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Environmental Exposure History and Vulvodynia Risk: A Population-Based Study

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Abstract

Background: Risk factors for vulvodynia continue to be elusive. We evaluated the association between past environmental exposures and the presence of vulvodynia.
Materials and Methods: The history of 28 lifetime environmental exposures was queried in the longitudinal population-based Woman-to-Woman Health Study on the 24-month follow-up survey. Relationships between these and vulvodynia case status were assessed using multinomial logistic regression.
Results: Overall, 1585 women completed the 24-month survey, the required covariate responses, and questions required for case status assessment. Screening positive as a vulvodynia case was associated with history of exposures to home-sprayed chemicals (insecticides, fungicides, herbicides—odds ratio [OR] 2.47, 95% confidence interval [CI] 1.71–3.58, $p < 0.0001$), home rodent poison and mothballs (OR 1.62, 95% CI 1.25–2.09, $p < 0.001$), working with solvents and paints (OR 2.49, 95% CI 1.68–3.70, $p < 0.0001$), working as a housekeeper/maid (OR 2.07, 95% CI 1.42–3.00, $p < 0.0001$), working as a manicurist/hairdresser (OR 2.00, 95% CI 1.14–3.53, $p < 0.05$), and working at a dry cleaning facility (OR 2.13, 95% CI 1.08–4.19, $p < 0.05$). When classified into nine individual environmental exposure categories and all included in the same model, significant associations remained for four categories (home-sprayed chemicals, home rodent poison or mothballs, paints and solvents, and working as a housekeeper).
Conclusions: This preliminary evaluation suggests a positive association between vulvodynia and the reported history of exposures to a number of household and work-related environmental toxins. Further investigation of timing and dose of environmental exposures, relationship to clinical course, and treatment outcomes is warranted.

Keywords: vulvodynia, environmental exposures, risk, population based

Introduction

Susceptibility to chronic pain conditions varies among individuals, but the specific etiologic mechanisms through which susceptibility results in chronic symptoms remain unclear. Vulvodynia is one such chronic pain disorder that affects ~7%–8.3% of women at any given time,[1,2] with ~4.2 new onset vulvar pain cases occurring per 100 women per year.[3] Vulvodynia has been linked to aberrant pain responses at the vulva and to central nervous system alterations in response to provoked stimuli. Associations with inflammatory alterations have similarly been demonstrated. Yet, the etiology of this pain disorder continues to be elusive. Environmental exposure to chemicals has been associated with neurologic disorders[4] as well as with acute and chronic pain in animals,[5–7] including other human populations.[8] Elucidating risk factors for acute and chronic pain is the focus of this substantial study, but to date the role of environmental exposures in susceptibility to vulvodynia has not been examined.

The Woman-to-Woman Health Study is a longitudinal population-based study of women in Southeast Michigan, designed to elucidate factors associated with vulvar pain onset and resolution. Twenty-eight questions regarding history of environmental exposures at home and at work were asked in the 24-month follow-up survey to assess whether past environmental exposures might be associated with the risk of vulvodynia. This article evaluates associations between the history of environmental exposures and the risk of having vulvodynia, or of having vulvar symptoms short of

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meeting case criteria, to assess these toxins as potential risk factors for vulvodynia.

Materials and Methods

The University of Michigan Woman-to-Woman Health Study is a prospective population-based study of 2277 women, aged 18 and over, living in Southeast Michigan, who were enrolled *via* random-digit dialing in 2008, and who received online or written surveys every 6 months regarding vulvodynia case status, health status, and exposures.[1] Funding was obtained from the National Institute of Child Health and Human Development at the Institutes of Health in the United States after scientific quality review (HD054767); this funder had no involvement in the conducting of research or manuscript preparation. Institutional Review Board (IRB) approval was obtained from the University of Michigan Medical IRB (#17098, January 23, 2008), and informed consent was obtained. At the time of the 24-month survey, questions were asked inquiring about 28 past environmental exposures at home and at work. Questions were an abbreviated listing of environmental exposures based on those used in the National Institute of Environmental Health Sciences Uterine Fibroid Study (D.D. Baird, pers. comm.).[9] Because vulvodynia case status is known to remit and relapse,[10] participant case status and covariate data for this analysis were based on responses received on the baseline, 6-, 12-, 18-, and 24-month follow-up surveys. Women were excluded from the analysis if they were missing information for any of the environmental exposures, for questions necessary to define case status, or for covariate data (age, ethnicity, or difficulty paying for basics data).

