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Incident thyroid disease in female spouses of private pesticide applicators

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Abstract

Background: Little is known about modifiable risk factors for thyroid disease. Several pesticides have been implicated in thyroid disruption, but clinical implications are not clear.

Objective: We assessed associations between pesticide use and other farm exposures and incident hypothyroidism and hyperthyroidism in female spouses of farmers in the Agricultural Health Study (AHS).

Methods: We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals for risk of thyroid disease in 24,092 spouses who completed at least one follow-up questionnaire.

Results: We identified 1627 hypothyroid and 531 hyperthyroid cases over 20 years of follow-up. The fungicides benomyl, maneb/mancozeb, and metalaxyl, the herbicide pendimethalin, and among those over 60 years of age the insecticides parathion and permethrin (applied to crops) were associated with elevated hypothyroidism risk, with HR ranging from 1.56–2.44. Conversely, the insecticide phorate, and the herbicides imazethapyr and metolachlor were associated with decreased risk (HR ranging 0.63–0.73), as were long-term farm residence and other farm-related activities (HR ranging 0.69–0.84). For hyperthyroidism, the insecticide diazinon, the fungicides maneb/mancozeb, and the herbicide metolachlor were associated with increased risk (HR ranging 1.35–2.01) and the herbicide trifluralin with decreased risk (HR: 0.57).

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Conflicts of interest

The authors declare they have no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.05.041.

Conclusions: Several individual pesticides were associated with increased risk of hypothyroidism and hyperthyroidism, although some pesticides were associated with decreased risk. Some of the findings, specifically associations with fungicides, are consistent with results from an earlier analysis of prevalent diseases in AHS spouses.

Keywords

Pesticides; Hypothyroidism; Hyperthyroidism; Agricultural Health Study

1. Introduction

Optimal levels of thyroid hormones (THs) are critical to many physiological processes. Excessive as well as decreased TH levels outside the optimal range may predispose individuals to adverse health outcomes including cardiovascular diseases, poor reproductive health, and impaired neurocognitive function (Cooper and Biondi, 2012; Klein and Ojamaa, 2001; Whybrow and Bauer, 2005a, 2005b). Some pesticides may alter thyroid function; for example, in humans, the organochlorine insecticides dichlorodiphenyltrichloroethane (DDT) and aldrin, the fungicide maneb, and metabolites of organophosphate insecticides have been linked with changes in circulating levels of thyroid-stimulating hormone (TSH) and THs (Blanco-Munoz et al., 2016; Campos and Freire, 2016; Freire et al., 2013; Lerro et al., 2017; Steenland et al., 1997). However, clinical implications remain unclear as findings from human studies are inconclusive, with null, inverse, as well as positive associations between specific thyroid function bio-markers and pesticides. While these biomarker-based studies provide some insight on the associations, these studies were generally limited due to smaller sample sizes, and mostly focused on euthyroid populations with inadequate power to look at clinical thyroid disease. Further, nearly all studies were cross-sectional, limiting causal inferences. Furthermore, only a limited number of pesticides were studied and data on many commonly used pesticides are lacking.

Pesticides are extensively used in the United States (US) (Atwood and Paisley-Jones, 2017). People may be exposed to pesticides via direct use or indirectly from environmental sources. Biomonitoring data from nationally representative surveys indicate that the general US population is exposed to numerous pesticides; some pesticides can be detected in > 50% of the population (Barr et al., 2005; Barr et al., 2010; CDC, 2009). Therefore, identifying links between pesticides and clinical thyroid conditions may have important implications.

The Agricultural Health Study (AHS), an ongoing prospective cohort study of private pesticide applicators (predominantly farmers) and their spouses, was conducted to examine health effects of pesticides and other farm-related exposures (Alavanja et al., 1996). Earlier AHS investigations have found that farmers exposed to pesticides, specifically organochlorines, had an elevated prevalence and incidence of hypothyroidism (Goldner et al., 2013; Shrestha et al., Submitted). Female spouses exposed to fungicides including maneb/mancozeb also had a higher prevalence of hypothyroidism and hyperthyroidism (Goldner et al., 2010).

The previous study of AHS spouses evaluated associations between ever-use of pesticides assessed at enrollment and thyroid diseases (mostly prevalent) identified from the enrollment

and first follow-up surveys (Goldner et al., 2010). Since then, the AHS has collected information on thyroid diseases at two additional follow-up surveys. With newly identified cases during this extended follow-up as well as incident cases from the first follow-up, here we examine pesticide use in relation to incident thyroid disease in female spouses of farmers in the AHS. We also explored associations with other farm-related exposures.

2. Methods

2.1. Study population

Between 1993 and 1997, 52,394 farmers from North Carolina and Iowa enrolled in the study by completing an enrollment questionnaire (Alavanja et al., 1996). At enrollment (Phase 1), farmers were given a questionnaire that asked about socio-demographics, pesticide use, and medical history, to be filled out by their spouse; 32,345 spouses (75% of married spouses, 219 male and 32,126 female) returned the questionnaire. Female spouses also provided information on reproductive history. Follow-up interviews were conducted in 1999–2003 (Phase 2), 2005–2010 (Phase 3), and 2013–2016 (Phase 4) to update information on pesticide use, socio-demographics, and health. We restricted the current analysis to the female spouses. All questionnaires can be accessed from the study website (https://aghealth.nih.gov/collaboration/questionnaires.)

2.2. Pesticide, farm exposures, and thyroid disease

At Phase 1, spouses were asked if they ever personally mixed or applied any pesticides in their lifetime; numbers of years and days per year they mixed or applied pesticides; and when pesticides were used, the percent of the time they personally spent mixing and applying them. Further, spouses were asked about ever-use of 50 named pesticides, with questions “In your lifetime, have you mixed or applied the following…” (questions presented in eFig. 1). Spouses were also asked about farm-related exposures including living on a farm, applying fertilizers, tilling soil, and sun exposure. Participants were asked about doctor-diagnosed thyroid diseases at all phases (eTable 1). At Phase 1, participants were asked if they had goiter, thyrotoxicosis/Grave’s disease, or other thyroid disease. In Phases 2, 3 and 4, participants were asked if they had hypothyroidism and/or hyperthyroidism, age at diagnosis, and if they ever received treatment for either condition.

2.3. Hypothyroidism and hyperthyroidism

Given that thyroid disease may have a varying natural history/disease course (for instance, hypothyroidism can develop after hyperthyroidism as a natural course of disease or after treatment, details in Supplemental Methods), we employed several decision rules to define “hypothyroidism” and “hyperthyroidism” when participants reported multiple thyroid disease types (eTable 2). For age at diagnosis, when participants provided different ages across the surveys, we used the age provided at the earliest follow-up survey, assuming reduced recall over time. For participants who did not provide age at diagnosis, we used the mid-point between the last disease-free phase and when they first reported disease to estimate age at diagnosis (estimated for 110 hypothyroidism and 34 hyperthyroidism cases).

