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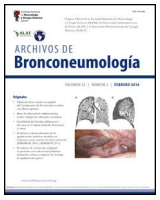

Discussion Letter

A Commentary on 'Effect of the Antibody-Mediated Immune Responses on COPD, Asthma, and Lung Function: A Mendelian Randomization Study'

To the Director,

We carefully read the article by Xu et al. published in *Archivos de Bronconeumología*.[1] The authors used Mendelian randomization (MR) to explore the relationship between antibody-mediated immune responses and chronic obstructive pulmonary disease (COPD), asthma, and lung function. This MR study identified 20 antibody-mediated immune responses with significant causal relationships to COPD, asthma, and certain lung function indicators. These findings provide a new perspective on understanding the genetic association between antibody-mediated immune responses and respiratory disease risk, offering genetic evidence for the prevention and treatment of COPD and asthma. We sincerely appreciate this innovative study, but would like to share some different perspectives on the research.

We believe that the methodology of this study still requires further improvement. Specifically, regarding the sample source, there may be overlap between the exposure and outcome data, which could introduce bias in the causal inference of the study. First, for the exposure data, Xu et al. used the GWAS summary statistics of antibody-mediated immune responses provided by Butler-Laporte et al.[2] This data originates from the genetic analysis of 20 types of microbiome antibody levels in 9724 British adults from the UK Biobank (UKB) database. However, for the outcome data, Xu et al. also used GWAS data from the UKB database,[3] including COPD, emphysema, bronchiectasis and asthma. Furthermore, for lung function-related indicators, including forced expiratory volume in 1-second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC, Xu et al. referenced the largest global GWAS data from 49 cohorts. However, 320,656 individuals (67% of the total sample) in this GWAS data also come from the UKB. This suggests that the MR results may still be primarily driven by data from the UKB.

MR is a powerful research method used to distinguish causal relationships, particularly demonstrating unique advantages when causal relationships cannot be clearly identified due to potential confounding bias in observational studies. However, the reliability of its results depends on strict adherence to a series of methodological assumptions, including the statistical independence of exposure and outcome data. Since both the exposure and some of the outcome data come from the UK Biobank, and most of the samples for lung function analysis are also from this database. If there is sample overlap, it could lead to significant bias in the MR analysis and a high type I error rate, resulting in an overestimation of causal relationships.[4] Previous studies have shown that when the sample overlap is low and the instrumental variable strength is high, its impact on the study conclusion may be limited.[5] Therefore, we recommend that the authors calculate the sample overlap between exposure and outcome to assess its potential impact on the study conclusions.

To enhance the robustness and reliability of the study results, we repeated the analysis in an independent external cohort. We used the recently released FinnGen R12 database (https://www.finngen.fi/en/access_results), which provides high-quality, UKB-independent samples that can be used for validation analysis, thus avoiding potential bias from sample overlap. In this analysis, we used the same exposure data as Xu et al., which is the GWAS summary statistics of antibody-mediated immune responses. For the outcomes, we used the GWAS data for COPD ($N = 433{,}208$) and asthma ($N = 301{,}060$) from the FinnGen R12 database. Additionally, we used the GWAS data for FEV_1/FVC ($N = 51{,}396$) and FEV_1 ($N = 44{,}671$) from the Within Family GWAS Consortium. For the data analysis, we selected SNPs significantly associated with immune response levels ($P < 1E{-}05$) according to the standards of Xu et al. To remove linkage disequilibrium, we also used the standard of $r^2 = 0.001$, kb = 10,000. Additionally, SNPs related to outcome variables were excluded ($P < 1E{-}05$).