The primary outcome was vulvodynia case status (vulvodynia case, intermediate symptoms, or asymptomatic). Cases were those who met validated case criteria,[11] including pain at the opening to the vagina lasting >3 months, on any of the five surveys from the baseline to the 24-month survey (''Cases''). Because characteristics of pain in vulvodynia may include both provoked and nonprovoked pain, which may also differ over time,[12] and because the location of vulvar pain as reported on a survey is often dissimilar to that reported during an examination, all cases meeting the stated criteria were included. Cases could have provoked, unprovoked, or mixed symptoms, primary or secondary onset, and could have symptoms localized to the introitus or more widespread symptoms. The intermediate group had some vulvar discomfort but never met case criteria in any of the surveys (''Intermediate symptoms''). Asymptomatic women were those who never reported having vulvar symptoms meeting case criteria nor reported intermediate symptoms (''Asymptomatic'').

Environmental exposure questions pertained to any lifetime exposures to toxins listed in the 28 questions included in the 24-month survey. (See complete listing in Supplementary Appendix A1; Supplementary Data are available online at www.liebertpub.com/jwh). They included items related to occupations such as dry cleaning, farming, working in salons, working as a housekeeper or maid (for at least 1 month), or occupational chemical class exposures, including solvents, pesticides, fumigants, and pharmaceuticals (at least once a week for at least a month). We also assessed exposures from the home environment, including ever spraying for rodents, insects, or bedbugs and products used on lawns (*e.g.*, ever using fungicides and herbicides). Other items included ever working with crops, aerial insecticide spraying, and personal use of bug sprays. Covariates included self-defined race/ethnicity and education level attained, which were assessed at baseline. Age, marital status, and a socioeconomic indicator that asked if women had difficulty paying for their basic expenses were assessed at the 24-month follow-up survey, or imputed from the 18-, 12-, 6-month, or baseline surveys if missing at 24 months.

Analysis

We calculated frequencies and distributions of demographic characteristics, environmental exposures, and case status (SAS, version 9.4, Cary, NC). Associations between vulvodynia case status and demographic characteristics were examined using chi-square tests. The association between each environmental exposure and vulvodynia case status was estimated in separate multinomial logistic regressions with adjustment for potential confounders.

In addition to the use of discrete environmental exposure items, we aggregated exposures into qualitatively similar composite categories. Six categories were defined by location (*i.e.*, occupational vs. home environment) and content (*i.e.*, types of chemicals or products). These six categories included (1) exposure to sprayed chemicals in or around the home (six items); (2) exposure to rodent poison or mothballs at home (two items); (3) exposure to pesticides, herbicides, or fumigants at work (three items); (4) ever worked on a farm (five items); (5) ever worked in a laboratory or medical setting (five items); and (6) ever worked with solvents or paints (two items). We also identified three single items (*i.e.*, worked as a manicurist or hairdresser, worked as a housekeeper or maid, and worked at a dry cleaning facility) that we considered distinct categories since they could not be aggregated by location and content. Three environmental questions that did not fit into any of the categories were reported by <3% of the population (working with grease or oil at work, working with welding fumes at work, or applying herbicides such as Agent Orange in the military). Since they were not individually associated with case status, they were not included in the final categorized groupings. We evaluated environmental exposure risk using each of the nine composite categories separately as well as by using the total number of categories to which women reported any exposure, using multinomial logistic regression models. Finally, we estimated whether specific categories of exposure were likely to be associated with case status when controlled for all of the other categories, using multinomial logistic regression with adjustment for potential confounders. Two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 2277 women completed the baseline survey in the Woman-to-Woman Health Study. Of these, 1832 (80.5%) completed the 24-month survey containing the environmental exposure questionnaire, 1585 (86.5%) of whom were included in this analysis. Four respondents were excluded who were missing data on difficulty paying for basics, two who were missing data required for defining case status, and 241 who had incomplete data for the environmental exposures.

Compared with those included, at baseline, women not included in this analysis were older (52.4% vs. 49.6% years, $p < 0.0001$), more likely to be Black or other race/ethnicity (33.9% vs. 22.5%, $p < 0.0001$), and to have difficulty paying for basics (43.2% vs. 34.8%, $p = 0.003$), and less likely to be college graduates (34.4% vs. 49.4%, $p \leq 0.0001$), or married (56.1% vs. 65.9%, $p \leq 0.001$).

