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Body mass index and fitness in late adolescence and risk of cardiovascular disease, respiratory disease, and overall death after COVID-19

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Abstract

Objective: Since obesity and poor fitness appear to be unfavorable for both cardiovascular health and coping with viral infections such as COVID-19, they are of specific interest in light of the increased risk of cardiovascular and respiratory events now seen after infection with SARS-CoV-2. Therefore, the aim of the present study was to investigate how body mass index (BMI) and cardiorespiratory fitness (CRF) in late adolescence are associated with the risk of cardiovascular disease (CVD), respiratory disease, and mortality after COVID-19.

Methods: In this study, 1.5 million 18-year-old Swedish men with BMI and CRF measured during enlistment for military service 1968–2005 were included. Hospitalized and non-hospitalized COVID-19 cases were identified through the Patient Register or positive polymerase chain reaction tests, and age-matched with non-infected controls. CVD, respiratory disease, and mortality after COVID-19 were divided into <60days, 60-180days, >180days post-infection. Cox regression models were used.

Results: Hospitalized COVID-19 cases (n = 9839), compared to controls, had >10-fold, 50 to 70-fold, and >70-fold hazards of CVD, respiratory disease, and mortality over the initial 60 days post-infection with little variation across BMI or CRF categories. The elevated risks persisted at declining levels >180 days. For non-hospitalized COVID-19 cases (n = 181,822), there was a 4- to 7-fold increased acute mortality risk, and high CRF was associated with lower risk of post-infectious respiratory disease.

Conclusions: The high hazards of adverse outcomes during the first two months after COVID-19 hospitalization, and across BMI and CRF categories, declined rapidly but were still elevated after six months. Adolescent CRF was associated with respiratory disease after COVID-19 without hospitalization, which gives further support to the health benefits of physical activity.

KEYWORDS
body-mass index, cardiovascular disease, infections, physical fitness, pulmonary disease

1 | INTRODUCTION

Obesity and physical inactivity resulting in poor cardiorespiratory fitness (CRF) have a negative impact on overall health and predispose to cardiovascular morbidity and mortality.[1,2] During the COVID-19 pandemic, caused by SARS-CoV-2, it became evident that these risk factors also play an important role in the development of severe COVID-19.[3,4] Obesity causes mechanical ventilation challenges and increased oxygen requirements,[5,6] while low CRF reduces the cardiopulmonary reserve,[1] both of which increase the likelihood of severe infection. A defect in immune cell function, impaired host defense, and systemic inflammation are also seen with obesity and low CRF, and may be counteracted by healthy weight and regular physical activity.[7–10] Recently, high body mass index (BMI) and poor CRF in late adolescence were found to be associated with a more severe course of COVID-19 many years later.[11,12] Gaining excess weight at a young age often results in a lifetime of overweight or obesity,[13] and CRF is similarly known to track over time probably due to a consistently sedentary lifestyle.[12,14] Since obesity and poor fitness appear to be unfavorable for both cardiovascular health and coping with viral infections such as COVID-19, they are of specific interest in light of the increased risk of cardiovascular and respiratory events now seen after infection with SARS-CoV-2.

In a study of more than 5 million participants from the national healthcare databases of the U.S. Department of Veterans Affairs, patients who survived 30 days after COVID-19 had a several-fold increased risk for cardiovascular disease (CVD) compared with uninfected individuals, including hypertension (hazard ratio (HR) 15.18 (95% confidence interval (CI) 11.53–18.62)), cardiac arrhythmias (8.41 (7.18–9.53)), coronary atherosclerosis (4.38 (2.96–5.67)), and heart failure (3.94 (2.97–4.80)).[15] In the same cohort, both hospitalized and non-hospitalized COVID-19 patients had an increased risk of cardiovascular events 30 days after infection.[16] Support for this is derived from a Swedish register study of 86,742 COVID-19 patients presenting an increased risk of acute myocardial infarction and ischemic stroke during two weeks after COVID-19 in both hospitalized and non-hospitalized patients.[17] Higher rates of long-term respiratory disease were also detected in the aftermath of SARS-CoV-2 infection.[18] Taken together, previous reports have found an association between COVID-19 and the subsequent risk of severe cardiovascular and respiratory diseases.

Since high BMI and poor CRF in late adolescence are associated with severe COVID-19 many years later, it was hypothesized in the present study that weight and fitness status early in life could also affect the risk of post-infectious CVD, respiratory disease, and mortality in the acute, post-acute and long-term phases after COVID-19. Additionally, the impact of BMI and CRF on cardiovascular and respiratory outcomes following hospitalized and non-hospitalized individuals with COVID-19 was explored. To this end, national Swedish population registers were linked and more than 1.5 million Swedish men born after 1950, with data on BMI and CRF at conscription to military service, and who were alive at the beginning of the COVID-19 pandemic, were included.

