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The association of overweight, obesity, and long-term obesity with SARS-CoV-2 infection: a meta-analysis of 9 population-based cohorts from the Netherlands Cohorts Consortium

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BACKGROUND: Obesity may affect an individual's immune response and subsequent risk of infection, such as a SARS-CoV-2 infection. It is less clear whether overweight and long-term obesity also constitute risk factors. We investigated the association between the degree and duration of overweight and obesity and SARS-CoV-2 infection.
METHODS: We analyzed data from nine prospective population-based cohorts of the Netherlands Cohorts Consortium, with a total of 99,570 participants, following a standardized procedure. Body mass index (BMI) and waist circumference (WC) were assessed two times before the pandemic, with approximately 5 years between measurements. SARS-CoV-2 infection was defined by self-report as a positive PCR or rapid-antigen test or as COVID-19 ascertained by a physician between March 2020 and January 2023. For three cohorts, information on SARS-CoV-2 infection by serology was available. Results were pooled using random-effects meta-analyses and adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements.
RESULTS: Individuals with overweight ($25 \leq BMI < 30$ kg/m^2) (odds ratio (OR) $= 1.08$, 95%-confidence interval (CI) 1.04-1.13) or obesity (BMI ≥ 30 kg/m^2) (OR $= 1.43$, 95%-CI 1.18–1.75) were more likely to report SARS-CoV-2 infection than individuals with a healthy body weight. We observed comparable ORs for abdominal overweight (men: 94 cm$\leq$WC < 102 cm, women: 80 cm$\leq$WC < 88 cm) (OR $= 1.09$, 95%-CI 1.04–1.14, $I^2 = 0\%$) and abdominal obesity (men: WC ≥ 102 cm, women: WC ≥ 88 cm) (OR $= 1.24$, 95%-CI 0.999–1.55, $I^2 = 57\%$). Individuals with obesity long before the pandemic, but with a healthy body weight or overweight just before the pandemic, were not at increased risk.
CONCLUSION: Overweight and obesity were associated with increased risk of SARS-CoV-2 infection with stronger associations for obesity. Individuals with a healthier weight prior to the pandemic but previous obesity did not have an increased risk of SARS-CoV-2, suggesting that weight loss in those with obesity reduces infection risk. These results underline the importance of obesity prevention and weight management for public health.

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INTRODUCTION

Obesity is associated with both the risk and severity of respiratory infections, which was clearly observed during the Swine flu pandemic in 2009 and the more recent COVID-19 pandemic [1, 2]. The underlying mechanism relates to an impaired immune response in those with obesity [3]. Therefore, obesity may increase the risk of getting infected with SARS-CoV-2, the virus that causes COVID-19 [4]. Results from a meta-analysis including 20 studies showed that individuals with obesity have a 46% higher odds of testing positive for SARS-CoV-2 than individuals with a healthy weight [5].

The risk of obesity-related comorbidities such as type 2 diabetes may depend on the length of time an individual has obesity, possibly due to longer exposure to inflammation and metabolic dysregulation [6, 7]. To our knowledge, the association between duration of obesity and SARS-CoV-2 infection has not yet been explored. An explanation for this may be the hospital-based designs of previous studies in which information on body weight was collected only during hospital admission [5]. In contrast, population-based cohorts often have repeatedly collected information on obesity-measures during a longer period prior to the pandemic. Therefore, these studies are ideally suited to investigate SARS-CoV-2 infection risk among individuals with long-term obesity [8]. Furthermore, population-based studies contribute to identifying high-risk groups for mild SARS-CoV-2 infections for which hospitalization was not necessary, but for which public health impact could be considerable.

Besides obesity, overweight might also increase SARS-CoV-2 infection risk [9, 10]. Today, more than a third of the population in Western countries are overweight, defined as a body mass index (BMI) ≥ 25 and <30 kg/m^2 [11]. Given this substantial prevalence, a higher risk of infection among those with overweight may have a large societal impact due to an increased burden of disease, and therefore warrants further study. Furthermore, one may hypothesize that the amount of abdominal fat (of which waist circumference (WC) is an indicator) is more important in relation to SARS-CoV-2 infection than general obesity (of which BMI is an indicator), because of its higher secretion rate of inflammation markers and worse immune response [12, 13]. So far, however, research on abdominal obesity and SARS-CoV-2 infection is scarce, and the few available studies into this topic have reported mixed results [14–16].

Therefore, the aim of this study was to investigate the association between the degree and the duration of (abdominal) overweight and obesity and the risk of SARS-CoV-2 infection among a large sample of Dutch adults by meta-analyzing data from nine population-based prospective cohort studies.

METHODS

Study population and design

We conducted a meta-analysis using data from nine prospective cohorts of the Netherlands Cohorts Consortium (NCC) [17]. NCC aims to include all population-based and population-representative Dutch cohort studies that provide longitudinal clinical phenotyping and biomedical data for research into the determinants of multimorbidity. The NCC currently consists of >450,000 participants from the Netherlands originating from 11 cohort studies. Two NCC cohorts could not participate in the current study because they did not collect data on infection with SARS-CoV-2. In the other nine cohorts, all active participants (n = 8) or a random subsample of active participants (n = 1) were invited to take part in one or more follow-up rounds during the pandemic. Table 1 presents an overview of the characteristics of the participating nine NCC cohorts. A brief description of the cohorts can be found in Supplementary Text S1 and a detailed description can be found in the cohort profiles [18–32]. All cohort studies were approved by an Institutional Review Board and written informed consent was obtained from all participants. Participating cohorts were asked to select adult participants with information on BMI and SARS-CoV-2 infection. Participants with missing information on age, sex and educational level were excluded from the study population. In total, 99,570 participants were included in the current study (see Fig. S1 for a flowchart of study participants). Per cohort, analyses were conducted by researchers of the individual cohorts following instructions from a standardized procedure.