Of the 1585 eligible women, 20.5% ($N = 325$) were defined as cases, of whom 171 (52.6%) met criteria for vulvodynia at baseline and 154 (47.4%) met criteria on a subsequent survey (6, 12, 18, or 24 months). Nineteen percent ($N = 301$) were defined as having intermediate symptoms, and 60.5% ($N = 959$) were defined as being asymptomatic.

Table 1 provides information on demographic characteristics of the study population by case status. Asymptomatic women were older, and less likely to be married, or to be a college graduate compared with cases or those with intermediate symptoms. Cases were less likely to be Black than either asymptomatic women or those with intermediate symptoms.

History of environmental exposures differed by age, ethnicity, and difficulty paying for basics (see Supplementary Table S1). In general, younger women were less likely to report home exposures to chemicals and pesticides, and to rodent poisons or mothballs ($p \leq 0.003$). Compared with other ethnic/racial groups, Black women tended to be less likely to report home exposure to most chemicals ($p = 0.03$ to <0.001), with the exception of exposure to mothballs, which they reported at a higher rate ($p < 0.001$). Black women also reported work associated with several of the farming questions less frequently than White women ($p = 0.03$–0.004), but had a greater likelihood of having worked as a housekeeper or maid or as a manicurist or hairdresser ($p < 0.01$–0.001). Women finding it hard to pay for basics were less likely to report using a weed killer in the yard ($p < 0.0001$), but were more likely to have had exposures of working as a housekeeper or maid ($p < 0.001$), working as a manicurist or hairdresser ($p = 0.01$), at a dry cleaner ($p = 0.02$), or being exposed to solvents, grease, or oils ($p = 0.03$) than women who did not have difficulty paying for basics. In general, there was little or no association between demographics and the other environmental exposures, including exposure to pesticides, herbicides, or fumigants at work, working on a farm, or working in a medical setting.

The frequency of reported environmental exposures and the odds ratios (ORs) between reported history of environmental exposures and case status adjusted for age, hard to pay for basics, and race/ethnicity are shown in Table 2. The most commonly reported exposures were chemical exposures at home—primarily insecticides, herbicides, fungicides, insect repellants, rodent poisons, and mothballs—each of which were statistically significantly associated with an increased odds of screening positive for vulvodynia. Working with solvents or paints, working at dry cleaners, and also working as a housekeeper/maid, or as a manicurist or hairdresser, which were less prevalent exposures than chemical exposures at home, were also statistically significantly associated with a greater odds of having vulvodynia compared with asymptomatic women. However, exposures to pesticides, herbicides, or fumigants at work, working in a medical/laboratory setting, and exposures during farming were not statistically significantly associated with case status. Of the 16 exposures that were more common in cases when compared with asymptomatic women, 7 were more common in women with intermediate symptoms compared with those who were asymptomatic.

To explore whether there was increased risk of vulvodynia associated with exposure to increasing numbers of categories of environmental chemical exposures, we assessed the number of categories (0–9) in which each participant reported exposure (Fig. 1). Most women reported exposures in 1–3 categories, with very few reporting exposure in none of the categories or in four or more categories. For each additional environmental exposure category reported, compared with those who were asymptomatic, women had 1.36 higher odds of being a case (95% confidence interval [CI] = 1.23–1.51, $p < 0.001$), and 1.19 higher odds of reporting intermediate symptoms (95% CI = 1.07–1.33, $p = 0.002$) after adjustment for age, race/ethnicity, and difficulty paying for basics.

When we jointly assessed exposure to each of the nine categories in a single model, controlling for age, ethnicity, and difficulty paying for basics (Fig. 2), four categories

Table 1. Demographic Characteristics by Case Status ($N = 1585$)

	Distributions as %				
	Overall (n = *1585*)	*Cases* (n = *325*)	*Intermediate symptoms* (n = *301*)	*Asymptomatic* (n = *959*)	p-*Value**
Age (years)					<0.0001
≤35	15.6	21.4	22.5	11.7	
>35–55	41.6	45.6	47.6	38.5	
>55	42.8	33.0	29.9	49.8	
Race/ethnicity					0.0001
White	76.2	82.1	75.8	74.5	
Black	16.5	8.8	15.6	19.9	
Hispanic	2.5	3.8	3.6	2.2	
Other	2.5	4.1	2.8	1.9	
Hard to pay for basics	34.8	32.1	33.2	36.1	0.3150
Married or living as married	65.9	77.6	76.4	59.0	<0.0001
College graduate	49.4	56.0	52.7	46.3	0.0022

