Assessing Causal Links Between Cytokines and Human Phenotypes: Mendelian-Randomization Study

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Abstract

Background: Cytokines have been implicated in the initiation of human complex diseases, and the causality between cytokines and human phenotypes has not been systematically explored.

Methods: Bidirectional mendelian randomization (MR) and multivariate mendelian randomization (MVMR) with Bayesian model averaging (MR-BMA) were performed to explore the causality of 41 cytokines and 83 human phenotypes.

Results: Inverse variance weighted (IVW) MR showed that MIG, SCGFb, SCF, and MIF had causal effects on ovarian, colon, breast cancer, and their subtypes. Similarly, MCP1, TRAIL, and SCGFb had causal effects on heart failure (HF), stroke and its subtypes, coronary heart disease (CHD), and myocardial infarction (MI). About neurological diseases: MIP1b had positively causal effects on Alzheimer's disease (AD) and Parkinson's disease (PD), and MIG increased the risk of AD. MR-BMA showed that MIP1b was the top priority risk factor for AD and PD; MCP1 was the top risk factor for HF, stroke, and gout; SCF was the top risk factor for ovarian cancer; PDGFbb and SCGFb were the top risk factor for ischemic stroke (IS) (cardioembolic) and type 1 diabetes, respectively. The results of bidirectional MR showed endocrine diseases and autoimmune diseases influenced the circulating levels of cytokines.

Conclusions: Our findings showed that cytokines have extensive causal effects on human complex diseases. Chemokines (MCP1, MIP1b) and growth factors (PDGFbb, SCGFb, SCF) could be recommended as valuable biomarkers of chronic diseases.

Introduction:

Cytokines are generally produced by stimulated cells, mainly immune cells [1]. As molecular messengers, cytokines allow immune system cells to communicate with each other to produce coordination of target antigens [2]. There have been many studies on proteomics and metabolomics in exploring human complex diseases [3, 4], and a series of important results have been achieved, but few studies were focused on cytokines, a special but vital human circulating substance. Exploring and discovering reliable and effective biomarkers from cytokines can bring tremendous benefits to public health practice.

Researchers concerned about this matter have successively reported the causality of cytokines to human complex diseases, such as Marios K Georgakis et al reported the causal relationship of MCP1 and stroke [5], a study of Shen Li et al on the causality of MCP1, MIP1b, IL13, and breast cancer [6]. However, these studies are only for one category of disease, up to now, there is no systematic study to investigate the bidirectional causality and prioritize true risk factors between cytokines and different categories of chronic diseases. To understand the potential causal role of cytokines for human complex diseases, a comprehensive analysis is needed.

The continuous development of MR methods has played a vital role in exploring the causality of exposure and outcome. In this study, we used the bidirectional MR and MR-BMA developed by Zuber V et

al [7] to jointly verify the causal effects of cytokines on human complex diseases. Screen the most prioritized cytokines could provide a scientific basis for them as valuable biomarkers. We implemented the most comprehensive cytokine genome-wide association study (GWAS), which evaluated 41 cytokines in 8293 healthy subjects of Finnish ancestry [8], and summary-level data on 40 human complex diseases and 43 risk factors that have been published by large GWAS from 36 consortiums.

The purpose of this study is to (1) evaluate the causal relationship between the circulating levels of cytokines and the risk of human complex diseases; (2) MR-BMA was used to screen out the most prioritized cytokines as biomarkers candidates; (3) evaluate the directionality and robustness evidence in the estimated etiological association.

Materials And Methods:

GWAS summary data for cytokines and outcomes

For the cytokines, the summary-level statistics were taken from the largest and most comprehensive GWAS for cytokines, which genotyped up to 8293 Finnish participants from three independent population cohorts: the Cardiovascular Risk in Young Finns Study, FINRISK1997, and FINRISK200225 [8]. We searched for GWAS and MR studies from PubMed to determine human complex diseases and risk factors, and the descriptive characteristics of the 40 human complex diseases and 43 risk factors are provided in Table S1.

Genetic instrumental variables

For each cytokine, the single nucleotide polymorphisms (SNPs) were filtered according to these criteria: (i) a genome-wide threshold of significance ($p < 5\times10^{-8}$); (ii) linkage disequilibrium (LD) ($R^2 < 0.1$, and < 10,000 kb physical distances) [5], which retaining SNPs with the lowest *p*-value as an independent instrument; (iii) find the corresponding SNPs related to cytokines in the GWAS database of the disease (outcome). Additionally, we computed the proportion of variance explained (R^2) for each pair of exposure and outcome. *F*-statistics were applied to quantify the strength of the selected instruments. In general, the *F*-statistic > 10 would be considered strong.

