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Assessing How Social Exposures Are Integrated in Exposome Research: A Scoping Review

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BACKGROUND: Exposome research aims to describe and understand the extent to which all the exposures in human environments may affect our health over the lifetime. However, the way in which humans interact with their environment is socially patterned. Failing to account for social factors in research exploring the exposome may underestimate the magnitude of the effect of exposures or mask inequalities in the distribution of both exposures and outcomes.

OBJECTIVES: We aimed to describe the extent to which social factors appear in the exposome literature, the manner in which they are used in empirical analyses and statistical modeling, and the way in which they are considered in the overall scientific approach.

METHODS: We conducted a scoping review of the literature using three databases (PubMed, Embase, and Web of Science) up to January 2022. We grouped studies based on the way in which the social variables were used in the analyses and quantified the type and frequency of social variables mentioned in the articles. We also qualitatively described the scientific approach used by authors to integrate social variables.

RESULTS: We screened 1,001 records, and 73 studies were included in the analysis. Fifty-five (~75%) used social variables as exposures or confounders or both, and a wide array of social variables were represented in the articles. Individual-level social variables were more often found, especially education and race/ethnicity, as well as neighborhood-level deprivation indices. Half of the studies used a hypothesis-free approach and the other half, a hypothesis-driven approach. However, in the latter group, of 35 studies, only 8 reported and discussed at least one possible social mechanism underlying the relationship observed between the social variable and the outcome.

DISCUSSION: Social factors in exposome research should be considered in a more systematic way, considering their role in structuring both the specific external and the internal exposome. Doing so could help to understand the mechanisms of construction and, potentially, alleviate social inequalities in health and mitigate the emergence of new ones. <https://doi.org/10.1289/EHP11015>

Introduction

Exposome research aims to describe and understand the extent and nature of all the exposures in human environments over the lifetime which may affect our health.¹ The exposome originally “encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards.”² The exposome can be classified into *a*) the external exposome, which refers to exposures outside of the body that can be general (broader social, cultural, and ecological contexts) or specific (chemical pollutants or lifestyle factors), and *b*) the internal exposome, which refers to exposures inside the body that are unique to the individual (metabolic processes, circulating blood biomarkers, hormones).³ These two domains are complementary, interrelated, and intertwined.

Increasingly, exposome scientists are taking an interest in social determinants of health—nonmedical factors that influence health outcomes, well-being, and quality of life (e.g., gender, race, education, income, housing, food security)—and how these may be included in the exposome framework, namely as part of the external exposome.⁴ A wide literature on social determinants of health has developed over many decades, predating the exposome concept,^{5,6} and which has established the relationship

between social inequalities and health inequalities, tracked trends in these inequalities over time and across contexts, and examined potential processes and mechanisms that may underlie the observed associations.⁷ Although behavioral and lifestyle factors are important determinants of mortality, several epidemiological studies have shown that social inequalities cannot fully be explained by traditional risk factors.^{8,9} One set of mechanisms linking social exposures to subsequent health is via differential activation of a wide range of physiological responses.¹⁰

The social-to-biological transition^{10,11} refers to how the social environment can lead to biological alterations and may be of particular interest to exposome science. Social environments may influence health through two main types of socially distributed initial exposures: *a*) exposures of exogenous origin, emerging from the specific external exposome (environmental exposures such as pollution, pesticides, work exposures; behaviors such as tobacco, alcohol, diet), and *b*) exposures of endogenous origin involving the subjective interpretation of conditions (challenges, interpersonal relationships, and so on) followed by the response of internal biological mechanisms, mainly linked to stress perception and stress response systems (especially psychosocial exposures) likely to modify the internal exposome.^{12,13} Therefore, the hypothesis of a biological embodiment of the social environment makes the link between social factors in the general external exposome and biological responses that make up the internal exposome and consequence on health while taking into account the specific external exposome.¹⁴