**p*-Value based on the chi-square test by vulvodynia case status.

Table 2. Relationship Between Environmental Exposures (Grouped and Individual) and Case Status ($N = 1585$)

Environmental exposures[a]	*% Exposed*		*Vulvodynia cases vs. asymptomatic women*	*Intermediate symptom group vs. asymptomatic women*
	Overall (%)	*Cases/intermediate symptoms/asymptomatic (%)*	*aOR (95% CI)*[b]	*aOR (95% CI)*[b]
Any exposure to spraying chemicals in or around the home	81.1	87.7/85.1/77.4	2.47 (1.71–3.58)****	2.02 (1.41–2.90)****
Use of products that kill weeds or pest plants on lawn	57.5	61.9/63.8/54.1	1.54 (1.17–2.02)**	1.88 (1.41–2.50)****
Use of products that kill mildew, blight, or fungus on law	24.5	31.1/25.9/21.8	1.83 (1.37–2.44)****	1.49 (1.09–2.03)*
Use of products that kill insects on lawn	45.9	49.1/52.5/42.8	1.42 (1.09–1.86)**	1.78 (1.36–2.35)****
Use of products that kill insects at home	60.1	67.1/61.8/57.3	1.70 (1.29–2.23)****	1.39 (1.06–1.83)*
Ever residing where insecticides were regularly sprayed	17.4	23.7/16.3/15.6	1.90 (1.38–2.62)****	1.26 (0.88–1.81)
Ever used insect repellant at least once a day for 5 days in a row	26.1	32.6/29.9/22.6	1.41 (1.06–1.88)*	1.22 (0.91–1.65)
Any exposure to rodent poison or mothballs at home	36.6	41.9/35.6/33.6	1.62 (1.25–2.09)***	1.33 (1.02–1.74)*
Household use of rodent poison	22.7	30.5/22.6/20.1	1.95 (1.45–2.61)****	1.34 (0.97–1.85)
Household use of mothballs	23.0	25.2/20.9/22.8	1.44 (1.07–1.96)*	1.14 (0.82–1.59)
Any exposure to pesticides, herbicides, or fumigants at work	3.5	3.4/3.7/3.4	0.92 (0.46–1.85)	1.22 (0.63–2.35)
Exposure to pesticides for at least once a week for at least a month	3.0	2.8/3.0/3.1	0.90 (0.42–1.94)	1.00 (0.46–2.18)
Exposure to herbicides for at least once a week for at least a month	2.2	2.5/2.7/2.0	1.19 (0.51–2.78)	1.31 (0.56–3.08)
Exposure to fumigants for at least once a week for at least a month	0.9	1.2/0.7/0.8	1.49 (0.44–5.04)	0.83 (0.17–3.95)
Ever worked on a farm	13.8	13.2/10.3/13.0	1.10 (0.78–1.57)	1.05 (0.72–1.52)
Exposure to chemical fertilizers for at least once a week for at least a month	1.9	1.5/3.0/1.7	0.97 (0.35–2.70)	1.96 (0.84–4.56)
Worked as a farmer, farm worker, or forestry worker for at least a month	3.3	4.0/2.3/3.3	1.12 (0.58–2.20)	0.69 (0.30–1.61)
Worked with farm animals at least once a week for at least 1 month	4.0	4.0/2.7/4.5	0.83 (0.43–1.57)	0.57 (0.26–1.24)
Worked with livestock or poultry for at least a month	3.3	3.4/2.3/3.6	0.90 (0.45–1.82)	0.66 (0.29–1.53)
Worked picking vegetables, fruits, tobacco, cotton, or other crops	8.8	9.9/6.3/9.2	1.23 (0.80–1.91)	0.80 (0.47–1.35)

(*continued*)

TABLE 2. (CONTINUED)