Bidirectional mendelian randomization

Causal estimates are presented per genetically predicted standard deviation (SD) of cytokines. In the current study, we applied the IVW method in the linear MR model. This conventional linear regression for each IV was weighted by inverse variance under a fixed-effect meta-analysis model. In the absence of directional pleiotropy, it provides robust causal estimates [9]. Further, Weighted Median Estimator (WME) and MR-Egger were used for alternative analyses. WME simultaneously assesses the robustness of causal findings [10], this could consider as one of the sensitivity analysis when multiple genetic variants were used as instrumental variables [11]. MR-Egger allows free estimation of the intercept, and a

statistically significant intercept term implies the presence of unbalanced pleiotropy and causal estimates in MR-Egger are less precise than those in IVW [12].

Multivariate mendelian randomization with Bayesian model averaging (MR-BMA) estimates

MR-BMA regards risk factor selection as a variable selection problem in a linear regression model and assumes that there are few real potential causal risk factors. This method: (I) considers all possible combinations of cytokines and generates posterior probability (PP) for each specific model, (□) uses BMA to calculate the marginal inclusion probability (MIP) of each cytokine, where MIP refers to the sum of PP in all possible models with risk factors, (□) will sort all cytokines according to the corresponding MIP to calculate the model average causal estimate (MACE) for each cytokine. (IV) will prioritize the best model according to the PP value of each model. More details are found in the article by Zuber V et al.[7], this multivariate MR method has been successfully used to ranking the priority of metabolites (risk factors) and age-related macular degeneration.

Finally, considering the number of tests in our research, a false-discovery rate (FDR) procedure was used to adjust multiple testing [13]. The consistent and significant results ($p < 0.05$) in main sensitivity analysis at least two different methods (meant consistent results under different assumptions) could also be viewed as robust associations. *p*-value above the corrected significance threshold but < 0.05 in at least one method was also considered as suggestive evidence. All analyses were two-tailed and performed using R software (Version 3.6.1) with packages 'TwoSampleMR'.

Results:

Figure 1 shows our study design and framework of this research. According to our criteria, a total of 217 SNPs were used as instrumental variables for the 27 cytokines which are divided into three categories: interleukin family, chemokines, and growth factors (supplement Table S1). For each pair of cytokines and outcomes, *F*-statistics were greater than or equal to 33.49, which is considered as no weak instrumental bias (supplement Table S6). The diseases (outcomes) included in the study (supplement Table S2) are divided into five categories: cancer and its subtypes, cardiovascular diseases, neurological and mental diseases, endocrine diseases, and autoimmune diseases.

Figure 2 shows IVW estimates of the causality between cytokines and human complex diseases. For cancers and its subtypes, MIG and SCF increased the risk of endometrioid ovarian and ER + breast cancer by 55% and 29% [ORs (95%CIs): 1.55 (1.05–2.30), 1.29 (1.06–1.57)], respectively. SCGFb was positively associated with high grade serous ovarian cancer (OR = 1.09, 95%CI = 1.00-1.19) and malignant neoplasm of colon (OR = 1.49, 95%CI = 1.01–2.19). However, MIF was negatively associated with low grade serous ovarian and breast cancer (Oncoarray) [ORs (95%CIs): 0.51 (0.27–0.95), 0.84 (0.75–0.95)], respectively. For cardiovascular diseases, MCP1 was positively associated with HF, stroke, ischemic stroke (IS) (large arteries), and IS (small blood vessels), [ORs (95%CIs): 1.16 (1.02–1.32), 1.09 (1.03–1.15), 1.22, (1.07–1.39), 1.15, (1.05–1.30)], respectively. TRAIL increased the risk of CHD (OR = 1.03,