Of the 28,046 female spouses who completed at least one follow-up survey (eFig. 2), we excluded participants with missing or inconsistent thyroid disease responses, thyroid cancer cases, prevalent disease, or unspecified thyroid disease. Of the 24,598 remaining disease free individuals at enrollment, 1627 (6.6%) participants developed (age at diagnosis > age at enrollment) hypothyroidism, 531 (2.2%) developed hyperthyroidism, 506 (2.1%) developed other or unknown thyroid conditions, and 21,934 did not report any thyroid disease.

2.4. Thyroid disease validation

To evaluate the quality of self-reported diagnoses, we re-contacted participants who had reported incident thyroid disease in Phases 3 and 4 to confirm their diagnosis, obtain details of medication use and treatments, and obtain consent for retrieval of medical records. We received confirmation questionnaires from 1174 participants (applicators and spouses). Of the 819 with self-reported hypothyroidism who completed the questionnaire, 82% confirmed their diagnosis; whereas of the 216 with self-reported hyperthyroidism (or both) who completed the questionnaire, only 51% confirmed their diagnosis. We have obtained medical records for 186 self-reported hypothyroidism and 43 hyperthyroidism (or both) cases to date. About 91% of self-reported hypothyroidism was confirmed by physicians/medical staff. We found low agreement for hyperthyroidism, however, with only 32% confirmed by medical records. This poor agreement may be because we did not reach the diagnosing physician or because, for some participants who were currently being treated for hypothyroidism after therapy for hyperthyroidism, records may have been incomplete or not thoroughly searched by the medical staff we reached.

2.5. Statistical analysis

We estimated odds ratios and 95% confidence intervals (CIs) for associations between covariates and hypothyroidism and hyperthyroidism using polytomous logistic regression. We used Cox proportional hazards models, separately for hypothyroidism and hyperthyroidism, to estimate hazard ratios (HRs) and 95% CIs for associations with pesticides and farm exposures. We used attained age as the time scale, with left-truncation at enrollment; the models were adjusted for state, education, and smoking status. For farm exposures, we additionally adjusted for ever-use of any pesticides. Time-at-risk was accrued until hypothyroidism or hyperthyroidism diagnosis, death, loss- or end- of follow-up. When proportional hazard assumptions were violated for covariates ($p\text{-}_{\text{interaction-attained-age-and-covariates}} < 0.10$), we used covariate-stratified Cox models, whereas for exposures, we allowed the HR to vary by median attained age (i.e., 60 years). Further, as 1273 spouses were missing information on smoking status and 3106 on education (2189 reported “something else” for education which was treated as a missing covariate), we used multiple imputation with the fully conditional specification method to impute these missing covariates (Lee and Carlin, 2010). We created five imputed datasets, performed regression analysis in each dataset, and obtained the pooled parameter estimates.

We performed several sensitivity analyses. For pesticide exposures, we adjusted for the top four pesticides (if more than four) whose Spearman correlation coefficient with the pesticide of interest was ≥0.40. For farm exposures, we performed two additional adjustments in separate models – adjusting for correlated farm exposures (≥0.40) and for all pesticides

associated with the thyroid disease of interest (farm exposures were not correlated with any pesticides with coefficient ≥ 0.40), in separate models. Other sensitivity analyses included adjusting for body mass index (BMI) and hormonal replacement therapy (HRT) use; and restricting hypothyroidism (n = 168 excluded) or hyperthyroidism (n = 121 excluded) cases to those who, in at least in one survey, reported receiving treatment.

We also restricted cases to those who reported having the same thyroid disease diagnosis at least two times across surveys, or whose diagnosis was confirmed in the validation study either through the participant questionnaire or medical records (850 hypothyroidism and 193 hyperthyroidism cases available) (referred to as a "stricter" case definition hereafter). We restricted our analyses to exposures with at least 10 thyroid disease cases in each exposure category for all but the stricter-case analyses for which we required only five exposed cases.

While we view our analyses as exploratory, for the main analyses and the analyses using the "stricter" case definition, we provide p-values adjusted for false discovery rate (FDR), with $p < 0.05$ considered statistically significant. We used SAS v.9.4 (SAS Inc., Cary, NC) for data analysis.

3. Results

Participants who developed hypothyroidism were older, more often identified as Whites, and more likely to report higher years of schooling, higher BMI, and HRT use (characteristics at enrollment presented in Table 1). Participants who developed hyperthyroidism were more often from North Carolina, and more often reported HRT use.

3.1. Hypothyroidism

The general pesticide use variables ever-use of any pesticides, number of years mixed or applied, and days per years of use were not associated with incident hypothyroidism (data not shown). After adjustment for state, education, and smoking, ever-use of each individual fungicides examined was associated with elevated hypothyroidism risk, although only the associations for benomyl, maneb/mancozeb, and metalaxyl were significant (Table 2). Because associations were elevated for all fungicides, we further adjusted for other fungicides even though none of the fungicides was correlated with coefficients ≥ 0.40. When mutually adjusted, the HRs for benomyl (HR = 1.21, 95% CI = 0.72–2.05), maneb/mancozeb (HR = 1.44, 95% CI = 0.98–2.22), and metalaxyl (HR = 1.51, 95% CI = 1.03–2.22) were attenuated but remained elevated whereas the HRs for captan (HR = 1.09, 95% CI = 0.78–1.51) and chlorothalonil (HR = 0.85, 95% CI = 0.50–1.45) were close to or below null. Of these five fungicides, association for maneb/mancozeb remained statistically significant when adjusted for FDR ($p = 0.03$).

The two insecticides, parathion and permethrin (applied to crops), were associated with increased hypothyroidism but only among those over age 60; the organophosphate insecticides fonofos and phorate were associated with decreased hypothyroidism risk. When accounting for multiple testing, only the association for parathion remained significant (FDR $p = 0.03$). For herbicides, ever-use of triazines and three individual herbicides, S-Ethyl-dipropylthiocarbamate (EPTC), imazethapyr, and metolachlor, were associated with

decreased hypothyroidism risk. All associations remained unchanged when additionally adjusted for correlated pesticides, except that the positive association with pendimethalin became stronger.

Hypothyroidism risk was modestly lower among those who lived on a farm 10 years before enrollment as well as among those who lived on a farm for > 45 years compared to those who lived on a farm 18 years or less (Table 3). Some farm-related tasks including tilling soil, driving combines, handpicking crops, milking cows, driving gasoline tractors or cleaning with gasoline, and increasing number of hours spent in the sun were also associated with modestly reduced hypothyroidism risk. When adjusted for correlated farm exposures (Table 3) or pesticides associated with hypothyroidism (data not shown), HR magnitudes remained similar but with wider CIs including the null (except for grinding metal which was positively associated among those aged > 60).