	% Exposed		Vulvodynia cases vs. asymptomatic women	Intermediate symptom group vs. asymptomatic women
Environmental exposures[a]	*Overall (%)*	*Cases/intermediate symptoms/asymptomatic (%)*	*aOR (95% CI)*[b]	*aOR (95% CI)*[b]
Ever worked in a laboratory/ medical setting	20.2	24.0/19.6/18.5	1.31 (0.98–1.75)	1.03 (0.75–1.40)
Worked with laboratory animals at least once a week for at least 1 month	1.0	0.9/1.0/1.0	0.74 (0.20–2.74)	0.78 (0.21–2.92)
Worked as a laboratory worker for at least a month	3.8	5.5/3.3/3.3	1.74 (0.95–3.19)	0.96 (0.46–2.02)
Worked with pharmaceuticals at least once a week for at least 1 month	11.7	12.6/11.6/11.4	1.14 (0.77–1.68)	1.05 (0.69–1.58)
Worked with chemicals to sterilize medical/dental instruments at least once a week for at least 1 month	4.3	4.9/4.3/4.1	1.20 (0.66–2.20)	1.05 (0.55–2.03)
Worked as a nurse or dental assistant for at least a month	11.6	12.6/13.6/10.5	1.21 (0.82–1.80)	1.36 (0.92–2.03)
Ever worked with solvents or paints	8.3	12.6/9.3/5.7	2.49 (1.68–3.70)****	1.49 (0.94–2.37)
Worked with solvents at least once a week for at least 1 month	5.9	9.2/6.0/4.8	2.03 (1.25–3.30)***	1.24 (0.70–2.20)
Worked with paints or varnishes at least once a week for at least 1 month	4.7	7.4/6.3/3.2	2.51 (1.43–4.38)**	2.17 (1.19–3.98)*
Ever worked as a manicurist or hairdresser	4.1	6.8/3.3/3.4	2.00 (1.14–3.53)*	0.91 (0.44–1.89)
Ever worked as a housekeeper or maid	12.4	12.4/15.6/9.9	2.07 (1.42–3.00)****	1.85 (1.25–2.73)***
Worked at dry cleaners for at least 1 month	3.2	4.6/4.3/2.4	2.13 (1.08–4.19)*	2.01 (0.99–4.08)

Multinomial logistic regression estimates for case status (three levels: cases, intermediate symptoms, or asymptomatic women [reference group]).
[a]Not included in the categorized groupings, due to small prevalence (<3%) and lack of association with case status were (1) working with grease or oil at least once a week for at least 1 month, (2) working with welding fumes at least once a week for at least 1 month, or (3) applied herbicides, such as Agent Orange, in the military.
[b]Odd ratios adjusted for age, race/ethnicity (White or not), and hard to pay for basics.
*$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.
aOR, adjusted odds ratio; CI, confidence interval.

remained statistically associated with screening positive for vulvodynia: home exposures to sprayed chemicals (OR = 1.88, $p = 0.002$), home exposure to rodent poison or mothballs (OR = 1.42, $p = 0.02$), exposure to solvents or paints (OR = 2.08, $p = 0.002$), and working as a housekeeper or maid (OR = 1.70, $p = 0.01$). Working as a manicurist or hairdresser, or at a dry cleaning facility was no longer statistically significant, although the ORs remained positive. Of note, younger age ($p < 0.001$) and White ethnicity ($p = 0.008$) remained positively associated with vulvodynia case status in this model.

Discussion

This is the first study to evaluate the potential impact of environmental exposures on the risk of vulvodynia. Notably, we found preliminary evidence of an association between vulvodynia and numerous reported exposures at home to chemicals, insecticides, and pesticides, as well as with occupational exposure to solvents/paints, and to occupations, including working as a housekeeper/maid, hairdresser/manicurist, and working at a dry cleaning facility. Working on a farm, at a laboratory or medical setting, or exposure to pesticides, herbicides, or fumigants at work was not statistically associated with vulvodynia case status.