95%CI = 1.01–1.06) and MI (OR = 1.03, 95%CI = 1.00-1.06). However, SCGFb decreased the risk of CHD (OR = 0.94, 95%CI = 0.90–0.99) and MI (OR = 0.94, 95%CI = 0.89-1.00). For neurological and mental diseases, MIG was positively associated with schizophrenia (OR = 1.17, 95%CI = 1.01–1.36) and AD (OR = 1.38, 95%CI = 1.10–1.72). Similarly, MIP1b increased the risk of AD (OR = 1.05, 95%CI = 1.01–1.09) and PD (OR = 1.06, 95%CI = 1.02–1.10), but decreased the risk of depression (OR = 0.95, 95%CI = 0.92–0.98). Additionally, the interleukin family include IL5, IL7, IL10, IL12p70 and IL13 increased the risk of anxiety disorders by 39%, 16%, 18%, 16% and 12%, [ORs (95%CIs): 1.39 (1.10–1.75), 1.16 (1.05–1.28), 1.18 (1.06–1.31), 1.16 (1.08–1.24), 1.12 (1.05–1.20)], respectively. And IL5, IL7, IL10 and IL13 decreased the risk of CHD by 12%, 6%, 7% and 4%, [ORs (95%CIs): 0.88 (0.78–0.99), 0.94 (0.89-1.00), 0.96 (0.92-1.00)], respectively.

Figure 3 shows the results of MR-BMA for selecting causal risk factors of human complex diseases from a large number of candidate cytokines. It shows the top models (i.e.sets of cytokines) ranked according to their model PP, and the top cytokines according to their MIP. In the interleukin family, IL2ra, IL13, IL16, IL18, and IL17 were the top risk factor for multiple sclerosis (MS) (OR = 1.27; PP = 0.13), anxiety disorders (OR = 1.12; PP = 0.22), ER- breast cancer (iCOGS) (OR = 1.11; PP = 0.07), systemic lupus erythematosus (SLE) (OR = 1.17; PP = 0.11), inflammatory bowel disease (IBD) (OR = 1.17; PP = 0.14), respectively. In the chemokines, MCP1 was the top risk factor for HF (OR = 1.18; PP = 0.08), stroke (OR = 1.09; PP = 0.16), and gout (OR = 1.16; PP = 0.17). MIP1b was the top risk factor for AD (OR = 1.05; PP = 0.21), PD (OR = 1.07; PP = 0.19), and rheumatoid arthritis (RA) (OR = 0.95; PP = 0.17). MIG and Eotaxin were the top risk factor for the IS (large artery) (OR = 1.21; PP = 0.12) and schizophrenia (OR = 0.94; PP = 0.31), respectively. For the growth factors, PDGFbb was the top risk factor for IS (cardioembolic) (OR = 1.16; PP = 0.17) and type 2 diabetes (OR = 0.91; PP = 0.11). SCGFb was the top risk factor for malignant neoplasm of colon (OR = 1.49; PP = 0.03) and type 1 diabetes (OR = 1.12; PP = 0.07), and SCF was the top risk factor for high grade serous ovarian cancer (OR = 1.13; PP = 0.2), clear cell ovarian cancer (OR = 1.29; PP = 0.04), and hypertensive diseases (OR = 1.07; PP = 0.08). More details about the results of MR-BMA can be found in the supplement Table S4.

As is shown in Fig. 4, the bidirectional MR study was used to test whether human complex diseases altered circulating cytokine levels. Most types of cancers were not associated with an increase or decrease of circulating cytokine levels, only high-grade serous ovarian cancer had a suggestive association with increased IL2ra (β = 0.112) and HGF (β = 0.088). However, endocrine diseases are causally related to a wide range of cytokines, such as type 1 diabetes influenced the circulating levels of IL16 (β = 0.048), IP10(β = 0.082), MIG (β = 0.101), CTACK (β=-0.047), and gout increased the circulating levels of IL5 (β = 0.145), MIF (β = 0.100). Autoimmune diseases include RA and SLE increased the circulating levels of chemokines and growth factors. RA increased the circulating levels of IL5 (β = 0.074), IL17 (β = 0.069), MIG (β = 0.105), MIP1b (β = 0.065), and SCGFb (β = 0.061). SLE increased the circulating levels of IP10 (β = 0.044), MIG (β = 0.054), and bNGF (β = 0.037).

We also performed the above statistical test on the causal relationship between cytokines and risk factors (anthropometric indicators, blood biochemistry, life behavior), which is found in the

supplementary Table S3, S5, S7 and Figure S1-S4. IVW results showed that all of the IL8, IL7, MIG, MIPb, Eotaxin, PDGFbb, and MIF have causal effects on more than four kinds of risk factors. For life behavior: IL10, IL18, GROa, and IP10 were the top risk factor for age at menopause, cigarettes per day, cognitive performance, systolic blood pressure. Eotaxin was the top risk factor for waist circumference and age of smoking initiation. About blood biochemistry, IL18, IL10, IL17, MIG, MIP1b, CTACK, and TRAIL were the top risk factor for Vitamin B12, Leptin, Lipoprotein A, Albumin, Urate, Apolipoprotein B, Omega-6 fatty acids, respectively.