Results were similar in analyses adjusting for BMI and HRT (data not shown). When hypothyroidism was defined by receipt of treatment, we found generally similar associations (eTable 4); two notable differences were lack of association with captan, and non-significant but elevated associations with the fungicide chlorothalonil and the herbicide paraquat among those aged > 60.

Associations were stronger in analyses using the stricter case definition, with higher-positive HRs ranging 1.53–3.46 for fungicides, 1.23–1.83 for organochlorines, 1.27–2.41 for carbamates, and 1.19–2.90 for organophosphates (eTable 5). Further, associations for the fumigant carbon tetrachloride/carbon disulfide 80/20 mix, any use of herbicides (among aged > 60 years), and the herbicides paraquat and glyphosate were also elevated, and associations for many pesticides remained significant when adjusted for FDR. For farm exposures, associations persisted for living on a farm for > 45 years, number of days worked in the field in the recent growing season, tilling soil, driving gasoline tractors, and sun exposure (data not shown).

3.2. Hyperthyroidism

General pesticide use variables were not associated with hyperthyroidism incidence (data not shown). Ever-use of maneb/mancozeb and ever use of metalaxyl (both fungicides) were each associated with elevated hyperthyroidism risk, although the association with metalaxyl was significant only after adjustment for use of correlated pesticides. The association with maneb/mancozeb among younger participants remained significant after correcting for FDR ($p = 0.04$). Hyperthyroidism risk was also elevated among those who ever-used the organophosphate insecticides diazinon or fonofos (Table 4). Several herbicides also showed positive associations in adjusted models; the strengths of these associations, however, were attenuated after further adjustment for correlated pesticides, except that metolachlor remained positively associated and remained significant after adjusting for FDR ($p = 0.04$). Each of the herbicides trifluralin and cyanazine was inversely associated with hyperthyroidism risk in models adjusting both for covariates and for correlated pesticides (Table 4).

For farm exposures (Table 5), those who spent more than half their childhood (under age 18) living on a farm had modestly reduced hyperthyroidism risk, but only among those aged ≤ 60. Applying chemical fertilizer and repairing engines were both associated with increased hyperthyroidism risk.

Results were similar in all sensitivity analyses. When restricted to cases who reported taking thyroid medications, associations were somewhat stronger; further, positive associations with DDT and atrazine were seen (eTable 6). With a stricter case definition, associations with some pesticides were much stronger, although estimates were imprecise (eTable 7); however, none of the associations remained significant when adjusted for FDR. With the stricter definition, associations for farm exposure were generally similar; however, the HR for use of chemical fertilizer was attenuated (HR = 1.28, 95% CI = 0.82–2.00) (data not shown).

4. Discussion

In this study of female spouses of farmers, 6.6% developed hypothyroidism and 2.2% developed hyperthyroidism over 20 years of follow up. Data on incident as well as prevalent thyroid disease in the US population are generally limited, and it is estimated that about 5–9% and 1.2% of the US population have hypothyroidism and hyperthyroidism (includes clinical and subclinical disease) respectively (Bahn Chair et al., 2011; Garber et al., 2012), with estimates coming from the Framingham study (Sawin et al., 1985), the Colorado thyroid disease prevalence study (Canaris et al., 2000), and the National Health and Nutrition Examination Survey (NHANES) (Aoki et al., 2007; Hollowell et al., 2002). For hypothyroidism, the prevalence estimate was 13.6% for women aged > 60 years in the Framingham study; ranged from 4% to 21% for women aged > 18 years (increasing with increasing age categories) in the Colorado thyroid prevalence study; and was 4.2% for females aged > 12 years in the NHANES 1999–2002 (Aoki et al., 2007). Hyperthyroidism prevalence was about 0.8% in females in the NHANES 1999–2002.

In this study, the fungicides benomyl, maneb/mancozeb, and metalaxyl, the herbicide pendimethalin, and, among those aged > 60 years, the insecticides parathion and permethrin (applied to crops) were each associated with modestly elevated hypothyroidism risk. The insecticide phorate, and the herbicides imazethapyr and metolachlor were associated with decreased risk. The insecticide diazinon, the fungicides maneb/mancozeb, and the herbicide metolachlor were associated with increased hyperthyroidism risk; and the herbicide trifluralin, with decreased risk. Some of these findings, specifically associations with fungicides, are consistent with a prior analysis of prevalent disease in the AHS spouses that included fewer years of follow-up and fewer cases. The current analyses included an additional 1252 incident hypothyroidism and 391 incident hyperthyroidism cases from two additional follow-up surveys.

4.1. Fungicides

Ever-use of the five fungicides we examined was associated with elevated hypothyroidism risk; associations for benomyl, maneb/mancozeb, and metalaxyl remained elevated even after mutual adjustment. Hyperthyroidism risk was elevated among those who ever-used

maneb/mancozeb or metalaxyl. These observations are generally consistent with the findings from the prevalent disease analysis in AHS spouses, but contrast with previous results in the farmers (except findings for captan that suggested positive associations with hypothyroidism) (Goldner et al., 2013; Lerro et al., 2017). Among the farmers, fungicides were not generally associated with thyroid disease, and those few that were associated were not consistent with the direction of association observed in AHS spouses (Goldner et al., 2013; Shrestha et al., Submitted). Although we do not know the reasons for the disparate findings between spouses and farmers, these two groups differ in exposure intensity and possible differences in predisposition to disease due to sex differences (Sawin, 2005). AHS farmers likely had much higher direct pesticide exposures than spouses. Women in general are disproportionately affected by thyroid dysfunction compared to men, possibly due to differences in sex hormones (for instance, estrogen alters THs and thyroxine (T_4)-binding globulin) (Tahboub and Arafah, 2009) and reproductive factors (for instance, parity may increase thyroid disease risk) (Carle et al., 2014).

Evidence on thyroid disruptive properties of these fungicides is limited, except for the manganese-based ethylenebis-dithiocarbamate fungicides maneb and mancozeb. These fungicides are metabolized to an anti-thyroid compound ethylene-thiourea (classified as a probable carcinogen by the US EPA based on cancer data) which may bring about hypothyroid-like effects in humans and animals (Axelstad et al., 2011; Goldner et al., 2010; Mallem et al., 2006; Steenland et al., 1997). Another hypothesis is involvement of heavy metal manganese in pathogenesis of autoimmune thyroid conditions, as suggested for rheumatoid arthritis, also an autoimmune disease, in the AHS (Murphy et al., 2016; Parks et al., 2016). Chlorothalonil may alter thyroid gland pathophysiology in frogs and increase serum T4 in female rats, although the Endocrine Disruptor Screening Program (EDSP) report concluded no convincing evidence for chlorothalonil-thyroid-pathway interaction (U.S. EPA, 2015a).