We found that the majority of women report some history of exposure to insecticides, weed killers, and/or mold deterrents at home, but that women who had vulvodynia as well as those who had intermediate symptoms were more than twice as likely to report having been exposed to one or more of these groups of chemicals. In humans, pesticide exposure

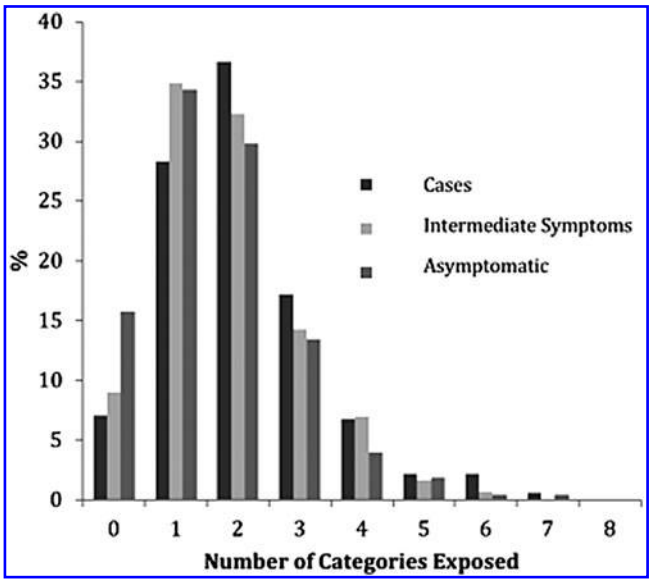

FIG. 1. Percentage of cases by number of positive responses to nine categories of environmental exposure ($N = 1585$).

(insecticides, herbicides, *etc.*) has been reported to be associated with lower cognitive performance, Parkinson's disease, Alzheimer's disease,[13,14] polyneuropathies, affective disorders, and suicide attempts,[4] as well as with delayed pain in studies on rats.[6] The possibility that the environmental exposures assessed here as well as other, less studied, environmental exposures[5] may have an impact on the risk not only of vulvodynia but also of other chronic pain disorders or affective disorders associated with vulvodynia[3,15–17] demands further study.

The route by which environmental exposures impact vulvodynia risk may be singular or multiple, and may impact mechanisms that have been previously reported to differ among women with vulvodynia than among those without this disorder.[18] Possible mechanisms include direct neurotoxicity or immune modulation, which have been reported after exposure to organophosphates[19,20] and hormone disrupting chemicals,[20] or due to differences in epigenetic susceptibility to environmental exposure effects.[21,22] It is conceivable that these mechanisms may be components of one or more pathways leading to the observed physiologic changes reported in vulvodynia, such as the peripheral nerve sprouting and sensitization,[23,24] the altered production of cytokines/neurokines,[25,26]