Discussion:

Our findings suggest that genetic predisposition to higher levels of the 24 cytokines (interleukin family: IL2ra, IL5, IL7, IL10, IL12p70, IL13, IL16, IL18, IL17; chemokines: IP10, MCP1, MIG, MIP1b, CTACK, Eotaxin, GROa; growth factors: bNGF, PDGFbb, SCGFb, VEGF, SCF, TNFb, TRAIL, and MIF) are associated with the risk of 31 human complex diseases. The results were robust in the alternative MR methods WME (in the supplement Figure S5). We also adopted MR-BMA to determine the top prioritized risk factors for every 31 diseases. Finally, we discovered a reverse causal relationship between certain diseases and the circulating levels of cytokines. Collectively, our findings showed that most cytokines have extensive causal effects on human complex diseases. Chemokines (MCP1, MIP1b) and growth factors (PDGFbb, SCGFb, SCF) could be used as promising biomarkers of chronic diseases.

From IVW analysis, our results showed that chemokines have a widespread causal relationship with cancers. MIG increased the risk of endometrioid ovarian cancer by 55%, which is consistent with animal experiment results of Denarda Dangaj et al. [14]. SCF and SCGFb increased the risk of ER + breast and high-grade serous ovarian cancer by 29% and 9%, respectively. Our literature search found no reports of observational studies on the correlation between SCF or SCGFb and breast or ovarian cancer incidence. SCF is the ligand of c-Kit, a member of the RTKs family, expression of the SCF/c-Kit axis is associated with tumor cell migration [15]. Invasive migration of tumor cells is stimulated by receptor tyrosine kinases (RTKs) and is regulated by growth factors [15]. SCF and SCGFb all belong to growth factors, the possibility of becoming biomarkers of these two cytokines on breast and ovarian cancer may need more evidence. However, MIF decreased the risk of breast cancer (oncoarray) and low-grade serous ovarian cancer by 16% and 49%. MIF is an important regulator of innate immunity [16]. Cell injury results in MIF release which then interacts with CD74. MIF-CD74 signaling activates pro-survival and proliferative pathways that protect the host during injury [17], the protective effect of MIF may cause the risk of breast and ovarian cancer to reduce. Besides, the biological functions of chemokines have been described in multiple malignancies [18–22]. The biological mechanism of chemokines and cancers needs to be confirmed by more biology experiments. For the extensive causality of cytokines and cardiovascular disease. Our results are consistent with Marios K. Georgakis et al.[5], and both showed that MCP1 had causal effects on stroke and its subtypes. In addition, we also found TRAIL and SCGFb had causal effects on CHD [ORs, 95%CIs: (1.03, 1.01–1.06); (0.94, 0.90–0.99)] and MI [ORs, 95%CIs: (1.03, 1.00-1.06); (0.94, 0.89-1.00)], respectively. TRAIL has been implicated as a pathogenic or protective factor in various cardiovascular diseases [23, 24]. H Björkbacka et al. demonstrates that subjects with high levels of stem

cell factors have a lower risk of cardiovascular events and death [25]. Therefore, reducing the TRAIL and SCGFb circulation levels could beneficial to the cardiovascular system. For neurological and mental diseases, MIG was positively associated with schizophrenia and AD. MIG was often regarded as a tumor biomarker, such as MIG/CXCL9 has been identified as a candidate biomarker of adoptive T cell transfer therapy in metastatic melanoma [26]. But our results show MIG was also significantly and positively associated with schizophrenia and AD. IVW showed MIP1b increased the risk of AD (OR = 1.05, 95%CI = 1.01–1.09) and PD (OR = 1.06, 95%CI = 1.02–1.10), but decreased the risk of depression (OR = 0.95, 95%CI = 0.92–0.98).

