health system will continue to have to navigate challenges until working conditions, appropriate wages and career development opportunities are addressed.

Implications for practice

A global undersupply of nursing and attrition rates that continue to climb means that nurse managers and policymakers need clear understanding of a range of financial, professional, and personal factors that keep nurses in nursing. Particularly, young nurses globally are looking for opportunities to develop professionally. It is important to them to have the opportunity to qualify at a university and gain increased autonomy. Strong and supportive workplace relationships seem to be one of the key factors to keep nurses in nursing not only in Germany but globally. Inadequate remuneration and the poor public image of the nursing profession seem to contribute to the intention to leave nursing profession. In addition, not being able to provide adequate patient care seem to be one of the main factors globally that leads to nurse turnover, particularly in young nurses. In order to address the nursing shortages, further research is needed to explore what young nurses are looking for, what motivates them to choose nursing, and what keeps them nursing worldwide.

Strengths and limitations

This study explored on factors that may push nurses to consider leaving the profession and pull factors that may keep them in nursing. In contrast to previous studies, which mostly focused on factors that contributed to intention to leave the nursing profession, this study provided a perspective on factors that kept nurses in nursing. Qualitative interviews are an important research tool to gain in-depth knowledge on the research subject and understanding of perspectives of targeted groups and was therefore considered as appropriate research method. Data analysis was guided by adequate methodological strategies aiming to minimize bias and reduce the risk of losing relevant content. Reporting of the qualitative findings was guided by the recommendation of the COREQ checklist [27].

Some limitations must be acknowledged. Although the qualitative design allowed an in-depth exploration of the nurses' perceptions on push and pull factors, findings of this study cannot be generalized beyond the study population. In addition, as the study was conducted in South Germany in two university hospitals and two smaller public hospitals, specific national and regional factors might have influenced the results. A similar study conducted elsewhere might get different results due to context. Even though data saturation was reached, higher number of nurses from different hospitals may have led to more diverse results. Although perceptions and experiences were relatively consistent within the study sample, these experiences may not be shared by all nurses. In addition, nurses who voluntary participated might have different perceptions and experiences compared nurses that choose not to participate. Social desirability in answers cannot be excluded. Quotes were translated from German into English; it is therefore possible that the meaning in translated quotes subtlely differed from the original meaning in German quotes. The results of the study must be interpreted with caution in terms of generalization and representativeness.

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Authors' contributions

CR and MW conceived the study. CR and SB developed the study protocol. MW was the principal investigator of the study. CR conducted the interviews, CR, AB and SB analysed the data. CR wrote the first draft manuscript. MW, SB, AB, KK, and CM provided critical input at every stage of the development of the manuscript. All authors provided substantial comments and approved the final version of the manuscript.

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Availability of data and materials

The dataset that was generated and analysed during the study will not be made publicly available due to German data protection law but may be made available by the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of the Medical Faculty of Heidelberg University (S-367/2019) prior to the start of the study. The staff council of each hospitals approved the study. Informed consent was provided prior to the interviews by all participants. Research conducted in this study was performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details
[1]Department of General Practice and Health Services Research, Heidelberg University Hospital, Marsilius Arcades, West Tower, Im Neuenheimer Feld 130, 69120 Heidelberg, Germany. [2]Department of Nursing Science, University Hospital Tuebingen, Hoppe-Seyler-Str. 9, 72076 Tuebingen, Germany. [3]Centre for Postgraduate Nursing Studies, University of Otago-Christchurch Campus, 2 Riccarton Ave, Christchurch 9140, New Zealand.

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