Indeed, well-defined socially structured exposures, such as occupation, education, or deprivation, have been examined in relation to biological measures,¹⁵ which, in turn, are related to morbidity or mortality.^{16–18} The way humans interact with their environment is socially patterned, meaning that external exposures that may elicit internal biological responses should be considered in their social context. This has led some

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epidemiologists to argue that social factors should be considered as “fundamental causes” of disease¹⁹ and some sociologists to propose the socio-exposome framework.⁶ The importance of including social factors in research exploring the exposome is evident if we are to understand health outcomes and health inequalities. Failing to account for social factors in environmental health research may lead to underestimating the magnitude of the effect of exposures and/or masking inequalities in the distribution of both exposures and outcomes. However, the way in which social variables are included deserves thoughtful consideration because their meaning, what they measure, and the mechanisms by which they can have an impact on health are different.¹¹ From an analytical point of view, exposome researchers may, on the one hand, want to take an “agnostic” and exploratory approach, using exposure-wide analyses to explore clusters of social exposures. On the other hand, they may have explicit reasons to include specific social variables based on previous research, aiming to test relevant pathways or to account for confounding. The debate among epidemiologists about the legitimacy of taking an agnostic approach and the choice of one method above another is not new,²⁰ and this could have had practical consequences for current knowledge on exposome and health inequities. Nevertheless, both approaches present challenges when using social variables that deserve to be specified.

We carried out a scoping review to describe *a*) the extent to which social factors appear in the exposome empirical literature, *b*) the manner in which social variables are used in empirical analyses and statistical modeling, and *c*) the way in which social factors are considered in hypotheses or the overall scientific approach. Our objective is to establish the role of social determinants in recent exposome science and to consider how research on the exposome may move forward in its aim to develop an understanding of how the social environment affects our health, building upon existing research on social determinants of health and health inequalities over the life course.

Methods

Search Strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines,²¹ a structured search strategy was developed to include title–abstract–keywords in a search string. The search strategy focused on articles related to both the social environment and the concept of the exposome. The full set of search terms was as follows:

(soci OR justice OR injustice OR equity OR inequity OR gender OR race OR ethnicity OR exclusion OR discrimination OR class OR oppression OR dominance OR geograph* OR housing OR “living conditions” OR urban OR “built environment” OR psychosoci* OR workplace OR education* OR income OR occupation* OR lifecourse OR “work conditions” OR rural) AND (exposom*)*.

The choice of keywords was based on the social epidemiology literature and is related to the socioeconomic determinants of health (material and psychosocial exposures), excluding behaviors. The search was limited to peer-reviewed articles from inception up until 3 January 2022 and was run using three databases: Pubmed, Embase, and Web of Science. All studies identified as suitable were extracted using Zotero (version 5.0.96.3; Zotero).

Eligibility Criteria

Eligible articles met the following inclusion criteria: *a*) peer-reviewed articles, *b*) empirical articles (controlled trials, cohort,

or cross-sectional study designs), *c*) on human populations, *d*) dealing with the concept of exposome—we used a broad definition of the exposome as multiple exposures (at least two), and *e*) using at least one variable related to the social environment. We excluded *a*) animal studies and *b*) books, book reviews, book chapters, conference abstracts, conference papers, editorials or letters to the editor, commentaries, and literature reviews. After applying the inclusion and exclusion criteria, all articles were written in English; therefore, no language restrictions were needed.

Screening and Extraction of Data

After removing duplicates, we conducted a screening process to select the papers to be fully reviewed. First, titles and abstracts were examined by four authors. L.N. fully screened the whole extraction and, in parallel, M.K.I., R.C., and L.M. conducted a second blind screening (one-third each) so that each abstract was screened twice. Then, studies classified as irrelevant in both the parallel screenings were excluded from further review. All disagreements regarding classification were resolved by discussion between reviewers. Extracted data included *a*) article identification (first author name, publication year, journal, publication title, keywords, and country), *b*) definition of the exposome, *c*) nature of the social variables and their usage, and *d*) suggested social mechanisms underlying the association.