MR-BMA can prioritize the risk of a group of risk factors with high genetic similarity [7]. Using this method, we further prioritize the cytokines that have been screened in TSMR to find the cytokine which is deserved the most attention. For the interleukin family, IL2ra, IL13, IL16, IL18, IL17 are just causally related to only one disease. Therefore, the results of interleukins in this study are still not stable enough compared to chemokines and growth factors. Previous studies have shown that MCP1 is a risk factor for stroke and its subtypes [5, 27], the MR-BMA further confirmed that MCP1 is the top risk factor for stroke and its subtypes. MCP1 may be a valuable biomarker and drug target for the treatment of stroke and its subtypes. Using this MVMR method, the results were consistent with IVW both showed that MIP1b was the causal and top risk factor for AD and PD. Previous studies such as John S. K. Kauwe et al. [28] found MIP1b and AD may have an association because it could induce the gathering of astrocytes and microglia in senile plaques. In a longitudinal study, MIP1b has been shown to predict their changes over time in older people with PD [29]. MIP1b is involved in neurodegeneration by promoting central nervous system (CNS) inflammation [30]. AD and PD have many similarities in pathology, and the role of neuroinflammation in the occurrence and development of these two diseases is becoming more and more important [31]. It is the first time that IVW and MR-BMA were jointly used to verify the causality of MIP1b and AD and PD. These diseases are the top two in the incidence of neurodegenerative diseases [32], MIP1b may become a new clinical drug target and a potential biomarker for AD and PD, and has great application prospects. However, IP10, MCP1, MIG, RANTES, and Eotaxin, which are also chemokines, were not among the top three risk factors for these two neurological diseases (the supplementary S1 for details). About the causality between chemokine family and neurological diseases, we are cautious here and look forward to more summary-level data sharing of GWAS studies on cytokines, and could more confidently determine the causal effects of chemokines on neurological diseases. In addition to the above, MR-BMA showed growth factors include PDGFbb was the top risk factor for IS (cardioembolic); SCGFb was the top risk factor for malignant neoplasm of the colon and type 1 diabetes; and SCF was the top risk factor for high grade serous ovarian cancer, clear cell ovarian cancer, and hypertensive diseases.

Last but not least, we adopted a bidirectional MR analysis to evaluated whether there is a reverse causal effect where disease status consequently altered circulating cytokine levels. Most types of cancer did not alter circulating cytokine levels. However, endocrine diseases are causally related to a wide range of cytokines, such as type 1 diabetes influenced circulating levels of IL16, IP10, MIG, CTACK. Autoimmune diseases include RA and SLE increased circulating levels of chemokines (IP10, MIG, and MIP1b) and

growth factors (bNGF, and SCGFb). These results suggest that cytokines may be a downstream consequence of endocrine diseases and autoimmune diseases. Further analysis of the association of upstream factors and other cytokines and inflammation on human complex diseases would provide more evidence for the etiology.

Regarding cytokines for the treatment of human complex diseases for a long time, the current more reliable cytokine therapy has been verified in melanoma and renal cell carcinoma. GWSA research has shown its advantages in exploring the association of human signs and risk factors with diseases [33], but true precision medicine hopes to find the molecular mechanism that is most concerned with human complex diseases [34]. Therefore, our systematic and comprehensive causal evaluation confirms the important role of cytokines in the development and progression of diseases.

Overall, our research has some advantages. First, we used the most comprehensive GWAS data set for cytokines and human complex diseases. Second, according to the literature review, our group combined the bidirectional MR methods and MR-BMA based on the Bayesian model framework to jointly explore the most promising cytokines. From the cytokines with established causal effects to find the most noteworthy of further research, this is very useful for reducing the failure rate of phase II and phase III clinical trials. Third, this study also showed the reverse causality of the human complex diseases and cytokines, suggest that cytokines may be a downstream consequence of endocrine diseases and autoimmune diseases. Of course, our research also has some limitations. Though the MR method could rule out confounding, it has trouble in dealing with horizontal pleiotropic effects, especially the common gene regulation mechanism across cytokines. Another limitation is that the causal effects of cytokines determined in this study are only statistically causality. Whether they can be transformed into clinical and public health benefits requires more animal experiments and clinical trials to assess. Despite these limitations, our research still provides an overview of relevant fields, and most of the results could be explained by biological mechanisms. The role of cytokine levels in human complex diseases needs further verification in causal inference studies with larger sample sizes.

Conclusion:

Collectively, our findings showed that most cytokines have extensive causal effects on human complex diseases. Chemokines (MCP1, MIP1b) and growth factors (PDGFbb, SCGFb, SCF) could be used as valuable biomarkers of chronic diseases.

Declarations

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Authors' contributions: Fuzhong Xue, Shucheng Si, and Kai Zhang have the conception. Shucheng Si did the statistical analyses and Kai Zhang drafted the initial manuscript. All authors participated in the interpretation of the results, edited and reviewed the manuscript.

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Ethics approval and consent to participate: Our research only involved summary-level statistics so ethical approval was not applicable but has been approved in the original research.

Availability of data and materials: Researchers may have access to this data from the original research shown in the supplement material.

