Research in China about the biological mechanisms that potentially link socioenvironmental changes and mental health: a scoping review

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Summary

China's rapid socioeconomic development since 1990 makes it a fitting location to summarise research about how biological changes associated with socioenvironmental changes affect population mental health and, thus, lay the groundwork for subsequent, more focused studies. An initial search identified 308 review articles in the international literature about biomarkers associated with 12 common mental health disorders. We then searched for studies conducted in China that assessed the association of the identified mental health related-biomarkers with socioenvironmental factors in English-language and Chinese-language databases. We located 1330 articles published between 1 January 1990 and 1 August 2021 that reported a total of 3567 associations between 56 specific biomarkers and 11 socioenvironmental factors: 3156 (88·5%) about six types of environmental pollution, 381 (10·7%) about four health-related behaviours (diet, physical inactivity, internet misuse, and other lifestyle factors), and 30 (0·8%) about socioeconomic inequity. Only 245 (18·4%) of the papers simultaneously considered the possible effect of the biomarkers on mental health conditions; moreover, most of these studies assessed biomarkers in animal models of mental disorders, not human subjects. Among the 245 papers, mental health conditions were linked with biomarkers of environmental pollution in 188 (76·7%), with biomarkers of health-related behaviours in 48 (19·6%), and with biomarkers of socioeconomic inequality in 9 (3·7%). The 604 biomarker-mental health condition associations reported (107 in human subjects and 497 in animal models) included 379 (62·7%) about cognitive functioning, 117 (19·4%) about anxiety, 56 (9·3%) about depression, 21 (3·5%) about neurodevelopmental conditions, and 31 (5·1%) about neurobehavioural symptoms. Improved understanding of the biological mechanisms linking socioenvironmental changes to community mental health will require expanding the range of socioenvironmental factors considered, including mental health outcomes in more of the studies about the association of biomarkers with socioenvironmental factors, and increasing the proportion of studies that assess mental health outcomes in humans.

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Introduction

Background

China has experienced rapid urbanisation and economic development during the last three decades. Like many other countries, rapid development in China has resulted in environmental pollution, including air pollution,[1] noise pollution,[2] heavy metal emissions,[3] and persistent organic pollutants.[4] Over the same period, the overall socioeconomic condition of Chinese citizens has improved dramatically, but socioeconomic inequality

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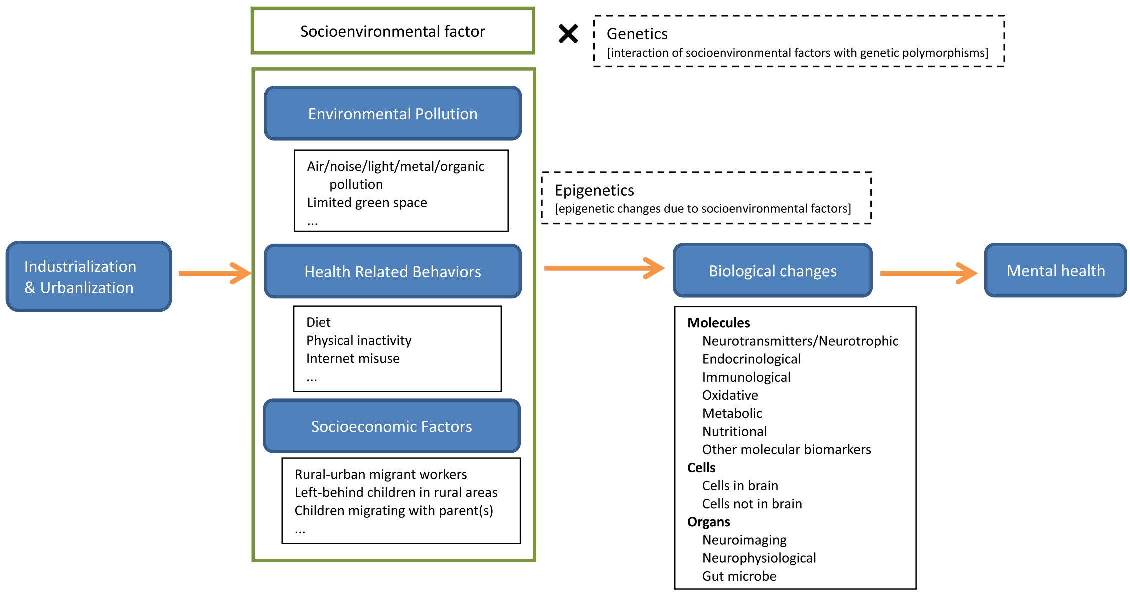

Figure 1. Framework of the relationship of socioenvironmental changes, biological changes, and mental health in China.

between different population subgroups has also increased. For example, rural-to-urban migration of young adults for work has resulted in a concurrent increase in the numbers of left-behind children and elderly relatives in rural communities.[5] These socioeconomic changes are accompanied by changes in health-related behaviours, including increased caloric intake,[6] decreased physical activity,[7] and increased screen-based activity (primarily in urban communities).[8] Moreover, these socioenvironmental changes are, in turn, closely related to population mental health. For example, air pollution increases hospital admissions for schizophrenia,[9] depression,[10] and anxiety[11]; the 'left-behind' experience increases the risk of experiencing several types of psychological problems[12]; and the synergetic effect of increased caloric intake, decreased physical activity, and excessive internet use has caused dramatic biological changes to China's youth, including earlier puberty,[13] metabolic abnormalities,[14] and perturbations of gut microbiota[15] —changes that can have direct and indirect effects on mental health. A recent national psychiatric epidemiological survey of adolescents 6 to 16 years of age[16] reported a 17·5% prevalence of any psychiatric disorder—the highest prevalence ever reported in China.

Numerous biomarkers of mental disorders have been identified.[17–21] Understanding the activity profiles of these biomarkers holds the (as yet unfulfilled) promise of improving the validity of psychiatric diagnoses and the specificity of treatments for mental disorders. At the same time, a growing literature is supporting the hypothesis that changes in socioenvironmental factors (including environmental pollutants, economic inequity, and human behavioural patterns) can induce changes in some of these mental health-related biomarkers that, in turn, affect biological processes which influence the incidence, severity, and course of a variety of mental disorders. These biomarkers could be the key to understanding the relationship between socioenvironmental changes and community mental health. Clarifying the biological mechanisms that link socioenvironmental change to mental health conditions would help develop early interventions to *prevent* mental disorders—a long-term goal of mental health professionals that has remained elusive. However, we are only beginning to investigate the complex, uncharted network of inter-relationships between socioenvironmental factors, biomarkers, and mental health. Our conceptual model of these hypothesised relationships is shown in Figure 1.

China has experienced the most rapid economic development of any country in the world. However, the gap in the socioeconomic status between different parts of the country (particularly between urban and rural communities) is one of the greatest in the world. This socioeconomic differential makes China an ideal setting to assess the complex relationships between changes in 'socioenvironmental agents' during socioeconomic development, biological mechanisms, and mental disorders. This scoping review is an initial step that aims to integrate the diverse research conducted in this field in China and, thus, lay the groundwork for subsequent, more focused studies.

Objectives

This scoping review aims to 1) systematically map currently available research and other information sources about the biological mechanisms that link socioenvironmental change and mental illnesses and 2) identify any critical gaps in current knowledge about this evolving field.

The specific research questions addressed in the review are:

1) *Which of the biomarkers associated with mental disorders are affected by socioenvironmental changes in China?*
2) *What links have been identified among socioenvironmental agents, biological changes, and mental health conditions in China?*

Methods

Protocol registration

Our protocol was drafted based on the methods described in the checklist of the PRISMA extension for scoping reviews (PRISMA-ScR)[22]; the article search strategy, article selection criteria, and data items extracted from selected documents were revised based on the findings of a pilot study. The final protocol was registered prospectively with the Open Science Framework on 23 August 2021 (https://osf·io/m8gzj).

Selection criteria

Inclusion criteria.

- Timeframe. From 1990 to 2021. China's dramatic social and environmental changes started three decades ago during China's economic reform era.
- Participants. General population or people with mental health problems living in mainland China OR animals OR cells involved in experiments conducted in mainland China.
- Socioenvironmental agents. Social and environmental factors that have both changed dramatically in China during the last three decades and gained attention due to their potential effect on mental health. As shown in our conceptual framework (Figure 1), they include six types of environmental pollution (air pollution, light pollution, noise pollution, heavy metals pollution, persistent organic pollutants, and limited green space), four types of health-related behaviours that have been associated with adverse effects on mental health (diet, physical inactivity, internet misuse, and other lifestyle factors), and one socioeconomic factor (socioeconomic inequality).
- Biomarkers. Biomarkers considered in this scoping review are those identified in review articles about biomarkers associated with mental health disorders. These articles were located using MeSH terms in the PUBMED database for reviews published between July 2016 and July 2021 that identified biomarkers associated with 12 mental health conditions: Schizophrenia Spectrum and Other Psychotic Disorders, Bipolar and Related Disorders, Mood Disorders, Anxiety Disorders, Personality Disorders, Feeding and Eating Disorders, Trauma and Stressor Related Disorders, Neurodevelopmental Disorders, Alzheimer's Disease and cognitive dysfunction, Sleep-Wake Disorders, Substance-related Disorders, and suicide. We used a broad definition of 'biomarker'[23–27] that includes both traditional biomarkers based on analytes or properties of biological systems (e.g., plasma, urine, cerebrospinal fluid) and other objectively measured characteristics of normal biological processes, including neuroimaging and neurophysiological markers. The function of a biochemical molecule in different tissues or cells can differ, so we only included studies that measured molecular biomarkers in tissues relevant to mental health (including the brain, cerebrospinal fluid, blood, urine, or gut) or *in vitro* cells commonly used to study mechanisms related to mental health (including brain cells, stem cells, or immunological cells). Based on the 308 relevant reviews located, we identified 56 specific biomarkers associated with the 12 mental health conditions that were classified into 13 categories of biomarkers: neurotransmitter, neurotrophic, endocrinological, oxidative, immunological, metabolic, nutritional, other molecular biomarkers, cells not in the brain, cells in the brain, neuroimaging, and gut microbe. The search terms to identify these reviews, the complete list of the identified biomarkers, and the mental health conditions the identified biomarkers are associated with are shown in Supplementary Table S1.
- Mental health condition. Any mental disorder or psychological distress reported in studies of human beings or studies of animal models of mental health disorders.
- Study design. No restriction. Policy documents are not likely to include evidence related to the interaction of socioenvironmental agents, biological markers, and mental health, so the search for eligible articles is limited to peer-reviewed publications and Chinese-language theses and dissertations that were not subsequently published in peer-review journals.

Exclusion criteria.

- The study is not published in English or Chinese.
- The report is a protocol or an abstract without a corresponding full-text article.
- The study is about SARS, COVID-19, or traditional Chinese medicine. There are many such reports, but they do not assess issues central to this review

(i.e., the biological mechanisms connecting socioenvironmental change and mental disorders), so they are excluded from the search.

Search strategy

Information sources. A systematic search was conducted in three English-language databases (Web of Science, Pubmed, PsychInfo) and two Chinese-language databases (CNKI and Wanfang) for peer-reviewed publications or Chinese-language theses and dissertations published between 1 January 1990 and 1 August 2021. In cases where a thesis or dissertation was published in a peer-reviewed journal, only the published paper was retained. The reference lists of included articles were reviewed to identify other potentially eligible studies not identified in the electronic searches. Only 'Core Journals' were included in the searches of Chinese databases. (Core Journals, classified by researchers in the Peking University library and experts of related institutions, are widely acknowledged as the highest quality Chinese-language journals, analogues to the journals listed in the Web of Science Core Collection.)

Search. The search strategies, including the terms used for each block of factors (socioenvironmental factors, biomarkers, mental health conditions, China-based reports, and excluded papers [about SARS, COVID, or traditional Chinese medicine]), used for the three English-language databases are shown in Supplementary Table S2. The corresponding search terms used for the two Chinese-language databases are shown in Supplementary Table S3.