Synthesis of Results

Given the heterogeneity among the studies, we used a descriptive approach to review the available evidence regarding the use of social factors in an exposome context. We grouped studies according to the manner in which social variables were used in the analyses (exposure, confounder, effect-modifier, descriptive). We used the following definitions. A confounder is a variable that causes both the exposure and outcome of interest.²² An effect-modifier modulates the effect of an exposure on the outcome across levels of this variable,²³ for example, the relationship between exposure to air pollution and respiratory health is different for children in low vs. high income and education groups.²⁴ We further quantified the type and frequency of social variables mentioned in the articles. We then built a word cloud using the package *ggwordcloud* in R software (version 4.0.5; R Development Core Team) as a visualization tool. We also qualitatively described the approach used by authors to integrate social variables into the exposome definition (agnostic or *a priori* hypothesis-driven) and the presence of a social hypothesis in the introduction and a social mechanism in the discussion. We considered agnostic/hypothesis-free approaches when researchers aimed to explore their data with no predefined hypothesis of interest, and hypothesis-driven approaches when researchers aimed to test an explicit hypothesis about the relationship between exposure(s) and outcome(s). We considered a social mechanism to be present if any underlying process linking the social factor(s) to the outcome(s) was mentioned in the discussion.

Results

Selection of Articles

The search yielded a total of 1,001 articles: 309 records in PubMed, 365 in Embase, and 327 records in Web of Science. Once all the articles were retrieved, 536 duplicates were identified and 465 articles were retained. The first screening stage—titles and abstracts—led to the exclusion of 382 articles that did not meet the eligibility criteria. The second screening stage—full-text assessment—led to the exclusion of an additional 10 articles, 7 of which did not contain social variables in the text

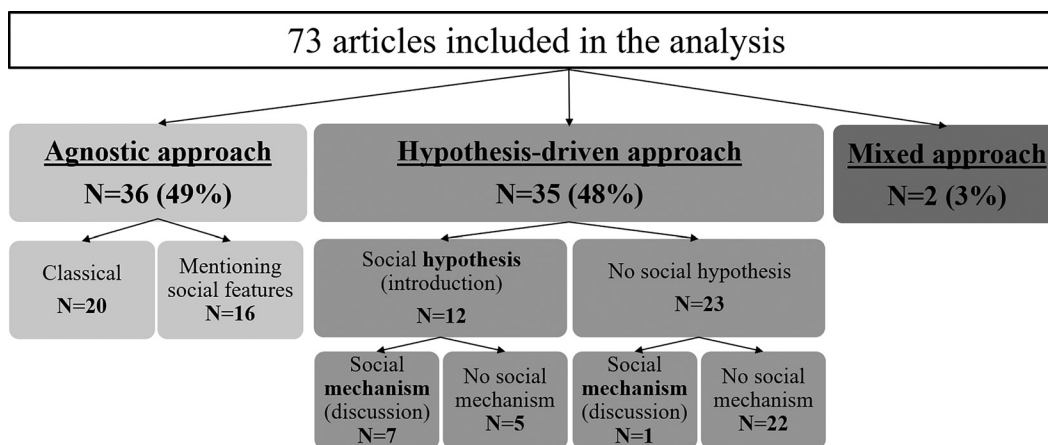


Figure 2. Social environment, *a priori* hypotheses and underlying mechanisms. Detailed table is available in Table S4. Note: Agnostic approach, data exploration with no predefined hypothesis of interest; hypothesis-driven approach, test of an explicit hypothesis about the relationship between exposure(s) and outcome(s).

between social variables and the outcome,^{25–32} among which seven also mentioned social hypothesis in the introduction.^{25–31} The mechanisms referred to different health behaviors^{27,31,32} (nutrition), different occupational^{26,28} (physical and chemical) and domestic^{26,32} (pesticides) exposures, or different psychosocial exposures^{25,29–32} (stress, social network), depending on social position. Two of the studies also mentioned epigenetics and the social-to-biological processes^{29,30}—or how social factors are associated with biological mechanisms. Of note, most of the studies using a hypothesis-driven approach did not mention any social hypothesis nor social-to-biological mechanism^{33–54} [$n = 22$ (63%)].