4.2. Organochlorine insecticides

Although we found limited evidence for organochlorine-hypothyroidism associations in our unrestricted analyses, with a stricter case definition, we saw elevated HR estimates for all individual organochlorines except for heptachlor. In earlier AHS investigations, generally significant positive associations between individual organochlorines and hypothyroidism were found for the farmers (Goldner et al., 2013; Lerro et al., 2017; Shrestha et al., Submitted), including associations with aldrin for TSH and total T_4 among 679 male farmers without self-reported thyroid diseases in the Biomarkers of Exposure and Effect in Agriculture (BEEA) study, a molecular epidemiologic sub-study within the AHS (Lerro et al., 2017). In the spouses, organochlorine associations with prevalent hypothyroidism were elevated, although imprecise (Goldner et al., 2010).

While the present study is among the largest to evaluate pesticide-thyroid disease associations among women, the lack of significant associations could still be due to limited study power because of the lower exposure prevalence among spouses compared to farmers. Further, the organochlorine insecticides evaluated were banned for use in the 1980s (except lindane which was banned in 2006) (Jones and de Voogt, 1999; U.S. EPA, 2006), likely

reducing direct exposure. On the other hand, elevated associations using a “stricter” case definition suggest that attenuation of associations could have resulted from misclassification of disease.

4.3. Organophosphate insecticides and permethrin

We found that ever-use of fonofos was associated with decreased hypothyroidism risk and increased hyperthyroidism risk. Among the other organophosphates, parathion was associated with increased and phorate with decreased hypothyroidism risk. Diazinon was associated with increased hyperthyroidism risk. The previous investigation of AHS spouses did not find associations between organophosphate insecticides and prevalent hypothyroidism or hyperthyroidism (Goldner et al., 2010). In the farmers, several individual organophosphate insecticides including diazinon, but not phorate, or parathion, were associated with hypothyroidism (Goldner et al., 2013; Shrestha et al., Submitted). The prior investigation in BEEA also found no robust associations between organophosphates and THs or subclinical hypothyroidism (Lerro et al., 2017). A study of Mexican floricultural workers, however, found associations between total organophosphate exposure, as measured by urinary dialkyl-phosphate species, and higher serum TSH and T4 (Lacasana et al., 2010).

Organophosphate insecticides are a class of chemicals that exert neurotoxicity primarily through their ability to inhibit the neurotransmitter acetylcholinesterase. Although these insecticides have been implicated in thyroid disruption (Campos and Freire, 2016), findings from animal studies are equivocal (for example, both decreased and increased T4 have been reported following malathion exposure) (U.S. EPA, 2015b, 2015d), and little is known about underlying mechanisms due to a paucity of studies. Diisopropylfluorophosphate could suppress TSH production in rats via pathways involving muscarinic and nicotinic receptors (Smallridge et al., 1991). So, it is possible these insecticides may alter thyroid function via common cholinergic pathways as suggested for diisopropylfluorophosphate. On the other hand, thyroid alterations can occur in mice exposed to the organophosphate insecticide chlorpyrifos at doses not inhibiting brain acetylcholinesterase (De Angelis et al., 2009), indicating these chemicals could act via other distinct pathways. An alternative pathway by which organophosphates can disrupt thyroid-homeostasis is by interfering with TH-binding protein transthyretin (Van den Berg et al., 1991). It is thus tempting to speculate that divergent associations for organophosphate insecticides observed in our study could be due to such distinct modes of action; nonetheless, these could also be chance findings.

The observed association of permethrin with hypothyroidism risk was consistent with earlier findings in AHS farmers (Shrestha et al., Submitted), but has not been explored in other human studies except for one cross-sectional study that found limited association between a urinary pyrethroid metabolite and thyroid biomarkers in men (Meeker et al., 2009).

4.4. Herbicides

We found that the herbicides EPTC, imazethapyr, and metolachlor were associated with decreased hypothyroidism risk; whereas, when adjusted for correlated pesticides, pendimethalin was associated with increased hypothyroidism risk. These associations were not seen in previous AHS studies except that metolachlor was previously associated with

reduced hypothyroidism prevalence in the spouses (Goldner et al., 2010). In the BEEA study, pendimethalin was associated with increased odds of subclinical hypothyroidism, higher TSH, and anti-thyroid-peroxidase positivity (Lerro et al., 2017). In contrast to the present study findings, EPTC was associated with higher TSH in the BEEA study. With a stricter case definition, we also detected elevated risks for paraquat and glyphosate; these associations were also seen in previous AHS studies (Goldner et al., 2010; Shrestha et al., Submitted).

For hyperthyroidism, positive associations for most herbicides were attenuated when adjusted for correlated pesticides, except for metolachlor for which positive association got stronger. The prior analysis in AHS spouses did not find any herbicide-hyperthyroidism associations (Goldner et al., 2010).

We are not aware of studies in other populations that examined these herbicides in relation to thyroid function. Non-human data reported by the EDSP suggested no convincing evidence for EPTC-thyroid-pathway interaction (U.S. EPA, 2015c), but suggested some evidence for metolachlor-thyroid-pathway interaction in mammals (U.S. EPA, 2015e). Specifically, metolachlor induced changes in thyroid histopathology and had sex-specific effects in rats – an increase in T4 in females with no change in TSH and an increase in TSH in males (U.S. EPA, 2015e). Pendimethalin has been shown to elicit a range of responses including increase in TSH levels, hepatic metabolism of T4, and thyroid hyperplasia in experimental studies – results that are consistent with our findings (Hurley, 1998).

4.5. Farm exposures

We found that living on a farm for a longer duration or in early life was associated with reduced risk of thyroid diseases. One might expect higher thyroid disease burden among those living on a farm due to greater likelihood for general pesticide exposure. However, given the autoimmune nature of some thyroid conditions (De Leo et al., 2016; Garber et al., 2012), early life farm exposures (for example, endotoxin exposures from livestock) may offer protection against later life auto-immune thyroid diseases (Okada et al., 2010). In the AHS, any childhood or current livestock exposure was associated with decreasing odds of rheumatoid arthritis and in some instances modified association between pesticides and other exposures and rheumatoid arthritis in a protective fashion (Parks et al., 2016). Additionally, for some farm-related tasks, we found generally reduced risks of hypothyroidism, consistent with the findings for living on a farm more generally. Protective association with increasing sun exposure may reflect potential benefit from vitamin D, as suggested for autoimmune thyroid conditions (Wang et al., 2015). Chemical fertilizer use was associated with increased hyperthyroidism risk, which may be related to exposure to nitrates. Nitrates are commonly found in high-nitrogen fertilizers and have been linked to hypothyroidism (Aschebrook-Kilfoy et al., 2012), albeit inconsistently (Ward et al., 2010). This may also be related to exposure to heavy metal cadmium present in fertilizers, as suggested for association between chemical fertilizer and rheumatoid arthritis (Murphy et al., 2016; Parks et al., 2016). Elevated thyroid disease risk associated with grinding metals observed in our study further supports this hypothesis.