2 | METHODS

2.1 | Study population

The study cohort included all individuals who were registered in the Swedish Military Service Conscription Register when they enlisted for military service between 1968 and 2005 (n = 1,949,891). Enlistment was mandatory for 18-year-old men in Sweden during the study period, except for prisoners or individuals with medical conditions incompatible with military service (2%–3% per year). Men with reused personal identification number (PIN) (n = 1233), women (n = 10,631), and men with missing information about the conscription test center (n = 118) were excluded. The cohort was divided into two analytic samples: one to analyze the effect of BMI and one to analyze the effect of CRF. In the first analytic sample, men with missing or invalid BMI (n = 188,392) and age <16 or >25 years (n = 3790) were excluded, while in the second analytic sample, men with missing fitness data (n = 203,065) and age <16 and >25 years (n = 5280) were excluded. Moreover, only men alive on 1 January 2020, and who had remained Swedish citizens were included (Figure S1). During the assessment at conscription, standardized physical examinations included measurements of weight, height, and blood pressure. Cardiorespiratory fitness was evaluated by a maximal bicycle ergometry test, in which the final work rate (Wmax) was divided by body mass (details described by Nordesjo and Schele).[19] A nine-level score based on Wmax served as a standardized measure of fitness. For the conscription years 2000–2005, the lowest three levels[1–3] were not recorded, and therefore, during this period, these levels were missing. Also, men with estimated values of fitness (considered as missing data) were excluded from the study. The final study cohort comprised 1,551,670 young men with valid data on BMI and 1,535,507 young men with available fitness data. To avoid registration bias in hospitalized COVID-19 cases, pre-existing comorbidities only, contracted before 1 January 2020, were collected from the National Patient Register, including CVD, respiratory disease, hypertension, diabetes mellitus, cancer, and obesity (Table S1). For diabetes mellitus, the National Diabetes Register was used for the identification of cases.

2.2 | Outcomes

The national health system in Sweden provides publicly financed health care at low cost to all citizens. Hospitalizations, hospital outpatient visits, and deaths are recorded in the National Patient Register and the Cause of Death Register, with diagnoses registered according to the International Classification of Diseases. Data from different sources were linked through the PIN unique to every Swedish citizen. Hospitalized patients with COVID-19 were identified through the National Patient Register and the Swedish Intensive Care Registry (https://www.icuregswe.org/en/) from 1 January 2020, to 1 January 2022. The diagnostic codes used were U07.1 (COVID-19, virus identified), and U07.2 (COVID-19, virus not identified). Hospitalizations were considered due to COVID-19 if 1) COVID-19 was the principal diagnosis or, 2) COVID-19 was a contributory diagnosis with a principal diagnosis probably related to COVID-19. These recognized principal diagnoses are listed in Table S2. Deaths due to COVID-19 during the same period were identified through the Cause of Death Register. Data on positive polymerase chain reaction tests for SARS-CoV-2 were collected from SmiNet (a registry for communicable disease surveillance in Sweden kept by the Swedish Public Health Agency) in order to identify non-hospitalized persons with COVID-19. Polymerase chain reaction testing was, however, severely restricted during the first months of the pandemic, and negative test results are not reported.

The index time was defined as the admission date of the first hospitalization due to COVID-19 in hospitalized individuals or as the date of laboratory-confirmed SARS-CoV-2 infection in non-hospitalized individuals. All had at least 60 days of follow-up. Incident cases of complications after being infected with SARS-CoV-2 were divided into three time periods: acute phase (<60 days after infection), post-acute phase (60–180 days after infection), and long-term phase (>180 days after infection until the end of follow-up). Late complications were divided into two groups: CVD (acute myocardial infarction, pulmonary embolism, heart failure, atrial flutter and fibrillation, hemorrhagic stroke, and ischemic stroke) and respiratory disease (interstitial lung disease, respiratory insufficiency, bronchitis, pulmonary emphysema, chronic obstructive pulmonary disease, asthma, and bronchiectasis) (Table S1). For each group, a cohort that was free of the related outcomes at the index time was identified to explore the risk of incident outcome during follow-up after COVID-19.

2.3 | Ethics statement

The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved the study (EPN Reference numbers: EPN Dnr 462-14 and Dnr 567-15; T 174-15/462-14; T 653-17/462-14; T196-17/567-15; T 2019–05875/462-14; T 2020–02420/462-14; T 2020-01325/462-14; T 2021-00797/462-14; T 2021–003310; T 2021–05638). The study conforms to the principles outlined in the Declaration of Helsinki. Because the individuals in the analyses were identified only through a code, informed consent was not possible or required for this type of study.