Studies that investigate the mechanisms via which the biological changes associated with socioenvironmental factors affect mental health conditions directly address the central issue considered in this report and, thus, are prioritised in our analyses. However, given the high cost of such studies, few studies simultaneously assessed all three components—socioenvironmental factors, biomarkers, and mental health conditions. Many of the available studies that provide indirect evidence about the effect of socioenvironmental factors on biomarkers for mental health focus on the relationship of these factors with other illnesses. For example, studies about air pollution-induced changes in inflammatory and oxidative biomarkers that focus on respiratory and cardiovascular diseases also provide indirect evidence of air pollution's effect on mental health because these biomarkers have been independently associated with mental health outcomes. To avoid excluding such studies from our review, studies included in the review did not necessarily need to consider mental health outcomes, but they did need to consider biomarkers that have previously been associated with one or more of the 12 mental health disorders of interest—that is, the biomarkers associated with mental disorders identified in our preliminary assessment of 308 review articles published in the international literature (discussed above).

Selection of Sources of Evidence. We initially screened identified records based on their titles and abstracts. The full texts were obtained for further screening if the eligibility criteria were met. Two independent reviewers carried out each step of this two-step screening process. The inter-rater reliability of pairs of reviewers was improved through iteratively revising the eligibility criteria in a pilot study until they achieved the desired level (ICC=0·90).[28] Any disagreements about inclusion were discussed, and if a consensus was not reached, a third (senior) reviewer made the final decision. Reasons for excluding papers are reported in the PRISMA flowchart[29] (Figure 2).

Data extraction

Data charting process. A data charting form for recording relevant information from included papers was developed and pilot-tested by the review team based on the recommendations of Arksey and O'Malley.[30] During the pilot study, four senior reviewers coded the same 50 eligible publications, discussed discrepancies, and subsequently finalised the items, definitions, and coding instructions in the data charting form. After the final version of the data charting form (Supplemental Table S4) was prepared, we recruited and trained 12 medical school graduate students to chart data from the 1330 papers included in the analysis. Each included paper was independently coded by one of the graduate students and checked by an experienced reviewer; disagreements were resolved by discussion between the two researchers or, if necessary, by a third (senior) researcher.

Items included in the data charting form.

1) characteristics of the study/report (date of publication, location of research, type of data, study design, time period(s) report refers to, geographic region(s) covered, sampling method, and sample size)
2) characteristics of human/animal subjects (*human*: age, gender, residence, cohort) (*animal*: species, disease model)
3) socioenvironmental agent. (types of socioenvironmental agents considered and method of assessing them)
4) biological markers (types of biomarkers considered, tissue used to assess biomarker [if relevant], and method of assessing the biomarker)

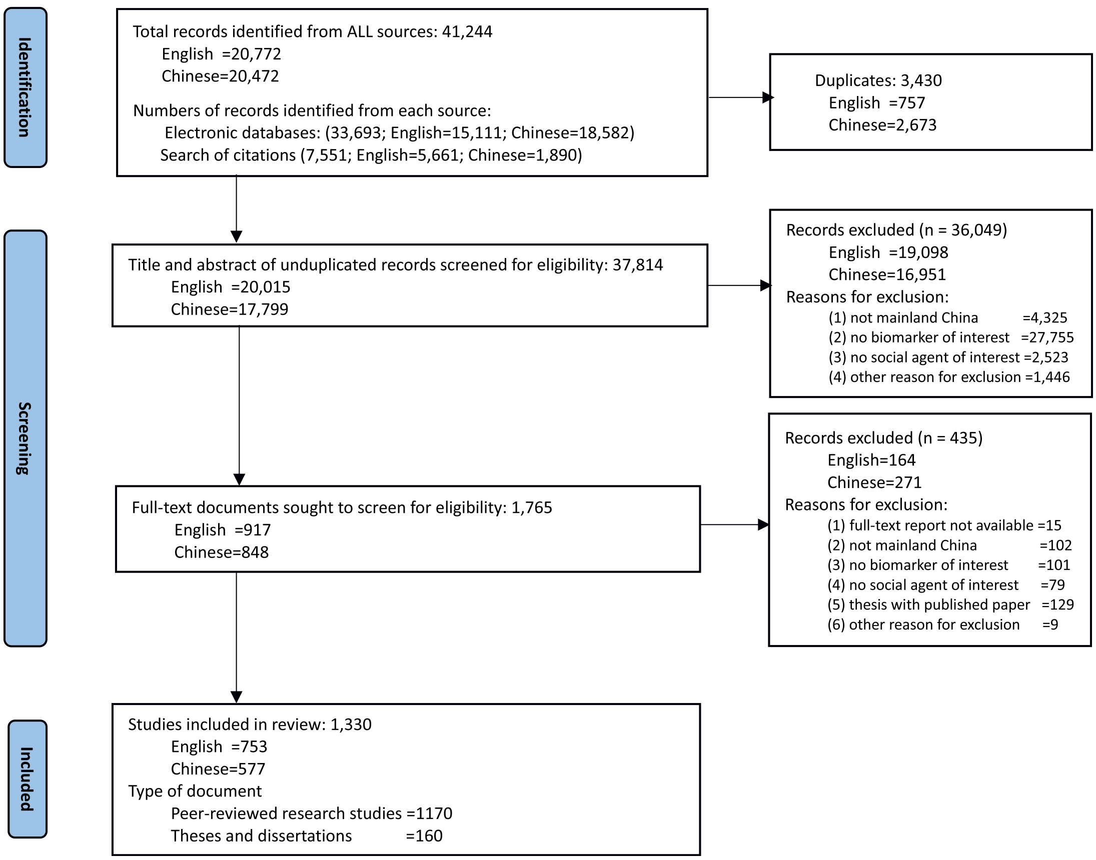

Figure 2. PRISMA flowchart.

5) mental health condition (method of assessing mental health status, specific diagnosis of mental disorder, reported mental health outcome of an exposure)
6) main goal/hypothesis of the study
7) main results of the study
8) reported relationship of socioenvironmental factors, biomarkers, and mental health conditions

Synthesis of results

We used the 'descriptive-analytical' method[30] from the narrative tradition and applied a common analytical framework to all the primary research reports. The analytic framework for synthesising the data included three categories of socioenvironmental factors subclassified as 11 specific socioenvironmental factors; 13 categories of biomarkers at the molecular, cellular, organ, and organism levels subclassified as 56 specific biomarkers; and five categories of mental health conditions subclassified as nine specific types of mental health conditions. The five categories of mental health conditions included three types of mental disorders (anxiety, depression, and neurodevelopmental disorders), cognitive functioning, and neurobehavioural symptoms; the three types of mental disorders and the cognitive functioning category are subclassified into conditions identified in animal-model studies and conditions identified in studies with human subjects. We report the specific biomarkers assessed in studies from mainland China, the socioenvironmental factors that affected these biomarkers, and the mental health conditions associated with each category of biomarker. Some descriptive statistics were based on the number of papers with specific characteristics (e.g., the proportion of papers originating in different Chinese provinces), but many of the included papers considered multiple categories of biomarkers, socioenvironmental factors, or mental health conditions, so several analyses were based on the number of reported biomarker*socioenvironmental factor associations with specific characteristics (e.g., the proportion of all reported associations related to air pollution) or the number of biomarker*mental health condition associations with specific characteristics (e.g., the proportion of all reported associations about depressive conditions). The R 4.1.0 software package was used to compute descriptive statistics and generate figures based on the data.

Role of the funding source

The funding sources were not involved in designing the study; in the collection, analysis, or interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Results

As shown in the PRISMA flowchart (Figure 2), the original search yielded 33,693 records, and 7,551 additional articles were identified after checking the citations of these records. After removing duplicates, screening titles and abstracts, and screening the full text of potentially relevant articles, 1330 records met the inclusion and exclusion criteria. Among these articles, 577 (43·4%) were Chinese-language research articles and theses. The citations for these 1330 papers are provided in the Supplementary Materials, and a description of the characteristics and types of factors assessed in the articles are listed in Supplementary Excel Table 1; interested readers can use the column-specific filter function of Excel to search for articles about specific biomarkers, socioeconomic factors, or mental health conditions.

Spatiotemporal distribution of included publications

As shown in Figure 3, the number of studies about the association of biomarkers and socioenvironmental factors of interest conducted in mainland China increased over time, particularly after 2005. Before 2012 Chinese-language publications exceeded English-language publications, but starting in 2012 English-language publications exceeded Chinese-language publications. As shown in Figure 4, most publications were from institutions located in China's more developed eastern provinces and provincial-level municipalities: the top five locations were Hubei (*n*=126), Beijing (*n*=123), Shanghai (*n*=114), Liaoning (*n*=110), and Jiangsu (*n*=102).

Target populations considered in included publications

Among the 1330 identified articles, 1317 articles considered a single target group, 11 articles considered two separate target groups (e.g., two kinds of cells; animals and humans), and two articles considered three separate target groups (shown in Supplementary Table S5), resulting in a total of 1345 distinct target-group-specific studies. Studies performed in humans accounted for 36·7% (493/1345) of all studies, including 346 cross-sectional studies, 100 longitudinal studies, 26 case-control studies, 18 clinical trials, and three retrospective studies (Figure 5A (1)).

Among these 493 studies in humans, 92 (18·7%) were community-based studies that randomly selected participants, while 174 (35·3%) were community-based studies that did not randomly select participants; 79 (16·0%) were exclusively conducted in rural areas (most were about socioeconomic inequity), and 160 (32·5%) were exclusively conducted in urban areas (most were about pollution); and 55 (11·2%) enrolled pregnant women, 78 (15·8%) enrolled workers with high exposure to pollution, 75 (15·2%) enrolled children, 7 (1·4%) enrolled adolescents, 35 (7·1%) enrolled college students, and 23 (4·7%) enrolled elderly adults.

Studies performed in animal models accounted for 57·0% (767/1345) of all studies (Figure 5A (2)): the most frequently used animals in these studies were rats (*n*=347), mice (*n*=330), and zebrafish (*n*=31). Studies that analysed specific cell types accounted for 6·3% (85/1345) of all studies (Figure 5A (3)). Among these studies, 57 used animals' brain cells (including neurons, astrocytes, microglia, and pituitary cells), four used human

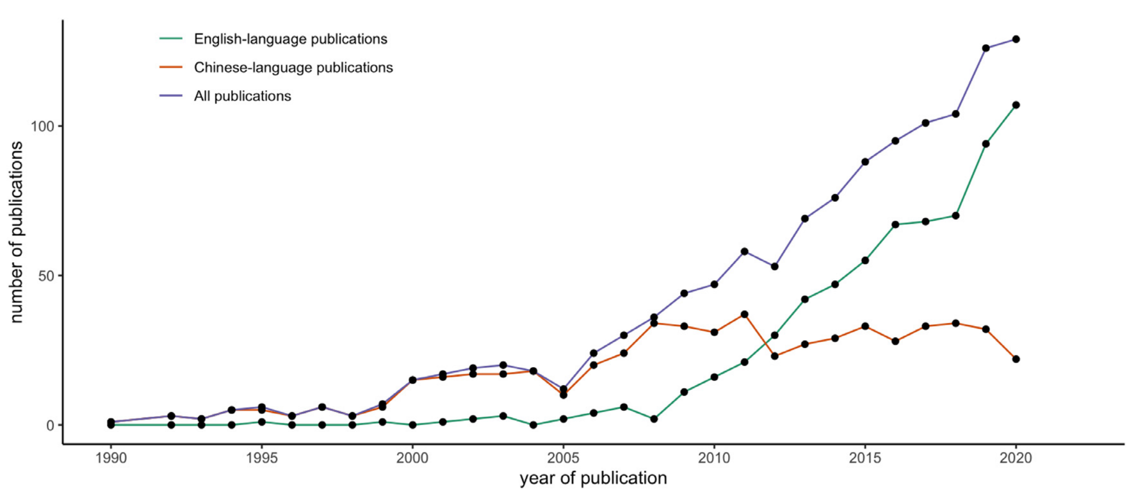

Figure 3. Annual number of articles included in the analysis published from 1990 to 2020. (*n*=1228; 102 articles published in 2021 were not included).

