

# SEVERITY OF COVID-19: CAUSES AND CONSEQUENCES — FROM OBESITY TO CHRONIC FATIGUE SYNDROME

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*In circumstances of COVID-19 epidemiological uncertainty, the causes and consequences of the disease remain important issues. The aim of this study was to investigate obesity as a potential predisposition and chronic fatigue syndrome (CFS) as a possible consequence of COVID-19. The study was conducted in two parts: a theoretical part, in which a literature review was performed, and an empirical part, in which COVID-19 patient survey data were analysed. To identify the main findings regarding the relationship between obesity and COVID-19, the literature review was focused on the investigation of systematic reviews and meta-analyses by three databases — Medline (via PubMed), Cochrane COVID-19 Study Register, and PROSPERO (International prospective register of systematic reviews). The patient survey was performed to investigate the relationship between obesity and severity of the disease, as well as the presence of CFS symptoms in COVID-19 patients in Latvia. The main findings of the literature review showed that obesity increases the risk of hospitalisation, disease severity, clinical complications, poor outcomes, and mortality. The results of the patient survey showed that overweight and obesity were more critical factors for men (males) suffering with COVID-19 than for women (females) in Latvia. The patient group with obesity caused almost half of all hospitalisations. The research data assumed that CFS patients were not a high-risk group for COVID-19, but COVID-19 caused CFS-like symptoms in patients and potentially increased the number of undiagnosed patients. In the context of further epidemiological uncertainty and the possibility of severe post-viral consequences, preventive measures are becoming increasingly important.*

**Keywords:** *epidemiological uncertainty, risk factor, body mass index, disease, literature review.*

## INTRODUCTION

In Latvia, incidence of the COVID-19 was relatively low during the first six months of infection intervention (March–August, 2020), but the epidemiological data of the following months showed a sharp increase in morbidity. In these circumstances, the importance of identifying and analysing the factors influencing the course of the disease is growing. Accordingly, the National Research Programme “COVID-19 Mitigation” project VPP-COVID-2020/1-0023 “Clinical, Bio-Chemical, Immunogenetic Paradigms of COVID-19 Infection and Their Correlation With Socio-Demographic, Etiological, Pathogenetic, Diagnostic, Therapeutically, and Prognostically Relevant Factors to Be In-

cluded in the Guidelines” was dedicated to identification of relevant factors correlated with COVID-19 infection paradigms. Within the scope of this project (inter alia), COVID-19 patients were surveyed and several biological parameters were determined during the recruitment of patients to the National Biobank — Genome Database of the Latvian population, maintained by the Latvian Biomedical Research and Study Centre. The preliminary data indicated several predispositions, such as overweight and obesity. At the same time, the study aimed to assess not only the causes, but also the consequences of COVID-19, and the survey was supplemented with additional questions to identify potential patients with chronic conditions such as the post-viral chronic fatigue syndrome (CFS). Rīga Stradiņš

University performed an analysis of the obtained data with the aim to investigate the causes and consequences of COVID-19 in Latvian circumstances. In light of this research, a scientific literature review was performed to obtain comparative data on impact of overweight on the course and severity of the COVID-19 disease.

## MATERIALS AND METHODS

The study consisted of two parts: a theoretical part, in which a literature review was performed, and an empirical part, in which the COVID-19 patient survey data were analysed. The survey data were obtained from the COVID-19 patients cohort established at the National Biobank – Genome Database of the Latvian population (Rovite *et al.*, 2018). The synthesis of these two parts should serve the aim of the research.

In the theoretical part, the purpose was to identify the main findings regarding the relationship between obesity and COVID-19, and the search was focused on systematic reviews and meta-analyses in databases. A search was performed in three databases — Medline (via PubMed), Cochrane COVID-19 Study Register, and PROSPERO (International prospective register of systematic reviews) — without time period restrictions. The following search key words were used in all databases without any other filters or restrictions: (“COVID-19”) OR (“coronavirus”) OR (“SARS-COV-2”) AND (“body mass index”) OR (“BMI”) OR (“obesity”) OR (“overweight”) AND (“systematic review”) OR (“meta-analysis”). The flow diagram of the studies selection process is shown in Figure 1.