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Figures

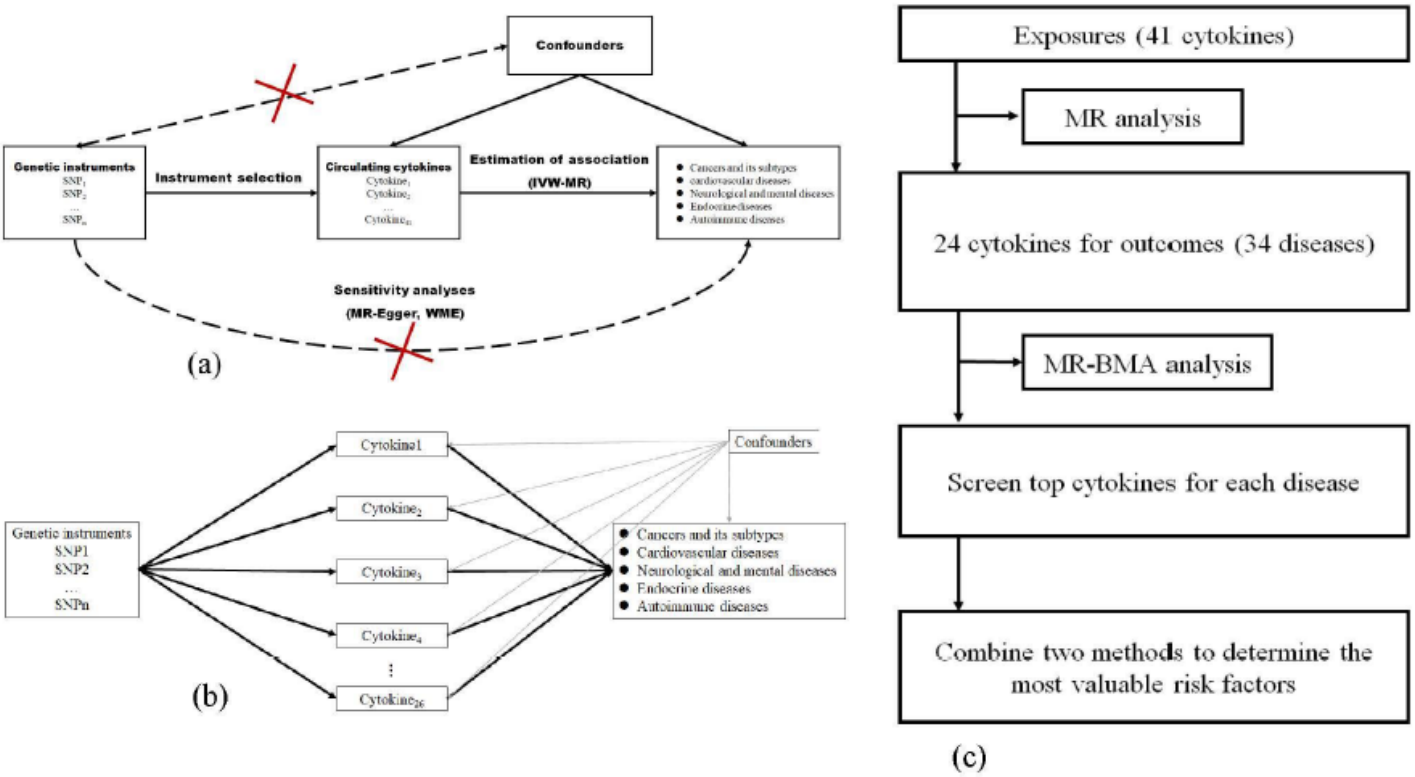

Figure 1

Study design and framework of this research. Panel (a) showed the framework of bidirectional Mendelian randomization. The causal effects of candidate exposure on outcome were calculated in turns. Panel (b) was the Multivariate mendelian randomization with Bayesian model averaging (MR-BMA) estimates. Panel (c) shows the brief process framework of our research. We first use the MR method to determine the causal relationship between cytokines and 40 kinds of diseases from the cytokines that have found instrumental variables. Then apply the MR-BMA method to rank the importance of these cytokines to determine the most valuable cytokines.