Figure 4. Provincial distribution of 1330 papers included in the analysis based on location of the institute that conducted the study.

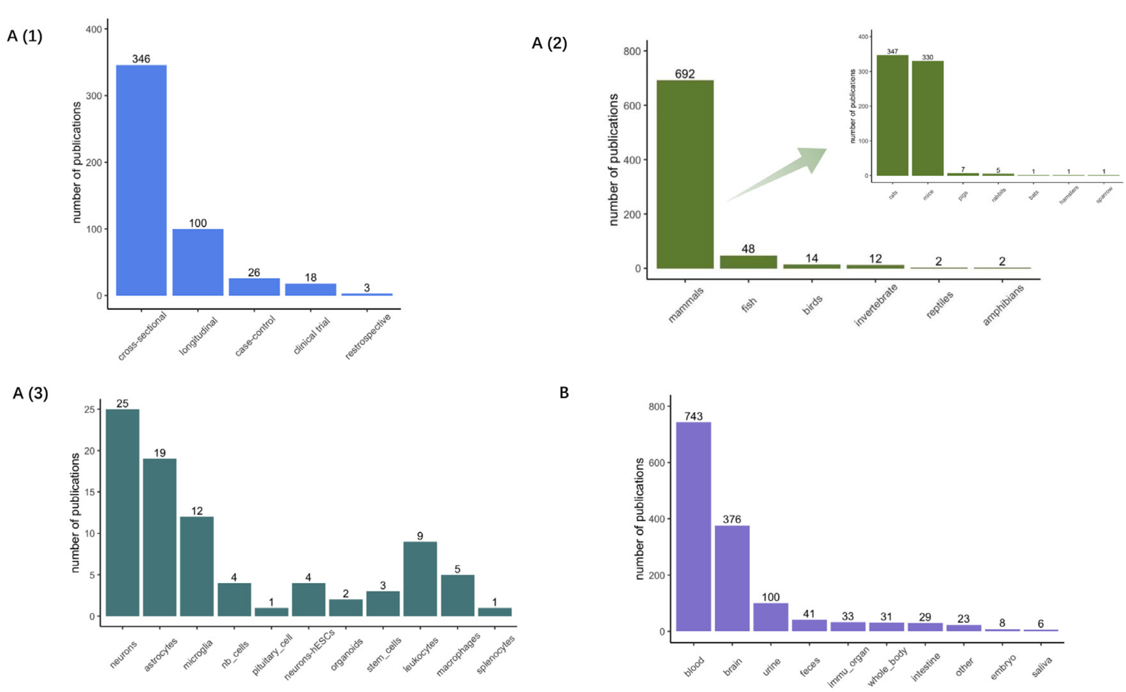

Figure 5. Characteristics of the 1330 articles included in the review.

Panel A. Number of distinct studies included in the review sorted by (1) study design of 493 human studies, (2) type of animal used in 767 animal-model studies, and (3) type of cell assessed in 85 cell-type studies.

Panel B. Type of biological samples used in 1407 reports about traditional biomarkers (i.e., biomarkers identified in biological samples) in the included articles.

neuroblastoma cells, four used neurons derived from human stem cells, two used brain organoids, and three used stem cells; the remaining 15 studies assessed the immunological effect of socioenvironmental exposures on leukocytes (*n*=9), macrophages (*n*=5), and splenocytes (*n*=1).

Socioenvironmental factors

Among the 1330 identified articles, 1250 considered a single socioenvironmental factor, 74 considered two different socioenvironmental factors (that is, two separate studies reported in a single article), and 6 considered three different socioenvironmental factors (shown in Supplementary Table S6). In total, the 1330 articles provided data from 1416 distinct studies about the 11 socioenvironmental factors, including 1230 (86·9%) about the six types of environmental pollution, 170 (12·0%) about the four types of health-related behaviours, and 16 (1·1%) about socioeconomic inequity. Many of the studies considered multiple biomarkers; the 1416 distinct studies reported data about 1835 associations between the 11 specific types of socioenvironmental factors and the 13 categories of biomarkers, and data about 3567 associations between the 11 socioenvironmental factors and the 56 specific types of biomarkers (Table 1). Among these 3567 reported associations, 3156 (88·5%) were about the six types of environmental pollution, 381 (10·7%) about the four types of health-related behaviours, and 30 (0·8%) about socioeconomic inequity.

As shown in Figure 6, the number of reported studies about environmental pollution began to increase around 2000, the number about health-related behaviours began to increase around 2007, and the number about socioeconomic inequality increased around 2015. Most of the 1230 reported studies about environmental pollution considered persistent organic pollutants, heavy metals pollution, and air pollution; relatively few reports considered noise pollution, light pollution, or green space reduction (Figure 7). Among the 170 reported studies about health-related behaviours, 111 (65·3%) assessed the association between diet and biomarkers associated with mental health disorders. All 16 studies about socioeconomic inequality assessed biomarkers associated with mental health disorders among adolescents and college students who had experienced (or were currently experiencing) being 'left behind' in rural communities when their parents migrated to cities for work.

The identified papers reported associations between environmental pollution and health-related behaviours with all 13 categories of biomarkers. However, no studies reported associations of socioeconomic inequality with four of the 13 types of biomarkers: neurotransmitters, neurotrophins, neurophysiological biomarkers, and gut microbiota (Supplementary Figure S1).

Biomarkers associated with socioenvironmental factors

The 13 categories of biomarkers associated with mental health conditions include eight molecular-level categories, two cellular-level categories, and three organ or organism-level categories. Among the 1835 reports of associations between the 13 categories of biomarkers and the 11 types of socioenvironmental factors, 1531 (83·4%) were about molecular biomarkers, 169 (9·2%) about cellular biomarkers, and 135 (7·4%) about organ- or organism-level biomarkers (including 66 about gut microbiota, 61 about neurophysiological measures, and eight about neuroimaging characteristics) (Table 1). Heart rate variability, one of the neurophysiological biomarkers, was the only organism-level biomarker considered.

Among the 1330 articles included in the review, 1193 (89·7%) reported studies about the association of socioenvironmental factors and 'traditional' biomarkers — that is, biomarkers related to mental health conditions identified in biological samples collected from humans or animals. Among these 1193 articles about traditional biomarkers, 1004 assessed biomarkers in a single type of biological sample, 165 articles assessed biomarkers in two types of samples, 23 articles assessed biomarkers in three types of samples, and one article assessed biomarkers in four types of samples (Supplementary Table S7), resulting in a total of 1407 distinct reports of sample-specific biomarker results. As shown in Figure 5B, among these 1407 reports, 743 (52·8%) used blood, 376 (26·7%) used brain tissue, 100 (7·1%) used urine, 41 (2·9%) used faecal material, 33 (2·4%) used samples from immunological organs (i.e., spleen, thymus, bursa of Fabricius, tonsils, and lymph nodes), 31 (2·2%) used whole-body homogenates of animal models (e.g., zebrafish and larvae), 29 (2·1%) used intestinal tissue, 8 (0·6%) used embryonic tissue, 6 (0·4%) used saliva, and 23 (1·6%) used other types of samples.

In addition to studies with candidate biomarkers, 44 (3·3%) studies used omics technology, including 34 studies about metabolomic biomarkers, two studies about epigenomic biomarkers, five studies about proteomic biomarkers, and three studies about transcriptomic biomarkers (Supplementary Table S8). Twenty-seven epigenetic studies (including the two epigenomics studies) investigated how socioenvironmental factors changed the expression of genes through DNA methylation or histone acetylation of candidate genes or global DNA. As shown in Table 2, 19 studies examined the relationship of socioenvironmental factors, genetic polymorphisms, and biomarkers associated with mental health or specific mental health conditions: nine of these studies considered environmental pollution and ten considered lifestyle factors such as adverse or stressful life events, unspecified stress, and the left-behind experience.

Biomarkers	Air pollution	Light pollution	Noise pollution	Heavy metals pollution	Persistent organic pollutants	Limited green space	Diet	Physical inactivity	Internet misuse	Other lifestyle factors	Socioeconomic inequality	Total number (%) of associations of each category of biomarker and of each specific biomarker with all socioenvironmental factors
Neurotransmitter [a]	***15***	***0***	***17***	***56***	***60***	***0***	***9***	***2***	***0***	***3***	***0***	***162 (8·8%)***
glutamic acid	14	0	11	29	49	0	4	0	0	0	0	107 (33·5%)
dopamine	5	0	6	22	14	0	1	0	0	0	0	48 (15·0%)
5-hydroxytryptamine	4	0	7	24	12	0	4	0	0	3	0	54 (16·9%)
noradrenaline and related	4	0	9	12	5	0	0	0	0	0	0	30 (9·4%)
gamma aminobutyric acid	1	0	6	7	9	0	3	0	0	0	0	26 (8·2%)
acetyl choline	3	0	0	20	17	0	0	1	0	0	0	41 (12·9%)
monoamines E	1	0	0	5	4	0	1	1	0	0	0	12 (3·8%)
galanin	0	0	0	0	0	0	1	0	0	0	0	1 (0·3%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**32 (10·0%)**	**0 (0·0%)**	**39 (12·2%)**	**119 (37·3%)**	**110 (34·5%)**	**0 (0·0%)**	**14 (4·4%)**	**2 (0·6%)**	**0 (0·0%)**	**3 (0·9%)**	**0 (0·0%)**	**319 (100·0%)**
Neurotrophic [a]	***14***	***0***	***0***	***21***	***29***	***0***	***10***	***1***	***0***	***0***	***0***	***75 (4·1%)***
BDNF	9	0	0	15	23	0	8	1	0	0	0	56 (64·4%)
nerve growth factor	5	0	0	1	3	0	1	0	0	0	0	10 (11·5%)
neurotrophin	0	0	0	0	2	0	1	0	0	0	0	3 (3·4%)
other	6	0	0	5	5	0	2	0	0	0	0	18 (20·7%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**20 (23.0%)**	**0 (0·0%)**	**0 (0·0%)**	**21 (24·1%)**	**33 (37·9%)**	**0 (0·0%)**	**12 (13·8%)**	**1 (1·1%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**87 (100·0%)**
Endocrinological [a]	***19***	***9***	***8***	***81***	***169***	***1***	***25***	***1***	***0***	***3***	***1***	***317 (17·3%)***
sex hormones	10	10	8	98	271	2	20	6	0	0	0	425 (60·6%)
thyroid hormone	8	1	2	35	136	0	11	0	0	6	0	199 (28·4%)
HPA	21	1	3	11	11	0	11	0	0	1	1	60 (8·6%)
other	2	4	3	5	1	0	2	0	0	0	0	17 (2·4%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**41 (5·8%)**	**16 (2·3%)**	**16 (2·3%)**	**149 (21·3%)**	**419 (59·8%)**	**2 (0·3%)**	**44 (6·3%)**	**6 (0·9%)**	**0 (0·0%)**	**7 (1·0%)**	**1 (0·1%)**	**701 (100·0%)**
Oxidative [a]	***73***	***2***	***3***	***143***	***154***	***0***	***31***	***1***	***0***	***3***	***1***	***411 (22·4%)***
antioxidase	50	2	5	141	138	0	31	0	0	0	1	368 (40·6%)
oxidative metabolites	59	3	3	91	115	0	15	0	0	0	0	286 (31·5%)
oxidant	22	1	0	47	62	0	14	1	0	3	0	150 (16·5%)
non-enzymatic antioxidants	17	1	0	30	28	0	11	0	0	0	0	87 (9·6%)
total antioxidant capacity	5	1	1	6	2	0	1	0	0	0	0	16 (1·8%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**153 (16·9%)**	**8 (0·9%)**	**9 (1·0%)**	**315 (34·7%)**	**345 (38·0%)**	**0 (0·0%)**	**72 (7·9%)**	**1 (0·1%)**	**0 (0·0%)**	**3 (0·3%)**	**1 (0·1%)**	**907 (100·0%)**