Exposures

Assessment of BMI and WC was conducted between 2000 and 2020, with specific periods of data collection varying between the cohorts (Table 1). Four exposure variables were used in this meta-analysis.

1. *Most recent BMI status* before the COVID-19 pandemic was defined as the most recent BMI measurement available before March 2020 (start of the COVID-19 pandemic in the Netherlands). International cut-off points were used to classify participants' BMI: healthy body weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) [33].
2. *Long-term obesity* was defined based on two BMI measurements before March 2020 and preferably with a period of about 5 years between both measurements. For all nine cohorts two measurements were available. Long-term obesity was classified into: 1) no obesity at both measurements (reference group), 2) only former obesity, i.e. obesity at the least recent measurement, but not the most recent measurement, 3) only recent obesity, i.e. obesity at the most recent measurement, but not the least recent measurement, and 4) long-term obesity, i.e. obesity at both measurements.
3. *Most recent WC status* before the pandemic was defined as the most recent WC measurement available before March 2020. For eight cohorts information on waist circumference was available. Sex-specific cut offs were used to classify participants' WC: healthy waist (men: WC < 94 cm, women: WC < 80 cm), abdominal overweight (men: 94 cm≤WC < 102 cm, women: 80 cm≤WC < 88 cm), and abdominal obesity (men: WC ≥ 102 cm, women: WC ≥ 88 cm) [33].
4. *Long-term abdominal obesity* was defined based on two WC measurements before March 2020 and preferably with a period of about 5 years between both measurements. For six cohorts two WC measurements were available. Long-term abdominal obesity was classified into: 1) no abdominal obesity at both measurements (reference group), 2) only former abdominal obesity, i.e. abdominal obesity at the least recent measurement, but not the most recent measurement, 3) only recent abdominal obesity, i.e. obesity at the most recent measurement, but not the least recent measurement, and 4) long-term abdominal obesity, i.e. abdominal obesity at both measurements.

Outcomes

Information on SARS-CoV-2 infection was collected between March 2020 and January 2023. The first outcome (**self-reported SARS-CoV-2 infection**) was based on having at least one SARS-CoV-2 infection (yes vs. no) confirmed with a positive PCR or rapid-antigen test based on self-report or ascertained by a physician based on self-report between March 2020-January 2023 (specific period depends on the individual cohort, see Table 1). Five cohorts collected information on SARS-CoV-2 infection once (Table 1). For the other cohorts, the mean number of SARS-CoV-2 infection measurements varied between 1.8-13.7 times per participant. The second outcome (**SARS-CoV-2 infection by serology**) was based on having at least one positive serological test for SARS-CoV-2 (yes vs. no) between March 2020-January 2022 (Table 1). SARS-CoV-2 infection by serology was available for three cohorts based on measurements in blood samples collected within the cohorts or based on linkage to existing registration data.

Confounders

Age (in years on March 1, 2020), sex and educational level were included as confounders, because men, older adults and the lower educated are known high-risk groups for (severe) COVID-19 [34, 35]. For one cohort (HELIUS), ethnicity was additionally included, because this cohort oversampled participants with a migration background [36]. Lastly, the available number of SARS-CoV-2 infection measurements was included, because the probability of reporting SARS-CoV-2 positive at least once is greater if the number of SARS-CoV-2 infection measurements is higher.

Table 1. Assessment of overweight and obesity and SARS-CoV-2 infection in the 9 cohorts included in the current meta-analysis.

Cohort	n (% response[a])	Assessment of overweight and obesity		Assessment of SARS-CoV-2 infection		
		Methodology	Period of data collection	Methodology	Period of data collection	Number of data collections (mean ± SD)
Doetinchem Cohort Study [22, 26, 31]	1238 (34%)	Measured	In 2003–2007, 2008–2012, 2013–2017 and 2018	Self-reported positive test and serology	March 2021–January 2022	3.4 ± 0.8
HELIUS [29]	2401 (22%)	Measured	In 2011–2015 and 2019–2020	Self-reported positive test or physician diagnosed infection and serology	June 2020–June 2021	1.8 ± 0.4
LASA [19, 20]	1280 (86%)	Measured	In 2011–2013, 2015–2016 and 2018–2019	Self-reported positive test or physician-diagnosed infection	June 2020–November 2022	2.5 ± 0.8
Leiden Longevity Study [32]	913 (70%)	Self-reported weight and height (no WC information)	In 2006–2008 and 2020–2021	Self-reported positive test or physician diagnosed infection	October 2020–July 2021	1
Lifelines [25, 27]	74049 (53%)	Measured	In 2007–2013, 2014–2017 and 2019–2020	Self-reported (physician-diagnosed) infection (until 12-2020) and positive test (from 12-2020 onwards)	March 2020–October 2022	13.7 ± 10.4
NTR [24, 30]	7647 (13%)	Measured and self-reported (dependent on round), WC always measured	In 2000–2016 and 2004–2020	Self-reported (physician diagnosed) infection	April 2020–August 2020	1
The Maastricht Study [28]	4591 (58%)	Self-reported weight and measured height and WC	In 2010–2016 and 2015–2020	Self-reported positive test	June 2021–January 2023	1
The NEO study [18]	3846 (61%)	Measured in 2008–2012; self-reported in 2020–2021	In 2008–2012 and 2020–2021	Self-reported positive test or physician diagnosed infection	February 2020–December 2020	1
The Rotterdam Study [21, 23]	3605 (41%)	Measured	In 2002–2005 and 2014–2017	Self-reported (physician diagnosed) infection and serology	April 2020–July 2020 (serology: until 01-2022)	1