2.4 | Statistical analyses

Statistical calculations were performed using R ver. 4.0.3 software (http://www.R-project.org). Body mass index, calculated as weight in kg divided by height in m squared (kg/m^2), was divided into four categories (BMI 15 to <20 = underweight, 20 to <25 = normal weight, 25 to <30 = overweight, ≥30 = obesity), with BMI 20–25 as reference. Cardiorespiratory fitness was trichotomized into low,[1–4] moderate,[5–7] and high,[8,9] with high fitness as reference. For the analyses, each hospitalized or non-hospitalized individual with COVID-19 was age-matched weekly with controls without registered COVID-19 from the Swedish Military Service Register. Hospitalized patients were matched 1:8 and non-hospitalized individuals were matched 1:4. In a sub analysis, COVID-19 patients in the intensive care unit were matched with 20 controls without COVID-19. Cox regression models were used to estimate HR and 95% CI for late complications after COVID-19 by comparing COVID-19 patients (non-hospitalized and hospitalized) with age-matched controls. Conscription test center and age in 2020 were considered as confounders and adjusted for in model 1. In model 2, further adjustments were made for preexisting comorbidities registered before 1 January 2020. The models were not adjusted for the year of conscription due to the strong collinearity with age in 2020. Statistical significance was set at 0.05.

3 | RESULTS

3.1 | Study population

In the final BMI sample of 1,551,670 men, born between 1950 and 1987 and alive on 1 January 2020, excluding men with missing BMI data, 191,661 cases of COVID-19 until 1 January 2022, were identified. Of these, 9839 were hospitalized (78,708 age-matched controls), and 181,822 were non-hospitalized (727,231 age-matched controls). Hospitalized, compared to non-hospitalized, individuals with COVID-19 were older (mean age 55.9 (8.8) versus 49.5 (9.0) years old) and had more preexisting comorbidities, including hypertension (18.9% vs. 4.9%),CVD (15.5% vs. 4.9%), and diabetes mellitus (15.4% vs. 4.1%). Moreover, hospitalized COVID-19 patients had more comorbidities than controls without COVID-19 (33.6% vs. 19.3% had any comorbidity), whereas non-hospitalized COVID-19 individuals were more similar to their controls in terms of comorbidities (11.3% vs. 11.8%). Mean BMI at conscription was similar for hospitalized and non-hospitalized COVID-19 patients (22.4 (SD 3.4) kg/m^2 versus 22.2 (SD 3.0) kg/m^2) (Table 1). In the final CRF sample of 1,535,507 men, excluding those with missing fitness data, findings were essentially similar to those in the BMI sample (Table S3). Among hospitalized COVID-19 cases, 20.9% performed at the lowest fitness level, while 14.2% of the non-hospitalized cases performed at the lowest level (Table S3).

3.2 | BMI in late adolescence and incident CVD following COVID-19

There were 808 cases (8.2%) of incident CVD during the first 60 days after infection among hospitalized COVID-19 patients, with 86.5% occurring during the initial hospital stay (Table S4). Using multivariable Cox regression models, a substantially increased risk of developing CVD in the acute phase (<60 days) after hospitalization due to COVID-19 was found compared with controls, and was roughly similar across all BMI categories (Figure 1, Table S4). Moreover, the risk of CVD after COVID-19 persisted in the post-acute phase (60–180 days post-infection), where 94 cases of CVD and a higher event rate of 41.4 per 1000 person-years compared to 10.3 among controls were found, again without much variation across BMI categories. The long-term risk of CVD (63 events after 180 days) was significantly higher in hospitalized COVID-19 patients who were overweight in youth compared to normal-weight

TABLE 1 Demographic data on COVID-19 cases with age-matched controls (1:8 for hospitalized and 1:4 for non-hospitalized) included in the body mass index (BMI) analyses.

