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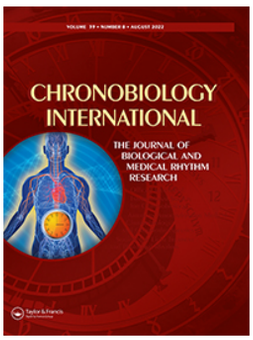

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Night-shift work is associated with increased susceptibility to SARS-CoV-2 infection

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ABSTRACT

Night-shift workers experience disturbances of their circadian rhythm and sleep, which may make them more susceptible to infectious diseases. Therefore, we studied whether night-shift workers are at higher risk of testing positive for SARS-CoV-2 infection than day workers. In this prospective study, data were used from 20 questionnaire rounds of the Dutch Lifelines COVID-19 cohort that was initiated in March 2020. In the different questionnaire rounds, 2285 night-shift workers and 23,766 day workers reported whether they had tested positive for SARS-CoV-2. Cox proportional hazards regression models adjusted for demographic, work, and health covariates were used to compare SARS-CoV-2 incidence between night-shift and day workers. From March 2020-January 2021, 3.4% of night-shift workers and 2.2% of day workers reported to have tested positive for SARS-CoV-2 ($p < .001$). After adjustment for covariates, night-shift workers had a 37% higher risk of testing positive for SARS-CoV-2 (hazard ratio: 1.37, 95% confidence interval: 1.05–1.77). In this study, we show that night-shift workers were more likely to test positive for SARS-CoV-2 than day workers, which adds to the growing evidence that night-shift work may influence the complex processes involved in infection susceptibility. Further mechanistic insight is needed to understand the relation between night-shift work and (SARS-CoV-2) infection susceptibility.

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Introduction

Nowadays, work takes place outside regular 9-to-5 working hours for many workers. In Europe, approximately one in five workers regularly works during the night (European Foundation for the Improvement of Living and Working Conditions (Eurofound) 2016). These night-shift workers are required to work and sleep at times that conflict with their circadian rhythm. Consequently, disturbances of the circadian rhythm and sleep have been proposed as likely drivers of the harmful effects of night-shift work, such as cardiovascular diseases and type 2 diabetes mellitus (Knutsson 2003; Moreno et al. 2019; Puttonen et al. 2010).

As circadian rhythm disturbances and disturbed sleep may negatively impact the immune system, interest has also been growing in whether night-shift work could increase susceptibility to infection (Almeida and Malheiro 2016). Earlier studies have found night-shift work to be associated with increased rates of common infections (Mohren et al. 2002; Prather and Carroll 2021). Furthermore, in a prospective study, we found healthcare workers who performed night-shift work to have 20% more respiratory infections than their day-working colleagues (Loef et al. 2019b). However, it is not yet known whether similar results can be expected outside healthcare and for specific types of infection.

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The COVID-19 pandemic has shown that infectious diseases can still have a major societal impact. Currently, a lot of research is being devoted to identifying risk factors for infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Multiple research groups worldwide have hypothesized night-shift work to be a potential risk factor for infection with SARS-CoV-2 (Belingheri et al., 2021; Lim et al. 2020; Silva et al. 2020). Correspondingly, the first (preliminary) studies report increased incidence of SARS-CoV-2 infection (Fatima et al. 2021; Rizza et al. 2021) and severe COVID-19 (Maidstone et al. 2021; Rowlands et al. 2021) among night-shift workers. However, since three of these studies used data from the same cohort with night-shift work exposure being assessed years before the start of the COVID-19 pandemic (Fatima et al. 2021; Maidstone et al. 2021; Rowlands et al. 2021), more prospective studies are needed that take into account workers' night-shift work status during the pandemic. Therefore, our aim was to determine whether night-shift workers are more susceptible to SARS-CoV-2 infection than day workers using data from a large prospective cohort study.

Methods

Study design and population

In this prospective study, data were used from the Lifelines COVID-19 cohort that aims to assess the impact of the COVID-19 pandemic and risk factors for SARS-CoV-2 infection and COVID-19 among the general Dutch population (Mc Intyre et al. 2021). In the Netherlands, the first SARS-CoV-2 cases occurred in February 2020. The Lifelines COVID-19 cohort started in March 2020 with (bi)weekly questionnaires about SARS-CoV-2 infection, health, lifestyle, work, and experiences during the pandemic. From July 2020, questionnaires were sent out monthly. The current study comprises the first 20 questionnaire rounds of the Lifelines COVID-19 cohort completed between March 2020-March 2021 (Table 1). Working participants aged 18–67 years who completed at least one questionnaire round and who had data available on SARS-CoV-2 infection, night-shift work, and covariates were included in the analysis.