HELIUS Healthy Life in an Urban Setting study, *LASA* Longitudinal Aging Study Amsterdam, *NEO* Netherlands Epidemiology of Obesity, *NTR* The Netherlands Twin Register, *WC* waist circumference.
[a] Proportion of individuals who were included in the meta-analysis out of the total number of individuals who were invited to participate in the COVID-19 sub-study of the particular cohort.

Statistical analysis

Analyses of the individual cohorts.   Analyses by the individual cohorts were performed between March-September 2023. Logistic regression analyses were conducted for all four exposures and the two outcome measures separately. The analyses were adjusted for age, sex, educational level, number of SARS-CoV-2 infection measurements, and, if applicable, ethnicity. Odds ratios (ORs) and 95% confidence intervals (95%-CI) were reported. To assess the potential for bias in each cohort specific analysis, the risk of bias for each included cohort was assessed using the ROBINS-E tool [37].

Meta-analysis.   ORs and 95%-CIs of the individual cohorts were transformed into log metrics. Subsequently, random-effects meta-analyses were conducted using restricted maximum likelihood as estimation method, as previously recommended [38, 39]. Individual study effects were pooled by applying the inverse variance method. Overall ORs and 95%-CIs were reported and forest plots were constructed. The I^2 statistic was evaluated to assess between-study heterogeneity. Based on the Cochrane Handbook cut-off points, an I^2 of 0%–40% was considered low heterogeneity, 30%–60% moderate heterogeneity, 50%–90% substantial heterogeneity, and 75%–100% high heterogeneity [40].

As 74% of all participants included in this meta-analysis were from one cohort (Lifelines), the meta-analyses were also performed without Lifelines to examine to which extent results were driven by this cohort.

Sensitivity analysis.   Sensitivity analyses were conducted on individual cohorts only for the most recent measurement of BMI and WC and results were meta-analyzed thereafter. First, we stratified for measurement before January 2021 and from January 2021 onwards. By doing so, we differentiated between the phase of the pandemic where vaccines were available, as the Dutch SARS-CoV-2 vaccination campaign started on January 6, 2021. In addition, stratification based on time point is also relevant because there were other variants of the SARS-CoV-2 virus prevalent over time [41]. Furthermore, the availability of rapid-antigen tests changed over time. All may have influenced the results.

Analyses were also stratified by sex (men vs. women) and age (< 70 years vs. ≥70 years), because men and older adults are known high-risk groups for (severe) COVID.

Analyses of the individual cohorts were conducted using IBM SPSS Statistics (IBM Corp, NY) and STATA (College Station, TX). STATA was used to conduct the meta-analyses. A p value < 0.05 was considered statistically significant.

RESULTS

Description of the cohorts

Participant characteristics of the nine cohorts are described in Table S1. The number of participants varied between 913 and 74,049 participants, resulting in a total of 99,570 participants. In total, 60% of the participants were women (range: 49.8%–71.7%). The mean age ranged between 48.1 and 74.2 years. On average, 39.6% of the participants had overweight (range: 29.5%–46.9%) and 16.7% had obesity (range: 9.8%–37.0%) on the most recent measurement before the pandemic. The percentage of participants with a self-reported SARS-CoV-2 infection varied between 0.9% and 24.7% across the nine cohorts (Table S1), depending on the timing and number of SARS-CoV-2 infection measurements (Table 1). In three cohorts with available data on serology (i.e. Doetinchem Cohort Study, HELIUS, The Rotterdam Study), the SARS-CoV-2 infection rate varied between 9.8% and 22.2%. The results of the risk of bias assessment of the 9 included cohorts is shown in Supplementary Text S2.

Association between overweight and SARS-CoV-2 infection

Overweight status.   The pooled results of the nine cohorts showed that individuals with overweight had a 1.08 times higher odds of a self-reported SARS-CoV-2 infection than individuals with a healthy body weight (OR = 1.08, 95%-CI 1.04–1.13, $I^2 = 0\%$) (Table 2, Fig. 1). The narrow confidence interval of this OR was largely due to the weight of Lifelines, and after excluding this cohort, the OR was similar, albeit no longer statistically significant (OR = 1.14, 95%-CI 0.99–1.30, $I^2 = 0\%$) (Table S2). The higher odds of having a SARS-CoV-2 infection among participants with overweight was not observed when using data from serological tests from three cohorts (OR = 1.02, 95%-CI 0.79–1.31, $I^2 = 54\%$) (Table 2, Fig. S4a).