To achieve the purpose of the empirical part — to investigate the relationship between obesity and severity of the COVID-19 disease in Latvian patients — the following tasks were defined:

- to determine the Body Mass Index (BMI) of patients participating in the project,
- to compare the obtained data with the relevant data of the Latvian population,
- to investigate the relationship of BMI and severity of the disease.

In order to compare the obtained data with the relevant data on the BMI in the Latvian population, the data of the Diseases Prevention and Control Centre’s Report “Health Behaviour Among Latvian Adult Population, 2018” were used (Latvian DPCC, 2019). The comparison was performed by age categories defined in the Report (15–24, 25–34, 35–44, 45–54, 55–64, 65–74 years) (Latvian DPCC, 2019).

Within the scope of this study, the standard BMI categories were used for adults: “Underweight = < 18.5”; “Normal weight = 18.5–24.9”; “Overweight = 25–29.9”, and “Obesity = BMI of 30 or greater”. For children until 19 years, the specific interpretation of BMI was used in accordance with

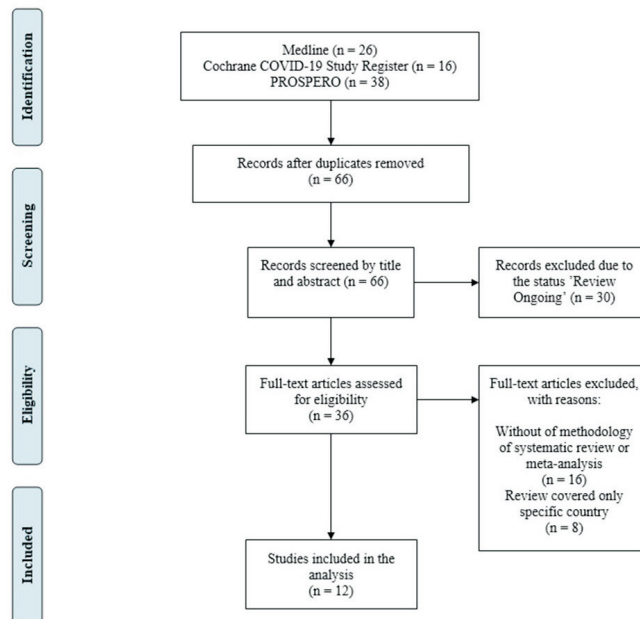


Fig. 1. Flow diagram of the selection process for systematic reviews and meta-analyses on relationship between obesity and COVID-19 prognosis.

the World Health Organisation’s “SD Scores for BMI Children 5–19 years”.

Hospitalisation was used as a criterion of disease severity.

The questionnaire for the purpose to identify potential CFS patients contained additional questions on CFS relevant symptoms, laboratory investigations, and quality of life.

Descriptive statistical methods were utilised for analyses of the obtained data.

Patient’s informed consent was obtained in accordance with the Central Medical Ethics Committee’s approval No 01-29.1/5034.

## RESULTS

In context of the theoretical research, the flow diagram of the selection process for systematic reviews and meta-analyses is shown in Figure 1.

A total of 80 articles were identified using the search strategies (Fig. 1). After the removal of duplicates using reference management software (EndNote, Clarivate Analytics), 66 articles studies were then screened for title and abstract and 30 were excluded due to the status “Review Ongoing”. The remaining 36 articles were screened against eligibility criteria. 24 full-text articles were excluded (16 were without methodology of systematic review or meta-analysis, and 8 reviews covered only specific countries, therefore they were not sufficiently eligible for objective evaluation).