Discussion

The first objective of our study was to describe the extent to which social factors appear in the exposome literature. Our review identified 73 articles where social variables had been included: relatively few compared with the overall number of articles in the field of exposome research. Although the social environment partly determines the level of exposure for many factors¹⁹ (physicochemical exposures, behaviors), this dimension is still poorly considered in the exposome literature. It is important to emphasize that this scarce consideration of the social environment may point toward an underappreciation of potentially important underlying mechanisms in some exposome research, such as the impact of socially distributed psychosocial exposures that may modify biological functioning (via the stress response system in particular) and may interact with other exposures.

Among the 73 studies matching the inclusion criteria for our scoping review, most [$n = 55$ (75%)] used social variables as exposures and/or confounders and a wide array of social variables were used across the articles. Individual-level social variables were more often found, especially education and race/ethnicity. Deprivation indices at the neighborhood level were also widely used. Around half of the studies used a hypothesis-free approach and the other half a hypothesis-driven approach. However, in the latter group, only 8 studies reported and discussed one or more possible social mechanisms underlying the relationship observed between the social variable and the outcome.

The wide range of potential social factors available present conceptual and methodological challenges given that their meanings may change over time, space, and in relation to socio-cultural contexts. When such variables were used as exposures, we observed two main approaches, each with their conceptual

and methodological advantages and challenges. First, agnostic, or hypothesis-free approaches, are common place in exposome research and mimic methods used in genomics. Often the aim in these studies is to identify internal omic signals of external exposures to pollutants or toxins,⁴ and an agnostic approach means that new and relatively unknown biomarkers or signals can be found and then replicated or subsequently examined in more depth. This approach may help researchers to establish the biological plausibility of relationships between external exposures and internal biomarkers.⁵⁵ The question arising is whether such exposure-wide approaches make sense when social variables are being considered. By agnostically treating exposure variables the same way in these types of analyses, any inherent structural or hierarchical relation between variables is ignored. Yet race/ethnicity or class are stratifying or “upstream” variables that affect the distribution of many other social factors, such as housing or psychosocial stressors.⁵⁶ By deciding to treat variables agnostically, does a hypothesis that these variables are “equivalent” and unrelated to each other not inevitably slip in?

The second approach we observed, commonly used in epidemiology, is where one or several hypotheses are tested. In the context of exposome research, the hypothesis would be that a social variable is associated with biomarkers or with a health outcome, or both. At present, there is a vast literature on the relationships between social factors of different types and a variety of biological markers through multiple mechanisms¹⁵ and decades of research on health inequalities.⁵⁷ In our review of the literature, we observed that relatively few of the hypothesis-driven papers, 12 of 35 (34%), put forward an explicit hypothesis about the relationship between the social variables and the outcome. When considering social-to-biological research, the underlying hypothesis and nature of the relationship is worth clarifying to facilitate the interpretation of findings and draw conclusions in terms of health inequalities.¹¹ Researchers working with social and health data within the exposome framework may be interested in examining their hypotheses using one of the many existing causal inference methods, including the use of instrumental variables, such as mendelian randomization, mediation analysis, and many others.⁵⁸