Individuals with obesity were also more likely to report a SARS-CoV-2 infection than individuals with a healthy body weight (OR = 1.43, 95%-CI 1.18–1.75, $I^2 = 56\%$) (Table 2, Fig. 2). The effect estimate was hardly affected after excluding Lifelines (OR = 1.52, 95%-CI 1.29–1.79, $I^2 = 0$) (Table S2). Higher odds for SARS-CoV-2 infection among individuals with obesity compared to individuals with a healthy weight were also observed by serological testing (OR = 1.22, 95%-CI 1.01–1.47, $I^2 = 0\%$) (Table 2, Fig. S4b).

For abdominal overweight, we observed similar associations with SARS-CoV-2 infection (based on both self-report and serology) as for general overweight based on BMI (Table 2, Fig. S2a). For abdominal obesity, however, slightly lower ORs were observed than for general obesity (Table 2). Individuals with abdominal obesity had a 1.24 times higher odds of a self-reported SARS-CoV-2 infection than individuals with a healthy waist (95%-CI 0.999–1.55, $I^2 = 57\%$) (Table 2, Fig. S2b). After excluding the Lifelines cohort, this OR was 1.35 (95%-CI 1.06-1.71, $I^2 = 28\%$) (Table S2).

Long-term obesity.   The results stratified on duration of obesity showed that individuals with recent obesity only (i.e. obesity on the most recent, but not on the least recent measurement prior to the pandemic) had a higher odds of SARS-CoV-2 infection than individuals without obesity on both measurements (OR = 1.51, 95%-CI 1.– 01–2.26, $I^2 = 57\%$ by self-report and OR = 1.61, 95%-CI 1.18–2.19, $I^2 = 0\%$ by serology) (Table 2 and Fig. 3 and S6b). A similar higher odds for a self-reported SARS-CoV-2 infection was observed among individuals with long-term obesity (i.e. obesity on both measurements) (OR = 1.48, 95%-CI 1.15–1.91, $I^2 = 65\%$) (Table 2, Fig. 4), though this was not observed for SARS-CoV-2 infection by serology (OR = 1.18, 95%-CI 0.95–1.46, $I^2 = 0\%$) (Fig. S6c). No association between former obesity only (i.e. obesity on the least recent, but not on the most recent measurement) and SARS-CoV-2 infection was found (Table 2, Fig. 5 and S6a).

The results regarding duration of abdominal obesity were similar to those of general obesity based on BMI, except for individuals with recent abdominal obesity only. For this group, a statistically significant higher odds of SARS-CoV-2 infection by serology was observed (OR = 1.49, 95%-CI 1.13–1.97) (Table 2, Fig. S7b), but not for SARS-CoV-2 infection by self-report (OR = 1.17, 95%-CI 0.90–1.52) (Fig. S3b). For general obesity, this association was found for both SARS-CoV-2 infection outcomes (by self-report and serology).

Sensitivity analysis

Stratification before January 2021 vs. January 2021 onwards.   Table S3 and Fig. S8 show that the effect estimates of the association between overweight and self-reported SARS-CoV-2 infection were similar before 2021 and from 2021 onwards. However, for obesity, the association was stronger before 2021 (OR = 1.59, 95%-CI 1.24–2.04, $I^2 = 44\%$) than from 2021 onwards (OR = 1.17, 95%-CI 0.96–1.43, $I^2 = 39\%$). For abdominal obesity, the same pattern was observed, but the differences in the magnitude of the associations between the two time periods was smaller (Table S3, Fig. S9). Results based on serology data, showed a similar pattern for the association with overweight (based on BMI or WC) before 2021 and from 2021 onwards (Table S4). However, these results should be interpreted with caution as they mostly rely on data from only two cohorts.

Table 2. Results of random-effects meta-analysis of the association between overweight/obesity and SARS-CoV-2 infection[a].

Exposures	SARS-CoV-2 positive by self-report			SARS-CoV-2 positive by serology		
	OR (95% CI)[b,c]	n[d]	I^2 (%)[e]	OR (95% CI)[b,c]	n	I^2 (%)[e]
Most recent BMI status[f]						
Healthy weight	1 (ref)			1 (ref)		
Overweight	**1.08 (1.04–1.13)**	9	0	1.02 (0.79–1.31)	3	54
Obesity	**1.43 (1.18–1.75)**	9	56	**1.22 (1.01–1.47)**	3	0
Long-term obesity[g]						
No obesity	1 (ref)			1 (ref)		
Only former obesity	1.08 (0.94–1.25)	8	1	1.33 (0.89–1.97)	3	0
Only recent obesity	**1.51 (1.01–2.26)**	9	57	**1.61 (1.18–2.19)**	3	0
Long-term obesity	**1.48 (1.15–1.91)**	9	65	1.18 (0.95–1.46)	3	0
Most recent WC status[h]						
Healthy waist	1 (ref)			1 (ref)		
Abdominal overweight	**1.09 (1.04–1.14)**	8	0	1.01 (0.79–1.28)	3	31
Abdominal obesity	1.24 (0.999–1.55)	8	57	1.15 (0.92–1.44)	3	33
Long-term abdominal obesity[g]						
No abdominal obesity	1 (ref)			1 (ref)		
Only former abdominal obesity	1.04 (0.96–1.12)	5	0	0.86 (0.58–1.28)	3	33
Only recent abdominal obesity	1.17 (0.90–1.52)	6	22	**1.49 (1.13–1.97)**	3	0
Long-term abdominal obesity	**1.31 (1.01–1.70)**	6	50	1.16 (0.96–1.39)	3	0

