Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Brief Report

Mendelian randomization study of obesity and type 2 diabetes in hospitalized COVID-19 patients

Hui-Qi Qu [a], Jingchun Qu [a], Joseph Glessner [a,b,c], Hakon Hakonarson [a,b,c,d,e,*]

[a] The Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[b] Department of Pediatrics, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[c] Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[d] Division of Pulmonary Medicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[e] Faculty of Medicine, University of Iceland, Reykjavik, Iceland

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ABSTRACT

Background: Both obesity and type 2 diabetes (T2D) are reported to be highly enriched in hospitalized COVID-19 patients. Due to the close correlation between obesity and T2D, it is important to examine whether obesity and T2D are independently related to COVID-19 hospitalization.
Objective: To examine the causal effect of obesity and T2D in hospitalized COVID-19 patients using Mendelian randomization (MR).
Research design and methods: This two-sample MR analysis applied genetic markers of obesity identified in the genome wide association study (GWAS) by the GIANT Consortium as instrumental variables (IVs) of obesity; and genetic markers of T2D identified by the DIAGRAM Consortium as IVs of T2D. The MR analysis was performed in hospitalized COVID-19 patient by the COVID-19 Host Genetics Initiative using the MR-Base platform.
Results: All 3 classes of obesity (Class 1/2/3) were shown as the causal risk factors of COVID-19 hospitalization; however, T2D doesn't increase the risk of hospitalization or critically ill COVID-19 as an independent factor.
Conclusions: Obesity, but not T2D, is a primary risk factor of COVID-19 hospitalization.

1. Introduction

The pandemic of Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [1]. SARS-COV-2 is not as virulent as SARS, and a large number of patients are asymptomatic or suffer only mild symptoms [2]. A large number of infected patients (~80%) have been asymptomatic or with mild symptoms [3], which has made the viral spread more difficult to control. On the other hand, a number of risk factors increased the severity and the rate of COVID-19-associated hospitalization, including obesity and type 2 diabetes (T2D) [4–7]. To investigate the risk factors of COVID-19-associated hospitalization is warranted for the development of effective preventive therapeutic approaches. In particular, obesity, especially patients with a body mass index (BMI) of ≥35 kg/m^2, has been shown as a strong and independent determinant of severe COVID-19 in large studies as reviewed by Stefan et al. [8].

Recently, genome wide association studies (GWAS) on severe COVID-19 have yielded important information on the disease pathogenesis [9–11]. The COVID-19 Host Genetics Initiative is a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the COVID-19 pandemic [11]. The summary statistics data are publicly available (https://www.covid19hg.org). Our recent analysis on the COVID-19 Host Genetics Initiative results demonstrated genetic correlations between COVID-19 and obesity as well as T2D [12]. However, it is hard to tell whether the correlations between COVID-19 and obesity/T2D are direct or indirect. Obesity contributes to metabolic syndrome [13], and increases the risk of T2D. Bearing in mind the close connection between obesity and T2D, it is important to examine whether the two reported risk factors are independently related to COVID-19 hospitalization.

Mendelian randomization (MR) uses genetic variants as proxies to simulate randomized clinical trial of risk factors and to determine causal effects [14], based on the results of well-designed genetic studies on each disease, e.g., large sample genome wide association studies (GWAS). By the two sample MR approach using the MR-Base platform [15], this study aims to investigate the causal effects of obesity and T2D in COVID-19-associated hospitalization in European populations based on two large GWASs on obesity and T2D, including the GWAS on obesity harboring 263,407 individuals of European ancestry [16], and the European T2D GWAS meta-analysis constituting 12,171 cases and 56,862 controls [17].

* Corresponding author at: Center for Applied Genomics, 3615 Civic Center Blvd, Abramson Building, Philadelphia, PA 19104, USA.
E-mail address: hakonarson@email.chop.edu (H. Hakonarson).