Table 1 *(Continued)*

Biomarkers	Air pollution	Light pollution	Noise pollution	Heavy metals pollution	Persistent organic pollutants	Limited green space	Diet	Physical inactivity	Internet misuse	Other lifestyle factors	Socioeconomic inequality	Total number (%) of associations of each category of biomarker and of each specific biomarker with all socioenvironmental factors
Immunological[a]	***82***	***3***	***3***	***66***	***54***	***0***	***39***	***4***	***0***	***3***	***3***	***257 (14·0%)***
cytokine	189	14	6	163	148	0	96	2	0	3	1	622 (78·6%)
immunoglobulin/antibody	20	0	4	24	21	0	1	0	0	0	3	73 (9·2%)
c-reactive protein	23	0	0	5	3	0	3	2	0	2	3	41 (5·2%)
cell adhesion molecule	15	0	0	2	0	0	1	0	0	0	0	18 (2·3%)
cluster of differentiation	6	0	0	0	1	0	6	0	0	0	0	13 (1·6%)
complement	3	0	0	1	2	0	0	2	0	0	2	10 (1·3%)
other	6	0	0	2	5	0	1	0	0	0	0	14 (1·8%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**262 (33·1%)**	**14 (1·8%)**	**10 (1·3%)**	**197 (24·9%)**	**180 (22·8%)**	**0 (0·0%)**	**108 (13·7%)**	**6 (0·8%)**	**0 (0·0%)**	**5 (0·6%)**	**9 (1·1%)**	**791 (100·0%)**
Metabolic[a]	***16***	***2***	***2***	***23***	***20***	***1***	***11***	***7***	***0***	***7***	***0***	***89 (4·9%)***
metabolomics	9	0	0	10	14	0	2	0	0	0	0	35 (33·7%)
carboxylic acids	5	0	2	15	6	0	2	0	0	0	0	30 (28·8%)
purines	3	1	0	6	2	1	7	1	0	7	0	28 (26·9%)
sphingolipid	5	1	0	4	0	0	1	0	0	0	0	11 (10·6%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**22 (21·2%)**	**2 (1·9%)**	**2 (1·9%)**	**35 (33·7%)**	**22 (21·2%)**	**1 (1·0%)**	**12 (11·5%)**	**1 (1·0%)**	**0 (0·0%)**	**7 (6·7%)**	**0 (0·0%)**	**104 (100·0%)**
Nutritional[a]	***1***	***0***	***0***	***9***	***13***	***1***	***0***	***0***	***0***	***1***	***6***	***31 (1·7%)***
mineral	0	0	0	13	23	0	0	0	0	0	7	43 (78·2%)
vitamin	1	0	0	3	4	1	0	0	0	1	2	12 (21·8%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**1 (1·8%)**	**0 (0·0%)**	**0 (0·0%)**	**16 (29·1%)**	**27 (49·1%)**	**1 (1·8%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (1·8%)**	**9 (16·4%)**	**55 (100·0%)**
Other molecular biomarkers[a]	***49***	***1***	***11***	***35***	***62***	***0***	***15***	***4***	***0***	***9***	***3***	***189 (10·3%)***
other molecules	31	1	11	28	39	0	15	4	0	0	2	131 (68·9%)
epigenetics	15	0	0	4	12	0	0	0	0	0	0	31 (16·3)
gene x environment	2	0	0	1	7	0	0	0	0	9	1	20 (10·5%)
proteomics/transcriptomics	1	0	0	2	4	0	1	0	0	0	0	8 (4·2%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**49 (25·8%)**	**1 (0·5%)**	**11 (5·8%)**	**35 (18·4%)**	**62 (32·6%)**	**0 (0·0%)**	**16 (8·4%)**	**4 (2·1%)**	**0 (0·0%)**	**9 (4·7%)**	**3 (1·6%)**	**190 (100·0%)**
Cells not in brain[a]	***19***	***0***	***1***	***37***	***24***	***0***	***1***	***0***	***0***	***1***	***1***	***84 (4·6%)***
lymphocyte	16	0	0	31	21	0	1	0	0	0	2	71 (67·0%)
mononuclear phagocyte system	4	0	1	5	3	0	0	0	0	0	0	13 (12·3%)
granulocytes	10	0	0	0	0	0	0	0	0	0	1	11 (10·4%)
white blood cells	1	0	0	3	1	0	0	0	0	1	0	6 (5·7%)

Table 1 *(Continued)*

Biomarkers	Air pollution	Light pollution	Noise pollution	Heavy metals pollution	Persistent organic pollutants	Limited green space	Diet	Physical inactivity	Internet misuse	Other lifestyle factors	Socioeconomic inequality	Total number (%) of associations of each category of biomarker and of each specific biomarker with all socioenvironmental factors
neutrophil-to lymphocyte ratio	1	0	0	1	1	0	0	0	0	0	0	3 (2·8%)
lymphocyte-to-monocyte ratio	0	0	0	1	0	0	0	0	0	0	0	1 (0·9%)
thymocyte	1	0	0	0	0	0	0	0	0	0	0	1 (0·9%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**33 (31·1%)**	**0 (0·0%)**	**1 (0·9%)**	**41 (38·7%)**	**26 (24·5%)**	**0 (0·0%)**	**1 (0·9%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (0·9%)**	**3 (2·8%)**	**106 (100·0%)**
Cells in brain[a]	***18***	***0***	***1***	***38***	***25***	***0***	***1***	***0***	***0***	***1***	***1***	***85 (4·6%)***
neuron	11	0	3	32	53	0	2	0	0	1	0	102 (61·8%)
glial cell	12	0	1	22	21	0	4	0	0	0	1	61 (37·0%)
neural stem cell	0	0	0	0	2	0	0	0	0	0	0	2 (1·2%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**23 (13·9%)**	**0 (0·0%)**	**4 (2·4%)**	**54 (32·7%)**	**76 (46·1%)**	**0 (0·0%)**	**6 (3·6%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (0·6%)**	**1 (0·6%)**	**165 (100·0%)**
Neuroimaging[a]	***0***	***0***	***2***	***0***	***0***	***1***	***0***	***0***	***1***	***2***	***2***	***8 (0·4%)***
functional MRI	0	0	2	0	0	1	0	0	0	1	1	5 (41·7%)
structural MRI	0	0	1	0	0	1	0	0	1	1	1	5 (41·7%)
diffusion tensor imaging	0	0	0	0	0	0	0	0	0	0	1	1 (8·3%)
PET	0	0	0	0	0	0	0	0	0	1	0	1 (8·3%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**0 (0·0%)**	**0 (0·0%)**	**3 (25·0%)**	**0 (0·0%)**	**0 (0·0%)**	**2 (16·7%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (8·3%)**	**3 (25·0%)**	**3 (25·0%)**	**12 (100·0%)**
Neurophysiological[a]	***25***	***0***	***5***	***13***	***6***	***1***	***1***	***5***	***5***	***0***	***0***	***61 (3·3%)***
heart rate variability	24	0	4	4	5	1	1	2	1	0	0	42 (65·6%)
EEG	0	0	2	9	1	1	0	3	4	0	0	20 (31·3%)
skin conductance level	0	0	1	0	0	1	0	0	0	0	0	2 (3·1%)
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**24 (37·5%)**	**0 (0·0%)**	**7 (10·9%)**	**13 (20·3%)**	**6 (9·4%)**	**3 (4·7%)**	**1 (1·6%)**	**5 (7·8%)**	**5 (7·8%)**	**0 (0·0%)**	**0 (0·0%)**	**64 (100·0%)**
Gut microbe[a,b]	***5***	***2***	***2***	***15***	***19***	***0***	***22***	***0***	***0***	***1***	***0***	***66 (3·6%)***
Total specific biomarker associations for each socioenvironmental factor and proportion of all such associations	**5 (7·6%)**	**2 (3·0%)**	**2 (3·0%)**	**15 (22·7%)**	**19 (28·8%)**	**0 (0·0%)**	**22 (33·3%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (1·5%)**	**0 (0·0%)**	**66 (100·0%)**
All biomarker category* socioenvironmental factor associations[a]	***336 (18·3%)***	***19 (1·0%)***	***55 (3·0%)***	***537 (29·3%)***	***635 (34·6%)***	***5 (0·3%)***	***165 (9·0%)***	***25 (1·4%)***	***6 (0·3%)***	***34 (1·9%)***	***18 (1·0%)***	***1835 (100·0%)***
All specific biomarker*socioenvironmental factor associations	***665 (18·6%)***	***43 (1·2%)***	***104 (2·9%)***	***1010 (28·3%)***	***1325 (37·1%)***	***9 (0·3%)***	***308 (8·6%)***	***26 (0·7%)***	***6 (0·2%)***	***41 (1·1%)***	***30 (0·8%)***	***3567 (100·0%)***

***Table 1*: Number of reported associations of 11 types of socioenvironmental factors with 13 categories of biomarkers and 56 specific types of biomarkers reported in the 1330 papers assessed in the review.**

[a] In most cases the number of associations for each category of biomarker is less than the sum of the associations of specific biomarkers included in the category because many studies assess the associations of multiple specific biomarkers within the same category of biomarkers

[b] There are no specific biomarkers reported for the ‘gut microbe’ category of biomarkers.

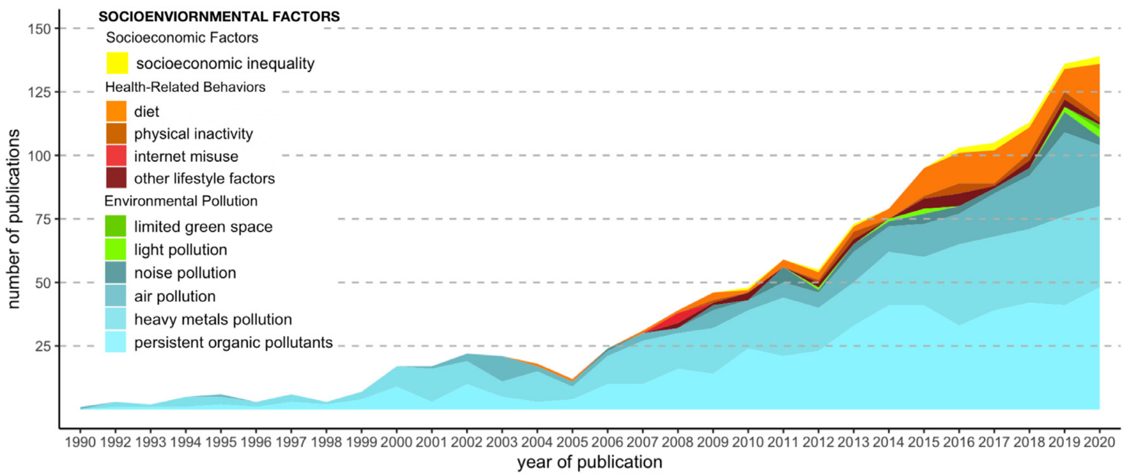

Figure 6. The number of papers that report associations of biomarkers with different socioenvironmental factors in China published from 1990 to 2020.

(Papers reporting associations of biomarkers with more than one of the 11 socioenvironmental factors were counted multiple times; after excluding 128 associations reported in 2021, data from 1288 associations were included in this figure).