BMI body mass index, *CI* confidence interval, *n* number of studies, *OR* odds ratio, *ref* reference, *WC* waist circumference.
[a]Figs. 1 and 2 and Supplementary Figs. S2–S7 show the accompanying forest plots of these results.
[b] **Bold** indicates statistical significance according to 95% CI.
[c] Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).
[d] Some results are based on less than nine studies, because waist circumference was not measured (twice) and/or because no cases were available in a particular exposure category.
[e] Heterogeneity can be considered low when $I^2 = 0\%$–40%, moderate when $I^2 = 30\%$–60%, substantial when $I^2 = 50\%$–90%, and high when $I^2 = 75\%$–100%.
[f] Healthy weight: BMI < 25 kg/m²; overweight: BMI ≥ 25 and <30 kg/m²; obesity: BMI ≥ 30 kg/m².
[g] No obesity: no obesity at both measurements; only former obesity: obesity at the least recent measurement, but not the most recent measurement; only recent obesity: obesity at the most recent measurement, but not the least recent measurement; long-term obesity: obesity at both measurements.
[h] Healthy waist: WC < 94 cm among men and <80 cm among women; abdominal overweight: WC ≥ 94 cm and <102 cm among men and ≥80 cm and 88 cm among women; abdominal obesity: WC ≥ 102 cm among men and ≥88 cm among women.

Study		OR with 95% CI	Weight (%)
Doetinchem Cohort Study		0.60 [0.32, 1.10]	0.43
HELIUS		1.37 [0.96, 1.95]	1.27
LASA		0.97 [0.65, 1.45]	1.00
Leiden Longevity Study		1.24 [0.43, 3.59]	0.14
Lifelines		1.08 [1.03, 1.12]	91.45
NTR		1.15 [0.89, 1.49]	2.41
The Maastricht Study		1.21 [0.96, 1.53]	2.90
The NEO study		0.57 [0.21, 1.53]	0.16
The Rotterdam Study		1.76 [0.77, 4.03]	0.23
Overall		1.08 [1.04, 1.13]	
Heterogeneity: $I^2 = 0.00\%$			

0.12 0.25 0.50 1.00 2.00 4.00 8.00
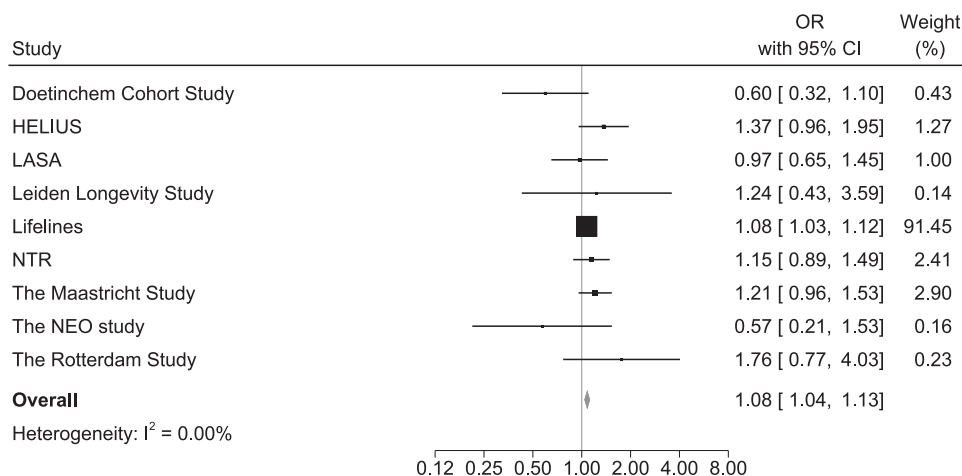
Fig. 1 Forest plot of the association between overweight (vs. healthy weight) and SARS-CoV-2 infection measured by self-report. CI confidence interval, HELIUS Healthy Life in an Urban Setting study, LASA Longitudinal Aging Study Amsterdam, NEO Netherlands Epidemiology of Obesity, NTR The Netherlands Twin Register, OR odds ratio. Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).

