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Causal Associations Between Body Fat Accumulation and Covid-19 Severity: A Mendelian Randomization Study

Satoshi Yoshiji, MD¹, Daisuke Tanaka, MD, PhD²,
Hiroto Minamino, MD², Tianyuan Lu, MSc¹,
Takaaki Murakami, MD, PhD², Yoshihito Fujita, MD, PhD²,
Brent J. Richards, MD, MSc¹, and Nobuya Inagaki, MD, PhD²
¹McGill University, Montreal, QC, Canada; ²Kyoto University,
Kyoto, Japan

Background: Previous studies reported associations between obesity measured by body mass index (BMI) and coronavirus disease 2019 (COVID-19). However, BMI is calculated only with height and weight and cannot distinguish between body fat mass and fat-free mass. Thus, it is not clear if one or both of these measures are mediating the relationship between obesity and COVID-19. **Aims:** To elucidate the independent causal relationships of body fat mass and fat-free mass with COVID-19 severity using Mendelian randomization (MR). **Results:** We identified single nucleotide polymorphisms associated with body fat mass and fat-free mass in 454,137 and 454,850 individuals of European ancestry from the UK Biobank, respectively. We then performed two-sample MR to ascertain their effects on severe COVID-19 (cases: 4,792; controls: 1,054,664) from the COVID-19 Host Genetics Initiative. We found that an increase in body fat mass by one standard deviation was associated with severe COVID-19 (odds ratio (OR)body fat mass = 1.61, 95% confidence interval [CI]: 1.28-2.04, P = 5.51×10⁻⁵; ORbody fat-free mass = 1.31, 95% CI: 0.99-1.74, P = 5.77×10⁻²). Considering that body fat mass and fat-free mass were genetically correlated with each other (r = 0.64), we further evaluated the independent causal effects of body fat mass and fat-free mass using multivariable MR and revealed that only body fat mass was independently associated with severe COVID-19 (ORbody fat mass = 2.91, 95%CI: 1.71-4.96, P = 8.85×10⁻⁵ and ORbody fat-free mass = 1.02, 95%CI: 0.61-1.67, P = 0.945). **Conclusions:** This study demonstrates the causal effects of body fat accumulation on COVID-19 severity and indicates that the biological pathways influencing the relationship between COVID-19 and obesity are likely mediated through body fat mass.

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