Neurotransmitters and neuropeptides. As shown in Table 1, 319 associations of socioenvironmental factors with specific neurotransmitters and neuropeptides were identified in the reviewed papers. These included associations with four types of monoamines and related enzymes (dopamine, 5-hydroxytryptamine, noradrenaline and related biomarkers [corticotropin-releasing factor and high vanillic acid], and monoamines enzymes), three types of amino acid neurotransmitters (gamma-aminobutyric acid, glutamic acid, and acetylcholine),

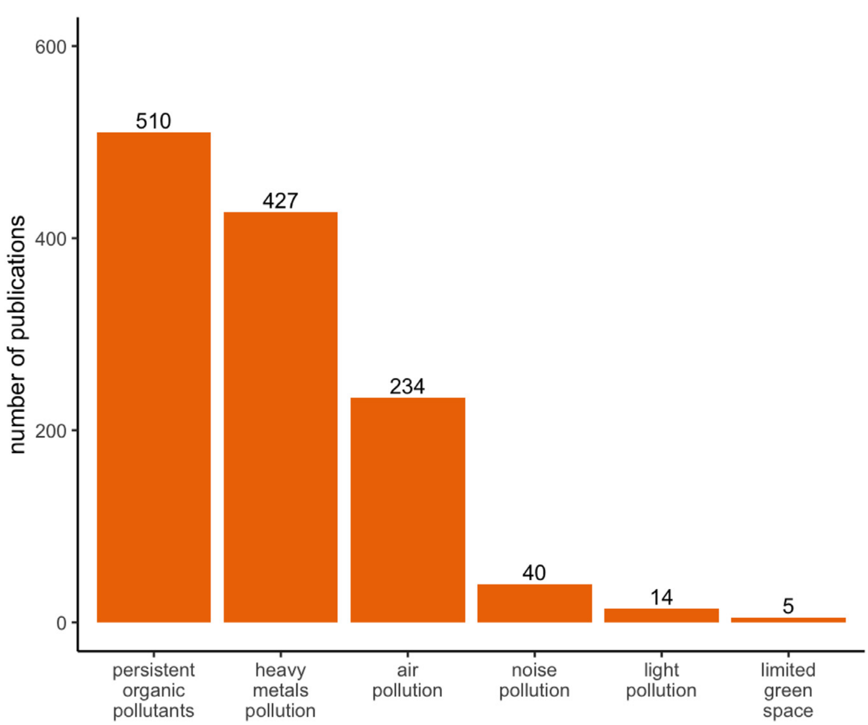

Figure 7. The number of included papers that considered different types of environmental pollution.

(Articles that analyze the association of biomarkers with multiple types of environmental pollutants are represented once for each type of pollutant considered).

ID[a]	Socioenvironmental category	Socioenvironmental factor considered	Gene(s) assessed	Type of outcome assessed	Mental health biomarker or mental health outcome assessed
R762	organic pollution	fluoride	*COMT* gene Val158Met polymorphism	mental health	cognitive decline
R764	organic pollution	fluoride	*ER-Alpha* gene rs3798577 polymorphism	biomarker	testosterone
R310	organic pollution	fluoride	polymorphisms of *CLU* and *TOMM40* genes	mental health	intelligence
R387	organic pollution	fluoride	*DRD2* gene Taq 1A polymorphism	mental health	IQ scores
R43	organic pollution	fluorine	*ER-Alpha* gene PvuII polymorphism	biomarker	magnesium
R44	organic pollution	fluorine	*FSHR* gene rs1394205 and rs6166 polymorphisms	biomarker	magnesium
R1133	organic pollution	PAH	*BDNF* gene Val66Me polymorphism	biomarker	oxidative stress
R1130	air pollution	PM2.5	*COMT* gene Val158Met polymorphism	biomarker	DNA damage
R1126	air pollution	PM2.5	*MTHFR* gene C677T polymorphism	biomarker	homocysteine
R45	lifestyle	left behind	*VDR* gene FOK I polymorphisms	biomarker	vitamin D
R364	lifestyle	negative life events	*TPH2* gene rs4570625, rs11178997 and rs120074175 polymorphisms	mental health	major depression
R368	lifestyle	negative life events	polymorphism of 5-*HTTLPR* and *5-HTR1A* genes	mental health	major depression
R367	lifestyle	negative life events	polymorphisms of *BDNF* and *GSK3B* genes	mental health	major depression
R363	lifestyle	negative life events	*BDNF* gene rs6265 polymorphism	mental health	major depression
R362	lifestyle	negative life events	polymorphisms of *GNB3* and *CREB* genes	mental health	major depression
R365	lifestyle	stress	*BDNF* gene Val66Met polymorphism	mental health	depression
R361	lifestyle	stress	*OXTR* gene rs53576 polymorphism	mental health	physical aggression and hostility
R370	lifestyle	stressful life events	*BDNF* gene Val66Met polymorphism	mental health	anxiety
R366	lifestyle	stressful life events	*BDNF* gene Val66Met polymorphism	mental health	depressive symptoms

***Table 2*: Summary of studies about the relationship of gene-socioenvironmental interactions with mental health-related biomarkers and mental health conditions.**

[a] ID numbers refer to ID numbers of references provided on page 34 in the Supplementary Materials.

and galanin (which was the only neuropeptide reported). Glutamic acid was the neurotransmitter most frequently studied, accounting for 33·5% (107/319) of all reported associations of socioenvironmental factors with neurotransmitters and neuropeptides. Most neurotransmitters and neuropeptides were assessed using blood or brain tissue, but one study measured 5-hydroxytryptamine, dopamine, and gamma-aminobutyric acid in urine samples.

Neurotrophic factors. There were 87 associations of socioenvironmental factors with neurotrophic factors identified in the reviewed papers (Table 1), including 56 reported associations with brain-derived neurotrophic factor (BDNF), ten with nerve growth factor, three with neurotrophin, and 18 with other types of neurotrophic factors (including glial cell line-derived neurotrophic factor, insulin-like growth factor-1, vascular endothelial growth factor, fibroblast growth factor-basic2, and transforming growth factor). Neurotrophic factors were mainly assessed in the blood and brain.

Endocrinological biomarkers. There were 701 associations of socioenvironmental factors with endocrinological factors identified in the reviewed papers. These included 425 associations with sex hormones, 199 with thyroid hormone, 60 with the HPA-axis hormones (including cortisol, adrenocorticotropic hormone, and norepinephrine), and 17 with other endocrinological factors (including melatonin, endothelin, growth hormone, and melanocyte-stimulating hormone). These biomarkers were mainly identified in blood, urine, and brain tissue.

Studies about estrogen and androgen receptors in brain tissue (all assessed in animal-model studies) were included in the review. However, studies that only assessed sex hormones in reproductive organs were excluded because sex hormones found in these organs are not considered biomarkers of mental disorders.

Norepinephrine is both a neurotransmitter and an HPA-axis hormone, so we categorised reports about norepinephrine as one of these two types of biomarkers based on the content of the specific studies, focusing on whether the study also assessed other neurotransmitters or other HPA-axis hormones. Among the 25 reports about the association of norepinephrine with socioenvironmental factors, 22 were classified as neurotransmitter associations, and three were classified as endocrinological associations (Supplementary Table S9).

Oxidative biomarkers. The 907 identified associations of socioenvironmental factors with oxidative biomarkers were subdivided into five groups: 368 associations with antioxidase biomarkers, 286 with metabolites of oxidative stress, 150 with oxidant, 87 with non-enzymatic antioxidants, and 16 with total antioxidant capacity. Oxidative biomarkers were measured in blood, brain, and urine samples.

Immunological biomarkers. The 791 associations of socioenvironmental factors with immunological biomarkers identified included 622 associations with cytokines, 73 with immunoglobulin/antibody biomarkers, 41 with C-reactive protein, 18 with cell adhesion molecules, 13 with clusters of differentiation, 10 with complement, and 14 with other immunological biomarkers (including toll-like receptors, prostaglandin E2, and nuclear factor kappa-B). The cytokines associated with socioenvironmental factors included 20 different types of interleukins (interleukin-6 was the most common), tumour necrosis factor, interferon, creatine kinase, transforming growth factor, and cerebrospinal fluid. Immunological biomarkers were assessed in the blood, brain, and immunological organs.

Metabolites. The 104 associations of socioenvironmental factors with metabolic biomarkers identified included 35 studies that performed metabolomic analyses for all metabolites and 69 studies that assessed associations with three specific types of candidate metabolites: 30 with carboxylic acids, 28 with purines, and 11 with sphingolipid. Among the 16 kinds of carboxylic acids assessed, 13 were amino acids. Uric acid (the only purine assessed) was the most frequently studied candidate metabolite. Eight different types of sphingolipids were examined. Metabolites were measured in blood, urine, and brain tissue.

Nutritional biomarkers. The 55 associations of socioenvironmental factors with nutritional biomarkers identified included 43 associations with minerals (including Ca, Me, Zn, and Se) and 12 associations with vitamins (including folate and vitamins D, A, B12, C, and E). The proportion of all assessed biomarkers for each socioenvironmental factor categorised as nutritional biomarkers was much higher for socioeconomic inequity (30·0% [9/30]) than for environmental pollution (1·4% [45/3156]) or health-related behaviours (0·3% [1/381]), providing indirect support for studies that find that left-behind children in rural China have higher malnutrition rates than children living in rural communities with their parents.[31,32] All nutritional biomarkers were measured in the blood.

Other molecular biomarkers. The 190 associations of socioenvironmental factors with other molecular biomarkers included 131 associations with 14 kinds of molecules that could not be grouped into the categories described above, 31 associations with epigenetic biomarkers, 20 associations with a measure of the interaction of gene and socioenvironmental factors, and eight associations assessed by using proteomic or transcriptomic technology. Among the 131 associations with other molecules, 113 were with five specific types of molecular biomarkers: 29 with camp-response element-binding protein, 29 with telomere length, 28 with mitochondrial molecules (including mitochondrial DNA copy number), 16 with the Alzheimer disease-related tau protein, and 12 with the Alzheimer disease-related amyloid beta protein. The remaining 18 reported associations considered links between socioenvironmental factors and nine other molecular biomarkers: glycogen synthase kinase 3β, fibrinogen, synaptosome-associated protein of 25, postsynaptic density protein 95, s100 calcium-binding protein B, amyloid precursor protein, neurofilament, beta-secretase 1, and synapsin. These molecules were mainly assessed in blood and brain tissue.

Cells not in the brain and cells in the brain. The 106 reported associations of socioenvironmental factors with cells not in the brain were all about cells related to immunological functioning. One reported association was about thymocytes; all the other 105 reported associations assessed the number, distribution, and function of white blood cells. Among these studies about white blood cells, 71 reported the association of socioenvironmental factors with lymphocytes, including B cells, T cells, and natural killer cells.

The 165 associations of socioenvironmental factors with cells in the brain included 102 associations with neurons, 61 with glial cells, and two with neural stem cells. The reports described the structure, number, and function of the brain cells of interest. For neurons, the ultrastructure of the synapse was of particular interest (reported in 24 papers). Astrocytes (reported in 29 papers) and microglia (reported in 23 papers) were the most frequently mentioned types of glial cells.

Neuroimaging, neurophysiology, and gut microbe. Associations of socioenvironmental factors with these organ-level and organism-level biomarkers included 12 associations with neuroimaging measures (including five with functional magnetic resonance imaging (MRI), five with structural MRI, one with diffusion tensor imaging, and one with positron emission tomography), 64 associations with neurophysiological measures (including 42 with heart rate variability, 20 with EEG results, and two with skin conductance level), and 66 associations with gut microbiota.

Distribution of associations of biomarkers across different socioenvironmental factors

Figure 8 provides a graphic representation of the distribution of all 1835 biomarker category*socioenvironmental factor links reported in the 1330 reviewed articles, and Supplementary Figure S2 shows the number of reports about each type of association stratified by socioenvironmental factor and biomarker category.

Fifty of the 56 specific mental health related-biomarkers considered in this review were associated with at least one of the three main types of environmental pollution: persistent organic pollutants, heavy metal pollutants, and air pollution (the exceptions were the four specific neuroimaging biomarkers, the neurophysiological skin conductance measure, and the neuropeptide galanin). The number and range of reported socioenvironmental-biomarker associations for the three other types of environmental pollution considered—noise pollution, light pollution, and green space reduction—are much smaller. There are no reports of the association of noise pollution with neurotrophic factors or nutritional biomarkers, and there are no reports of the association of light pollution with neurotransmitters, neurotrophic factors, nutritional biomarkers, cells inside or outside the brain, neuroimaging biomarkers, or neurophysiological biomarkers. Moreover, reduced green space (rarely studied in China) has only been associated with endocrinological, metabolic, nutritional, neuroimaging, and neurophysiological biomarkers. (Supplementary Figure S2).