Stratification by sex and age. We observed similar results for men and women (Table S5). Stratifying the results by age did not lead to different conclusions for individuals aged <70 vs. ≥70 years for (abdominal) overweight and abdominal obesity (Table S6). However, the association between obesity based on BMI and self-reported SARS-CoV-2 infection seemed to be stronger in individuals ≥70 years than in individuals <70 years (OR 2.15, 95%-CI 1.30–3.55, $I^2 = 28\%$ vs. OR 1.35, 95%-CI 1.09–1.68, $I^2 = 0\%$).
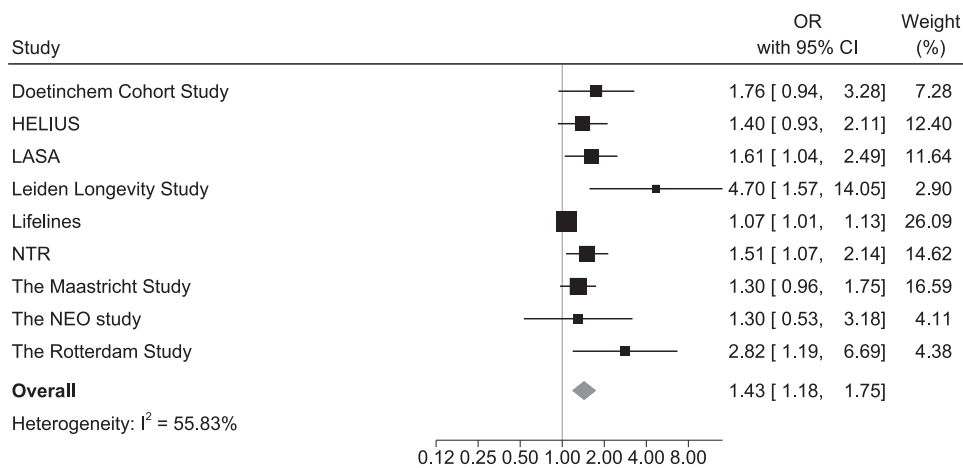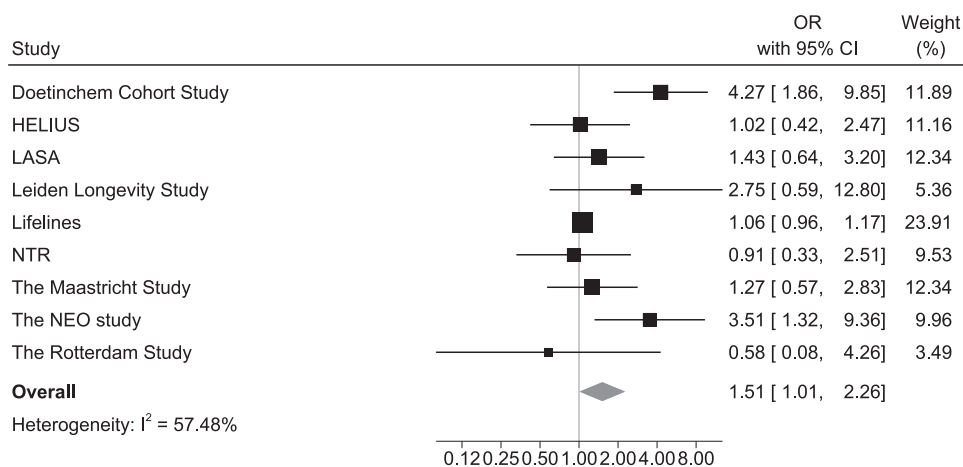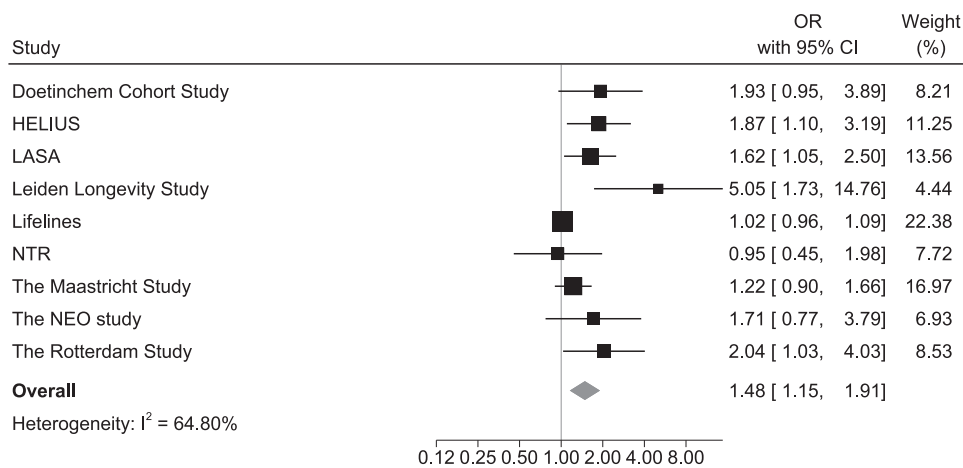
Fig. 2 Forest plot of the association between obesity (vs. healthy weight) and SARS-CoV-2 infection measured by self-report. CI confidence interval, HELIUS Healthy Life in an Urban Setting study, LASA Longitudinal Aging Study Amsterdam, NEO Netherlands Epidemiology of Obesity, NTR The Netherlands Twin Register, OR odds ratio. Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).
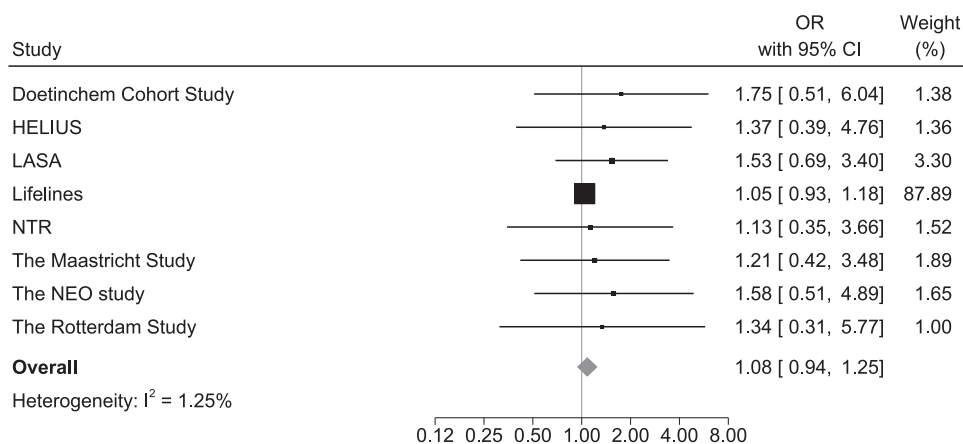

Fig. 3 Forest plot of the association between only recent obesity (vs. no obesity) and SARS-CoV-2 infection measured by self-report. CI confidence interval, HELIUS Healthy Life in an Urban Setting study, LASA Longitudinal Aging Study Amsterdam, NEO Netherlands Epidemiology of Obesity, NTR The Netherlands Twin Register, OR odds ratio. Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).