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2. Research design and methods

2.1. Data sources

This is a two-sample MR study designed to assess whether obesity or T2D was causally related to the risk of COVID-19-associated hospitalization. Single nucleotide polymorphisms (SNP) that were systematically identified by large sample GWASs served as the IVs to represent the exposures, i.e., obesity or T2D.

IVs for obesity: The SNPs associated with obesity were identified by the large scale GWAS on obesity in European populations by the Genetic Investigation of ANthropometric Traits (GIANT) Consortium [16]. The obesity phenotype was further divided into 3 clinical classes [18], e.g. class 1 obesity ($30 \le BMI < 35$, kg/m^2) including 55,229 cases and 104,894 controls; class 2 obesity ($35 \le BMI < 40$) including 15,334 cases and 97,858 controls; class 3 obesity ($BMI \ge 40$) including 3986 cases and 67,010 controls. The GIANT meta-analysis included multiple cohorts, while some cohorts had no class 2 and/or class 3 cases. The controls for the 3 classes of obesity were subjects with $BMI < 25$.

IVs for T2D: The SNPs associated with T2D were identified by the large sample European T2D GWAS meta-analysis [17], including 12,171 cases and 56,862 controls of European ancestry from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium [19].

The outcome measure was COVID-19-associated hospitalization based on the study of the COVID-19 Host Genetics Initiative Release 4 on 6406 cases and 902,088 controls of European ancestry (Dataset ID GCST010779, Released on October 20, 2020, https://www.covid19hg.org/results/r4/) [11], contained in the MR-Base platform (https://www.mrbase.org/) [15]. Consequently, the MR results were re-examined in the most recent data release by the COVID-19 Host Genetics Initiative, COVID19-hg GWAS meta-analyses round 6 (Released on June 15, 2021, https://www.covid19hg.org/results/r6/), including 24,274 hospitalized cases and 2,061,529 controls from different human populations [20]. In addition, we further assessed the causal effects of obesity and T2D in critically ill cases of COVID-19, i.e. individuals requiring respiratory support in hospital or deceased due to the disease, including 8779 cases and 1,001,875 controls [20].

All the above GWAS studies have been performed in adult populations.

2.2. SNP selection

SNPs for obesity: autosomal SNPs were selected by P value $< 1E-05$ from the obesity association analysis, in addition to being informative in the association test with COVID-19 hospitalization. Based on these results, 1361 SNPs were associated with class1 obesity; 1133 SNPs were associated with class 2 obesity; and 252 SNPs were associated with class 3 obesity (Supplementary Table 1). After the clumping procedure to obtain independent significant using MR-Base [15] (Supplementary Table 2),

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(1) 52 SNPs were left as the IVs for class 1 obesity: 25 SNPs were also associated with class 2/3 obesity, or were in linkage disequilibrium (LD) $r^2 > 0.277$ with an IV SNP for class 2/3 obesity; and 27 SNPs were specifically associated with class 1 obesity.
(2) 41 SNPs were left as the IVs for class 2 obesity: 3 SNPs were also associated with both class 1 and 3 obesity; 20 additional SNPs were also associated with class 1 obesity, or in LD with a class 1 SNP; 3 additional SNPs were also associated with class 3 obesity, or in LD with a class 3 SNP. 15 SNPs were specifically associated with class 2 obesity.
(3) 15 SNPs were left as the IVs for class 3 obesity: 7 SNPs were also associated with class 1/2 obesity, or in LD with class 1/2 SNPs; and 8 SNPs were specifically associated with class 3 obesity.

SNPs for T2D: 637 autosomal SNPs had P value $< 1E-05$ from the T2D association analysis, and were informative in the association test of COVID-19 hospitalization (Supplementary Table 3). After the clumping procedure to obtain independent significance using MR-Base [15], 55 SNPs were left as IVs for T2D (Supplementary Table 4). Among these IVs, 3 SNPs were also associated with obesity, i.e., rs4506565 in LD with the obesity SNP rs10885402 with $r^2 = 0.515$; rs9936385 in LD with the obesity SNP rs9923233 with $r^2 = 1.000$; and rs9947403 in LD with the obesity SNP rs8084515 with $r^2 = 0.968$. The biological explanation of the pleiotropy of these 3 IVs is that they may increase the risk of T2D by causing obesity.

