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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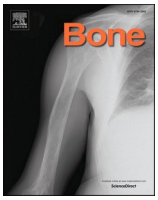

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Total body bone mineral density and severe COVID-19: A Mendelian randomization analysis in five age strata

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To the Editor

Kottlors et al. [1] conducted a multicenter feasibility study to verify whether bone mineral density (BMD) is a significant predictor of COVID-19. Using a univariate logistic regression model, they found that low BMD was a risk factor for intensive care unit (ICU) admission of COVID-19 patients. However, BMD was excluded from a multivariate regression analysis as a significant predictor after accounting for gender and age or other interaction terms. The average age of the sample in this study was 59.3 ± 16.2 years. The high correlation between age and BMD may have led to BMD being excluded from the multivariate analysis which was the most relevant limitation. Similarly, Battisti et al. [2] found that vertebral fractures with low spinal trabecular bone density were not significantly associated with mortality in the COVID-19 group of 239 people after age and gender adjustment compared to this effect was remained significant in non-COVID-19 group. However, Tahtabasi et al. [3] reported that vertebral BMD and lower BMD were significant independent predictors of COVID-19 mortality in both univariate and multivariate regression analysis but their study included 63 patients of low BMD and the mean age was 72.1 ± 12.6 years. Thus, the main take-home message is whether the prognostic relevance of low BMD as a risk factor for SARS-CoV-2 infected patients persists in a selected age group. In this study, we want to present some information in potential association between total body BMD (TBBMD) stratified by five levels of age and COVID-19, and then discuss the causality.

The causality of the association between BMD and severe COVID-19 has not been established because observational studies are prone to the effects of confounding factors. Mendelian randomization (MR) exploits genetic variants as instrumental variables to bring down confusion about environmental or other disease factors because alleles are randomly assigned to offspring. In this study, we performed a two-sample MR analysis for the association of TBBMD with severe COVID-19 to validate the authors' findings.

Summary statistics of TBBMD were obtained from the Genetic Factors for Osteoporosis (GEFOS) Consortium [4]. Age strata comprised 0–15 years (N = 11,807), 15–30 years (N = 4,180), 30–45 years (N = 10,062), 45–60 years (N = 18,805), and 60 or more years (N = 22,504). Summary-level genetic data for COVID-19 were acquired from The COVID-19 Host Genetics Initiative genome-wide association meta-analysis (release 6, 15 June 2021; without the 23andMe study) [5], which included 8779 very severe respiratory confirmed COVID-19 cases versus 1,001,875 population controls. The MR analyses were performed using the inverse-variance weighted method, but the multiple-SNP test is not applicable to features that contain only one instrumental variable, in which case we use the Wald ratio test [6]. All summary data used in this work are publicly available. They were obtained with relevant participant consent and ethical approval. Single-nucleotide polymorphisms (SNPs) at $p < 5 \times 10^{-8}$ were selected as instrumental variables. The linkage disequilibrium threshold was set to $r^2 = 0.001$ within a distance of 10,000 kb.

The MR analyses (Fig. 1) showed that severe COVID-19 was associated with low TBBMD in people over 60 years of old (OR = 0.88 [95% CI, 0.78–0.99], p value = 0.0352), 20 SNPs were used as instrumental variables (Table 1). There were no strong evidences supporting associations of COVID-19 with TBBMD in the four different age strata, namely 0–15, 15–30, 30–45, and 45–60 years. Our results showed that potential association between BMD and severe COVID-19 in aged population and revealed that the higher TBBMD is a protective factor for COVID-19 in people over 60 years of age compared to other age groups. It meant that the higher BMD is in people over 60 years of age, the less likely they are to develop more severe COVID-19. We demonstrated that BMD could be a predictor of severe COVID-19 in aged population to identify cases with severe progressions and to predict whether a patient should be treated in an ICU within the observation period. It was confirmed that BMD was eliminated from the multivariate logistic regression of Kottlors et al. [1] primarily due to a high collinearity between age and BMD.

In conclusion, we investigated the impacts of age-stratified TBBMD risk on severe COVID-19 using large-scale genetic summary data. With performing a more homogenous patient age, the potential effects between low BMD and COVID-19 in aged population were illustrated. The findings may help shed light on the clinical implications. BMD can provide guidance for clinical treatment to predict whether infected patients need to be treated in the intensive care unit (ICU), and more attention should be paid to elderly patients with low BMD.

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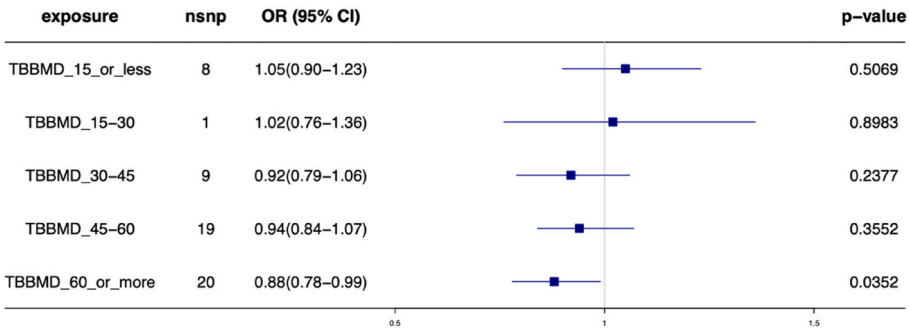

Fig. 1. Associations of TBBMD with coronavirus disease 2019 (COVID-19). Abbreviations: CI, confidence interval; TBBMD, total body bone mineral density; OR, odds ratio; SNP, single-nucleotide polymorphism.

Table 1
Summary genetic instrumental variables between TBBMD in individuals ≥60 years and severe COVID-19.