DISCUSSION

In this meta-analysis of nine population-based cohort studies, individuals with obesity were at increased risk of SARS-CoV-2 infection compared to those with a healthy weight. To a lesser extent, this risk was also increased among individuals with overweight. The higher odds of SARS-CoV-2 infection was primarily observed in individuals with obesity at the most recent measurement prior to the COVID-19 pandemic. Individuals who previously had obesity, but no longer had obesity at the most recent measurement before the pandemic did not have an increased risk of SARS-CoV-2 infection. The association between obesity and SARS-CoV-2 infection appeared to be stronger in the period before 2021 than from 2021 onwards, when vaccines became available.

Our findings are in line with the results of an earlier meta-analysis that reported an increased risk of testing positive for SARS-CoV-2 among individuals with obesity [5]. The current study extends this work by covering a longer follow-up period during the COVID-19 pandemic and including other overweight-related exposures which have been studied less frequently. Two previous studies reported an association between overweight and SARS-CoV-2 infection [9, 10], and the present study supports their

findings. In the present study, the association between overweight and SARS-CoV-2 infection was weaker than that of obesity. The effects of overweight were also less consistent, as no association was found when measuring SARS-CoV-2 infection by serology. However, serology was only available among 7200 individuals from three cohorts. A study among 235,928 participants of the UK Biobank cohort did find an association based on **serology**, but all data for this study were obtained in the beginning of the pandemic [9]. Therefore, more studies using data on SARS-CoV-2 obtained during a longer period of the pandemic are needed to confirm whether overweight is associated with higher SARS-CoV-2 infection susceptibility.

The current meta-analysis also identified abdominal overweight/obesity as possible risk factors for SARS-CoV-2 infection, but this was also not fully supported by serology data. Two earlier studies provided evidence for a (causal) association between abdominal fat and susceptibility for SARS-CoV-2 infection [14, 16]. Body fat, in particular visceral fat, is associated with high secretion of inflammation markers such an adipokines and cytokines and probably therefore a higher infection risk [12, 13]. Therefore, one could speculate that effect estimates of associations between WC, as a marker for abdominal fat, and SARS-CoV-2 infection would be

Fig. 4 Forest plot of the association between long-term obesity (vs. no obesity) and SARS-CoV-2 infection measured by self-report. CI confidence interval, HELIUS Healthy Life in an Urban Setting study, LASA Longitudinal Aging Study Amsterdam, NEO Netherlands Epidemiology of Obesity, NTR The Netherlands Twin Register, OR odds ratio. Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).

Fig. 5 Forest plot of the association between only former obesity (vs. no obesity) and SARS-CoV-2 infection measured by self-report. CI confidence interval, HELIUS Healthy Life in an Urban Setting study, LASA Longitudinal Aging Study Amsterdam, NEO Netherlands Epidemiology of Obesity, NTR The Netherlands Twin Register, OR odds ratio. Odds ratios are adjusted for age, sex, educational level, and number of SARS-CoV-2 infection measurements (and ethnicity for one cohort).

larger than effect estimates for BMI as a marker of overall body fat. However, we did not observe such differences, which is in line with the results of an earlier study that used genetic instruments for BMI and WC assessment [15]. A postulated hypothesis in literature is that abdominal obesity is related to COVID-19 disease severity rather than risk of getting infected with SARS-CoV-2, which is supported by the results of two observational studies [42, 43]. Taken together further research is needed to assess the potential added risk of abdominal obesity compared to general obesity in the development of SARS-CoV-2 infection.

Earlier work on overweight and SARS-CoV-2 infection has mostly been conducted in hospital-based studies [5]. An advantage of the population-based cohorts in the current study is that they have prospective data, with multiple exposure-measurements from before the pandemic, which allowed us to examine duration of obesity. An interesting finding is that the SARS-CoV-2 infection risk was not higher in individuals who had obesity a long time before the pandemic (> 5 years) but not shortly before the pandemic. This implies that obesity at the time of exposure to the infectious agent is more important than long-term obesity and that weight loss resulting in overweight or a healthy body weight leads to a lower risk. This is in line with a previous Korean study that found weight loss to be associated

with a reduced SARS-CoV-2 infection rate [44]. Also supportive of our findings is a large prospective study that identified weight gain as a risk factor for pneumonia [45]. From a public health perspective, the indication that losing weight to obtain a healthier body weight may be associated with reduced infection risk underlines the importance of obesity prevention and management.