Participants of the Lifelines COVID-19 cohort were recruited from the larger Lifelines population cohort (Scholtens et al. 2015). This is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical/socio-demographic/behavioral/physical/psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Approval of the Lifelines Cohort study was obtained from the Medical Ethics Committee of the University Medical Center Groningen, The Netherlands. Informed consent was obtained from all participants.

Measures

Night-shift work

Information on night-shift work since the start of the COVID-19 pandemic was collected with one question in round 7 (May 2020) ("Since the start of the corona-crisis in the Netherlands (mid-March), did/do you work in

Table 1. Questionnaire rounds lifelines COVID-19 cohort from March 2020 to March 2021.

Round[1]	Date[2]	SARS-CoV-2 infection questions[3]	Night-shift work questions[4]
1	Mar to Apr 2020	Tested, diagnosed, self-reported	-
2	Apr to May 2020	Tested, diagnosed, self-reported	-
3	Apr to May 2020	Tested, diagnosed, self-reported	-
4	Apr to May 2020	Tested, diagnosed, self-reported	-
5	Apr to May 2020	Tested, diagnosed, self-reported	-
6	Apr to May 2020	Tested, diagnosed, self-reported	-
7	May 2020	Tested, diagnosed, self-reported	Night shifts March 2020 until now
8	May to Jun 2020	Tested, diagnosed, self-reported	Night shifts in the last 14 days
9	Jun 2020	Tested, diagnosed, self-reported	Night shifts in the last 14 days
10	Jul 2020	Tested	-
11	Jul to Aug 2020	Tested, diagnosed, self-reported	-
12	Jul to Sep 2020	Tested, diagnosed, self-reported	-
13	Sep 2020	Tested, diagnosed, self-reported	Night shifts in the last 14 days
14	Oct to Nov 2020	Tested	-
15	Nov 2020	Tested, self-reported	-
15b	Nov to Dec 2020	Tested, self-reported	-
16	Dec 2020	Tested, self-reported	-
16b	Dec 2020 to Jan 2021	Tested, self-reported	-
17	Jan to Feb 2021	Tested, self-reported	Night shifts in the last 14 days
18	Feb to Mar 2021	Tested, self-reported	Night shifts March 2020 until now

[1]Number of questionnaire round; [2] Month(s) during which the questionnaire round was completed; [3] Questions on SARS-CoV-2 infection that were included in the questionnaire round (tested: having tested positive, diagnosed: being diagnosed by a physician, self-reported: self-reporting whether one believes one (has) had a SARS-CoV-2 infection); [4] Questions on night-shift work that were included in the questionnaire round, "-" means that no night-shift work questions were included in that particular round.

night shifts?") and round 18 (February-March 2021) ("Did you work in night shifts in the period between March 2020 and now?") of the Lifelines COVID-19 cohort among participants who indicated to work in their daily life. Participants who answered "yes, regularly" or "yes, occasionally" to this question in round 7 and/or round 18 were labelled night-shift workers (Supplementary Table S1A-E). Participants who answered "no" in round 7 and round 18, or who answered "no" in one of these rounds with a missing value in the other round, were labelled day workers (Table S1F-H). Participants who reported night-shift work in round 18, and not in round 7, were included as night-shift workers from round 8 onwards (Table S1B). Participants who had missing values on the night-shift work question in both rounds (either because they did not work or they skipped this question) were excluded (Table S1I).

Besides the primary night-shift work questions, in four rounds in between round 7 and 18, participants were asked whether they worked in night shifts in the last 14 days (Table 1). Participants who were labelled day workers, but reported to have worked night shifts in one or more of these additional questions were excluded (Table S1J-L). Participants who reported night-shift work in round 7, but not in round 18 were only labelled night-shift workers if they also reported night-shift work in the rounds between 7 and 18 (Table S1E), otherwise they were excluded (Table S1M).