A total of 248 associations of the four types of health-related behaviours with the 13 categories of biomarkers were identified in the reviewed papers. Diet, the most frequently assessed health-related behaviour (accounting for 66·5% [165/248] of all health-related behaviour*-biomarker category associations), was associated with 11 of the 13 categories of mental health-related biomarkers (neuroimaging and nutritional biomarkers were the exceptions). Reduced physical activity was associated with all categories of biomarkers except for nutritional and neurophysiological biomarkers. Other lifestyle factors (which included smoking, drinking alcohol, chronic stress, means of daily commuting, work type [sedentary, light physical, or physical], and sleep patterns) were associated with all categories of biomarkers except for neurotrophic and neurophysiological biomarkers. Internet abuse was the least frequently studied health-related behaviour; to date, it has only been associated with changes in neuroimaging and neurophysiological biomarkers.

This review only identified 30 linkages between socioeconomic inequality and specific types of mental health-related biomarkers. Most of these studies assess the relationship between socioeconomic inequality and nutritional biomarkers. No associations have yet been reported about the association of socioeconomic inequality with neurotransmitter, neurotrophic, oxidative, or metabolic biomarkers.

Biomarkers and mental health conditions

All 1330 included studies assessed the association of the 56 mental health-related biomarkers with socioenvironmental

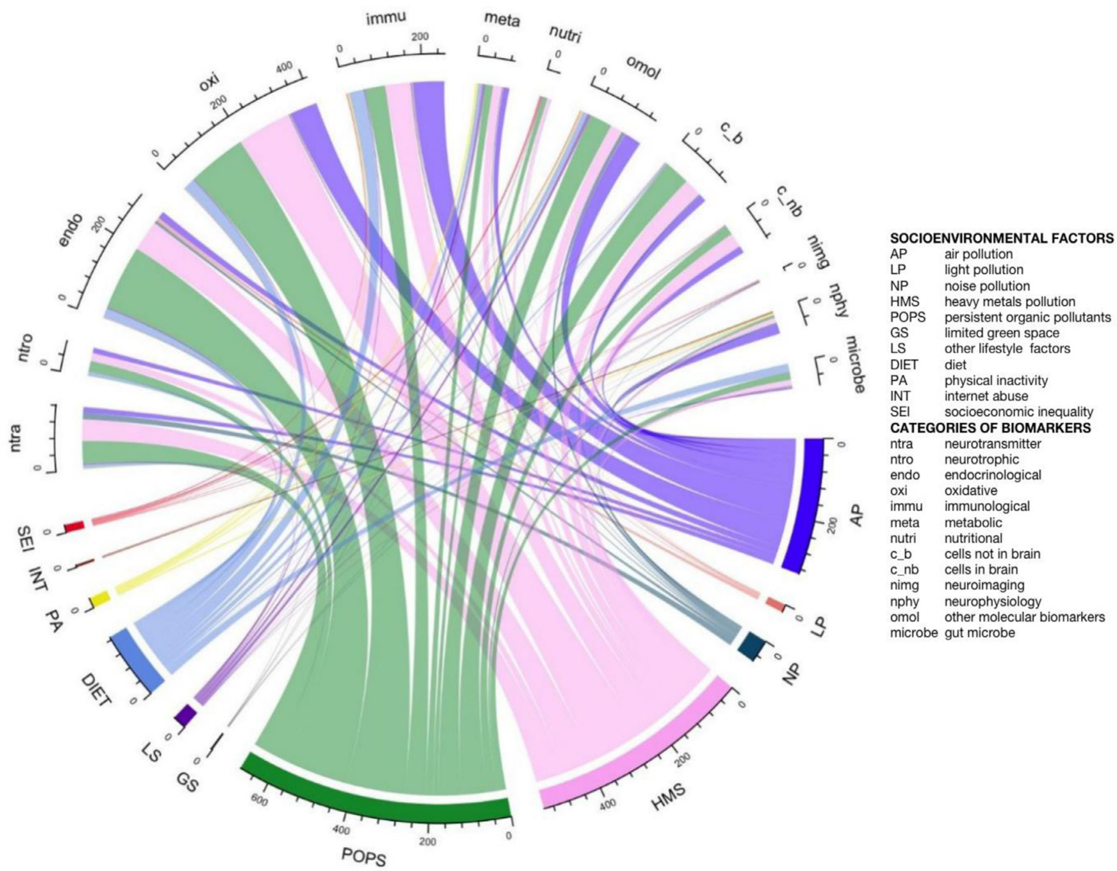

Figure 8. Graphic representation of the distribution of all 1835 biomarker category*socioenvironmental factor links reported in the 1330 reviewed articles.

Biomarkers (with lower case labels) and socioenvironmental factors (with upper cases labels) are shown in the upper and lower half of the circle, respectively. The circumference of the circle is dissected into intervals, each interval representing 40 reported links. The colored band associated with each socioenvironmental factor in the bottom half of the circle is projected upwards branching into the various biomarkers it has been associated with in the top half of the circle, with the width of each branch representing the corresponding number of reported links).

factors, but only 245 (18·4%) of the studies also considered the association of the biomarkers with mental health conditions. Moreover, in most studies that consider mental health conditions, biomarkers were assessed in animal models of mental disorders, not in human subjects. The detailed breakdown of biomarker*mental health condition associations reported in these studies is shown in Table 3.

Among the 245 papers, 188 (76·7%) considered the association of mental health conditions with biomarkers of environmental pollution, 48 (19·6%) considered the association of mental health conditions with biomarkers of health-related behaviours, and 9 (3·7%) considered the association of mental health conditions with biomarkers of socioeconomic inequity (Supplementary Excel Table 1). These studies reported 604 unique associations between mental health conditions and the 56 specific biomarkers (107 in human subjects and 497 in animal models), including 379 (62·7%) about cognitive functioning (353 in animal models), 117 (19·4%) about anxiety (103 in animal models), 56 (9·3%) about depression (31 in animal models), 21 (3·5%) about neurodevelopmental conditions including ADHD and autism (10 in animal models), and 31 (5·1%) about neurobehavioural symptoms including internalising and externalising symptoms, mobile phone dependence, and social interaction symptoms (none in animal models).

The categories of biomarkers that accounted for most of the 604 reported biomarker*mental health condition associations were neurotransmitter biomarkers (146, 24·2%), oxidative biomarkers (136, 22·5%), cells in the brain (66, 10·9%), endocrinological biomarkers (61, 10·1%), and other molecular biomarkers (48, 7·9%). The specific biomarkers most frequently reported in these studies were neurons (*n*=52), glutamic acid (*n*=46), oxidative metabolites (*n*=44), antioxidase (*n*=38), and cytokine (*n*=36).

Biomarkers	Cognition [A]	Cognition [H]	Anxiety [A]	Anxiety [H]	Depression [A]	Depression [H]	Neurodevelopmental [A]	Neurodevelopmental [H]	Neurobehavioural [H]	Total number (%) of associations of each category of biomarker and of each specific biomarker with all mental health conditions
Neurotransmitter [b]	***54***	***1***	***16***	***2***	***8***	***2***	***2***	***0***	***4***	***89 (19·6%)***
glutamic acid	30	0	8	1	3	1	0	0	3	46 (31·5%)
dopamine	11	1	5	1	1	1	1	0	1	22 (15·1%)
5-hydroxytryptamine	12	0	5	1	3	1	1	0	0	23 (15.8%)
noradrenaline and related	7	0	4	0	1	0	0	0	0	12 (8·2%)
gamma aminobutyric acid	8	0	4	1	1	1	1	0	0	16 (11·0%)
acetyl choline	14	0	2	0	0	0	0	0	0	16 (11·0%)
monoamines E	6	0	1	1	1	1	0	0	0	10 (6·8%)
Galanin	0	0	1	0	0	0	0	0	0	1 (0·7%)
Total specific biomarker associations for each mental health condition *and proportion of all such associations*	**88 (60·3%)**	**1 (0·7%)**	**30 (20·5%)**	**5 (3·4%)**	**10 (6·8%)**	**5 (3·4%)**	**3 (2·1%)**	**0 (0·0%)**	**4 (2·7%)**	**146 (100·0%)**
Neurotrophic [b]	***26***	***1***	***4***	***0***	***4***	***0***	***0***	***1***	***1***	***37 (8·1%)***
BDNF	19	1	4	0	4	0		1	1	30 (76·9%)
nerve growth factor	5	0	0	0	0	0	0	0	0	5 (12·8%)
neurotrophin	1	0	0	0	0	0	0	0	0	1 (2·6%)
other	3	0	0	0	0	0	0	0	0	3 (7·7%)
Total specific biomarker associations for each mental health *condition and proportion of all such associations*	**28 (71·8%)**	**1 (2·6%)**	**4 (10·3%)**	**0 (0·0%)**	**4 (10·3%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (2·6%)**	**1 (2·6%)**	**39 (100·0%)**
Endocrinological [b]	***25***	***3***	***11***	***1***	***9***	***1***	***1***	***1***	***6***	***58 (12·8%)***
sex hormones	13	0	5	0	3	0	0	0	4	25 (41·0%)
thyroid hormone	6	3	1	0	1	0	0	1	1	13 (21·3%)
HPA	6	0	6	1	6	1	1	0	1	22 (36·1%)
other	1	0	0	0	0	0	0	0	0	1 (1·6%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**26 (42·6%)**	**3 (4·9%)**	**12 (19·7%)**	**1 (1·6%)**	**10 (16·4%)**	**1 (1·6%)**	**1 (1·6%)**	**1 (1·6%)**	**6 (9·8%)**	**61 (100·0%)**

Table 3 *(Continued)*

Biomarkers	Cognition [A]	Cognition [H]	Anxiety [A]	Anxiety [H]	Depression [A]	Depression [H]	Neurodevelopmental [A]	Neurodevelopmental [H]	Neurobehavioural [H]	Total number (%) of associations of each category of biomarker and of each specific biomarker with all mental health conditions
Oxidative [b]	***57***	***2***	***10***	***0***	***0***	***0***	***0***	***2***	***2***	***73 (16·1%)***
antioxidase	28	2	7	0	0	0	0	1	0	38 (27·9%)
oxidative metabolites	33	2	7	0	0	0	0	1	1	44 (32·4%)
oxidant	19	0	5	0	0	0	0	1	1	26 (19·1%)
non-enzymatic antioxidants	15	1	4	0	0	0	0	0	0	20 (14·7%)
total antioxidant capacity	5	1	1	0	0	0	0	1	0	8 (5·9%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**100 (73·5%)**	**6 (4·4%)**	**24 (17·6%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**4 (2·9%)**	**2 (1·5%)**	**136 (100·0%)**
Immunological [b]	***22***	***0***	***9***	***1***	***2***	***2***	***1***	***1***	***0***	***38 (8·4%)***
cytokine	21	0	7	1	2	2	1	2	0	36 (81·8%)
immunoglobulin/antibody	0	0	0	0	0	1	0	0	0	1 (2·3%)
c-reactive protein	0	0	0	0	0	1	0	0	0	1 (2·3%)
cell adhesion molecule	0	0	1	0	0	0	0	0	0	1 (2·3%)
cluster of differentiation	2	0	0	0	0	0	0	0	0	2 (4·5%)
complement	1	0	0	0	0	1	0	0	0	2 (4·5%)
other	0	0	1	0	0	0	0	0	0	1 (2·3%)
Total specific biomarker associations for each mental health condition and proportion of all such associations	**24 (54·5%)**	**0 (0·0%)**	**9 (20·5%)**	**1 (2·3%)**	**2 (4·5%)**	**5 (11·4%)**	**1 (2·3%)**	**2 (4·5%)**	**0 (0·0%)**	**44 (100·0%)**
Metabolic [b]	***2***	***0***	***0***	***1***	***0***	***1***	***0***	***0***	***0***	***4 (0·9%)***
metabolomics	0	0	0	0	0	0	0	0	0	0 (0·0%)
carboxylic acids	2	0	0	1	0	1	0	0	0	4 (100·0%)
purines	0	0	0	0	0	0	0	0	0	0 (0·0%)
sphingolipid	0	0	0	0	0	0	0	0	0	0 (0·0%)