4.6. Age-specific associations for pesticides

We found age-specific associations for the insecticides parathion and permethrin (applied to crops) in relation to hypothyroidism in the main analyses and for several other pesticides in analyses using the stricter case definition, with associations being stronger among older groups. There could be several explanations for this. For instance, older women may be more vulnerable to pesticide exposure due to comorbidity or they may have had higher and more extended exposures to some of these earlier toxic pesticides.

4.7. Strengths and limitations

Our study has several strengths. The prospective design likely reduced biases associated with differential reporting. The enrollment questionnaire asked about use of a wide-range of pesticides and detailed information on numerous covariates, which allowed us to examine thyroid disease risk in relation to multiple pesticides and to explore the influence of potential confounders. Further, we corroborated our findings in sensitivity analyses.

Several limitations of the study warrant consideration. We relied on self-report of doctor-diagnosed thyroid disease instead of obtaining diagnostic medical records, likely resulting in some disease misclassification. Because we asked about thyroid disease multiple times across the surveys, we were able to minimize false positives by excluding inconsistencies. In our validation study, about 91% of hypothyroidism self-reports were confirmed by medical records, but our attempt to validate hyperthyroidism cases was less successful. Although 80% of participants reporting hypothyroidism on prior surveys confirmed having any thyroid disease in the validation questionnaire, only 51% reported having hyperthyroidism specifically or having ever received treatment for hyperthyroidism. Further, among those whose medical records were obtained, only 32% of hyperthyroidism self-reports were confirmed by medical personnel. Nevertheless, the records indicated that > 95% participants with self-reported hyperthyroidism at some time in the past were currently taking exogenous THs which would be expected following thyroid ablation or radiation therapy. If current physicians or staff reviewed relatively recent medical records (rather than older records), they may have missed information on hyperthyroidism diagnosis or treatment in the past. We are reasonably confident that bias due to disease misclassification had limited impact on the results for hypothyroidism, whereas this impact may be more of a concern for the findings for hyperthyroidism. Still, in sensitivity analyses using a stricter case definition, findings for some pesticides were similar, but stronger, supporting for the credibility of our observations. Validation studies performed in the Nurses' Health Study II found good agreement between thyroid disease self-reports and medical records, indicating that thyroid disease self-reports are likely reliable (Kang et al., 2013).

Our exposure data were also based on self-reports and lacked pesticide-specific information on intensity or duration of exposure, and thus prone to misclassification. Because pesticide information was collected before diagnosis, misclassification of outcome and exposure was likely non-differential and would tend to attenuate measures of association (Blair et al., 2011). Pesticide self-reports were found to be reliable in the AHS applicators (Blair et al., 2011; Hoppin et al., 2002) but we do not have data to support this for their spouses. Still, it is likely that self-reports by farm spouses are more reliable than those in the general

population due to greater familiarity with and reliance on pesticides. Exposure misclassification may also have occurred because we only considered pesticide use before enrollment, and did not account for pesticide use that occurred later; we are uncertain about the direction of any resulting bias. Participants may also have been exposed to pesticides indirectly via their applicator spouses as well as from other environmental sources that we did not account for, for example, if they lived near other farms. Further, participants were exposed to multiple pesticides, and our single pollutant models, though they adjust for correlated pesticides, do not address joint effect of exposure to pesticide mixtures or how these pesticides interact. These should be explored in future studies, although finding suitable statistical methods accommodating the complex exposure scenarios in the AHS is challenging.

Another limitation of the study is that we do not have data on dietary iodine intake or iodine sufficiency status, a known risk factor for thyroid diseases. Although we assume that iodine sufficiency status would not differ by geographical regions at present due to fortification of salt with iodine (Pearce, 2007) and that adjusting for state in the analysis that would account for any regional differences in iodine enrichment in food, we cannot rule out residual confounding as we do not have individual level iodine intake data.

We have emphasized results unadjusted for multiple testing as this is among the first reports to consider thyroid disease and pesticide associations, but some of these associations could be due to chance. Nonetheless, we also presented p-values correcting for the false discovery rate for multiple comparisons for pesticides-thyroid disease associations for some analyses. Lastly, our study is limited in that we were not able to assess specific thyroid disease conditions such as auto-immune or subclinical conditions.

5. Conclusions

Our findings suggest that exposures to certain pesticides are associated with risk of hypothyroidism and hyperthyroidism. Some findings such as elevated hypothyroidism risk among users of fungicides are consistent with previous AHS findings, whereas findings such as reduced thyroid disease risk in users of some pesticides are novel. Because many of these pesticides are still used, confirmation of these findings in longitudinal studies as well as in mechanistic studies would be valuable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of spouses by thyroid disease status in the Agricultural Health Study (n = 24,092).

Characteristics	Non-cases (n = 21,934)	Hypothyroidism (n = 1627)		Hyperthyroidism (n = 531)	
	n (%)	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]
Age (years)					
≤ 30 years	1699 (7.7)	90 (5.5)	Ref	35 (6.6)	Ref
31–40 years	6164 (28.1)	445 (27.4)	1.42 (1.10, 1.83)	136 (25.6)	1.11 (0.73, 1.67)
41–50 years	6329 (28.9)	539 (33.1)	1.56 (1.21, 2.01)	153 (28.8)	1.11 (0.73, 1.68)
51–60 years	4884 (22.3)	369 (22.7)	1.30 (0.99, 1.71)	146 (27.5)	1.29 (0.83, 2.00)
> 60years	2858 (13)	184 (11.3)	1.25 (0.93, 1.68)	61 (11.5)	0.89 (0.55, 1.44)
State					
Iowa	15,316 (69.8)	1177 (72.3)	Ref	340 (64)	Ref
North Carolina	6618 (30.2)	450 (27.7)	0.93 (0.81, 1.05)	191 (36)	1.22 (0.99, 1.50)
Race[b]					
White	21,014 (98.2)	1585 (99.4)	Ref	506 (97.3)	Ref
Other	381 (1.8)	10 (0.6)	0.46 (0.23, 0.90)	14 (2.7)	1.45 (0.78, 2.72)
Education[c]					
≤ High school	8549 (40.5)	538 (34.1)	Ref	235 (45.6)	Ref
1–3 years beyond high school	5824 (27.6)	469 (29.8)	1.30 (1.13, 1.49)	132 (25.6)	0.87 (0.68, 1.10)
≥ College graduate	4715 (22.4)	422 (26.8)	1.45 (1.25, 1.68)	102 (19.8)	0.82 (0.63, 1.07)
Something else	1996 (9.5)	147 (9.3)	1.22 (1.00, 1.49)	46 (8.9)	0.79 (0.55, 1.14)
Smoking status[d]					
Never smoker	15,222 (73.3)	1138 (73.6)	Ref	362 (71.5)	Ref
Former smoker	3464 (16.7)	294 (19)	1.14 (0.99, 1.31)	90 (17.8)	1.00 (0.77,1.30)
Current smoker	2080 (10)	115 (7.4)	0.70 (0.56, 0.87)	54 (10.7)	1.02 (0.74,1.39)
Body mass index (kg/m^2)[e]					
< 25	10,110 (50.1)	677 (45.1)	Ref	251 (51.6)	Ref
25–< 30	6472 (32.1)	520 (34.6)	1.24 (1.09, 1.41)	147 (30.2)	0.91 (0.73, 1.14)
≥30	3595 (17.8)	305 (20.3)	1.28 (1.10, 1.48)	88 (18.1)	0.98 (0.75, 1.27)
Ever-use of hormonal replacement therapy[f]					