Two additional questions about night-shift work frequency ("How many night shifts did you work on average per month in the period between March 2020 and now?") and history ("Did you work in night shifts in the 6 months prior to the start of the corona-crisis (September 2019-February 2020)?") were asked in round 18. Participants who were day workers during the COVID-19 pandemic, but reported to work night shifts in the six months before the pandemic were also excluded. Night-shift work frequency (answer options: <1; 1; 2; 3; 4; 5; 6; ≥7 night shifts/month) was categorized into working ≤2, 3–4, or ≥5 night shifts/month, similar as in earlier work (Loef et al. 2019b).

SARS-CoV-2 infection

In every round, participants were asked whether they experienced a SARS-CoV-2 infection (either by having tested positive, being diagnosed by a physician, and/or self-reporting whether one believes one (has) had a SARS-CoV-2 infection) (Table 1). First, participants were asked whether they had been tested for "the coronavirus (COVID-19)" (since the last time they participated in a Lifelines COVID-19 questionnaire). Participants who answered "yes" were subsequently asked if they had tested positive for the coronavirus (COVID-19). Up until round 13, participants who answered "no" were subsequently asked if a physician had said that they had a coronavirus/COVID-19 infection. Up until round 7, participants who had not been tested were also asked if they thought they (had) had a coronavirus/COVID-19 infection. From round 8 onwards, all participants were asked if they thought they had ever had a coronavirus/COVID-19 infection.

As testing positive for SARS-CoV-2 is the most reliable measure of a SARS-CoV-2 infection being present and has been consistently assessed throughout the different rounds, this was the primary outcome measure. As a secondary outcome measure, the combination measure of testing positive, being diagnosed by a physician, and/or believing one (has) had a SARS-CoV-2 infection was used.

Covariates

Demographic (age/sex/educational level/household composition), work (occupation/occupational class/working (partly) from home/occupation involving frequent contact with others), and health (behavior) (BMI/smoking/general perceived health/chronic health conditions) variables were included as covariates. Information on age, sex, education, occupation, and occupational class was retrieved by linking data from the Lifelines COVID-19 cohort with data from the Lifelines population cohort. Information on all other covariates was based on one or more questionnaire rounds of the Lifelines COVID-19 cohort. A full description of the included covariates is provided in Supplementary Text S1.

In round 18 (February/March 2021), participants were asked whether they had received a SARS-CoV-2 vaccination (yes, only the first injection; yes, both injections; no). On 6 January 2021, the first people in the Netherlands received the SARS-CoV-2 vaccine. As round 16b ended on 5 January 2021, participants could only have received the SARS-CoV-2 vaccine in round 17 or 18. In this period (January-March 2021), only healthcare workers, those aged over 75 years, and those with serious medical conditions were eligible for vaccination. Based on this information, our primary analysis was conducted excluding the rounds during which SARS-CoV-2 vaccination could have influenced the association between night-shift work and SARS-CoV-2 infection. This decision was further supported by previous work indicating that the antibody response to the SARS-CoV-2 vaccine is influenced by the circadian clock (Zhang et al. 2021).

Statistical analysis

Characteristics of the study population were compared between night-shift and day workers using the independent-samples t-test and the chi-square test.

To study the association between night-shift work and testing positive for SARS-CoV-2, Cox proportional hazards regression models were used. For every participant, time at risk was calculated in months from enrolment in the Lifelines COVID-19 cohort (March/April 2020) until either a SARS-CoV-2 infection was reported, the participant stopped participating in the study, or the last questionnaire round was completed. If a SARS-CoV-2 infection was reported during multiple rounds of the study, the first reporting of the infection was leading in the analysis. If a SARS-CoV-2 infection was reported in a particular round, and the participant did not participate in the previous round, the date of the SARS-CoV-2 infection was centered between the last known date without infection and the first-known date with infection.

First, a Cox regression model was developed including questionnaire rounds 1–18 (March 2020-March 2021). However, since the vaccination campaign is likely to have influenced the association between night-shift work and testing positive for SARS-CoV-2, the primary Cox regression model in this study included rounds 1–16b (March 2020-January 2021). Thus, rounds 17 and 18 during which participants could have potentially been vaccinated were excluded.

Besides testing positive for SARS-CoV-2, an additional Cox regression model was completed with the SARS-CoV-2 combination measure (testing positive, being diagnosed by a physician, and/or believing one (has) had a SARS-CoV-2 infection) as outcome measure.

Adjustment for covariates in the analyses for both outcomes was completed in four different models:

- Model 1: unadjusted;
- Model 2: adjusted for age, sex, educational level, and household composition;
- Model 3: additionally adjusted for occupation, occupational class, working (partly) from home, and occupation involving frequent contact with others;
- Model 4: additionally adjusted for BMI and smoking.