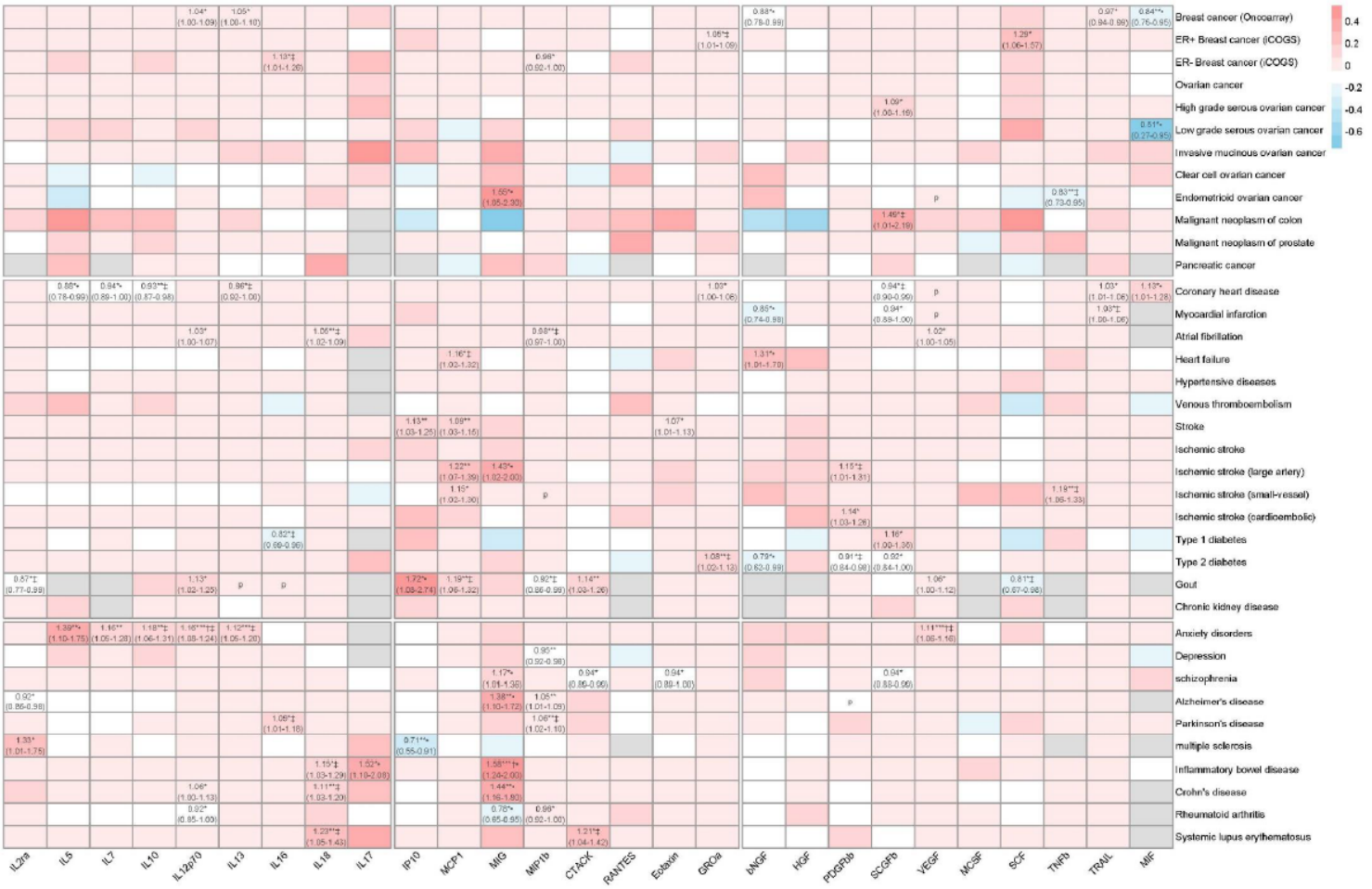

Figure 2

Causal effects of genetically determined cytokines on human complex diseases by IVW-MR analysis. The heat map showed the Odds Ratios (ORs) and confidence intervals (CIs) of cytokines on human complex diseases. The depth of the color represents the size of the effect values (log OR), where red represented the positive association and blue represented the negative association. Here, only significant results ($p<0.05$) were marked with values of OR (95%CI). • for one instrumental variable, only Wald ratio method was applied; * $p<0.05$; ** $p<0.01$; *** $p<0.001$; † $p<0.05$ in both IVW and WME MR analysis; ‡ p-value passed the FDR correction