Of note, it is entirely plausible when using social variables in relation to health outcomes that reverse causation may occur.⁵⁹ As well as social factors causing health outcomes, health conditions can impact conditions such as where people live, through access to care or socioeconomic factors, or lead people to change

their employment status, among many other examples. This is a standard problem in any quantitative analysis and deserves attention from the researchers performing the analyses. When longitudinal data collected from childhood are used, as is the case for some exposome analysis, the temporal sequence of early life experiences helps to some extent to avert the problem of reverse causation.⁶⁰

As well as using social variables as exposures in either hypothesis-free or hypothesis-driven approaches, many of the studies in our sample used them as confounding factors. This means that the authors wanted to adjust their statistical associations for a social variable, potentially associated with their exposure and outcome, to avoid spurious results. Controlling for social variables as potential confounders may be necessary; however, it is important to avoid interpreting the association between the confounding variable and outcome in multivariable analyses. Such interpretations may lead to table 2 fallacy, and lead to mistakes in the interpretation of these estimates.⁶¹ Moreover, such practice has been considered as inappropriate by some epidemiologists who argue that social variables should instead be systematically treated as “fundamental causes.”^{19,62}

Beyond the question of integrating social variables in exposome studies, it is fundamental to recognize that the choice of an agnostic or hypothesis-driven approach brings with it a different theoretical framework that will influence how exposome researchers consider the question of the origins of social inequalities in health.^{63–65} Many pragmatic issues arise regarding the availability of social variables and their comparability or harmonization across data sets. As such, it was unsurprising to see that many of the papers we reviewed used education (individual or parental) as a social variable. Education is often used as a measure of socioeconomic position, a global concept that captures both resources and prestige.⁶⁶ It is relatively straightforward to collect, often measuring the number of years of education or level of diploma, and therefore seemingly easy to harmonize across data sets. However, there are a number of considerations to bear in mind when using education as a social variable. Over time, the proportion of people attending school, achieving a high school-level diploma and attending further education has increased, thus the way in which educational attainment relates to other social factors and health outcomes has evolved.⁵⁷ Therefore, we must consider a number of questions: Is the quality of education equivalent across context and time? In a specific country at a specific time, who was able to achieve a high level of education? What was the mandatory legal school age limit? Did this vary according to gender, race, class? What kind of benefits does a high level of education offer over time, between countries?⁶⁷ When education is used in relation to health outcomes, it is important to consider the mechanisms that may underlie the association, such as behavioral, psychosocial, and material pathways,⁶⁸ a point we will return to in our recommendations below.

The second most used variable was race/ethnicity. In our scoping review, we found that race/ethnicity variables were most often used as a confounder. Although this type of adjustment may reduce bias, it does not help to understand the role or the meaning of race/ethnicity. Race and ethnicity variables may be used at the individual and neighborhood levels as socially constructed categories reflecting societal and individual histories of discrimination and dispossession experienced by minoritized people⁶⁹ and vary according to the socio-political history of each country. Providing that researchers understand the theoretical bases upon which race/ethnicity affects health and disease along the life course, the exposome research framework can provide the opportunity to explore the relationships between minoritized groups

within a population and their physical and social environments. Given the potential harms of discrimination to health that may operate through social-to-biological pathways,⁷⁰ using a conceptually clear race/ethnicity variable in relation to biological and health measures may elucidate important connections between the social experience of minoritized people and the consequences of this upon their health in the aim of understanding and redressing inequalities.⁷⁰