Table 3 *(Continued)*

Biomarkers	Cognition [A]	Cognition [H]	Anxiety [A]	Anxiety [H]	Depression [A]	Depression [H]	Neurodevelopmental [A]	Neurodevelopmental [H]	Neurobehavioural [H]	Total number (%) of associations of each category of biomarker and of each specific biomarker with all mental health conditions
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**2 (50·0%)**	**0 (0·0%)**	**0 (0·0%)**	**1 (25·0%)**	**0 (0·0%)**	**1 (25·0%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**4 (100·0%)**
***Nutritional*[b]**	***1***	***0***	***0***	***0***	***0***	***0***	***0***	***2***	***0***	***3 (0·7%)***
mineral	1	0	0	0	0	0	0	1	0	2 (66·7%)
vitamin	0	0	0	0	0	0	0	1	0	1 (33·3%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**1 (33·3%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**2 (66·7%)**	**0 (0·0%)**	**3 (100·0%)**
***Other molecular biomarkers*[b]**	***23***	***7***	***4***	***1***	***1***	***7***	***1***	***1***	***2***	***47 (10·4%)***
other molecules	18	3	2	0	0	1	1	1	1	27 (56·3%)
epigenetics	5	0	1	0	0	0	1	0	0	7 (14·6%)
gene x environment	0	3	0	1	0	7	0	0	1	12 (25·0%)
proteomics/transcriptomics	0	1	1	0	0	0	0	0	0	2 (4·2%)
Total* specific biomarker *associations for each mental health condition and proportion of all such associations	**23 (47·9%)**	**7 (14·6%)**	**4 (8·3%)**	**1 (2·1%)**	**0 (0·0%)**	**8 (16·7%)**	**2 (4·2%)**	**1 (2·1%)**	**2 (4·2%)**	**48 (100·0%)**
***Cells not in brain*[b]**	***1***	***1***	***2***	***1***	***1***	***1***	***0***	***0***	***3***	***10 (2·2%)***
lymphocyte	1	1	2	1	1	1	0	0	3	10 (71·4%)
mononuclear phagocyte system	0	0	0	0	0	0	0	0	1	1 (7·1%)
granulocytes	1	0	1	0	1	0	0	0	0	3 (21·4)
white blood cells	0	0	0	0	0	0	0	0	0	0 (0·0%)
neutrophil-to lymphocyte ratio	0	0	0	0	0	0	0	0	0	0 (0·0%)
lymphocyte-to-monocyte ratio	0	0	0	0	0	0	0	0	0	0 (0·0%)
thymocyte	0	0	0	0	0	0	0	0	0	0 (0·0%)

***Table 3** (Continued)*

Biomarkers	Cognition [A]	Cognition [H]	Anxiety [A]	Anxiety [H]	Depression [A]	Depression [H]	Neurodevelopmental [A]	Neurodevelopmental [H]	Neurobehavioural [H]	Total number (%) of associations of each category of biomarker and of each specific biomarker with all mental health conditions
Total specific biomarker associations for each mental health *condition and proportion of all such associations*	**2 (14·3%)**	**1 (7·1%)**	**3 (21·4%)**	**1 (7·1%)**	**2 (14·3%)**	**1 (7·1%)**	**0 (0·0%)**	**0 (0·0%)**	**4 (28·6%)**	**14 (100·0%)**
***Cells in brain*[b]**	***45***	***1***	***12***	***0***	***1***	***0***	***2***	***0***	***2***	***63 (13·9%)***
neuron	37	1	10	0	1	0	1	0	2	52 (78·8%)
glial cell	11	0	2	0	0	0	1	0	0	14 (21·2%)
neural stem cell	0	0	0	0	0	0	0	0	0	0 (0·0%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**48 (72·7%)**	**1 (1·5%)**	**12 (18·2%)**	**0 (0·0%)**	**1 (1·5%)**	**0 (0·0%)**	**2 (3·0%)**	**0 (0·0%)**	**2 (3·0%)**	**66 (100·0%)**
***Neuroimaging*[b]**	***2***	***1***	***1***	***1***	***1***	***0***	***0***	***0***	***2***	***8 (1·8%)***
functional MRI	1	1	0	0	0	0	0	0	2	4 (30·8%)
structural MRI	1	1	1	1	1	0	0	0	1	6 (46·2%)
diffusion tensor imaging	1	0	1	0	1	0	0	0	0	3 (23·1%)
PET	0	0	0	0	0	0	0	0	0	0 (0·0%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**3 (23·1%)**	**2 (15·4%)**	**2 (15·4%)**	**1 (7·7%)**	**2 (15·4%)**	**0 (0·0%)**	**0 (0·0%)**	**0 (0·0%)**	**3 (23·1%)**	**13 (100·0%)**
***Neurophysiological*[b]**	***0***	***3***	***0***	***1***	***0***	***2***	***0***	***0***	***5***	***11 (2·4%)***
heart rate variability	0	1	0	1	0	1	0	0	2	5 (29·4%)
EEG	0	2	0	1	0	2	0	0	4	9 (52·9%)
skin conductance level	0	0	0	1	0	1	0	0	1	3 (17·6%)
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	**0 (0·0%)**	**3 (17·6%)**	**0 (0·0%)**	**3 (17·6%)**	**0 (0·0%)**	**4 (23·5%)**	**0 (0·0%)**	**0 (0·0%)**	**7 (41·2%)**	**17 (100·0%)**

Table 3 *(Continued)*

Biomarkers	Cognition [A]	Cognition [H]	Anxiety [A]	Anxiety [H]	Depression [A]	Depression [H]	Neurodevelopmental [A]	Neurodevelopmental [H]	Neurobehavioural [H]	Total number (%) of associations of each category of biomarker and of each specific biomarker with all mental health conditions
Gut microbe[b,c]	*8*	*1*	*3*	*0*	*0*	*0*	*1*	*0*	*0*	*13 (2·9%)*
Total specific biomarker *associations for each mental health condition and proportion of all such associations*	8 (61·5%)	1 (7·7%)	3 (23·1%)	0 (0·0%)	0 (0·0%)	0 (0·0%)	1 (7·7%)	0 (0·0%)	0 (0·0%)	13 (100·0%)
All biomarker category mental health condition associations*[b]	*266 (58·6%)*	*21 (4·6%)*	*72 (15·9%)*	*9 (2·0%)*	*27 (5·9%)*	*16 (3·5%)*	*8 (1·8%)*	*8 (1·8%)*	*27 (5·9%)*	*454 (100·0%)*
*All specific biomarker*mental health condition associations*	*353 (58.4%)*	*26 (4.3%)*	*103 (17.1%)*	*14 (2.3%)*	*31 (5.1%)*	*25 (4.1%)*	*10 (1.7%)*	*11 (1.8%)*	*31 (5.1%)*	*604 (100·0%)*

***Table 3*: Number of reported associations of 9 types of mental health conditions[a] with 13 categories of biomarkers and 56 specific types of biomarkers reported in the 237 papers assessed in the review that assessed the relationships of mental health conditions with biomarkers.**

[a] Mental health conditions specified as '[A]' were assessed in studies that used animal models of human mental disorders while those specified as '[H]' were conducted with human subjects.

[b] In most cases the number of associations for each category of biomarker is less than the sum of the associations of specific biomarkers included in the category because many studies assess the associations of multipe specific biomarkers within the same category of biomarkers.

[c] There are no specific biomarkers reported for the 'gut microbe' category of biomarkers.

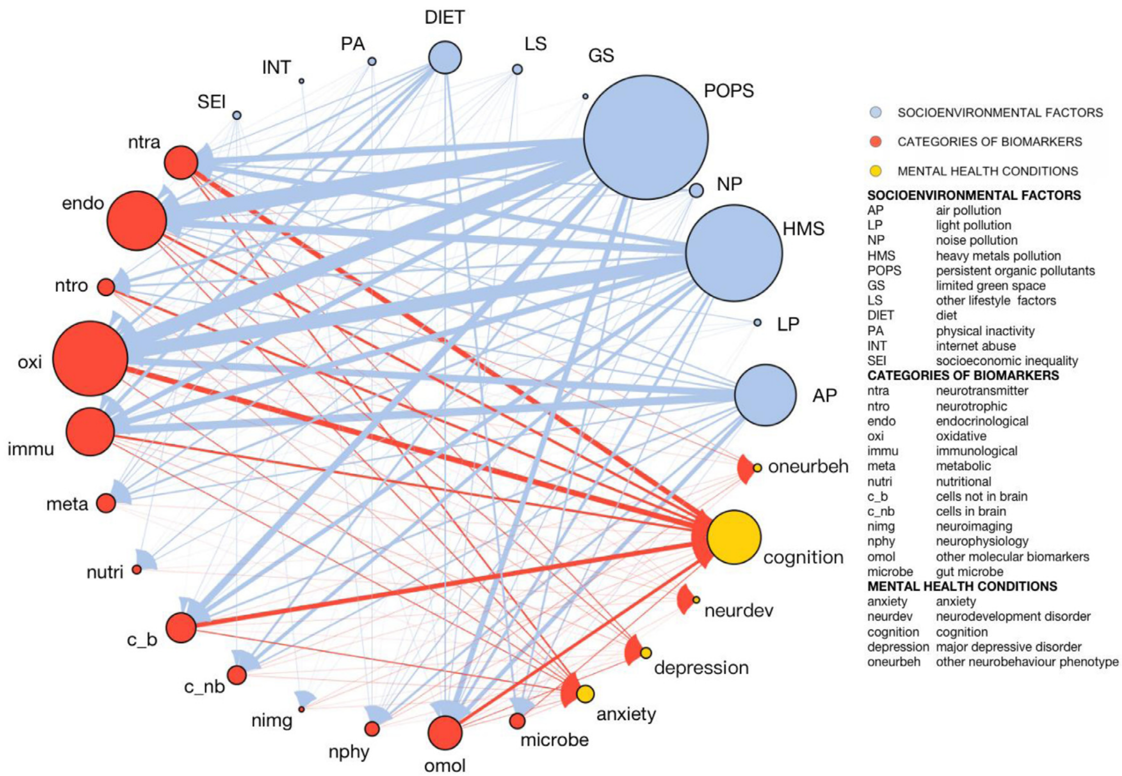

Figure 9. Links bridging socioenvironmental factors, biomarkers, and mental health conditions.

(Around the circumference of the circle, blue dots represent socioenvironmental factors, red dots categories of biomarkers, and yellow dots mental health conditions; the size of the dots correspond to the number of papers among the 1330 papers included in this review that report on the specific factor/biomarker/condition. The width of blue lines represents the number of papers that identified linkages between socioenvironmental factors and biomarkers and the width of red lines represents the number of papers that identified linkages between biomarkers and mental health conditions. For each of the five mental health conditions considered, the papers using human subjects and those using animal models are combined).

Figure 9 provides a graphic representation of the links identified between the 11 socioenvironmental factors, 13 categories of mental health-related biomarkers, and five mental health conditions reported in publications by mainland China authors (in English or Chinese) from 1990 to the middle of 2021. In summary, measures of cognitive function and anxiety were linked to all 13 categories of biomarkers; depression was linked to 12 of the 13 categories (excluding gut microbiota biomarkers); neurodevelopmental disorder-related phenotypes were linked to 9 of the 13 categories (excluding metabolic, cells not in the brain, neuroimaging, and neurophysiological biomarkers); and neurobehavioural symptoms were linked to 10 of the 13 categories (excluding immunological, metabolic, nutritional, and gut microbe biomarkers). Biomarkers for immunological cells not in the brain are most frequently associated with neurobehavioural symptoms, nutritional biomarkers are most frequently associated with neurodevelopmental disorder phenotypes, and the 11 remaining categories of biomarkers are most frequently associated with measures of cognitive functioning. For 10 of the 13 categories of biomarkers, anxiety was the second most frequently measured mental health outcome; the exceptions were neurotrophic biomarkers that have the same reported associations between depression and anxiety (4, 10·3%), other molecular biomarkers that have more reported associations with depression than anxiety (8, 16·7% vs 5, 10·4%), and nutritional biomarkers that have no reported associations with anxiety.