Characteristics	Non-cases (n = 21,934)	Hypothyroidism (n = 1627)		Hyperthyroidism (n = 531)	
	n (%)	n (%)	OR (95% CI)[a]	n (%)	OR (95% CI)[a]
No	14,600 (72.6)	996 (66)	Ref	330 (67.3)	Ref
Yes	5521 (27.4)	513 (34)	1.40 (1.23, 1.60)	160 (32.7)	1.24 (0.99, 1.55)

Abbreviations: OR, odds ratio; CI, confidence intervals.

Note: Due to missing covariates, the ORs are based on n = 18,148 non-cases, 1371 hypothyroidism case, and n = 439 hyperthyroidism case.

[a] Estimated using polytomous logistic regression; each covariate adjusted for all others in the table.

[b] n = 582 missing overall; 539 (2.5%) in non-cases, 32 (2%) in hypothyroidism, and 11(2.1%) in hyperthyroidism.

[c] n = 917 missing overall; 850 (3.9%) in non-cases, 51 (3.1) in hypothyroidism, and 16 (3%) in hyperthyroidism.

[d] n = 1273 missing overall; 1168 (5.3%) in non-cases, 80 (4.9%) in hypothyroidism, and 25 (4.7%) in hyperthyroidism.

[e] n = 1927 missing overall; 1757 (8%) in non-cases, 125 (7.7%) in hypothyroidism, and 45 (8.5%) in hyperthyroidism.

[f] n = 1972 missing overall; 1813 (8.3%) in non-cases, 118 (7.3%) in hypothyroidism, and 41 (7.7%) in hyperthyroidism.

Table 2

Ever-use of pesticides and risk of incident hypothyroidism in AHS spouses.

Pesticide	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Any fungicide[c]	1457	99	1.26 (1.02, 1.54)	
Benomyl	1527	21	1.56 (1.01, 2.40)	
Captan	1501	50	1.27 (0.96, 1.69)	
Chlorothanolil	1528	20	1.29 (0.83, 2.00)	
Maneb/Mancozeb	1508	40	1.71 (1.24, 2.35) **	
Metalaxyl	1509	35	1.64 (1.16, 2.30) *	1.82 (1.25, 2.66)
Any insecticide[c]	903	686	1.04 (0.94, 1.14)	
Organochlorine				
Age ≤ 60[d]	1012	54	0.80 (0.61, 1.06)	
Age > 60[d]	414	75	1.17 (0.91, 1.49)	
Aldrin	1509	19	1.43 (0.91, 2.26)	1.55 (0.88, 2.72)
Chlordane				
Age ≤ 60[d]	1020	34	0.87 (0.62, 1.22)	
Age > 60[d]	439	38	1.10 (0.79, 1.54)	
DDT	1470	59	0.97 (0.74, 1.26)	
Heptachlor	1515	12	0.92 (0.52, 1.64)	0.77 (0.41, 1.47)
Lindane	1519	29	1.08 (0.75, 1.56)	
Toxaphene	1512	15	1.25 (0.75, 2.08)	
Carbamate	1039	545	1.04 (0.93, 1.15)	
Aldicarb	1531	11	1.44 (0.80, 2.62)	
Carbaryl	1033	535	1.04 (0.94, 1.16)	1.02 (0.90, 1.15)
Carbofuran	1517	29	0.86 (0.60, 1.25)	0.97 (0.62, 1.54)
Organophosphate	1135	454	1.03 (0.92, 1.15)	
Chlorpyrifos	1475	72	1.10 (0.87, 1.40)	1.28 (0.96, 1.71)
Coumaphos	1519	26	1.18 (0.80, 1.74)	
Diazinon	1382	168	0.96 (0.82, 1.13)	

Pesticide	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Dichlorvos	1505	41	0.83 (0.61, 1.14)	
Fonofos	1521	23	0.70 (0.46, 1.06)	0.74 (0.46, 1.20)
Malathion	1205	362	1.10 (0.97, 1.24)	1.08 (0.94, 1.24)
Parathion				
Age ≤ 60[d]	1051	11	1.00 (0.55, 1.81)	
Age > 60[d]	469	14	2.44 (1.43, 4.16) **	
Phorate	1519	22	0.63 (0.41, 0.96)	0.64 (0.41, 1.01)
Terbufos	1502	43	0.87 (0.64, 1.17)	0.87 (0.59, 1.30)
Pyrethroid				
Permethrin (livestock)	1490	54	0.86 (0.65, 1.12)	
Permethrin (crops)				
Age ≤ 60[d]	1042	21	0.83 (0.54, 1.28)	
Age > 60[d]	468	15	1.68 (1.01, 2.82)	
Any fumigant[c]	1530	30	1.04 (0.72, 1.49)	
Methyl bromide	1542	18	1.02 (0.64, 1.62)	0.75 (0.44, 1.28)
Carbon tetrachloride/carbon disulfide 80/20 mix	1544	12	1.12 (0.63, 1.98)	
Any herbicide[c]	936	641	1.03 (0.93, 1.15)	
Alachlor	1475	69	0.91 (0.71, 1.16)	1.15 (0.83, 1.59)
Butylate	1521	18	0.74 (0.46, 1.17)	0.75 (0.43, 1.32)
Chlorimuron ethyl	1517	24	0.81 (0.54, 1.21)	0.89 (0.55, 1.44)
Dicamba	1480	63	0.90 (0.70, 1.16)	1.17 (0.85, 1.60)
EPTC	1527	14	0.58 (0.34, 0.99)	0.70 (0.37, 1.30)
Glyphosate	987	585	1.05 (0.94, 1.16)	1.07 (0.95, 1.20)
Imazethapyr	1505	36	0.72 (0.51, 1.00)	0.63 (0.40, 0.97)
Metolachlor	1502	40	0.70 (0.51, 0.96)	0.72 (0.48, 1.08)
Paraquat	1514	25	1.27 (0.86, 1.90)	
Pendimethalin	1499	41	1.10 (0.81, 1.50)	1.77 (1.19, 2.62)
Petroleum	1477	59	0.93 (0.72, 1.21)	
Trifluralin	1454	86	0.95 (0.76, 1.18)	1.15 (0.87, 1.52)

Pesticide	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Phenoxy	1308	241	0.93 (0.81, 1.07)	
2,4-D	1305	238	0.93 (0.80, 1.07)	0.90 (0.77, 1.05)
2,4,5-T	1516	16	1.25 (0.76, 2.05)	
Triazine	1468	78	0.78 (0.62, 0.98)	
Atrazine	1476	69	0.86 (0.67, 1.09)	0.99 (0.71, 1.36)
Cyanazine	1504	39	0.78 (0.57, 1.08)	0.84 (0.55, 1.27)
Metribuzin	1517	25	0.82 (0.55, 1.22)	1.04 (0.64, 1.69)

Abbreviation: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; CI, confidence intervals; DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl dipropylthiocarbamate; HR, hazard ratio.