The main findings of the review are presented in a summary of findings table (Table 1). This table provides key information concerning the research authors, number of covering

Table 1. Characteristics of the included systematic reviews and meta-analyses assessing severe COVID-19 according to Body Mass Index (BMI) and obesity

Authors	Number of articles (studies) included in review or meta-analysis	Main results and conclusions
Chang <i>et al.</i> , 2020, June	16 observational studies	BMI was found to be higher in patients with severe disease than in those with mild or moderate disease in China. Elevated BMI was associated with invasive mechanical ventilation (IMV) use in Western countries. Additionally, there were increased odds ratios of IMV use and hospitalisation in patients with obesity. In conclusion, obesity or high BMI increased the risk of hospitalisation, severe disease and IMV in COVID-19.
Yang, <i>et al.</i> , 2020, June	9 articles	Results show that severe COVID-19 patients had a higher BMI than non-severe ones; COVID-19 patients with obesity were more severely affected and have a worse outcome than those without. Obesity may aggravate COVID-19.
Földi, <i>et al.</i> , 2020, July	24 retrospective cohort studies	Obesity was a significant risk factor for intensive care unit (ICU) admission in a homogenous dataset, as well as for IMV in COVID-19. Comparing BMI classes with each other, it was found that a higher BMI always carries a higher risk. Obesity may serve as a clinical predictor for adverse outcomes.
Malik <i>et al.</i> , 2020, July	14 studies	The results of the current study show that BMI plays a significant role in COVID-19 severity in all age groups, especially the older individuals. Study finding showed that the population and patients with high BMI have moderate to high risk of medical complications with COVID-19.
Hussain, <i>et al.</i> , 2020, July-August	14 studies	Patients with obesity are at high risk of mortality from COVID-19 infection. All the primary points (including the age 70; BMI $25 \text{ kg/m}^2$ ; severe comorbidities) and gender are significantly associated with COVID-19 mortality.
Huang, <i>et al.</i> , 2020, August	A total of 45 650 participants from 33 studies	Univariate analyses showed significantly higher ORs of severe COVID-19 with higher BMI: for hospitalisation, for ICU admission, for IMV requirement, and for death. Multivariate analyses revealed increased ORs of severe COVID-19 associated with higher BMI for the same positions. Conclusion: Obesity increases risk for hospitalisation, ICU admission, IMV requirement and death among patients with COVID-19.
Peres, <i>et al.</i> , 2020, August	9 studies (6 cohorts and 3 cross-sectional)	Most of the included studies showed some degree of association to: (a) higher BMI and worse clinical presentation and (b) obesity and need of hospitalisation. The results were inconsistent about the impact of obesity on mortality. Based on limited methodological quality studies, obesity seems to predict poor clinical evolution in patients with COVID-19.
Seidu, <i>et al.</i> , 2020, August	9 cohort studies with data on of 4920 patients	Conclusions: Excess adiposity is a risk factor for severe disease and mortality in people with SARS-CoV-2 infection. This was particularly pronounced in people 60 and older. It should be taken into account when considering individual and population risks and when deciding on which groups to target for public health messaging on prevention and detection measures.
Malik, P. <i>et al.</i> , 2020, September	10 studies with 10 233 confirmed COVID-19 patients	The overall prevalence of obesity in the study was 33.9%. In meta-analysis, COVID-19 patients with obesity had higher odds of poor outcomes compared with better outcomes with a pooled OR, with 86% heterogeneity between studies. The study suggests a significant association between obesity and COVID-19 severity and poor outcomes.
J.V.V. de Siqueira, <i>et al.</i> , 2020, September-October	20 articles, with a population total estimated from 1 to 7671 patients	Conclusions: In the current review, obesity and overweight were represented an unfavourable factor for infection of novel coronavirus, where the higher the BMI the worse the outcomes. This occurred by worsening the infection itself, as well as increasing the prevalence of hospitalisations, worst outcomes and greater lethality; especially when co-occurring with other chronic conditions and in the elderly as well.
Soeroto, <i>et al.</i> , 2020, November-December	16 studies	Conclusion: Obesity is a risk factor of composite poor outcome of COVID-19. On the other hand, COVID-19 patients with composite poor outcome have higher BMI. BMI is an important routine procedure that should always be assessed in the management of COVID-19 patients and special attention should be given to patients with obesity.
Chu <i>et al.</i> , 2020, December	22 studies (12 591 patients)	BMI was higher in severe/critical COVID-19 patients than in mild COVID-19 patients. Additionally, obesity in COVID-19 patients was associated with poor outcomes, which comprised severe COVID-19, ICU care, IMV use, and disease progression. Obesity as a risk factor was greater in younger patients. However, obesity did not increase the risk of hospital mortality.