	BMI analytic sample (*n* = 1551670)			
	Hospitalized COVID-19 cases *n* = 9839	Controls *n* = 78708	Non-hospitalized COVID-19 cases *n* = 181822	Controls *n* = 727231
Age (years), mean (SD)	18.4 (0.8)	18.3 (0.6)	18.3 (0.6)	18.3 (0.6)
Height (cm), mean (SD)	179.2 (6.8)	179.1 (6.5)	179.6 (6.5)	179.3 (6.6)
Weight (kg), mean (SD)	72.0 (12.1)	69.7 (10.5)	71.6 (11.0)	70.9 (11.2)
BMI (kg/m^2), mean (SD)	22.4 (3.4)	21.7 (2.9)	22.2 (3.0)	22.0 (3.1)
Systolic blood pressure (mmHg), mean (SD)	127.9 (10.9)	128.4 (11.1)	128.5 (11.0)	128.7 (11.0)
Diastolic blood pressure (mmHg), mean (SD)	68.4 (9.8)	67.8 (9.9)	66.8 (9.9)	67.0 (9.9)
Age in 2020 (years), mean (SD)	55.9 (8.8)	55.9 (8.8)	49.5 (9.0)	49.5 (9.0)
BMI, n (%)				
BMI 15 to <20	2268 (23.1)	22093 (28.1)	40350 (22.2)	181249 (24.9)
BMI 20 to <25	5884 (59.8)	48283 (61.3)	117123 (64.4)	451474 (62.1)
BMI 25 to <30	1329 (13.5)	6959 (8.8)	20098 (11.1)	76410 (10.5)
BMI ≥30	358 (3.6)	1373 (1.7)	4251 (2.3)	18098 (2.5)
Preexisting comorbidities[a], *n* (%)				
Any comorbidity	3304 (33.6)	15203 (19.3)	20576 (11.3)	85869 (11.8)
Cardiovascular disease[b]	1529 (15.5)	6856 (8.7)	8825 (4.9)	36727 (5.1)
Respiratory diasease[c]	1046 (10.6)	3480 (4.4)	7428 (4.1)	29020 (4.0)
Hypertension	1856 (18.9)	7518 (9.6)	8899 (4.9)	37574 (5.2)
Diabetes mellitus[d]	1517 (15.4)	5731 (7.3)	7367 (4.1)	32082 (4.4)
Cancer	560 (5.7)	2780 (3.5)	3664 (2.0)	14667 (2.0)
Obesity diagnosis	406 (4.1)	1221 (1.6)	2162 (1.2)	8985 (1.2)

[a]Diagnoses received from the National Patient Register.

[b]Including acute myocardial infarction, pulmonary embolism, heart failure, atrial flutter and fibrillation, hemorrhagic stroke, and ischemic stroke.

[c]Including interstitial lung disease, respiratory insufficiency, bronchitis, pulmonary emphysema, chronic obstructive pulmonary disease, asthma, and bronchiectasis.

[d]Diagnoses received from the National Patient Register and the National Diabetes Register.