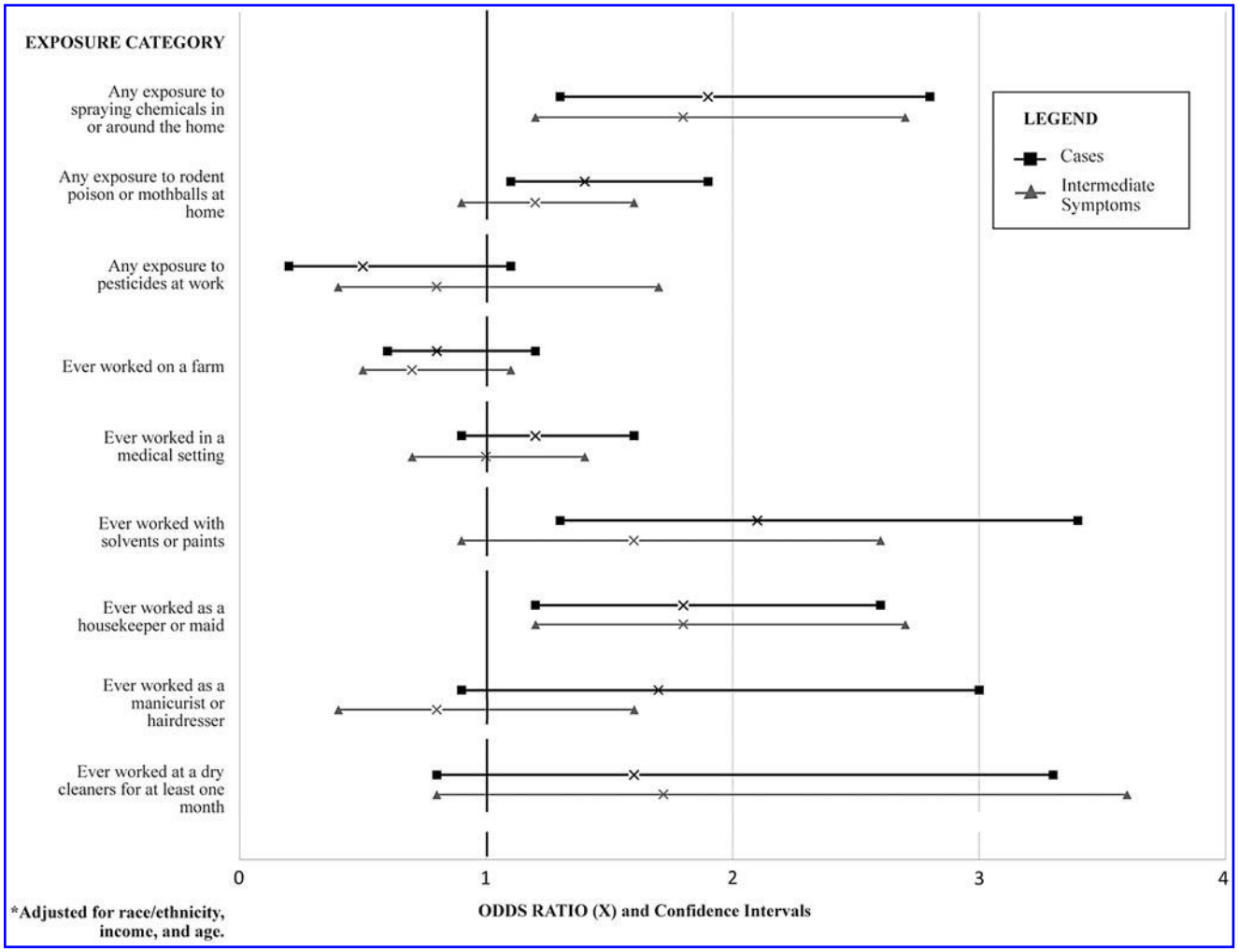

FIG. 2. Relationship between case status (three levels: cases, intermediate symptoms, and asymptomatic [reference group]) and environmental exposures, with all nine exposure categories in the model ($n = 1585$).

and/or mast cell release,[27,28] which may impact both peripheral and central neurophysiology, and the changes in neurotransmitter and cellular receptor production and activity, thereby impacting pain sensitivity. If relationships between past exposures and vulvodynia are confirmed in other studies, this information may suggest more targeted treatments.

Data are limited in women with vulvodynia. Harlow et al. found an increase in reported allergic reactions (hives, reactions to insect bites, and seasonal allergies) among women with vulvodynia compared with those without.[29] Leclair et al. noted a difference in T-cell subtypes in vulvar biopsies of women with vulvodynia compared with unaffected women, and suggested that this may be related to ''infectious, allergic, or autoimmune triggers.''[30] Others have suggested an altered immunologic response to common exposures such as candida among women with this disorder.[31] Whether these indicate a predisposition among some women to vulvodynia based on their responsivity to external exposures is unclear, and it demands further study.

This study has some limitations. Thirteen percent of potential participants were excluded due to incomplete data on the survey that included the environmental questions. Those excluded were older, more likely to be Black, and were more likely to report having difficulty paying for basics—characteristics associated with both increased and decreased reporting of exposure to various environmental toxins. Participants were asked to recall their history of environmental exposures over their lifetimes, and the accuracy of these recalled exposures may differ among individuals. Although we controlled for age, ethnicity, and a socioeconomic status variable, the potential for recall bias cannot be ruled out. In addition, the timing of each exposure is not clear, and hence in some cases one or more exposures may have occurred after the onset of vulvar symptoms. Although we did not adjust for multiple comparisons, when we jointly assessed categories of exposure, four of the nine categories were significantly associated with vulvodynia. This study also has several strengths. As this was a population-based study broadly addressing women's health, women were not aware of our hypothesis. Also, the outcome was based on validated screening criteria, and we were able to assess who met criteria for vulvodynia even though most women had never been diagnosed for this condition—thereby decreasing the likelihood of recall differing by case status.

Conclusion

In summary, histories of exposures to a variety of environmental toxins were associated not only with vulvodynia case status but also with those having intermediate symptoms not currently meeting the vulvodynia screen-based diagnosis. Further research is needed to verify these findings, and to more carefully assess the impact of timing and dose of exposure, as well as how exposures may alter the clinical course of vulvodynia or its treatment. Given our limited scientific understanding of the etiology of and modifiable risk factors for vulvodynia, further investigation of the role of environmental exposures is warranted.

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Author Disclosure Statement

No competing financial interests exist.

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