SNPs for T2D: 637 autosomal SNPs had P value $< 1E-05$ from the T2D association analysis, and were informative in the association test of COVID-19 hospitalization (Supplementary Table 3). After the clumping procedure to obtain independent significance using MR-Base [15], 55 SNPs were left as IVs for T2D (Supplementary Table 4). Among these IVs, 3 SNPs were also associated with obesity, i.e., rs4506565 in LD with the obesity SNP rs10885402 with $r^2 = 0.515$; rs9936385 in LD with the obesity SNP rs9923233 with $r^2 = 1.000$; and rs9947403 in LD with the obesity SNP rs8084515 with $r^2 = 0.968$. The biological explanation of the pleiotropy of these 3 IVs is that they may increase the risk of T2D by causing obesity.

2.3. Statistical analysis

The MR analysis was done using the MR-Base platform [15]. The conventional random effects inverse variance weighted (IVW) analysis was used for the MR analysis. Heterogeneity of the causal estimates across all SNPs was tested by Q statistics. The effect of each SNP is presented in a forest plot. MR Egger analysis is also shown in the forest plots, which suffers from low statistical power. The effect of each single instrument on the overall effect was shown in the plot of the leave-one-out analysis.

3. Results

The MR analysis acquired significant P values for all the 3 classes of obesity, suggesting each class of obesity as a causal risk factor of COVID-19 hospitalization (Table 1). No significant heterogeneity was seen across different SNPs. The leave-one-out analysis showed that no single instrument had significant impact on the overall effect (Supplementary Figs. 1–3). The causal effect of each SNP is represented in the forest plots (Supplementary Figs. 4–6).

The MR analysis on T2D and COVID-19 hospitalization was not significant with a negative β value. The leave-one-out analysis and forest plots are shown in Supplementary Figs. 7–8. Considering the potential bias by the 3 pleiotropic IVs also associated with obesity, we re-performed the MR analysis with the rest of the 52 SNPs, and repeated the non-significance with a negative β value (Table 1).

To confirm the above results, we retested the above sets of obesity and T2D IVs in the most recent data release by the COVID-19 Host

Table 1
The MR analysis on obesity and type 2 diabetes in COVID-19 hospitalization.

Inverse variance weighted	N of SNP	β	Se	P value	Q statistics	Q_df	Q_pval
European populations (6406 cases and 902,088 controls)							
Class 1 obesity	52	0.105	0.041	0.0114	58.47	51	0.220
Class 2 obesity	41	0.085	0.032	0.0086	46.26	40	0.230
Class 3 obesity	15	0.078	0.029	0.0062	12.59	14	0.559
Type 2 diabetes	55	0.012	0.027	0.6527	48.14	54	0.699
Type 2 diabetes minus 2 obesity SNPs	52	0.008	0.030	0.7854	46.37	51	0.658
Different human populations (24,274 cases and 2,061,529 controls)							
Class 1 obesity	42	0.106	0.023	3.39E−06	47.21	41	0.234
Class 2 obesity	35	0.066	0.020	9.84E−04	55.59	34	0.011
Class 3 obesity	14	0.054	0.015	2.33E−04	12.16	13	0.514
Type 2 diabetes	48	−0.025	0.017	0.1441	43.92	47	0.601
Type 2 diabetes minus 2 obesity SNPs	45	−0.030	0.020	0.1288	43.24	44	0.504

Abbreviations: se, standard error of β; df, degrees of freedom.