All results are detailed in Fig. 1. The results show that, after false discovery rate adjustment, only the level of anti-toxoplasma gondii IgG seropositivity remained significantly negatively associated with FEV_1/FVC. When false discovery rate adjustment was not applied to the *P*-values, we found that Epstein–Barr virus VCA p18 antibody levels, toxoplasma gondii p22 antibody levels, anti-chlamydia trachomatis IgG seropositivity, anti-helicobacter pylori IgG seropositivity, and helicobacter pylori catalase antibody levels were associated with COPD; Anti-Toxoplasma gondii IgG seropositivity, anti-human herpes virus 6 IE1A IgG seropositivity, anti-bk polyomavirus IgG seropositivity and toxoplasma gondii p22 antibody levels were associated with asthma; Helicobacter pylori cagA antibody levels were associated with FEV_1; and Toxoplasma gondii p22 antibody levels, anti-herpes simplex virus 2 IgG seropositivity, and helicobacter pylori UREA antibody levels were associated with FEV_1/FVC, indicating potential causal relationships.

Similar to the results of Xu et al., we also found potential causal relationships between Epstein–Barr virus VCA p18 antibody levels and toxoplasma gondii p22 antibody levels with COPD. However, we did not observe any significant statistical differences for the remaining results of Xu et al., and we additionally identified three new results: Anti-chlamydia trachomatis IgG seropositivity, anti-helicobacter pylori IgG seropositivity, and helicobacter pylori catalase antibody levels. For the MR analysis of asthma, FEV_1, and FEV_1/FVC, we did not obtain the same results as Xu et al., and most of the results did not pass the false discovery rate test.

In conclusion, we greatly admire the efforts of Xu et al. in exploring the causal relationship between immune responses and respiratory diseases. This provides new insights for further