[a] Adjusted for education, state, and smoking.

[b] Adjusted for education, state, smoking, and correlated pesticides, wherever applicable (See eTable 3 for correlated pesticides, exposed and unexposed n may differ due to missing values in correlated exposures).

[c] Any insecticide indicates use of any of insecticides including organochlorines, carbamates, organophosphate, and pyrethroids; any fumigant indicates use of any two fumigants listed in the table and others not shown due to a small number of exposed cases; any fungicide indicates use of any five fungicides listed; and any herbicide indicates use of any herbicides listed.

[d] Hazard ratio allowed to vary by the median age (i.e., 60 years) for exposures that did not meet proportional hazards assumptions ($p \leq 0.10$).

* False discovery rate adjusted p-value < 0.10.

** False discovery rate adjusted p-value < 0.05.

Table 3

Farm exposures and risk of incident hypothyroidism in AHS spouses.

Exposure	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Lived at least half the life on a farm before 18	641	944	0.92 (0.83, 1.02)	–
Living on a farm 10 years ago	321	1265	0.82 (0.72, 0.93)	–
No. of years lived on a farm (years)				
0–18		400	Ref[c]	–
19–31		411	0.97 (0.84, 1.12)	–
32–45		420	0.89 (0.77, 1.02)	–
> 45		348	0.84 (0.71, 1.00)	–
Worked in the field recent growing season				
No		784	Ref[c]	Ref
< 10 days		326	0.92 (0.81, 1.05)	0.88 (0.74, 1.03)
10–30 days		283	0.95 (0.82, 1.09)	0.93 (0.76, 1.12)
31–100 days		150	0.78 (0.65, 0.93)	0.82 (0.63, 1.05)
> 100 days		33	0.72 (0.51, 1.02)	0.69 (0.42, 1.11)
Tasks in the last growing season				
Till soil	1212	363	0.86 (0.76, 0.97)	0.88 (0.76, 1.02)
Planting	1226	348	0.93 (0.82, 1.05)	0.98 (0.82, 1.16)
Apply natural fertilizer	1380	192	1.01 (0.87, 1.18)	1.04 (0.87, 1.24)
Apply chemical fertilizer	1387	184	1.05 (0.89, 1.23)	1.11 (0.91, 1.35)
Drive combines	1415	154	0.82 (0.70, 0.98)	–
Handpick crops	1212	365	0.87 (0.77, 0.99)	0.86 (0.74, 1.00)
Other tasks, at least monthly				
Milk cows	1488	36	0.69 (0.50, 0.97)	–
Grind animal feed	1450	78	0.84 (0.67, 1.06)	–
Veterinary procedures	1339	192	0.91 (0.78, 1.07)	–
Drive trucks	972	560	0.93 (0.84, 1.04)	–
Drive diesel tractor	1015	521	0.97 (0.87, 1.08)	1.20 (1.03, 1.39)
Drive gasoline tractor	1158	375	0.85 (0.75, 0.96)	0.82 (0.71, 0.94)
Weld	1516	10	0.67 (0.36, 1.25)	0.59 (0.29, 1.19)

Exposure	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Grind metal[d]	1510	19	0.98 (0.62, 1.54)	–
Age ≤ 60			–	0.79 (0.40, 1.55)
Age > 60			–	2.25 (1.14, 4.44)
Clean with gasoline	1310	221	0.87 (0.75, 1.00)	0.88 (0.74, 1.04)
Clean with solvents	1227	306	0.92 (0.81, 1.04)	1.02 (0.86, 1.20)
Paint	1050	488	0.91 (0.82, 1.02)	0.97 (0.84, 1.11)
Hours/day in the sun, recent growing season				
Up to 1 h		359	Ref	
1–5 h		745	0.88 (0.78, 1.00)	–
>6h		126	0.77 (0.63, 0.95)	–
Hours per day in the sun, 10 years ago[d]				
Up to 1 h		243	Ref	
1–5 h (Age < 60)		465	0.81 (0.68, 0.96)	–
(Age > 60)		240	0.79 (0.63, 0.99)	–
> 6 h (Age < 60)		149	0.93 (0.72, 1.21)	–
(Age > 60)		76	0.75 (0.54, 1.04)	–

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for education, state, smoking, and ever mixed or applied pesticides.

[b]Adjusted for education, state, smoking, and correlated farm exposures; entry '–' indicates that the exposures either not correlated with other farm exposures (exposed and unexposed n may differ due to missing values in correlated exposures).

[c]P-trend < 0.05.

[d]Hazard ratio allowed to vary by the median age (i.e., 60 years) for pesticides that did not meet proportional hazards assumptions (p ≤ 0.10).

Table 4

Ever-use of pesticides and risk of incident hyperthyroidism in AHS spouses.

Pesticide	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Any fungicide[c]	484	31	1.11 (0.77, 1.6)	
Captan	503	11	0.89 (0.49, 1.61)	
Maneb/mancozeb (all)[d]	496	16	1.74 (1.05, 2.88)	
Age ≤ 60	318	11	2.63 (1.43, 4.86)**	
Age > 60	178	5	0.99 (0.40, 2.42)	
Metalaxyl	498	13	1.48 (0.85, 2.60)	1.89 (1.03, 3.46)
Any insecticide[c]	308	211	0.98 (0.82, 1.17)	
Organochlorine	469	44	1.07 (0.78, 1.47)	
Chlordane	485	20	0.89 (0.57, 1.40)	
DDT	478	26	1.35 (0.91, 2.02)	
Carbamate	354	165	0.94 (0.78, 1.14)	
Carbaryl	357	161	0.93 (0.77, 1.12)	0.91 (0.73, 1.12)
Carbofuran	500	13	1.22 (0.70, 2.12)	0.89 (0.44, 1.82)
Organophosphate	371	147	1.09 (0.90, 1.32)	
Chlorpyrifos	487	24	1.13 (0.75, 1.71)	0.99 (0.6, 1.64)
Diazinon	438	72	1.35 (1.05, 1.73)	
Dichlorvos	491	11	0.77 (0.42, 1.41)	
Fonofos	498	15	1.56 (0.93, 2.63)	1.48 (0.77, 2.82)
Malathion	410	107	1.01 (0.82, 1.26)	1.08 (0.85, 1.39)
Phorate	500	12	1.14 (0.64, 2.02)	0.98 (0.52, 1.87)
Terbufos	493	20	1.33 (0.85, 2.09)	1.14 (0.62, 2.11)
Pyrethroid				
Permethrin (livestock)	480	24	1.30 (0.86, 1.96)	
Permethrin (crops)	498	16	1.45 (0.88, 2.38)	
Any herbicide[c]	332	185	0.91 (0.76, 1.09)	
Alachlor (all)[d]	474	31	1.39 (0.96, 2.00)	1.27 (0.76, 2.11)