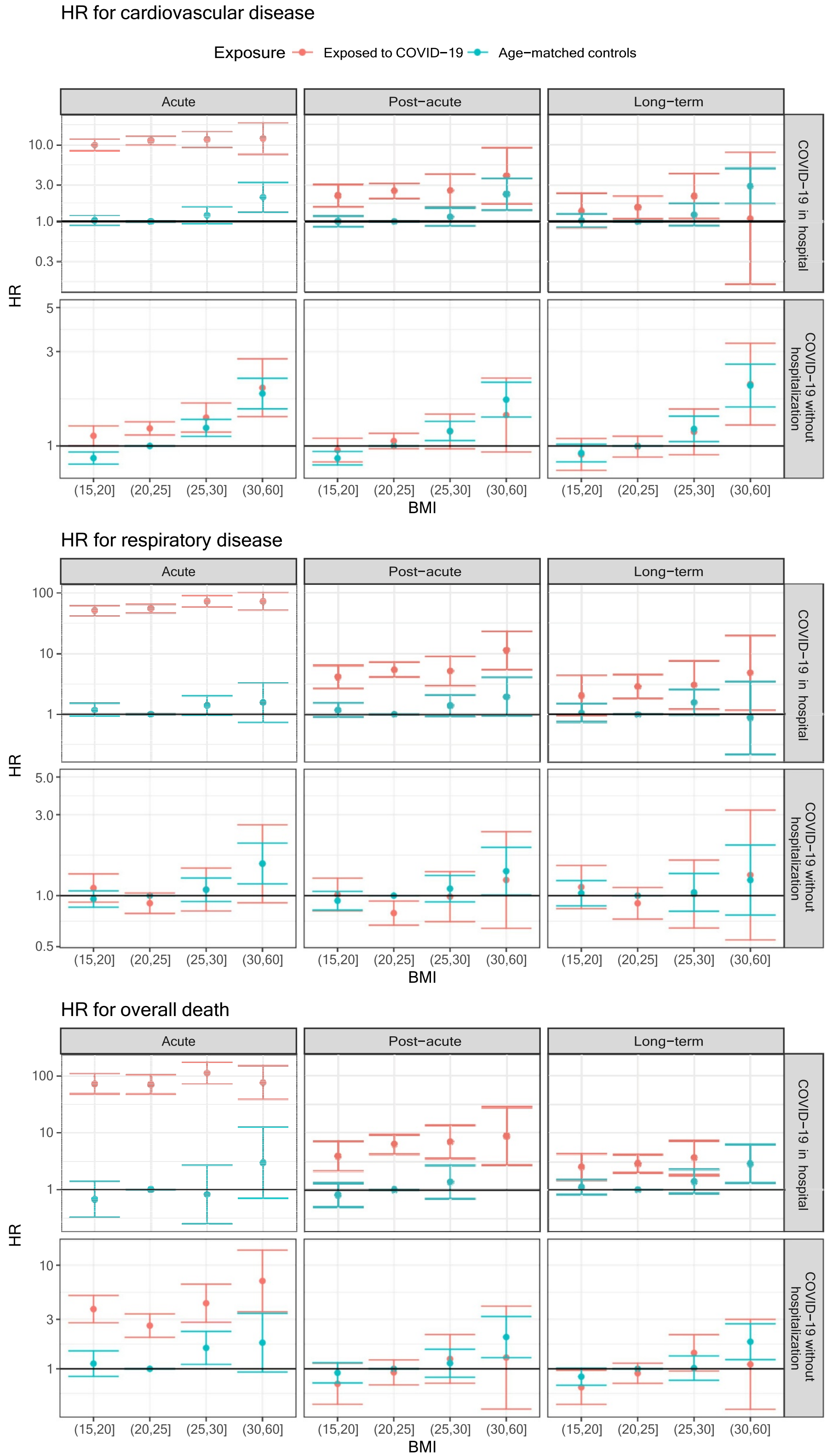

FIGURE 1 Hazard ratios (HR) and 95% confidence intervals for cardiovascular disease, respiratory disease, and overall death after COVID-19 divided by body mass index (BMI) category. Adjusted for test center, age in 2020, and preexisting comorbidities registered before 1 January 2020. The time periods post-infection are shown from left to right: acute (<60 days), post-acute (60–180 days), and long-term (>180 days). The top row within each outcome is COVID-19 cases in hospital and the bottom row is non-hospitalized COVID-19 cases. Red is individuals with COVID-19 and blue is age-matched controls without COVID-19.

controls, but not as pronouncedly as in earlier phases (Figure 1, Table S4). A subgroup analysis including only COVID-19 patients admitted to an intensive care unit showed that this group had a similar burden of CVD following infection as the entire group of hospitalized patients (Figure S2).

There were 446 cases (0.2%) of incident CVD during the initial 60 days after infection among non-hospitalized individuals (Table S5). Similar to hospitalized COVID-19 patients, non-hospitalized individuals with COVID-19 had an increased risk of CVD in the acute phase after infection compared with controls with BMI 20–25 at conscription (Figure 1, Table S5). Men who were obese at age 18 had a 2-fold increased risk of post-infection CVD, however, a similar risk increase was seen for obese controls. The 2-fold increased risk of obesity was persistent in the long-term phase (Figure 1, Table S5).

3.3 | CRF in late adolescence and incident CVD following COVID-19

Independent of CRF at conscription, hospitalization due to COVID-19 was associated with a 10-fold increased risk of CVD compared with controls during the first 60 days after infection in Cox regression models (Figure 2, Table S6). The risk increase persisted across all CRF categories in the post-acute phase but not in the long-term phase. Moreover, for non-hospitalized individuals with COVID-19, CRF in youth did not affect the risk of a post-infectious cardiovascular event (Figure 2, Table S7).

Taken together, hospitalization due to COVID-19 was the strongest risk factor for CVD in the acute and post-acute phases, whereas the long-term risk more than 180 days post-infection was significant but not as pronounced. Body mass index and fitness in adolescence were of minor importance for the risk of post-infectious CVD, with no systematic variation across categories of weight and fitness. For COVID-19 cases not requiring hospital care, there was an increased CVD risk in the acute phase but not in the post-acute and long-term phases. Compared to normal weight, obesity at age 18 was associated with a markedly increased risk of CVD in the acute phase in both non-hospitalized COVID-19 cases and their controls. Thus, obesity early in life appears to be a strong risk factor for CVD regardless of having had a previous infection or not. In hospitalized cases, severe COVID-19 per se was more important for the short-term risk of CVD, substantially overshadowing the effect of obesity.

3.4 | BMI in late adolescence and incident respiratory disease following COVID-19

During the first 60 days after infection, incident respiratory disease was seen in 1644 of the hospitalized COVID-19 patients (16.7%) (Table S4). Irrespective of BMI in late adolescence, using Cox regression models, there was an excessive risk for developing respiratory disease in the acute phase after hospitalization due to COVID-19 compared with controls. Infected patients who were overweight and obese in adolescence had a more than 70-fold increased risk of post-infectious respiratory disease compared to normal-weight controls (Figure 1, Table S4). The increased risk persisted in all BMI categories in the post-acute phase following infection, and the event rate was 37.2 per 1000 person-years among individuals with COVID-19 compared to 3.8 among controls. In the long-term phase, there was still an almost 5-fold increased risk of respiratory disease after COVID-19 among patients with adolescent obesity (HR 4.88 (1.20–19.79)). The event rate for individuals with COVID-19 during this period was 10.2 per 1000 person-years versus 3.5 among controls (Table S4).