While our results provide further support for an association of overweight with SARS-CoV-2 infection, it remains to be seen whether this points to a causal mechanism or if there are other factors explaining this association. Differences in self-reported SARS-CoV-2 infection by weight status could for example result from differences in testing behavior. Individuals with obesity were already targeted as medical/high risk group for a more severe COVID-19 prognosis early in the pandemic [46]. Therefore, they may have been more likely to do a PCR or rapid-antigen test or visit a physician and be diagnosed with a SARS-CoV-2 infection than individuals with a healthy body weight. However, our results based on serology generally support the existence of a biological mechanism between obesity and acquiring a SARS-CoV-2 infection. Evidence from literature supports such a causal link. First of all, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor (ACE2), which is highly expressed in adipose tissue [3]. In

addition, ACE2 is overexpressed among those having obesity which may determine greater viral entry and replication [13]. This suggests a role for adipose tissue as a virus reservoir, enhancing viral spread which is also known from other infectious diseases [47]. Furthermore, ACE2 expression is enhanced by several proinflammatory cytokines [12], the levels of which are already elevated in individuals with obesity. The state of chronic low-grade inflammation and associated impaired immune response in individuals with obesity contributes to being more susceptible to infections like SARS-CoV-2 [4]. Furthermore, our results also indicate that weight loss may reduce infection risk, which also supports a biological mechanism. Still, it needs to be confirmed whether weight loss itself or an associated healthier lifestyle, such as increased physical activity might be the primary protective factor against SARS-CoV-2 infection. However, Yoon et al. [44] observed an association between weight loss and reduced infection risk even after adjusting for physical activity [44]. This supports the hypothesis of weight loss to be directly responsible for the observed lower risk.

Interestingly, the observed increased SARS-CoV-2 infection risk among individuals with obesity, was higher in the period before 2021 than from 2021 onwards. Several differences between these periods exists. First, SARS-CoV-2 vaccines became available in the Netherlands in the beginning of 2021. In the Netherlands, individuals with severe obesity were considered a risk group for severe COVID-19 and had earlier access to the vaccine than the general population. In addition, individuals with obesity may have been more willing to receive the vaccine, which was shown in England, where vaccine uptake in 2021 has been found to be higher among those with overweight and obesity compared to those with a healthy weight [48]. This may have reduced the SARS-CoV-2 infection risk and/or symptoms in individuals with obesity from 2021 onwards, which may have resulted in a weaker association between obesity and SARS-CoV-2 infection in this period. Second, rapid-antigen tests also became available in the beginning of 2021. This may have led to an increase in the identification of a-symptomatic or mild SARS-CoV-2 cases, particularly among low-risk individuals with a healthy weight who might not have visited a testing facility or physician otherwise. This could also partly explain the weaker association between obesity and SARS-CoV-2 infection observed from 2021 onwards. Furthermore, subjective self-report is dependent on recall and testing behavior [49]. Therefore, serology is possibly a more objective measure to assess SARS-CoV-2 infections, especially early in the pandemic. Unfortunately, serology data in the present study did not allow the stratification according to period (before 2021 and from 2021 onwards) due to limited data. Lastly, dominant SARS-CoV-2 variants changed over time. While before 2021 almost all infections in The Netherlands were caused by the original strain, from 2021 onwards new variants emerged, which had higher transmissibility but resulted in less severe disease [41]. When more patients became asymptomatic, this may have resulted in more misclassification of cases and therefore weaker associations with overweight and obesity.

Methodological considerations
We pooled the results from protocolized analyses in nine individual cohort studies, resulting in a large study population covering a large share of the geographical and cultural variation within the Netherlands. Although we have no reason to assume that our results would not be generalizable to other high-income countries with similar or higher obesity rates, more research is needed to confirm this. Compared to most meta-analyses that combine results from published studies, we used a different approach in which individual studies conducted the same analyses based on a standardized protocol. Therefore, these analyses are more comparable in terms of the classification of the exposures, the adjustments to the models that were performed, and the sensitivity analyses that were carried out. This is also

visible in the results of these particular domains of the risk of bias assessment (Text S2). Together, this might have contributed to the relatively low heterogeneity (I^2) in most analyses. Nevertheless, the risk of bias assessment did reveal a high risk of bias due to missing data, which may have caused selection bias. Both non-response bias and attrition bias are common and inevitable in prospective cohorts such as those included in the current meta-analysis, though this does not necessarily cause biased results [50–52].

Despite the standardized protocol aiming to increase comparability between cohorts and analyses, the cohorts still varied in the timing and assessment of exposure and outcome and in the characteristics and numbers of included participants. The timing and method (measured or self-reported) of the BMI and WC assessment varied between cohorts, though in the majority of individuals the most recent BMI and WC status was objectively measured within 5 years before the start of the pandemic. Some cohorts only had one SARS-CoV-2 measurement in the first months of the pandemic (when testing opportunities were more limited), whereas others had multiple measurements throughout the pandemic. As a result, the number of self-reported SARS-CoV-2 infections also strongly differed between the cohorts. To take this into account, analyses were adjusted for the number of SARS-CoV-2 infection measurements. Besides assessment time, the cohorts also varied in size. Lifelines contained almost three quarters of all participants included in the current meta-analysis, and may as a consequence have dominated the results. After excluding Lifelines from the meta-analysis, effect estimates were in general slightly higher and heterogeneity was somewhat lower. However, the overall conclusion remained similar with and without Lifelines.

CONCLUSION
This study showed that individuals with (abdominal) obesity, and to a lesser extent individuals with (abdominal) overweight, were at increased risk of SARS-CoV-2 infection. Individuals with obesity long before the pandemic, but a healthier body weight just before the pandemic were not at increased risk. This indication that weight loss may be associated with reduced infection risk suggests that targeting overweight and obesity may not only contribute to improving population health by lowering the risk of chronic diseases, but also the risk of infectious diseases. Since it is likely that infectious diseases will continue to emerge and re-emerge in the future, these results therefore underline once more the importance of overweight prevention and weight reduction for public health.

DATA AVAILABILITY

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ADDITIONAL INFORMATION

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