Discussion

Summary of evidence

In this scoping review, we first identified a wide range of biomarkers linked to mental health outcomes reported in the international literature and then identified 1330 studies conducted in mainland China that assess the association of these biomarkers with various socioenvironmental factors that have been rapidly changing in parallel with China's economic development over the past three decades. The number of related studies increased over time, with most contributions coming from institutions in the economically developed parts of the country. Most studies were about the biological effects of environmental pollution — particularly air pollution, heavy metal emissions, and persistent organic pollutants; few studies considered the biological effects of the increasing socioeconomic inequality that has accompanied China's rapid economic development. There was no specificity in the biological systems affected by different types of socioenvironmental factors: environmental pollution affected almost all categories of biomarkers considered. Only 18·4% (245/1330) of the studies considered any type of mental health condition, and most of the studies that did assess mental health conditions used animal models of mental disorders.

The rapid increase in published articles over time is related to the significantly increased volume of government-funded medical research in China over recent decades and to increasing awareness of the potential adverse biological effects of rapid urbanisation and economic development. The increase in the proportion of identified reports published in English-language journals over time is related both to the desire of researchers (and their institutions) to increase their international footprint and, importantly, to the expectation of many institutions that graduate students publish their research in English-language journals listed on the Science Citation Index (i.e., journals that have published impact factors).

The predominance of reports about the biological effects of environmental pollution (88·5%, 3156 of all 3567 reported associations of biomarkers with socioenvironmental factors) is related to the early recognition in China of the adverse health effects of the pollution that has accompanied rapid economic development — effects which were previously reported widely in other countries. The inclusion of mental health outcomes in such studies has only occurred more recently, inspired mainly by similar research in western countries.[33] Unlike changes in health-related lifestyle behaviours and socioeconomic inequity, it is relatively easy to objectively measure environmental pollution (with the possible exception of reduced green space), and pollution-related changes are typically more evident to community members (e.g., the number of haze days in cites and cyanobacteria blooms in lakes). Thus, the scientific feasibility of studying environmental pollution and the social and governmental support for such studies makes it much easier to conduct studies about pollution than studies about other types of socioenvironmental factors.

The relative lack of studies about the biological and mental health effects of lifestyle changes and socioeconomic inequity may be due to the difficulty of conducting and funding such studies, but this does <u>not</u> indicate that they are less important. Socioeconomic inequity and the type and prevalence of health-related lifestyle behaviours are related, but the nature of this relationship and the biological mechanisms that connect the combined effect of these factors to mental health outcomes remain largely unknown. The predominance of studies that use animal models is another problem. For example, the 111 reports about diet, which account for 65·3% of all reports about biomarkers associated with health-related behaviours, typically use animal models to assess the biological effects of extreme high-fat or extreme high-sugar diets — designs that increase the effect size of the results but may not be relevant for the less extreme diets consumed by humans.

Most research about the relationship between socioeconomic inequity and mental health in China and elsewhere has been conducted by social psychiatrists or other social scientists who identify social factors such as bad parenting practices[34] and traumatic experiences[35] that increase the risk of subsequent mental disorders. It is only recently that biological psychiatrists have become interested in the biological mediators connecting these social factors to mental health outcomes.[36] This trajectory in the focus of research about socioeconomic inequity combined with the relative difficulty of conducting such research is probably the main reason that only 30 (0.8%) of all 1330 reports included in this review assessed socioeconomic inequality. It has, for example, long been recognised that the 'left-behind' experience of China's rural children and adolescents (associated with the massive rural-to-urban migration of their parents for work) is a risk factor for mental disorders,[34,37-39] but very few studies have been conducted on the biological mechanisms that mediate this relationship (including a study about changes in brain structures[35] and another about changes in cortisol levels[40]). Moreover, the number of left-behind rural elderly — who often bear the combined stress of poverty and the responsibility of parenting grandchildren — likely equals or even exceeds the number of left-behind children; their plight and the mental health consequences of their plight have, to date, been largely ignored by the scientific community.

The biomarker profiles—the proportional distribution of the 13 categories of biomarkers—vary considerably between the three types of socioenvironmental factors and between the five types of mental health conditions. These differences are more likely related to the relatively small number of associations identified for most of the categories (less than 50 associations for socioeconomic inequality and for three of the five mental health conditions) than to the varying biological effects of the biomarkers on different socioenvironmental factors or on different mental disorders. Nevertheless, comparison of the biomarker profiles can provide useful information. For example, despite the much greater number of studies about air pollutants, heavy metal emissions, and persistent organic pollutants than about noise pollution, two studies about noise pollution consider neuroimaging biomarkers, while none of the studies about the three more commonly researched pollutants assessed neuroimaging biomarkers. Numerous studies have proven that air pollutants, heavy metal emissions, and persistent organic pollutants affect molecular and cellular biomarkers, including cells in the brain; these findings indicate the potential value of using neuroimaging to identify alterations in brain structure or function caused by these pollutants. Similarly, there were over 100 studies about the biomarkers associated with diet, but none used neuroimaging to assess the effect of diet on the brain. The failure to do so may be due to the prohibitively high cost of neuroimaging. One potential future direction for neuroimaging research in China would be to support studies that employ functional near-infrared spectroscopy (fNIRS) to assess the relationship between environmental factors and mental health conditions. This recently developed neuroimaging technique for measuring haemoglobin changes in the brain has been identified as a potential biomarker for schizophrenia[41] and major depressive disorder[42]; it has also been used to assess the psychological and cognitive effects of different types of urban spaces[43] and of being a left-behind child.[44]

Our preliminary review of the international literature to identify biomarkers associated with mental health disorders identified many more biomarkers for severe mental disorders such as schizophrenia spectrum disorders than for cognition or anxiety, so we were expecting to locate more studies from mainland China that identified biomarkers in individuals with severe mental disorders. However, the opposite was the case, possibly because of the lack of well-established experimental animal paradigms of schizophrenia. Among the 604 biomarker-mental health condition associations reported in the 245 papers that assessed mental health conditions, 497 (82·3%) were the results of studies that used animal models of mental health conditions: 93·1% (353/379) for studies about cognition functioning, 88·0% (103/117) for anxiety, 55·4% (31/56) for depression, 47·6% (10/21) for neurodevelopmental disorders, and 0% (0/31) for neurobehavioural symptoms. Modelling mental disorders in animals is more complex than modelling other types of diseases, so the use of animal-model paradigms of mental disorders in research is controversial. More studies assessing the relationship of socioenvironmental factors, biomarkers, and mental disorders – particularly severe mental disorders such as schizophrenia – need to enrol human subjects.

All socioenvironmental factors affect multiple biological symptoms, so it is important to move away from studies that focus on specific pairings of a single biomarker with a single socioenvironmental factor to multifaceted studies that simultaneously consider different classes of biomarkers, different types of socioenvironmental factors, and different types of psychological problems. A few studies identified in this review provide potential options for achieving these goals. One example is the Allostatic Load method (reported in 1 of the 1330 identified studies[45]) of combining the effects of multiple biomarkers from different biological systems, such as the HPA-axis, immune system, metabolic system, and cardiovascular systems. Another somewhat costly solution is to use omics technology that simultaneously assesses a wide range of potential biomarkers in the available biological sample rather than *a priori* selecting a specific candidate biomarker (reported in 44 reviewed studies, see Supplementary Table S8). One promising area is research on the interaction between genetics and socioenvironmental factors; for example, 19 studies (Table 2) considered how genetic polymorphism influences the effect of socioenvironmental factors on biomarkers of mental health conditions. The effect of these genetic polymorphisms on the association of socioenvironmental factors and mental health outcomes is mediated by different biomarkers, including the extent of DNA damage, homocysteine, and vitamin D. More epigenomic studies are also needed; preliminary results from studies using candidate epigenetic biomarkers reported changes in global DNA methylation levels, global histone acetylation levels, and candidate genes, but only two of the identified studies[46,47] performed epigenomic analyses.

Strengths and limitations

This report is a scoping review, so our goal is to identify available literature and critical gaps in the available literature, not to summarise the findings of the available literature. We have successfully identified and characterised a large corpus of work about this important topic – the biological mechanisms that link socioenvironmental changes to mental health, but the review has several limitations. In our preliminary search for biomarkers associated with mental disorders in the international literature, the volume of available studies was so great that we had to limit our search to review articles; this may have excluded some rarely reported or recently identified biomarkers. Based on the review of the current literature about research in China and discussions with relevant experts, our selection of socioenvironmental factors of interest was limited to different types of pollution, a short list of lifestyle behavioural changes, and a single socioeconomic variable; it is certainly possible that other types of socioenvironmental changes that have not yet been studied in China result in biological changes that directly or indirectly affect mental health. To ensure the quality of included Chinese-language studies, we limited our search of Chinese-language studies to those reported in 'Core Journals', so some relevant studies published in local journals may have been missed. Finally, our findings are limited to the association of socioenvironmental factors with biomarkers in mainland China; similar analyses from other countries may identify additional biological factors linking socioenvironmental factors with mental disorders.

Conclusions

Few studies have directly assessed the biological mechanisms linking socioenvironmental changes and mental health. There are, however, many studies in the international literature that assess the relationship of a wide variety of biomarkers with mental disorders and a large and growing literature in China about the biological effects of China's rapid environmental and socioeconomic changes. To identify potential biological mediators of the effects of socioenvironmental factors on mental health outcomes, we adopted the novel approach of identifying all biomarkers previously associated with mental disorders in the international literature and then searched English- and Chinese-language databases for studies conducted in mainland China that reported associations between these mental-health-related biomarkers and socioenvironmental factors. We identified 1330 relevant papers that reported 3567 specific biomarker-socioenvironmental associations, but only 245 (18%) of these papers simultaneously reported the association of the biomarker(s) with mental health conditions. The inclusion of many studies that did not directly evaluate the association of biomarkers with mental health conditions but did assess the effect of socioenvironmental factors on biomarkers associated with mental health disorders greatly improved our power to map a network of reported relationships between socioenvironmental factors, biological changes, and mental health outcomes.

There are numerous studies in China about the effects of air pollution, heavy metal emissions, and persistent organic pollutants on biological markers associated with mental health outcomes, but relatively few studies about the biological effects of other important socioenvironmental factors that have been changing rapidly as China develops. Some promising areas — such as gene by environment interactions and the epigenetic effects of environmental changes — remain understudied. Moreover, available research does not identify socioenvironmental factor-specific biomarker profiles or mental health condition-specific biomarker profiles, possibly because most studies consider candidate biomarkers in limited categories, most results are based on animal-model studies, and relatively few studies simultaneously assess socioenvironmental factors, biomarkers, and mental health outcomes. One possible way to overcome these limitations is to focus more financial and personnel resources on studies about mental health outcomes in human subjects exposed to different socioenvironmental changes using omics technologies. These technologies do not need to select candidate biomarkers and, thus, might be the best solution for interpreting the complicated, interrelated effects of socioenvironmental factors on the biological systems that influence different mental health outcomes.

Contributors

YZ, QL, YY, and HW conducted the literature search and data extraction. YZ and YY cross-checked extracted data. YZ made the figures. YZ, QL, and YY made the tables. MAB, MRP, and TL contributed extensively to the interpretation and write-up of the data. All authors contributed to the study design, data analysis, data interpretation, and preparation of the manuscript.

Declaration of interests

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2022.100610.

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