Since the health variables chronic health conditions and general health were only available for a subsample of the study population, these variables were not included in the main analysis. Instead, a sensitivity analysis among the participants with complete data on these health variables was conducted to determine whether additionally adjusting for chronic health conditions and general health influenced the effect estimate (model 5).

Lastly, incidence rates of testing positive for SARS-CoV-2 were compared by frequency of night-shift work (day worker; ≤2, 3–4, or ≥5 night shifts/month), using day workers as reference group.

Analyses were conducted using IBM SPSS Statistics, version 25.0 (IBM Corporation, New York, New York).

Results

Study population

All 140,145 active adult participants in the Lifelines population cohort were invited to participate in the Lifelines COVID-19 cohort (Figure 1). Of these, 76,421 participants completed at least one of the 20 questionnaires. Subsequently, participants who did not work, participants aged >67 years, and participants who did not have complete and consistent information on night-shift work, SARS-CoV-2 infection, and covariates, were excluded. In total, 2285 night-shift workers and 23,766 day workers were included in the current study (Figure 1).

Night-shift workers were younger (49.3 years vs. 50.9 years), less often female (58.4% vs. 62.1%), and less often higher educated (31.7% vs. 45.7%) than day workers (Table 2). Night-shift workers were more likely to have a blue-collar occupation (19.0% vs. 12.7%) than day workers. Most night-shift workers had care and welfare occupations (51.1%), while business economic and administrative occupations was the most common occupational class among day workers (25.0%). Night-shift workers were less likely to work (partly) from home (11.2% vs. 55.1%) and more likely to have an occupation involving frequent contact with others (73.9% vs. 43.8%) than day workers. Furthermore, night-shift workers were more likely to smoke (14.3% vs. 10.8%) and had a higher BMI (26.5 kg/m^2 vs. 26.0 kg/m^2) than day workers. Data from the 60% of the participants who reported their vaccination status in round 18 indicated that night-shift workers had received the SARS-CoV-2 vaccination much more often than day workers (27.8% vs. 7.5% received one or both doses).

Night-shift work and SARS-CoV-2 infection

From March 2020-March 2021 (rounds 1–18), 6.7% of night-shift workers tested positive for SARS-CoV-2 compared to 4.6% of day workers ($p < .001$). The