Deprivation indices are another type of very commonly used social variable. Deprivation, covering the various conditions, independent of income, experienced by people who are poor, is a multi-dimensional concept, closely related to poverty.⁷¹ Ecological indices of deprivation are mainly constructed from population census data and are often used as a way to deal with an absence of individual socioeconomic data collected alongside biological or health data.^{72,73} These indices measure relative deprivation at a given geographical level, as opposed to other measures of relative poverty and deprivation that require individual-level survey questions. Once the respective scores are constructed and divided into a suitable variable, such as quintiles, each ward or postal code is attributed a deprivation quintile. Inhabitants of that place may be attributed the corresponding deprivation quintile to represent the deprivation level of their place of residence and possibly as a proxy-variable for their social position, should individual-level data be unavailable. Both the Carstairs and Townsend indices,⁷⁴ developed in the 1980s in the UK and on which many other deprivation indices are based, have shown that a higher level of deprivation is associated with an increased risk of mortality and morbidity.⁷⁴ Even if the geographical scale being used is small, it is important to consider the potential for error when using ecological indices to approximate individual socioeconomic position, which may lead to an underestimation of the extent of social inequality that would be observed with individual-level indicators.^{73,75} We think that exposome studies using such social variables would benefit from outlining the respective strengths and limitations of specific variable, and the underlying hypothesis the variable is being used to test, in the case of hypothesis-driven work (see the “recommended questions” in Figure 3).

Regarding parental characteristics, we found that maternal characteristics were more often considered than paternal characteristics. This lack of attention paid to paternal exposures has been discussed by Sharp et al.⁷⁶ who underlined that empirical literature on paternal exposures is rare. Often the data regarding the father are lacking, and where they do exist, tend to be of lower quality. Moreover, the emphasis on maternal exposures and the lack of available data on paternal exposures reflect in part gender imbalances in power and health inequities that result from broader structural power imbalances.

Limitations

Some limitations of this review should be mentioned. By using the term “exposomsm” in our literature review, we may have restricted our search to the most recent articles using this concept and left out older articles where multiple exposures were being considered before the term “exposome” was coined. We also acknowledge that other social variables may not have been captured by the search terms we used; therefore, we most likely selected a subset of the exposome studies using social variables. Finally, we restricted our scoping review to peer-reviewed articles published in English and did not consider the gray literature nor the bibliographies of studies included in our pool. This may have biased our selection of papers. However, this scoping review did not aim to be systematic but, rather, to provide an overall picture of the use of social variables in exposome research.