articles (or studies), and the sum of available data on the main outcomes.

The time period for literature was not defined, but the real systemic reviews and meta-analyses started to appeared in June 2020 and continued until the end of 2020 (the current study was completed by December 2020).

In the empirical part of the study on investigation of the relationship between obesity and severity of the COVID-19 disease in Latvian patients, the data of 190 women (female) and 123 men (male) were investigated. The data of the comparative analysis between the prevalence of BMI in the overall Latvian population and patient groups, in each of the defined age categories, are shown in Figure 2 for females and in Figure 3 for males.

Figures 2 and 3 indicate the age categories in which the BMI of the patient group exceeded that of the overall Latvian population and which can indicate risk groups in both the female and male populations. In Table 2, the data on hospitalisations as a COVID-19 disease severity criterion are shown.

The most critical values are marked in bold in Table 2. High importance is also given to the results showing that hospitalisation for the BMI category “Obesity = BMI of 30 or greater” accounted for 46% of the total number of hospitalisations; the BMI categories “Overweight = 25–29.9” and “Normal weight = 18.5–24.9” accounted for 28.1% of the total number of hospitalisations; and 1.2% were for the BMI category “Underweight = < 18.5”.

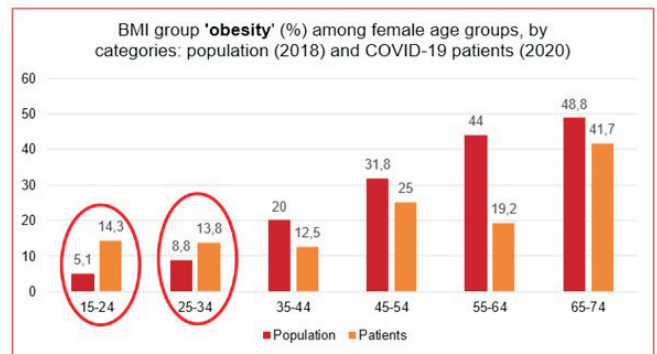
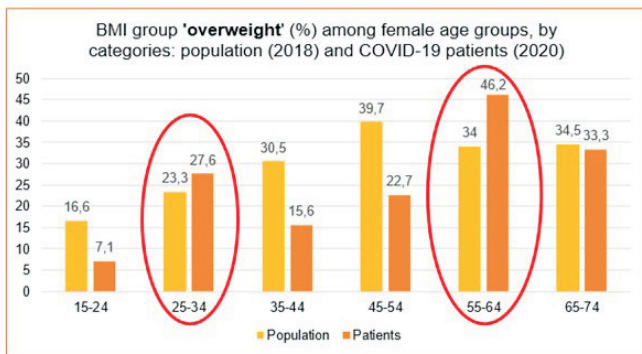
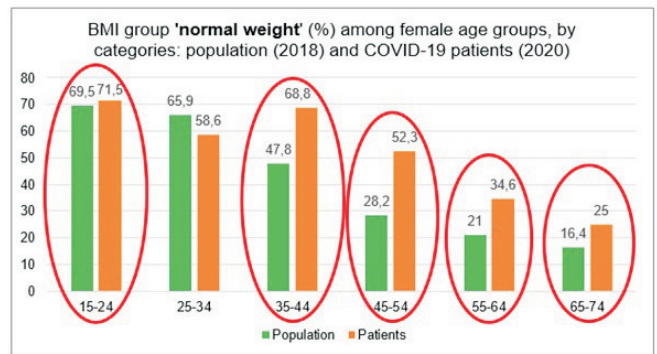
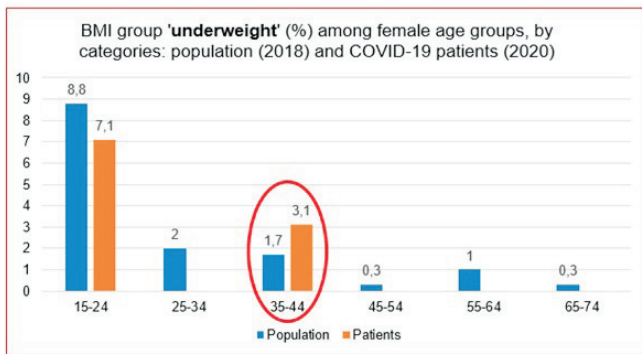