The risk of respiratory disease among non-hospitalized COVID-19 patients, compared with controls, was not increased in any of the time periods following the infection. Moreover, BMI in adolescence did not affect the risk (Figure 1, Table S5).

3.5 | CRF in late adolescence and incident respiratory disease following COVID-19

Regardless of the CRF category, hospitalized patients with COVID-19 displayed an approximately 70-fold higher hazard in the Cox regression model for respiratory disease in the acute phase compared with their controls (Figure 2, Table S6). The increased risk of respiratory disease after hospitalization persisted in the post-acute and long-term phases even among those with high CRF previously in life. In a subgroup analysis, COVID-19 patients admitted to the ICU displayed a similar risk of respiratory disease after infection as the entire group of hospitalized patients, irrespective of youth CRF (Figure S3). Among non-hospitalized COVID-19 cases, low or moderate CRF in adolescence was associated with a slightly higher risk of respiratory disease in all three phases after SARS-CoV-2 infection compared to men with high CRF (Figure 2, Table S7).

3.6 | BMI in late adolescence and overall death after COVID-19

In total, 513 deaths (5.2%) among hospitalized COVID-19 cases were identified during the first 60 days after infection, of which 82.7% occurred during the initial hospital stay (Table S4). Using Cox regression, there was an increased mortality risk of hospitalized COVID-19 patients compared with their controls, particularly in the acute phase but also in the following two time periods, and across all BMI categories (Figure 1, Table S4). After COVID-19 hospitalization, the death rate per 1000 person-years was 24.0 in the post-acute phase compared to 3.6 among controls, and 12.5 in the long-term phase compared to 4.6 among controls (Table S4).

In the acute phase, 189 deaths (0.1%) were registered among non-hospitalized individuals with COVID-19, with the highest adjusted hazard of mortality after infection relative to controls seen among those who were obese in adolescence (HR 7.04 (3.55–13.97)) although with wide confidence intervals (Figure 1, Table S5). Meanwhile, no increased risk of death was seen in the post-acute and long-term phases following non-hospitalized COVID-19, regardless of BMI in youth (Figure 1, Table S5).

3.7 | CRF in late adolescence and overall death after COVID-19

Irrespective of CRF at a young age, hospitalization due to COVID-19 was associated with an increased mortality risk in the acute