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Exposures	Outcoms	Nsnp	OR(95%CI)	b	P	P_fdr
Significant results						
Epstein−Barr virus VCA p18 antibody levels	COPD	37	0.94(0.90 to 0.98)	−0.059	0.008	0.233
Toxoplasma gondii p22 antibody levels	COPD	38	1.02(1.00 to 1.04)	0.021	0.014	0.286
Anti−chlamydia trachomatis IgG seropositivity	COPD	19	0.97(0.95 to 1.00)	−0.028	0.032	0.453
Anti−helicobacter pylori IgG seropositivity	COPD	16	1.04(1.00 to 1.08)	0.039	0.037	0.453
Helicobacter pylori Catalase antibody levels	COPD	17	0.97(0.93 to 1.00)	−0.035	0.046	0.474
Anti−Toxoplasma gondii IgG seropositivity	Asthma	19	1.03(1.01 to 1.06)	0.034	0.003	0.169
Anti−human herpes virus 6 IE1A IgG seropositivity	Asthma	21	0.97(0.95 to 0.99)	−0.032	0.007	0.233
Anti−BK polyomavirus IgG seropositivity	Asthma	14	0.99(0.97 to 1.00)	−0.014	0.019	0.357
Toxoplasma gondii p22 antibody levels	Asthma	38	1.02(1.00 to 1.03)	0.015	0.035	0.453
Helicobacter pylori CagA antibody levels	FEV1	15	0.98(0.96 to 0.99)	−0.024	0.012	0.273
Anti−Toxoplasma gondii IgG seropositivity	FEV1/FVC	14	0.97(0.96 to 0.99)	−0.028	<0.001	0.026
Toxoplasma gondii p22 antibody levels	FEV1/FVC	26	0.98(0.97 to 0.99)	−0.018	0.001	0.057
Anti−herpes simplex virus 2 IgG seropositivity	FEV1/FVC	13	0.98(0.96 to 0.99)	−0.021	0.007	0.233
Helicobacter pylori UREA antibody levels	FEV1/FVC	19	0.98(0.96 to 1.00)	−0.022	0.042	0.453
Non−significant results						
Herpes simplex virus 2 mgG−1 antibody levels	COPD	17	0.98(0.96 to 1.00)	−0.020	0.102	0.596
Human herpes virus 6 IE1A antibody levels	COPD	24	0.96(0.91 to 1.01)	−0.044	0.105	0.596
Epstein−Barr virus EBNA−1 antibody levels	COPD	23	0.97(0.93 to 1.01)	−0.034	0.121	0.596
Chlamydia trachomatis PorB antibody levels	COPD	76	1.00(1.00 to 1.01)	0.004	0.190	0.665
Epstein−Barr virus ZEBRA antibody levels	COPD	33	1.03(0.98 to 1.08)	0.029	0.203	0.684
Helicobacter pylori GroEL antibody levels	COPD	13	0.98(0.94 to 1.02)	−0.024	0.251	0.699
Varicella zoster virus glycoproteins E and I antibody levels	COPD	21	0.97(0.92 to 1.02)	−0.028	0.284	0.767
Cytomegalovirus pp150 antibody levels	COPD	22	1.02(0.98 to 1.06)	0.020	0.293	0.767
Anti−herpes simplex virus 2 IgG seropositivity	COPD	17	0.99(0.97 to 1.01)	−0.011	0.345	0.775
Helicobacter pylori UREA antibody levels	COPD	21	0.99(0.96 to 1.01)	−0.013	0.347	0.775
Anti−Toxoplasma gondii IgG seropositivity	COPD	19	1.01(0.99 to 1.04)	0.012	0.373	0.775
Anti−human herpes virus 6 IgG seropositivity	COPD	16	0.99(0.97 to 1.01)	−0.008	0.389	0.775
Cytomegalovirus pp52 antibody levels	COPD	24	0.97(0.92 to 1.03)	−0.026	0.394	0.775
Chlamydia trachomatis tarp−D F2 antibody levels	COPD	22	0.99(0.95 to 1.03)	−0.012	0.516	0.844
Cytomegalovirus pp28 antibody levels	COPD	20	0.98(0.94 to 1.03)	−0.015	0.538	0.844
Chlamydia trachomatis pGP3 antibody levels	COPD	20	0.99(0.96 to 1.02)	−0.009	0.587	0.864
BK polyomavirus VP1 antibody levels	COPD	24	0.99(0.94 to 1.05)	−0.008	0.791	0.907
Helicobacter pylori OMP antibody levels	COPD	16	1.01(0.96 to 1.05)	0.006	0.798	0.907
Anti−Epstein−Barr virus IgG seropositivity	COPD	12	1.00(0.98 to 1.02)	0.001	0.872	0.943
Anti−polyomavirus 2 IgG seropositivity	Asthma	16	1.03(1.00 to 1.06)	0.029	0.054	0.481
Polyomavirus 2 JC VP1 antibody levels	Asthma	27	1.04(1.00 to 1.09)	0.040	0.064	0.516