Fig. 2. Prevalence of BMI in the overall Latvian population, left column in each segment (Latvian DPCC, 2019), and patient groups, right column in each segment (authors, 2020), in each of the defined age categories, for females

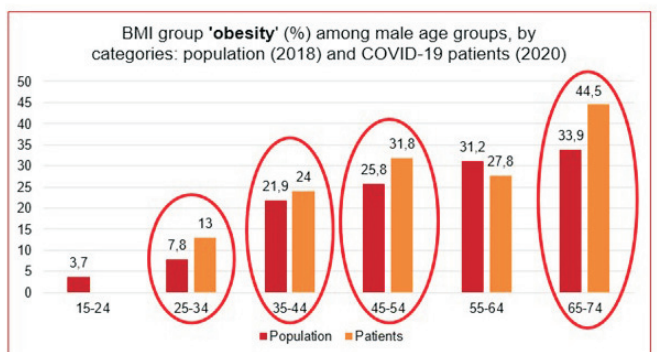
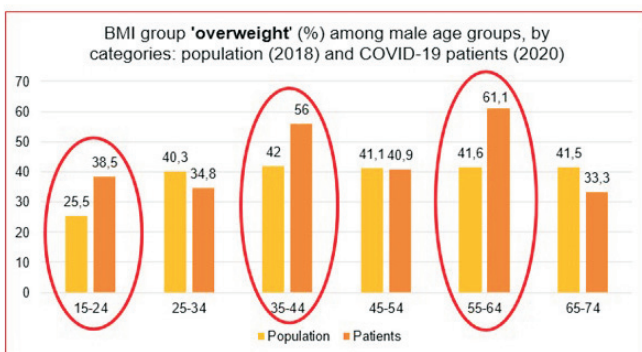
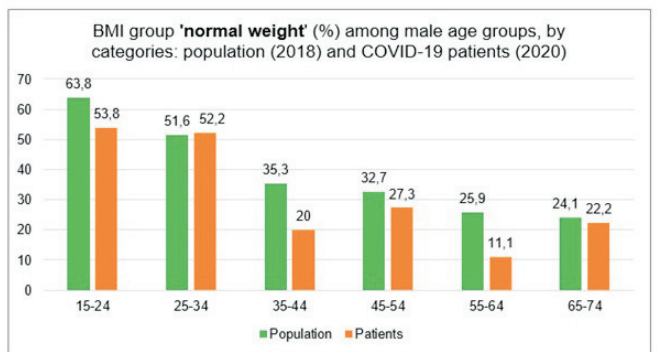
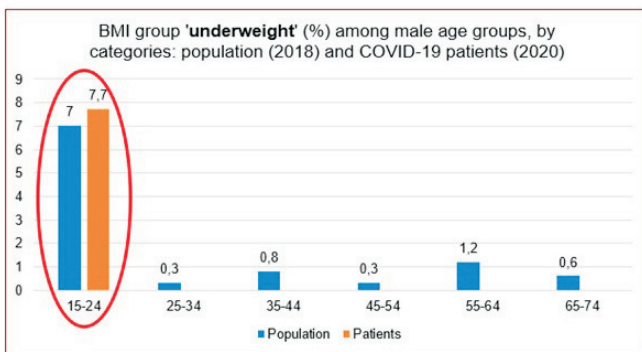