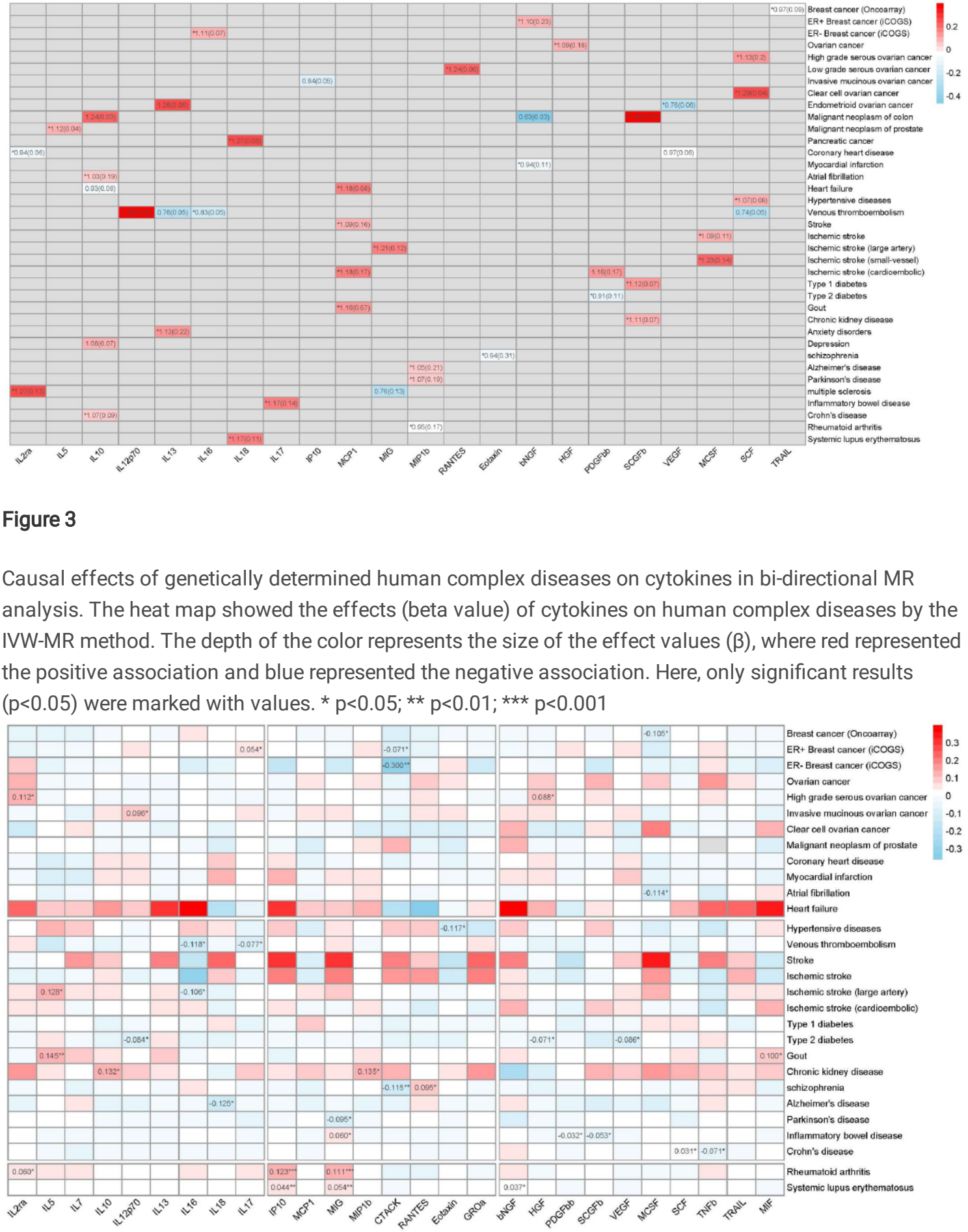

Figure 3

Causal effects of genetically determined human complex diseases on cytokines in bi-directional MR analysis. The heat map showed the effects (beta value) of cytokines on human complex diseases by the IVW-MR method. The depth of the color represents the size of the effect values (β), where red represented the positive association and blue represented the negative association. Here, only significant results ($p<0.05$) were marked with values. * $p<0.05$; ** $p<0.01$; *** $p<0.001$

Figure 4

Results of top models in MR-BMA analysis for genetically determined cytokines on human complex diseases. The heat map showed the Odds Ratios (ORs) of blood cell traits on breast cancer. The depth of the color represents the size of the effect values (log OR), where red represented the positive association and blue represented the negative association. Each row of the heat map represents a multivariate model. The cytokines marked with color and values represent the factors included in the multivariate MR analysis while the gray grid indicated the factors not included in the top model by MR-BMA. The number in parentheses indicates the posterior probability (PP) of this model. *top risk factors with the largest marginal inclusion probability (MIP).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.pdf