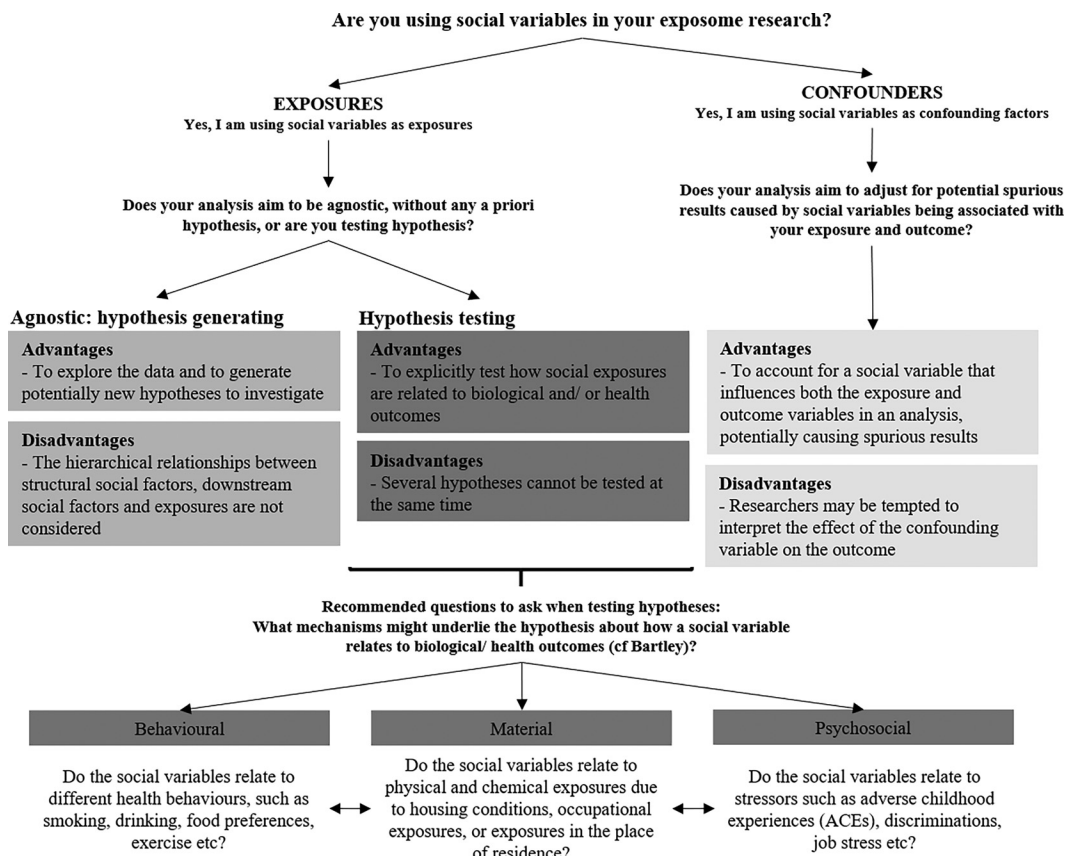


Figure 3. Recommendations regarding the use of social variables in the exposome context.

Recommendations

Based on our review, we developed a set of recommendations to guide exposome researchers when using social variables based on the health inequalities literature (Figure 3). The first decision researchers may need to make is about whether the social variables are being used as exposures or confounders, the two most common usages found in our review. When using them as exposures, there are two main approaches used in exposome research that deserve to be made explicit, each with their advantages and disadvantages: agnostic or hypothesis-driven approaches. The agnostic approach may be helpful for generating hypotheses to be subsequently tested using a hypothesis-driven approach. Based on the health inequalities and social-to-biological literature,^{10,11} we suggest that researchers using social variables as exposures in hypothesis-driven studies first make explicit their hypothesis about how a social variable relates to biological/health outcomes and after which develop a theoretical model for testing this hypothesis, with the use of resources such as Bartley (2015),⁵⁷ including potential underlying mechanisms. Only then should they select which social variables are most appropriate to carry out their analyses.⁶⁷ To help develop this theoretical model, it may be useful to consider three broad explanatory models, the behavioral, material, and psychosocial.⁵⁷

The behavioral model suggests that the social variable in question is related to different health behaviors, such as smoking, drinking, food preferences, or exercise. The material model suggests that the social variable is related to physical and chemical exposures due to housing conditions, occupational exposures, or exposures in the place of residence, for example. When considering social-to-biological processes, these two models refer to mechanisms of exogenous origin, consisting of processes through

which socially patterned conditions external to the body enter the body and elicit a physiological response from it and/or a physical effort. Finally, the psychosocial model pertains to social variables being related to stressors, such as adverse childhood experiences, discriminations, or job stress. This last model underlines a mechanism of endogenous origin that refers to internal biological processes that occur as a consequence of sensory and neurobiological signals triggered by perceptions and emotions. These mechanisms driving social-to-biological processes may operate simultaneously (e.g., poor material conditions and psychosocial adverse experiences) but also interact with each other (material conditions, as well as psychosocial experiences, are likely to influence behaviors). All three processes are likely to contribute to “how we literally incorporate, biologically, the world around us.”⁶⁵

Conclusion

Our scoping review established the small but growing role of social variables in recent exposome science.⁷⁷ Overall, we conclude that researchers in the exposome field are increasingly aiming to integrate social variables into their studies, which is important considering the social distribution of various dimensions of the exposome. However, the role of these social variables is not always made explicit, and their use is often not placed within the context of an appropriate body of literature on the social determinants of health. Based on our findings, we have made recommendations to guide researchers when using social variables in their exposome study, and suggest that, when appropriate, they make their hypothesis about the relation between the social variable and outcome clear. Moving toward a more interdisciplinary exposome framework, for example, by including social scientists in environmental health research,

could accelerate the development of theoretical approaches to specifying social forces that should be included in exposome research.

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