Genetics Initiative, COVID19-hg GWAS meta-analyses round 6 [20]. As shown by the MR re-analysis (Table 1), more significant P values were acquired for all the 3 classes of obesity, while non-significance was repeated for T2D. These results suggest that T2D itself is not a causal risk factor of COVID-19 hospitalization. In addition, we further assessed the causal effects of obesity and T2D in critically ill cases of COVID-19, including 8779 cases and 1,001,875 controls [20]. As the results, we acquired statistical significance in both the IVs for class 1 obesity and those for class 3 obesity. A trend of association is seen in the IVs for class 2 obesity, but lack of statistical significance. Instead, no association was seen with type 2 diabetes (Table 2).

4. Discussion

Obesity has been reported as a risk factor of COVID-19 severity by previous studies [4,7,21,22]. Obesity is a common health problem, affecting about 315 million people world-widely [23]. Obesity may cause metabolic syndrome [13], and increases the risk of a number of chronic diseases, including but not limited to T2D and hypertension, both have been reported as risk factors of severe COVID-19 in clinical studies [4,24]. However, T2D is closely related to obesity-induced insulin resistance. It is therefore difficult to differentiate any independent effects of T2D in COVID-19 hospitalization, without the confounding effect of obesity by an epidemiological approach. The MR analysis using obesity or T2D specific genetic markers as the instrumental variables is a robust approach to address this issue.

In the recent publication by the COVID-19 Host Genetics Initiative [20], BMI, but not T2D, has been identified of association with increased risk of COVID-19 severity. With genetic effect estimates of BMI from the UK Biobank, Leong et al. have also shown that higher BMI is a causal risk factor for COVID-19 susceptibility and severity [25]. With these interesting findings, some important topics warrant further investigation. In the previous two studies [20,25], the single nucleotide polymorphisms (SNPs) associated with BMI and T2D were mainly identified in the European populations, while the COVID-19-associated SNPs were identified in multi-ethnic samples. For the causal effect of BMI, which class of obesity is it from, i.e., from only severe obesity, or from all classes of obesity? Obesity-associated SNPs may also be associated with T2D. Does these SNPs bias the MR results of T2D? In both the previous reports [20,25], BMI/T2D-associated SNPs with genome-wide significance (i.e., P ≤ 5E−08) were used as the instrumental variables (IVs). According to our study, the overall genetic risk of a complex disease/trait may be better captured at the cutoff of P-value ≤ 1E−05, while stricter cutoff may cause the missing of informative SNPs, and looser may introduce noise by including SNPs with spurious association [26]. Could the null effect of T2D be due to missing genetic information?

Table 2
The MR analysis on obesity and type 2 diabetes in critically ill cases of COVID-19.[a]

Inverse variance weighted	N of SNP	β	Se	P value	Q statistics	Q_df	Q_pval
Class 1 obesity	42	0.113	0.037	0.0024	37.77	41	0.615
Class 2 obesity	35	0.055	0.030	0.0623	38.83	34	0.261
Class 3 obesity	14	0.060	0.025	0.0170	7.41	13	0.880
Type 2 diabetes	48	−0.018	0.025	0.4831	35.18	47	0.898
Type 2 diabetes minus 2 obesity SNPs	45	−0.024	0.028	0.4001	34.01	44	0.861

[a] The COVID-19 Host Genetics Initiative, COVID19-hg GWAS meta-analyses round 6, including 8779 cases and 1,001,875 controls.