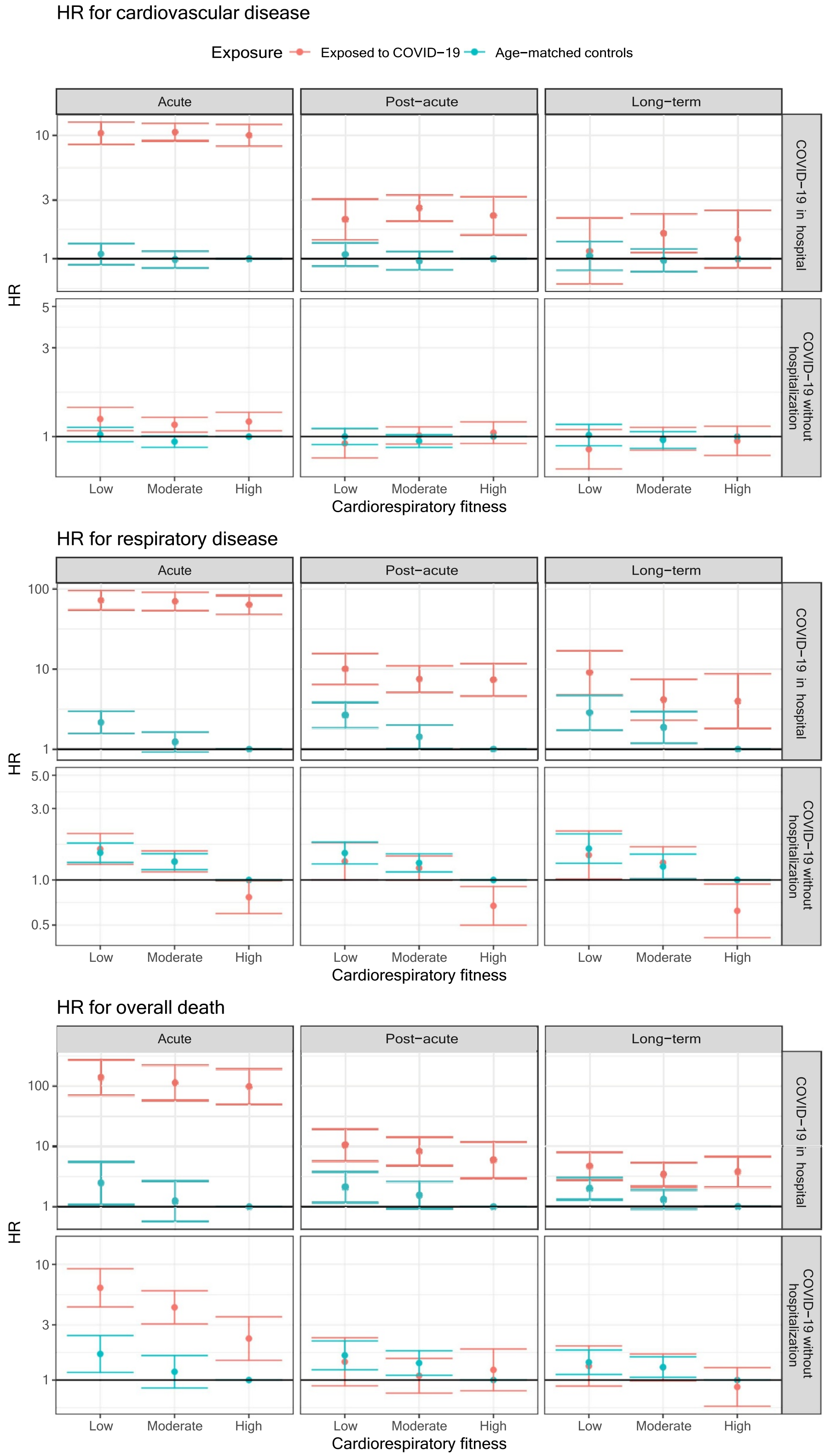

FIGURE 2 Hazard ratios (HR) and 95% confidence intervals for cardiovascular disease, respiratory disease, and overall death after COVID-19 divided by fitness category. Adjusted for test center, age in 2020, and preexisting comorbidities registered before 1 January 2020. The time periods post-infection are shown from left to right: acute (<60 days), post-acute (60–180 days), and long-term (>180 days). The top row within each outcome is COVID-19 cases in hospital and the bottom row is non-hospitalized COVID-19 cases. Red is individuals with COVID-19 and blue is age-matched controls without COVID-19.

phase up to 60 days following the infection compared to controls without COVID-19 in Cox regression models. The elevated risk persisted in hospitalized cases, regardless of adolescent CRF, in the post-acute and long-term phases (Figure 2, Table S6). For non-hospitalized cases, poorer CRF at conscription entailed a gradually increased risk of death in the acute phase but did not affect the mortality risk in the post-acute and long-term phases (Figure 2, Table S7).

4 | DISCUSSION

In this large register-based cohort study, comprising over 1,5 million men, it was found that BMI and CRF in late adolescence had no impact on the increased risk of post-infectious cardiovascular and respiratory disease as well as overall death, following severe COVID-19 requiring hospitalization. In cases with infection without the need of hospital care, an overall increased short-term risk of death was found over the first 2 months in comparison with non-infected controls, but with an increase in risk that did not vary systematically across BMI and fitness categories. Interestingly, low or moderate CRF in adolescence was associated with a higher risk of respiratory disease in all three phases after SARS-CoV-2 infection compared to high CRF.

Both obesity and physical inactivity with poor CRF established early in life are known to be persistent traits over the course of a lifetime,[13,14] probably representing unfavorable long-term lifestyle with negative impact on cardiovascular health and the ability to cope with viral infections such as COVID-19.[1–4,20–26] Our research group has previously found high BMI in late adolescence to be associated with severe COVID-19 many years later, with an elevated risk starting already at BMI $\geq$22.5 and with a gradual risk increase with increasing BMI.[11] Additionally, high CRF at a young age seems to protect from severe COVID-19 with OR 0.76 (95% CI 0.67–0.85) for hospitalization, and 0.61 (0.48–0.78) for intensive care.[12] However, the impact of weight and fitness status early in life on the risk of serious complications in the aftermath of COVID-19 has not been evaluated until now. To investigate these relationships, the Swedish Military Service Conscription Register was used, which provided us with objective data on BMI and CRF in late adolescence in a large population-based cohort.

In the present study, it was found that regardless of BMI and CRF at a young age, men who had been hospitalized due to COVID-19 had an increased risk of cardiovascular and respiratory disease, as well as overall death, within 180 days after infection. Likewise, Xie et al found that people who survived COVID-19 exhibited an increased 1-year risk of incident CVD irrespective of current obesity status and several CVD risk factors,[16] indicating that hospitalization due to severe COVID-19 poses far greater risk than other CVD risk factors. The underlying mechanisms may be direct virus-induced effects on endothelial cells such as dysfunction and apoptosis,[27] but also virally induced systemic inflammation (cytokine storm) leading to cardiovascular events through ACE2 receptor downregulation, platelet activation, and hypercoagulability,[28,29] all of which are difficult to counteract with high fitness and healthy weight.