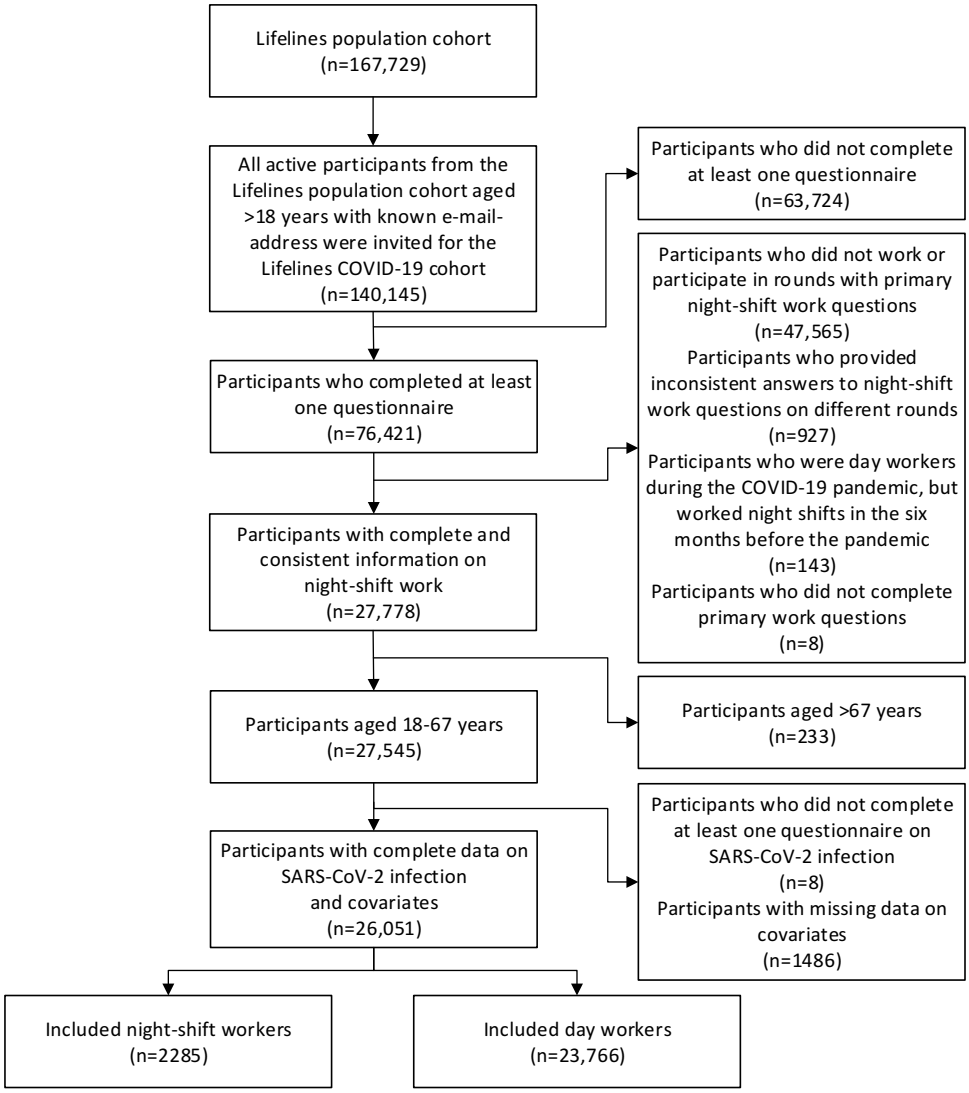

Figure 1. Flowchart of study participants.

crude Cox regression model shows that night-shift workers had a 54% higher risk to test positive for SARS-CoV-2 than day workers (hazard ratio (HR): 1.54, 95% confidence interval (CI): 1.30–1.82) (Table 3). After adjustment for demographic, work, and health variables, this reduced to a non-statistically significant 18% higher risk of testing positive for SARS-CoV-2 (HR: 1.18, 95% CI: 0.98–1.41).

Table 2 shows that there was a large discrepancy in vaccination status between night-shift and day workers, with 1 in 5 night-shift workers being fully vaccinated compared to less than 1 in 22 day workers in March 2021. This emphasizes the need to perform the analysis excluding the questionnaire rounds after the start of the vaccination campaign. From March 2020-January 2021 (rounds 1–16b), 3.4% of night-shift workers and 2.2% of day workers tested positive for SARS-CoV-2 ($p < .001$). The unadjusted hazard ratio indicates a 69% higher risk of testing positive for SARS-CoV-2 among night-shift workers compared to day workers (HR: 1.69, 95% CI: 1.33–2.14) (Table 3). After adjustment for all covariates, night-shift workers still had a 37% higher risk of testing positive for SARS-CoV-2 (HR: 1.37, 95% CI: 1.05–1.77). Thus, in the period without implementation of vaccination, night-shift workers had an increased SARS-CoV-2 incidence.

Additional adjustment for chronic health conditions and general health among the 22,409 participants with information on these variables, did not influence the association between night-shift work and testing positive for SARS-CoV-2 (Supplementary Table S2).

No difference in the combination measure (testing positive, being diagnosed by a physician, and/or believing one (has) had a SARS-CoV-2 infection) was observed between night-shift and day workers. Based on this combination measure, 13.6% of night-shift workers and 13.5%

Table 2. Characteristics study population stratified for night-shift workers and day workers (n = 26,051).