In our analysis, all 3 classes of obesity were shown to be causal risk factors of COVID-19 hospitalization with positive and significant β values, although the effect size of the association with COVID-19 hospitalization is not comparable across different classes of obesity due to the application of different sets of IVs. In further, we repeated the statistical significances of the IVs for class 1 obesity and those for class 3 obesity in critically ill cases of COVID-19, despite the smaller sample size and the decreased statistical power. Our study implies that obesity itself is the primary risk factor of COVID-19 hospitalization, independent of complications caused by more severe classes of obesity. As reviewed by Popkin et al. [21], obesity is associated with severe form of the 2009 H1N1 influenza [27], the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) infection [28], and severe COVID-19. In addition to risk of severe COVID-19 caused by obesity-related chronic metabolic diseases, hormone and nutrient dysregulation, respiratory dysfunctions, and immune/inflammatory dysfunctions in obesity, may all contribute to the risk of severe COVID-19 [21]. This viewpoint is supported by our MR analysis results, showing all 3 tiers of obesity correlated with COVID-19 hospitalization. As a limitation of the current study, the role of metabolically healthy obesity (MHO) in COVID-19 remains to be investigated. Individuals with MHO have metabolically healthy fat distribution, e.g. increased gluteofemoral and leg fat mass [29]. If MHO could be demonstrated of no association with severe COVID-19, precise prevention of severe COVID-19 could be practiced towards cases with metabolically unhealthy obesity, rather than a particular class of obesity.

Interestingly, our MR analysis showed that T2D doesn't increase the risk of COVID-19 hospitalization as an independent factor. Clinically observed risk of T2D in severe COVID-19 might be due to underlying obesity. However, compared with obesity, T2D tends to develop on the basis of long term obesity and insulin resistance, and is therefore associated with aging [30]. Individuals with genetic susceptibility of T2D may develop T2D disease as they age. Due to this reason, the risk effect of T2D in COVID-19 hospitalization may be underestimated by the MR approach. With this possibility, however, previous studies observed no evidence of increased hospitalization rate for COVID-19 in type 1 diabetes (T1D) children [31,32]. These observations may suggest diabetes itself is not a significant risk factor of COVID-19 hospitalization.

In conclusion, this MR analysis showed that obesity, but not T2D, is the risk factor of COVID-19 hospitalization. While obesity is a risk factor of severe COVID-19, information supported by the previous clinical studies, the null effect of diabetes is also supported by the lack of association between T1D and COVID-19 hospitalization. The outcome data of this study, the COVID-19 Host Genetics Initiative Release 4, was released on October 20, 2020. In contrast, the first approval of the use of any COVID-19 vaccine was by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) with a temporary regulatory approval on 2 December 2020 (https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/conditions-of-authorisation-for-pfizerbiontech-covid-19-vaccine). Therefore, the null effect of diabetes observed in this study was not biased by prioritized vaccination in T2D patients. It is worth to

emphasize that the null association between T2D and COVID-19 hospitalization needs to be explained with caution, considering limitations of the current MR approach. Previous retrospective observational studies have shown that T2D is associated with hospitalization and severe COVID-19 [33,34]. T2D is characterized by low-grade inflammation [35]. Poorly glycemic control and long diabetes duration could contribute to severe COVID-19. The T2D GWAS data may predict the risk of T2D, but contain no information about glycemic control and diabetes duration in the patients. These factors as the potential risk of severe COVID-19 couldn't be excluded by the null effect of T2D in this MR study, and warrant for large scale epidemiological study. In addition, both T2D and T1D have long term complications that are clinically reported of association with the risk of COVID-19 hospitalization, e.g. diabetic nephropathy and chronic renal failure [36]. The effect of T2D may be underestimated due to the limitation of the current MR approach. In addition, the current genetic information on obesity and T2D biased towards white Europeans. It would be interesting to perform a MR analysis based on the genetic information identified in non-white Ethnic groups to avoid the exacerbation of health disparities due to the lack of genomic information in minorities.

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CRediT authorship contribution statement

Hui-Qi Qu: Conceptualization, Methodology, Data analysis, Writing - Original draft preparation
Jingchun Qu: Data analysis, Writing - Original draft preparation
Joseph Glessner: Data analysis, Investigation
Hakon Hakonarson: Conceptualization, Writing - Reviewing and editing, Supervision.

Declaration of competing interest

The authors have no competing interests to declare.

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