SNPs	Beta	SE	p.value	Beta	SE	p.value
	TBBMD_60_or_more			severeCOVID-19		
rs10824760	0.0886	0.0149	3.05E−09	−0.0238	0.0301	0.4299
rs11228240	−0.0848	0.0114	1.12E−13	−0.0008	0.0228	0.9725
rs1936792	0.0607	0.0110	3.72E−08	−0.0072	0.0226	0.7495
rs2371447	−0.0711	0.0099	6.58E−13	−0.0025	0.0211	0.9044
rs2566752	−0.0776	0.0101	1.55E−14	−0.0259	0.0210	0.2185
rs2741856	0.1391	0.0194	7.03E−13	−0.0279	0.0394	0.4788
rs34670419	−0.1603	0.0265	1.40E−09	0.0532	0.0516	0.3028
rs34920465	−0.1008	0.0126	9.41E−16	0.0542	0.0227	0.0166
rs3801387	−0.1337	0.0108	2.82E−35	−0.0009	0.0202	0.9631
rs55983207	−0.1409	0.0255	3.37E−08	0.1491	0.0665	0.0250
rs56104760	0.0715	0.0127	2.00E−08	−0.0204	0.0251	0.4163
rs61884328	−0.1063	0.0168	2.46E−10	−0.0091	0.0313	0.7724
rs6557155	−0.0981	0.0102	5.18E−22	0.0205	0.0213	0.3349
rs6942191	−0.0645	0.0103	4.23E−10	−0.0140	0.0222	0.5289
rs6978070	0.0641	0.0103	4.73E−10	0.0150	0.0214	0.4847
rs7131442	−0.0762	0.0119	1.81E−10	0.0166	0.0260	0.5221
rs7548588	−0.0617	0.0099	3.80E−10	0.0001	0.0215	0.9959
rs7740042	−0.0741	0.0121	9.05E−10	0.0095	0.0266	0.7206
rs7787512	0.0849	0.0101	3.56E−17	−0.0199	0.0208	0.3378
rs9533094	0.0688	0.0097	1.30E−12	−0.0324	0.0189	0.0870

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Declaration of competing interest

None.

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References

[1] J. Kottlors, N.G. Hokamp, P. Fervers, J. Bremm, F. Fichter, T. Persigehl, O. Safarov, D. Maintz, S. Tritt, N. Abdullayev, Early extrapulmonary prognostic features in chest computed tomography in COVID-19 pneumonia: bone mineral density is a relevant predictor for the clinical outcome-a multicenter feasibility study, Bone 144 (2021).
[2] S. Battisti, N. Napoli, C. Pedone, M. Lombardi, G. Leanza, F. Tramontana, M. Faraj, V. Agnoletti, M. Verna, L. Viola, E. Giampalma, R. Strollo, Vertebral fractures and mortality risk in hospitalised patients during the COVID-19 pandemic emergency, Endocrine 74 (3) (2021) 461–469.
[3] M. Tahtabasi, N. Kilicaslan, Y. Akin, E. Karaman, M. Gezer, Y.K. Icen, F. Sahiner, The prognostic value of vertebral bone density on chest CT in hospitalized COVID-19 patients, J. Clin. Densitom. 24 (4) (2021) 506–515.
[4] C. Medina-Gomez, J.P. Kemp, K. Trajanoska, J. Luan, A. Chesi, T.S. Ahluwalia, D. O. Mook-Kanamori, A. Ham, F.P. Hartwig, D.S. Evans, R. Joro, I. Nedeljkovic, H. F. Zheng, K. Zhu, M. Atalay, C.T. Liu, M. Nethander, L. Broer, G. Porleifsson, B. H. Mullin, S.K. Handelman, M.A. Nalls, L.E. Jessen, D.H.M. Heppe, J.B. Richards, C. Wang, B. Chawes, K.E. Schraut, N. Amin, N. Wareham, D. Karasik, N. Van der Velde, M.A. Ikram, B.S. Zemel, Y. Zhou, C.J. Carlsson, Y. Liu, F.E. McGuigan, C. G. Boer, K. Bonnelykke, S.H. Ralston, J.A. Robbins, J.P. Walsh, M.C. Zillikens, C. Langenberg, R. Li-Gao, F.M.K. Williams, T.B. Harris, K. Akesson, R.D. Jackson, G. Sigurdsson, M. den Heijer, B.C.J. van der Eerden, J. van de Peppel, T.D. Spector, C. Pennell, B.L. Horta, J.F. Felix, J.H. Zhao, S.G. Wilson, R. de Mutsert, H. Bisgaard, U. Styrkarsdottir, V.W. Jaddoe, E. Orwoll, T.A. Lakka, R. Scott, S.F.A. Grant, M. Lorentzon, C.M. van Duijn, J.F. Wilson, K. Stefansson, B.M. Psaty, D.P. Kiel, C. Ohlsson, E. Ntzani, A.J. van Wijnen, V. Forgetta, M. Ghanbari, J.G. Logan, G. R. Williams, J.H.D. Bassett, P.I. Croucher, E. Evangelou, A.G. Uitterlinden, C. L. Ackert-Bicknell, J.H. Tobias, D.M. Evans, F. Rivadeneira, Life-course genome-wide association study meta-analysis of total body BMD and assessment of age-specific effects, Am. J. Hum. Genet. 102 (1) (2018) 88–102.
[5] C.-H.G. Initiative, The COVID-19 host genetics initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic, Eur. J. Hum. Genet. 28 (6) (2020) 715–718.
[6] S. Burgess, D.S. Small, S.G. Thompson, A review of instrumental variable estimators for mendelian randomization, Stat. Methods Med. Res. 26 (5) (2017) 2333–2355.

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