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Pesticide	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Age ≤ 60	302	22	1.60 (1.04, 2.47)	1.41 (0.80, 2.46)
Age > 60	172	9	1.04 (0.53, 2.04)	1.00 (0.46, 2.17)
Chlorimuron ethyl	491	13	1.46 (0.84, 2.53)	0.97 (0.49, 1.90)
Dicamba	477	27	1.35 (0.91, 1.99)	1.11 (0.66, 1.86)
Glyphosate	345	170	0.93 (0.77, 1.12)	0.90 (0.73, 1.11)
Imazethapyr	484	20	1.39 (0.88, 2.19)	1.05 (0.55, 1.99)
Metolachlor	476	29	1.80 (1.24, 2.63)**	2.01 (1.17, 3.44)
Pendimethalin	487	18	1.51 (0.94, 2.41)	1.18 (0.64, 2.17)
Petroleum oil (all)[d]	484	21	1.10 (0.71, 1.71)	
Age ≤ 60	309	16	1.33 (0.81, 2.21)	
Age > 60	175	5	0.71 (0.29, 1.74)	
Trifluralin	481	23	0.87 (0.57, 1.32)	0.57 (0.33, 0.99)
Phenoxy	435	74	0.96 (0.74, 1.23)	
2,4-D	434	74	0.97 (0.75, 1.24)	1.04 (0.78, 1.38)
Triazine	471	34	1.16 (0.82, 1.65)	
Atrazine	476	29	1.23 (0.84, 1.80)	1.08 (0.65, 1.82)
Cyanazine	491	14	0.96 (0.56, 1.64)	0.55 (0.28, 1.07)

Abbreviation: 2,4-D, 2,4-dichlorophenoxyacetic acid; CI, confidence intervals; DDT, dichlorodiphenyltrichloroethane; HR, hazard ratio.

[a]Adjusted for education, state, and smoking.

[b]Adjusted for education, state, smoking, and correlated pesticides, wherever applicable (See eTable 3 for correlated pesticides, exposed and unexposed n may differ due to missing values in correlated exposures).

[c]Any insecticide indicates use of any of insecticides including organochlorines, carbamates, organophosphate, and pyrethroids; any fumigant indicates use of any two fumigants listed in the table and others not shown due to a small number of exposed cases; any fungicide indicates use of any five fungicides listed; and any herbicide indicates use of any herbicides listed.

[d]Hazard ratio allowed to vary by the median age (i.e., 60 years) for exposures that did not meet proportional hazards assumptions (p ≤ 0.10), but n in each category < 10, so overall (all) HR also presented.

**False discovery rate adjusted p-value < 0.05.

Table 5

Farm exposures and risk of incident hyperthyroidism in AHS spouses.

Exposure	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Lived at least half the life on a farm before 18				
Age ≤ 60[c]	163	166	0.78 (0.63, 0.98)	–
Age > 60[c]	50	135	1.10 (0.79, 1.52)	–
Living on a farm 10 years ago	104	415	0.88 (0.69, 1.10)	–
No. of years lived on a farm (years)[d]				
0–31		263	Ref	
> 31		249	0.89 (0.73, 1.08)	–
Worked in the field recent growing season				
No		242	Ref	Ref
< 10days		96	0.92 (0.72, 1.17)	0.95 (0.71, 1.27)
10–30 days		102	1.11 (0.88, 1.40)	1.02 (0.73, 1.42)
31–100 days		59	0.98 (0.73, 1.31)	0.91 (0.59, 1.40)
> 100 days		14	0.90 (0.52, 1.56)	0.56 (0.24, 1.31)
Tasks in the last growing season				
Till soil	385	124	1.02 (0.82, 1.26)	0.96 (0.75, 1.24)
Planting	373	137	1.11 (0.90, 1.38)	0.91 (0.68, 1.21)
Apply natural fertilizer	444	62	0.98 (0.75, 1.29)	0.80 (0.58, 1.09)
Apply chemical fertilizer	427	81	1.47 (1.15, 1.90)	1.58 (1.16, 2.17)
Drive combines	448	57	1.06 (0.80, 1.41)	–
Handpick crops	360	147	1.14 (0.93, 1.40)	1.11 (0.86, 1.42)
Other tasks, at least monthly				
Milk cows	487	10	0.58 (0.31, 1.08)	–
Grind animal feed	469	24	0.82 (0.54, 1.24)	–
Veterinary procedures	432	66	1.05 (0.80, 1.37)	–
Drive trucks	293	207	1.15 (0.96, 1.38)	–
Drive diesel tractor	335	167	1.02 (0.84, 1.24)	1.08 (0.83, 1.40)
Drive gasoline tractor	375	123	0.93 (0.75, 1.15)	0.87 (0.68, 1.12)

Exposure	Unexposed cases	Exposed cases	HR (95% CI)[a]	HR (95% CI)[b]
Repair engines	486	14	2.23 (1.31, 3.82)	2.14 (1.15, 3.98)
Grind metal	488	10	1.66 (0.88, 3.11)	-[e]
Clean with gasoline	413	83	1.15 (0.90, 1.47)	1.13 (0.84, 1.51)
Clean with solvents	399	102	1.04 (0.83, 1.30)	0.86 (0.64, 1.15)
Paint	327	173	1.13 (0.94, 1.37)	1.15 (0.90, 1.47)
Hours/day in the sun, recent growing season				
Up to 1h		112	Ref	
1–5 h		233	0.90 (0.71, 1.13)	–
>6h		52	0.96 (0.68, 1.34)	–
Hours/day in the sun, 10years ago				
Up to 1 h		59	Ref	
1–5 h		230	1.19 (0.89, 1.59)	–
>6h		82	1.11 (0.79, 1.57)	–

Abbreviation: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for education, state, smoking, and ever mixed or applied pesticides.

[b]Adjusted for education, state, smoking, and correlated farm exposures; entry "-" indicates exposures either not correlated with other farm exposures (exposed and unexposed n may differ due to missing values in correlated exposures).

[c]Hazard ratio allowed to vary by the median age (i.e., 60 years) for pesticides that did not meet proportional hazards assumptions ($p \leq 0.10$).

[d]Different cut-off used for "no. of years lived on a farm" for hyperthyroidism than hyperthyroidism.

[e]Not sufficient n for HR to vary by the median age.