	Night-shift workers (n = 2285)		Day workers (n = 23766)	
	Mean or %	SD or n	Mean or %	SD or n
Demographic variables				
Age (in years)	49.3*	9.5	50.9*	8.9
Sex (% female)	58.4*	1334	62.1*	14769
Educational level (%)				
Low	16.5*	377	14.1*	3348
Middle	51.8*	1184	40.3*	9568
High	31.7*	724	45.7*	10850
Household composition (%)				
Living alone	7.7	176	7.9	1880
Living together with adults	44.6*	1018	49.3*	11718
Living together with children (and adults)	35.1	801	33.1	7869
Living together but unknown with whom	12.7*	290	9.7*	2299
Work variables				
Occupation (%)				
High skilled white collar	54.9*	1254	58.2*	13830
Low skilled white collar	26.1*	596	29.1*	6920
High skilled blue collar	7.6*	173	6.2*	1469
Low skilled blue collar	11.5*	262	6.5*	1547
Occupational class (%)				
Care and welfare occupations	51.1*	1168	20.0*	4765
Technical occupations	16.0*	365	10.3*	2442
Business economics and administrative occupations	7.2*	164	25.0*	5944
Transport and logistics occupations	7.0*	161	2.5*	588
Public administration, security, and legal occupations	6.2*	141	3.7*	878
Other occupations	12.5*	286	38.5*	9149
Working (partly) from home (% yes)	11.2*	255	55.1*	13104
Occupation involving frequent contact with patients/clients/children/ general public (% yes)	73.9*	1689	43.8*	10409
Health variables				
Smoking (% yes)	14.3*	327	10.8*	2564
BMI (in kg/m^2)	26.5*	4.4	26.0*	4.2
Chronic health condition (% yes)[1]	25.9	489	27.0	5547
General health (% mediocre/poor)[1]	3.0*	57	4.2*	854
Vaccination status against SARS-CoV-2 (%)[2]				
Unvaccinated	72.2*	1002	92.5*	13120
Received only first dose	7.9*	109	3.1*	437
Received both first and second dose	20.0*	277	4.4*	629

* Statistically significant difference ($p < 0.05$) between night-shift workers and day workers tested with independent-samples t-test and chi-square test.
[1]Among subsets of 1889 night-shift workers and 20520 day workers.
[2]Among subsets of 1388 night-shift workers and 14186 day workers. Vaccination status reported in round 18 (February/March 2021).

of day workers reported a SARS-CoV-2 infection from March 2020-January 2021 (p = .888). The corresponding hazard ratio was 1.04 (95% CI: 0.93–1.17) in the crude model and 0.98 (95% CI: 0.87–1.11) in the fully adjusted model (Supplementary Table S3).

Information on night-shift work frequency was available for 1258 of the 2285 night-shift workers. Compared to day workers, night-shift workers with ≤2, 3–4, and ≥5 night shifts/month all had a somewhat higher risk of testing positive for SARS-CoV-2 with hazard ratios of 1.51 (95% CI: 0.95–2.42), 1.93 (95% CI: 1.20–3.10), and 1.25 (95% CI: 0.76–2.06) in the fully adjusted models

Table 3. Hazard ratios for testing positive for SARS-CoV-2 for night-shift workers versus day workers including and excluding rounds 17 and 18 (rounds after start vaccination) (n = 26,051).

	Night-shift workers vs. day workers (n = 26,051)					
	March 2020-March 2021 Rounds 1–18			March 2020-January 2021 Round 1–16b		
	HR	95% CI		HR	95% CI	
Model 1: crude	1.54*	1.30	1.82	1.69*	1.33	2.14
Model 2: adjusted for demographic variables	1.45*	1.22	1.71	1.59*	1.25	2.02
Model 3: model 2 + work variables	1.18	0.99	1.42	1.36*	1.05	1.76
Model 4: model 3 + health (behavior) variables	1.18	0.98	1.41	1.37*	1.05	1.77

CI, confidence interval; HR, hazard ratio.
Model 1: crude model without adjustment for covariates; Model 2: adjusted for age, sex, educational level, and household composition; Model 3: additionally adjusted for occupation, occupational class, working (partly) from home, and occupation involving frequent contact with others; Model 4: additionally adjusted for BMI and smoking.
* $p < 0.05$.

Table 4. Hazard ratios for testing positive for SARS-CoV-2 for average number of night shifts per month in night-shift workers versus day workers (March 2020-January 2021) (n = 25,024).

	Frequency of night shifts								
	≤2 night shifts/ month (n = 461)			3–4 night shifts/ month (n = 298)			≥5 night shifts/ month (n = 499)		
	HR	95% CI		HR	95% CI		HR	95% CI	
Crude model	1.96*	1.24	3.10	2.62*	1.66	4.13	1.36	0.84	2.21
Fully adjusted model[1]	1.51	0.95	2.42	1.93*	1.20	3.10	1.25	0.76	2.06

Reference group: day workers. CI, confidence interval; HR, hazard ratio.
[1]Adjusted for age, sex, educational level, household composition, occupation, occupational class, working (partly) from home, occupation involving frequent contact with others, BMI, and smoking.
* $p < 0.05$.

respectively (Table 4). However, no dose-response association could be observed between frequency of night shifts and SARS-CoV-2 incidence.