Chlamydia trachomatis momp D antibody levels	Asthma	10	1.02(0.99 to 1.05)	0.021	0.115	0.596
Varicella zoster virus glycoproteins E and I antibody levels	Asthma	22	0.97(0.92 to 1.01)	−0.034	0.135	0.607
Anti−human herpes virus 7 IgG seropositivity	Asthma	19	1.01(1.00 to 1.02)	0.007	0.157	0.658
Cytomegalovirus pp28 antibody levels	Asthma	20	1.03(0.98 to 1.09)	0.034	0.181	0.665
Chlamydia trachomatis tarp−D F1 antibody levels	Asthma	24	1.01(0.99 to 1.03)	0.013	0.184	0.665
Helicobacter pylori CagA antibody levels	Asthma	15	0.98(0.96 to 1.01)	−0.016	0.187	0.665
Human herpes virus 6 p101k antibody levels	Asthma	21	0.99(0.96 to 1.01)	−0.014	0.192	0.665
Merkel cell polyomavirus VP1 antibody levels	Asthma	24	0.98(0.94 to 1.01)	−0.024	0.228	0.699
Helicobacter pylori VacA antibody levels	Asthma	21	0.99(0.97 to 1.01)	−0.012	0.278	0.763
Cytomegalovirus pp150 antibody levels	Asthma	22	1.02(0.98 to 1.05)	0.018	0.296	0.767
Helicobacter pylori OMP antibody levels	Asthma	14	0.98(0.94 to 1.02)	−0.019	0.330	0.775
Herpes simplex virus 2 mgG−1 antibody levels	Asthma	17	0.99(0.97 to 1.01)	−0.011	0.339	0.775
Chlamydia trachomatis tarp−D F2 antibody levels	Asthma	22	0.99(0.95 to 1.02)	−0.014	0.394	0.775
Helicobacter pylori UREA antibody levels	Asthma	22	1.01(0.98 to 1.04)	0.013	0.399	0.775
Anti−Epstein−Barr virus IgG seropositivity	Asthma	12	1.01(0.99 to 1.02)	0.007	0.428	0.787
Anti−herpes simplex virus 2 IgG seropositivity	Asthma	17	0.99(0.97 to 1.01)	−0.008	0.448	0.792
Epstein−Barr virus EBNA−1 antibody levels	Asthma	22	1.02(0.97 to 1.07)	0.017	0.495	0.837
Anti−Merkel cell polyomavirus IgG seropositivity	Asthma	19	1.01(0.98 to 1.03)	0.007	0.612	0.872
Anti−varicella zoster virus IgG seropositivit	Asthma	16	1.00(0.98 to 1.03)	0.004	0.749	0.907
Human herpes virus 6 IE1A antibody levels	Asthma	24	0.99(0.94 to 1.05)	−0.008	0.767	0.907
Helicobacter pylori Catalase antibody levels	Asthma	17	1.00(0.97 to 1.02)	−0.002	0.846	0.938
Herpes simplex virus 1 mgG−1 antibody levels	Asthma	31	1.00(0.96 to 1.03)	−0.002	0.914	0.961
BK polyomavirus VP1 antibody levels	FEV1	18	1.04(1.00 to 1.09)	0.043	0.054	0.481
Anti−BK polyomavirus IgG seropositivity	FEV1	9	1.01(1.00 to 1.02)	0.009	0.125	0.596
Toxoplasma gondii sag1 antibody levels	FEV1	30	0.98(0.96 to 1.00)	−0.017	0.126	0.596
Anti−varicella zoster virus IgG seropositivit	FEV1	13	1.01(1.00 to 1.03)	0.013	0.131	0.602
Chlamydia trachomatis tarp−D F1 antibody levels	FEV1	19	0.99(0.97 to 1.01)	−0.013	0.165	0.658
Helicobacter pylori Catalase antibody levels	FEV1	13	0.98(0.96 to 1.01)	−0.017	0.168	0.658
Human herpes virus 6 IE1B antibody levels	FEV1	22	0.98(0.95 to 1.02)	−0.017	0.319	0.775
Anti−herpes simplex virus 2 IgG seropositivity	FEV1	13	0.99(0.97 to 1.01)	−0.008	0.389	0.775
Helicobacter pylori GroEL antibody levels	FEV1	10	0.98(0.93 to 1.03)	−0.019	0.486	0.836
Cytomegalovirus pp28 antibody levels	FEV1	12	0.99(0.94 to 1.03)	−0.013	0.542	0.844
Anti−human herpes virus 6 IgG seropositivity	FEV1	13	1.00(0.99 to 1.02)	0.004	0.550	0.844
Cytomegalovirus pp52 antibody levels	FEV1	19	1.01(0.98 to 1.04)	0.008	0.616	0.872
Human herpes virus 6 p101k antibody levels	FEV1	18	1.00(0.98 to 1.03)	0.004	0.674	0.907
Epstein−Barr virus ZEBRA antibody levels	FEV1	28	1.01(0.97 to 1.04)	0.007	0.724	0.907