Fig. 3. Prevalence of BMI in the overall Latvian population, left column in each segment (Latvian DPCC, 2019), and patient groups, right column in each segment (authors, 2020), in each of the defined age categories, for males

Simultaneously, COVID-19 can induce long-lasting complications and chronic conditions such as the post-viral CFS, which is a poorly understood, serious, complex, multi-system disorder, characterised by symptoms lasting at least six months, with severe incapacitating fatigue not alleviated by rest, and other symptoms, many autonomic or cognitive in nature, including profound fatigue, cognitive dysfunction,

sleep disturbances, muscle pain, and post-exertional malaise, which lead to substantial reductions in functional activity and quality of life (Pheby *et al.*, 2020).

For this reason, the questionnaire for the purpose to identify the potential CFS patients contained additional questions on the CFS relevant symptoms, laboratory investigations and

Table 2. Hospitalisations as a COVID-19 disease severity criterion, by age category, as a percentage of the total number of hospitalisations and as a percentage of number of hospitalisations in each age category. The most critical values are marked in bold

Age category	As a percentage of the total number of hospitalisations	As a percentage of number of hospitalisations in age category
until 14 years	0	0
15–24	1.3%	3.7%
25–34	12%	17.3%
35–44	4%	5.3%
45–54	16%	18.2%
55–64	16%	27.3%
<b>65–74</b>	<b>28%</b>	<b>63.6%</b>
75–84	10.7%	<b>80%</b>
85–93	12%	<b>100%</b>

quality of life. The data of this survey showed that none of the 120 respondents was diagnosed with CFS, but 53 respondents (44.2%) indicated at least one of the symptoms characteristic of CFS. Of these 53 respondents, 20 respondents (37.7%) reported 4 to 8 CFS specific symptoms simultaneously. Significantly, 19 of these 20 respondents (95%) reported the launching of symptoms after COVID-19, in the period from March 2020.

## DISCUSSION

Due to topicality and variability of the situation, new scientific publications have appeared, and the majority of relevant studies identified that obesity increases the risk of hospitalisation, disease severity, clinical complications, poor outcomes, and mortality. Only one of 12 investigated articles indicated that obesity did not increase the risk of hospital mortality.

The data of this study survey showed that BMI of the COVID-19 patients did not have strong relation to the BMI data of overall Latvian population. The situation for men (males) suffering from COVID-19 was more critical concerning overweight and obesity, in comparison with women (females) in Latvia.

The excess of BMI in the category “Obesity” for female patients compared to the overall Latvia female population was observed in the age groups from 15 until 34 years, and in the category “Overweight” for age groups from 25 to 34 years and from 55 to 64 years. Male patients had a much higher prevalence of obesity — excess of BMI in the category “Obesity” for male patients compared to the overall Latvian male population was observed in the age groups from 25 until 54 years and from 65 to 74 years. However, the male age groups from 15 to 24 years, from 35 to 44 years and from 55 to 64 were represented by dominance of the BMI category “Overweight”. It is remarkable that for female patients in the age from 35 to 44 years the “Underweight” was characteristic, but for male patients this age group was dominated by the categories “Overweight” and “Obesity”.