Discussion

In this large prospective study, night-shift workers had a 37% higher risk of testing positive for SARS-CoV-2 during the pandemic (March 2020-January 2021) than day workers. Based on the combined outcome of testing positive, being diagnosed by a physician, and/or believing one had a SARS-CoV-2 infection, night-shift workers did not have a higher SARS-CoV-2 incidence than day workers. Night-shift workers' increased risk of testing positive for SARS-CoV-2 was irrespective of night-shift work frequency.

In accordance with our results, two previous studies have also reported an increased risk of testing positive for SARS-CoV-2 among night-shift workers, with odds

ratios varying between 1.79 and 3.05 (Fatima et al. 2021; Rizza et al. 2021). These effect estimators are somewhat higher than in our study. This could be partly explained by the fact that these previous studies did not (or only to a limited extent) adjust for work variables, while adjusting for exposures at work substantially reduced the size of the effect estimator (with 33%) in the current study. Nevertheless, the combined results of our study and these previous studies indicate that night-shift workers are likely to be at higher risk to develop SARS-CoV-2 infection than day workers. Furthermore, an association between night-shift work and severe COVID-19, defined as testing positive for SARS-CoV-2 in hospital (Maidstone et al. 2021; Rowlands et al. 2021) and/or dying from COVID-19 (Rowlands et al. 2021) has also been reported previously. However, these studies and the study of Fatima et al. on SARS-CoV-2 incidence are all based on data from the UK Biobank in which night-shift work exposure was assessed years before the start of the pandemic (Fatima et al. 2021; Maidstone et al. 2021; Rowlands et al. 2021). This warrants further investigation in other cohorts that take into account workers' night-shift work status during the pandemic. The current study meets this need and is, to our knowledge, the first study with multiple measurements during one year of the COVID-19 pandemic to study SARS-CoV-2 incidence among night-shift workers.

Our main finding is in line with studies on the association between night-shift work and increased incidence of common (respiratory) infections conducted before the pandemic (Loef et al. 2019b; Mohren et al. 2002; Prather and Carroll 2021), which suggests that night-shift work may increase infection susceptibility in general. Possible mechanisms underlying this relation are impaired immune system functioning because of circadian rhythm disturbances and disturbed sleep among night-shift workers (Belingheri et al., 2021; Cermakian et al. 2022; Cuesta et al. 2016; Lim et al. 2020; Silva et al. 2020). Both the adaptive (or acquired) immune system and innate immune system have been found to display circadian rhythms (Cermakian et al. 2022). Therefore, circadian rhythm disturbances caused by night-shift work may affect immune system functioning (e.g. altered regulation of circulating cytokines, depressed proliferative responses of immune cells, and altered and desynchronized immune cell counts), which could potentially enhance infection susceptibility (Cermakian et al. 2022; Cuesta et al. 2016; Liu et al. 2021; Loef et al. 2019a). Furthermore, as evidence suggests that circadian clock pathways influence viral replication, disturbances of the circadian rhythm caused by night-shift work could also impact the extent to which a virus can infect and replicate in host cells (Zhuang et al. 2022). Reduced sleep and poorer sleep quality may further contribute to an impaired immune system functioning among night-shift workers (Mello et al. 2020; Richter et al. 2021). To illustrate, we previously found poorer sleep quality among night-shift workers in healthcare to explain part of their increased risk of respiratory infections (Loef et al. 2020). Earlier studies have also suggested that disturbed sleep may result in less awareness of health and safety measures and thereby increase infection susceptibility (Fatima et al. 2021; Maidstone et al. 2021). However, more research is needed to further unravel the physiological, and possibly behavioral, mechanisms linking night-shift work and infectious diseases.

When also including the vaccination implementation period January-March 2021 in the analysis, an increased SARS-CoV-2 incidence of 18% instead of 37% based on the criterion of testing positive was observed among night-shift workers. This lower increased incidence may be partly explained by the higher vaccination rates among night-shift workers compared to day workers, which has prevented infections to occur. However, more research is needed to confirm our findings in studies with preferably even longer follow-up periods and more information on vaccination status.