Epstein−Barr virus EBNA−1 antibody levels	FEV1	17	0.99(0.95 to 1.04)	−0.006	0.768	0.907
Herpes simplex virus 1 mgG−1 antibody levels	FEV1/FVC	26	1.02(1.00 to 1.04)	0.020	0.100	0.596
Anti−helicobacter pylori IgG seropositivity	FEV1/FVC	13	0.99(0.97 to 1.00)	−0.014	0.104	0.596
Toxoplasma gondii sag1 antibody levels	FEV1/FVC	30	0.99(0.97 to 1.00)	−0.014	0.107	0.596
Epstein−Barr virus EBNA−1 antibody levels	FEV1/FVC	17	1.02(0.99 to 1.06)	0.025	0.115	0.596
Anti−human herpes virus 6 IgG seropositivity	FEV1/FVC	13	1.01(1.00 to 1.02)	0.008	0.168	0.658
Chlamydia trachomatis momp D antibody levels	FEV1/FVC	8	0.99(0.97 to 1.01)	−0.013	0.204	0.684
Cytomegalovirus pp150 antibody levels	FEV1/FVC	14	1.02(0.99 to 1.05)	0.019	0.238	0.699
BK polyomavirus VP1 antibody levels	FEV1/FVC	18	1.02(0.99 to 1.05)	0.020	0.243	0.699
Human herpes virus 6 IE1A antibody levels	FEV1/FVC	18	1.02(0.98 to 1.05)	0.019	0.295	0.767
Helicobacter pylori VacA antibody levels	FEV1/FVC	14	0.99(0.98 to 1.01)	−0.008	0.309	0.775
Varicella zoster virus glycoproteins E and I antibody levels	FEV1/FVC	17	1.02(0.98 to 1.06)	0.020	0.337	0.775
Anti−human herpes virus 6 IE1A IgG seropositivity	FEV1/FVC	17	0.99(0.98 to 1.01)	−0.007	0.370	0.775
Polyomavirus 2 JC VP1 antibody levels	FEV1/FVC	23	0.99(0.96 to 1.01)	−0.011	0.383	0.775
Chlamydia trachomatis momp A antibody levels	FEV1/FVC	26	1.00(0.99 to 1.00)	−0.004	0.390	0.775
Anti−cytomegalovirus IgG seropositivity	FEV1/FVC	12	0.99(0.97 to 1.01)	−0.010	0.400	0.775
Human herpes virus 7 U14 antibody levels	FEV1/FVC	16	1.02(0.98 to 1.06)	0.017	0.417	0.787
Cytomegalovirus pp52 antibody levels	FEV1/FVC	19	1.01(0.98 to 1.04)	0.010	0.432	0.787
Helicobacter pylori CagA antibody levels	FEV1/FVC	15	0.99(0.98 to 1.01)	−0.007	0.445	0.792
Epstein−Barr virus ZEBRA antibody levels	FEV1/FVC	28	0.99(0.97 to 1.02)	−0.007	0.542	0.844
Cytomegalovirus pp28 antibody levels	FEV1/FVC	12	0.99(0.95 to 1.03)	−0.012	0.582	0.864
Helicobacter pylori Catalase antibody levels	FEV1/FVC	13	1.00(0.98 to 1.01)	−0.005	0.593	0.864
Epstein−Barr virus VCA p18 antibody levels	FEV1/FVC	29	1.01(0.98 to 1.03)	0.006	0.692	0.907
Human herpes virus 6 IE1B antibody levels	FEV1/FVC	22	0.99(0.97 to 1.02)	−0.006	0.701	0.907
Anti−BK polyomavirus IgG seropositivity	FEV1/FVC	9	1.00(0.99 to 1.01)	−0.002	0.710	0.907
Epstein−Barr virus EA−D antibody levels	FEV1/FVC	13	0.99(0.95 to 1.04)	−0.006	0.774	0.907

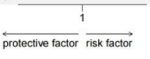

Fig. 1. Forest plot of the MR analysis results for antibody-mediated immune responses and respiratory diseases. All results were obtained using the inverse-variance weighted method. COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1-second; FVC, forced vital capacity; MR, Mendelian randomization; FDR, false discovery rate; CI, confidence interval; OR, odds ratio.

understanding the relationship between immune responses and respiratory diseases. However, we hope that adjusting the sample data sources can further strengthen the conclusions of this study and potentially yield new results to advance the field.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Conflict of Interests

The authors declare that they have no competing interests.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article.

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