The hospitalisations as a COVID-19 disease severity criterion, by age category, showed that a critical situation increased rapidly from the age of 65 years. However, the patient group with obesity caused almost half of all hospitalisations.

The study data assumed that CFS patients are not a high-risk group for COVID-19, but that COVID-19 disease causes CFS-like symptoms in patients. This increases the need for monitoring of patients for even longer after recovering from COVID-19 symptoms, to prevent complications and progression of chronic diseases, including CFS.

## CONCLUSIONS

In the context of further epidemiological uncertainty and the possibility of severe post-viral consequences, preventive measures are becoming significantly important. The increased risk of poor outcomes from COVID-19 disease in people with obesity should be taken into account in decision-making on individual and population risk prevention and detection measures. Regular physical activities, a balanced diet, and emotional stability can be effective tools to mitigate, prevent, and avoid the COVID-19 consequences.

## ACKNOWLEDGEMENTS

The study is supported by the National Research Programme’s project “COVID-19 Consequences Mitigation”, No VPP-COVID-2020/1-0023, “Clinical, Bio-Chemical, Immunogenetic Paradigms of COVID-19 Infection and Their Correlation With Socio-Demographic, Etiological, Pathogenetic, Diagnostic, Therapeutically, and Prognostically Relevant Factors to Be Included in the Guidelines” and by the Latvian Science Council’s Fundamental and Applied Research project No lzp-2019/1-0380 “Selection of Biomarkers in ME/CFS for Patient Stratification and Treatment Surveillance/Optimisation”. We acknowledge the Genome Database of Latvian Population, the Latvian Biomedical Research and Study Centre, for providing survey data.

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Received 22 March 2021

Accepted in the final form 2 November 2021

## COVID-19 SMAGUMS: CĒLOŅI UN SEKAS — NO APTAUKOŠANĀS LĪDZ HRONISKĀ NOGURUMA SINDROMAM

COVID-19 epidemioloģiskās nenoteiktības apstākļos jautājumi par slimības cēloņiem un sekām joprojām ir aktuāli. Šī pētījuma mērķis bija izpētīt aptaukošanos kā potenciālu predispozīciju un hroniska noguruma sindromu (HNS) kā iespējamās COVID-19 sekas. Pētījums tika veikts divās daļās: teorētiskajā daļā, kurā tika veikts literatūras apskats, un empīriskajā daļā, kurā tika analizēti COVID-19 pacientu aptaujas dati. Lai identificētu galvenos secinājumus par aptaukošanās un COVID-19 saistību, literatūras pārskats tika koncentrēts uz sistemātisku pārskatu un meta-analīžu izpēti trīs datu bāzēs — *Medline* (caur *PubMed*), *Cochrane COVID-19 Study Register* un *PROSPERO* (*International prospective register of systematic reviews*). Pacientu aptauja tika veikta, lai izpētītu saistību starp aptaukošanos un slimības smagumu, kā arī HNS simptomu klātbūtni COVID-19 pacientiem Latvijā. Galvenie literatūras pārskata secinājumi liecina, ka aptaukošanās palielina hospitalizācijas, slimības smaguma, klīnisko komplikāciju, nelabvēlīgu rezultātu un mirstības iespējamību. Pacientu aptaujas rezultāti rāda, ka vīriešu, kuri cietuši no COVID-19, dati ir kritiskāki attiecībā uz lieko svaru un aptaukošanos, salīdzinot ar sievietes datiem Latvijā. Pacientu grupa ar aptaukošanos izraisa gandrīz pusi no visām hospitalizācijām. Pētījuma dati pierāda, ka HNS pacienti nav COVID-19 augsta riska grupā, tomēr COVID-19 pacientiem izraisa HNS līdzīgus simptomus un potenciāli palielina nediagnosticēto pacientu skaitu. Saistībā ar epidemioloģisko nenoteiktību un nopietnu pēcvirusa seku iespējamību preventīvie pasākumi kļūst arvien nozīmīgāki.