Interestingly, the combination measure of testing positive, being diagnosed by a physician, and/or believing one had a SARS-CoV-2 infection was not increased among night-shift workers. In the total study population, this combination measure resulted in a much higher incidence (13.5%) than the measure that only included testing positive for SARS-CoV-2 (2.3%). This can be explained by the fact that a relatively large part of the population indicated to believe they had had a SARS-CoV-2 infection and this component made up the vast majority of cases in the combination measure. However, this self-report component is the least reliable component of the combination measure, because it is highly subjective in comparison with the more objective test results and physician diagnosis. This is also reflected by the erratic course of the self-report component within the total Lifelines COVID-19 cohort (Lifelines Corona Research 2021a), indicating that people may believe to have had a SARS-CoV-2 infection in one questionnaire round and change their mind in the next round. Therefore, inclusion of the self-report component in the combination measure may have diluted its association with night-shift work.

No previous study has investigated frequency of night-shift work in relation to SARS-CoV-2 incidence. Although the strongest association with infection

incidence might be expected in the group that works the most night shifts, we did not observe a dose-response association between night-shift work frequency and testing positive for SARS-CoV-2. Similarly, in our earlier study on the association between night-shift work and respiratory infections, this was also not observed (Loef et al. 2019b). One explanation for the relatively low hazard ratio among night-shift workers working ≥5 night shifts/month could be a healthy worker effect (Knutsson 2004) where workers who are able to work a high number of night shifts/month represent a relatively healthy group. In addition, a disadvantage of the frequency measure used in the current study is that it does not take into account the number of consecutive night shifts and the number of rotations between day and night shifts, while these are important aspects of night-shift work (Garde et al. 2020). Earlier work on SARS-CoV-2 and common infections also shows that rotating night-shift work was associated with higher infection rates than permanent night-shift work (Maidstone et al. 2021; Prather and Carroll 2021), indicating that night-shift system may be of influence in the association with infection susceptibility, and should ideally be taken into account in future work.

Strengths and limitations

Strengths of this study are its prospective design and its follow-up period of one year with frequent measurements during the COVID-19 pandemic. To our knowledge, this is the first prospective study designed to study the association between night-shift work and SARS-CoV-2 infection that also takes into account workers' current night-shift work status during the pandemic. Another strength is the wide range of covariates that were taken into account in the analyses. Furthermore, the large, population-based study population adds to the generalizability of our findings.

A limitation of the current study lies in the fact that determinant, covariates, and outcome were measured by self-report. Participants were asked about their night-shift work status in the previous 3 months in round 7 and the previous 12 months in round 18. Therefore, this measure is susceptible to recall bias. However, since the recall period was relatively short and night-shift work significantly influences participants' life and is therefore easy to remember, we expect the impact of recall bias to be minimal.

In the current study, participants were labeled as night-shift workers if they reported to have worked night shifts during the first year of the COVID-19 pandemic, and as day workers if they reported they had not. However, no information on working hours was available to validate this categorization, which may have led to misclassification. For example, participants who worked late evening shifts (e.g. until 3 a.m.) may have not reported to work night shifts, while they would have been categorized as night-shift workers based on their working hours. This misclassification may have led to an underestimation of the association between night-shift work and testing positive for SARS-CoV-2.

For the outcome measure testing positive for SARS-CoV-2, positive test results reported by the participants were not confirmed by registration data. We also do not have information on whether positive test results were based on polymerase chain reaction tests or for example antigen tests. Furthermore, in the beginning of the pandemic, night-shift workers (who were often healthcare workers) may have had more access to testing facilities and may have been more motivated to get tested than day workers, which could have led to a differential underestimation of SARS-CoV-2 cases in day workers. However, it was only up until May 2020 that specific groups such as healthcare workers had increased access to testing facilities. From June onwards, all people in the Netherlands were able to get tested. Because SARS-CoV-2 infections were relatively rare in the beginning of the pandemic in the north of the Netherlands (Lifelines Corona Research 2021b), the impact of the limited access to testing during this period on the current findings is probably small. Furthermore, adjusting analyses for occupational class (including care and welfare occupations) will have further reduced this potential bias.

Conclusion

In conclusion, night-shift workers were more likely to test positive for SARS-CoV-2 than day workers in a large population of Dutch workers. This suggests that additional efforts may be needed to protect night-shift workers from SARS-CoV-2 infection and infectious diseases in general. In this context, vaccination and prevention strategies may need to be specifically targeted at night-shift workers. Furthermore, further research should be undertaken to study the mechanisms linking night-shift work and SARS-CoV-2 infection.

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Data availability statement

The data analyzed in this study were obtained from Lifelines (https://www.lifelines.nl/researcher). Requests to access these data should be directed to Lifelines Research Office (research@lifelines.nl).

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