In line with this, several recent reports have presented an increased risk of cardiovascular long-term complications after hospitalization due to COVID-19. Negreira-Caamano et al found that one out of 16 hospitalized patients suffered from a cardiovascular event such as acute coronary syndrome, cerebrovascular event, thrombosis, heart failure, and death in the first year after discharge from hospital.[30] One third of these occurred during the initial 30 days. Accordingly, in the present study, most cases were identified during the first 60 days. Another report showed higher rates of diabetes mellitus, respiratory disease,CVD, chronic kidney disease, and liver disease months after hospital admission compared to the general population not exposed to SARS-CoV-2, and not only in the elderly.[18] Similarly, a higher long-term risk of incident CVD, respiratory disease, and overall death following COVID-19 was observed in our cohort consisting of middle-aged men (mean age 55 years during the relevant period) without preexisting cardiovascular or respiratory disease. Studies on other viral infections, such as influenza, have also shown an increased risk of post-infectious cardiovascular events.[31,32] However, the risk seems to be higher with COVID-19 than with influenza,[33] which probably can be related to the exclusive pathophysiological mechanisms.[28]

Interestingly, a protective effect associated with high CRF on post-infectious respiratory disease following COVID-19 not in need of hospital care was found in the present study, which is, as far as we know, a novel finding. This is supported by previous reports suggesting that regular physical exercise improves the immune function and reduces systemic inflammation[34]—the main contributor to lung injury caused by SARS-CoV-2. Also, an enhanced cardiopulmonary reserve related to high CRF may contribute to an increased capacity to recover from a mild infection without contracting respiratory complications.[1] Moreover, an overall increased mortality risk in the acute phase after COVID-19 without hospitalization compared to non-infected controls was presented in the current study. Previous data have shown elevated adolescent BMI to be recognized as a risk factor for infectious disease mortality,[35] and also for cardiovascular death among Israeli conscripts.[36] Likewise, low aerobic fitness in late adolescence has been associated with an increased risk of early death from any cause.[37] In the present report, the statistical power was not sufficient to detect differences in mortality risk after non-hospitalized COVID-19 across BMI and fitness categories.

4.1 | Strengths and limitations

The strengths of this study are the population-based study design including large national registers with high coverage and validity,[38] and the complete follow-up of confirmed hospitalized and non-hospitalized COVID-19 cases, and later complications. The use of laboratory-confirmed diagnoses of non-hospitalized COVID-19 cases increases the reliability of the diagnosis. Moreover, weekly matching of controls without COVID-19 decreases the risk of time-specific factors during the pandemic, such as differences in testing procedures and vaccination availability. Even so, there are some limitations that must be highlighted. First, new virus subtypes evolving during the study period were not taken into consideration. Second, there were limited possibilities to test symptomatic individuals throughout the initial months of the pandemic. This might have caused underdiagnosing of COVID-19 cases, particularly mild cases not requiring hospital care, and if so, leading to an underestimation of the true risk of late cardiovascular and respiratory disease following infection with SARS-CoV-2. Also, cases of cardiovascular or respiratory disease after COVID-19 were collected from hospital registers only, and not from primary care, which likely underrates the number of those. A further limitation is the lack of generalizability regarding sex and ethnicity. It was not mandatory for women to conscript for military service during the study period, and the minor fraction of enlisting women was not representative of the general Swedish female population and was thus excluded in the present study. Because adult immigrants to Sweden are not conscripted, they were not included in this cohort. Therefore, our results may not be representative of other populations or for women. Also, data on BMI, fitness, and other lifestyle factors during life were not available in the study, making it impossible to exclude potential residual confounding by unmeasured factors between conscription and 2020.

4.2 | Conclusions

The high hazards of adverse outcomes seen over the first two months after being hospitalized with COVID-19, and across all BMI and CRF categories, declined rapidly but were still elevated after 6 months. In men with COVID-19 who were not hospitalized, mortality was substantially elevated over the first two months but not thereafter, with no significant variation across BMI and fitness categories. Interestingly, high adolescent CRF was associated with lower risk of post-infectious respiratory disease in all three time periods following COVID-19 not requiring hospital care, which gives further support to the health benefits of physical activity.

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AUTHOR CONTRIBUTIONS

Josefina Robertson, Maria Åberg, and Martin Adiels were responsible for the conception and design of the study as well as for the acquisition and analysis of data. Martin Adiels and Anders Muszta performed the statistical analyses. All authors took part in drafting the manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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