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Non-occupational exposure to pesticides and health markers in general population in Northern Finland: Differences between sexes

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ABSTRACT

Background: Occupational exposure to pesticides has been reported among general population worldwide. However, little is known about the associations between non-occupational exposure to pesticides, and biological markers of health and their response by sex.

Objectives: We aimed to assess the associations between non-occupational overall pesticide exposure, length of exposure and specific pesticides reported with 35 biological markers of health representing cardiometabolic, haematological, lung function, sex hormones, liver and kidney function profiles, and vitamin D in Finnish cohort.

Methods: 31-year cross-sectional examination of the Northern Finland Birth Cohort 1966 provided blood samples for biomarker measurements in 1997–1998. Number of subjects varied between 2361 and 5037 for given exposures and certain outcome associations. Multivariable regression analyses were performed to examine associations between overall pesticide exposure (OPE), length of pesticide exposure in months (PEM), in years (PEY), and specific pesticides use (PEU) or not with cardiometabolic [SBP, DBP, TC, LDL, HDL, triglycerides, fasting glucose, insulin, HOMA-IR, HOMA-B, HOMA-S, hs-CRP], hematological [WBC, RBC, Hb, HCT, MCV, MCH, MCHC, platelets], lung function (FVC, FEV1), sex hormones [luteinizing hormone (LH), testosterone (TT), sex-hormone binding globulin (SHBG)], liver and kidney function profiles [total protein, albumin, globulin, ALP, ALT, GGT, urea, creatinine], and vitamin D adjusting for sex, BMI, socioeconomic position (SEP) and season of pesticide use.

Results: This cohort study on up to 5037 adults with non-occupational OPE, PEM, PEY and PEU differed by sex and SEP. In regression analyses, all the exposures were positively associated with total cholesterol and low-

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransaminase; BMI, body mass index; DBP, diastolic blood pressure; EDCs, endocrine disrupting chemicals; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; GGT, gamma-glutamyl transferase; Hb, haemoglobin; HCT, haematocrit; HDL, high-density lipoprotein cholesterol; HOMA, Homeostatic model assessment; HOMA-IR, HOMA for insulin resistance; HOMA-β, HOMA for assessing β-cell function; HOMA-S, HOMA for insulin sensitivity; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; LH, luteinizing hormone; MCH, mean corpuscular haemoglobin; MCHC, MCH concentration; MCV, mean corpuscular volume; NFBC1966, Northern Finland Birth Cohort 1966; OPE, overall pesticide exposure; PEM, pesticide exposure in months; PEU, specific pesticides; PEY, pesticide exposure in years; RBC, total red blood cell; SBP, systolic blood pressure; SHBG, sex-hormone binding globulin; SEP, socioeconomic position; TC, total cholesterol; TG, triglycerides; TT, testosterone; WC, waist circumference; WBC, total leukocyte count..

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density lipoprotein cholesterol, and PEU was negatively associated with high-density lipoprotein cholesterol in females. OPE and PEM were positively associated with haematocrit in females and PEU with platelets in males. PEU was negatively associated with mean corpuscular haemoglobin. OPE and PEM were positively associated with LH in males. OPE was negatively associated with total protein and albumin in males.
Discussion: In Finnish young adults, non-occupational overall pesticide exposure, length of exposure and specific pesticides were associated with multiple biological markers of health. The biological markers seem to be indicative of adverse effects of pesticides and warrant for further studies to replicate the findings and determine the underlying mechanisms.

1. Introduction

The generic term "pesticides" includes over 1000 various chemical substances, which can be grossly classified as insecticides, herbicides, and fungicides according to their targets. They are increasingly used since the 1950 and provide one of the most effective and accepted global strategies for crops protection that has enhanced agricultural production worldwide (Kangas et al., 1995). However, the pesticide exposure may contribute with several adverse metabolic health outcomes in humans and wildlife and some of them are endocrine disrupting chemicals (EDCs) (Evangelou et al., 2016; Lauretta et al., 2019). Epidemiological investigations, although very limited, have reported associations between occupational exposure to pesticides and chronic diseases including diabetes (Parrón et al., 2011; Yan et al., 2016), neurodegenerative diseases (Mamane et al., 2015), increased risk of respiratory symptoms (asthma and chronic bronchitis) (Bao et al., 2020; Berg et al., 2019), cardiovascular diseases (Bao et al., 2020), all-cause mortality (Gangemi et al., 2016; Mathur et al., 2002; Silva et al., 2016), several kinds of cancers (Kaur and Kaur, 2018; Van Der Plaat et al., 2018) and DNA methylation changes (Gangemi et al., 2016; Parrón et al., 1996). In addition, effects of pesticides directly on endocrine, nervous and immune systems have also been reported (Banerjee et al., 1999; Hernández et al., 2006; Mostafalou and Abdollahi, 2013). However, the underlying mechanisms by which the pesticides interfere biological pathways contributing to chronic diseases remain largely unknown as reported by both epidemiological and experimental studies (Anwar, 1997; Benford et al., 2000). Assessing biological markers of human exposure to pesticides has received some attention (Dalmolin et al., 2020) and dysfunctions in circulating biomarkers of health could reflect cytotoxicity in relation to pesticides exposure (Anwar, 1997; Gangemi et al., 2016). The alterations in biological markers could also be used to document either preclinical alterations or early adverse metabolic health effects elicited by the external exposure to pesticides and/or absorption of certain chemicals from pesticides.

Despite the growing evidences suggesting that occupational exposure to pesticides is linked to adverse metabolic health outcomes, the association between non-occupational, expectedly less severe exposure and biological markers of health in general population is largely lacking. The consequences of short- and long-term exposure to pesticides and effects of different types of pesticides on biological markers remain to be determined. In addition, the Global Burden of Disease study 2017 has reported an elevated risk in exposure-outcome associations in relation to most occupational risks in men (Stanaway et al., 2018). However, different response to exposure to pesticides by sex has not received much attention. Furthermore, little is known about the complex role of low dose exposure to pesticides in the early development of metabolic diseases in young adulthood through alteration of circulating biological markers of health.

In the present study, we used data from a Finnish general adult population to examine the associations of reported non-occupational overall pesticide exposure (OPE), length of pesticide exposure [in months (PEM) or in years (PEY)] and specific pesticides (PEU) with biological markers of health representing cardiometabolic, haematological, lung function, sex hormones, liver and kidney function profiles and their response by sex.

2. Methods

2.1. Study population

The Northern Finland Birth Cohort 1966 (NFBC1966) is a population-based, homogeneous, longitudinal birth cohort study which comprised of offspring of pregnant women (n = 12,055) with expected delivery dates during 1966, residing in two Northernmost provinces of Finland (Oulu and Lapland) (Cohort NFBC, 1966; Paula, 1969; Rantakallio, 1988). There were 12,058 live births and these children were followed-up until the age of 46 year (Järvelin et al., 2004). The current study focuses on the 31-year follow-up data, i.e. young adult age of disease development. In 1997, at 31-year of age, participants health, lifestyle and occupation were assessed by postal questionnaires (n = 11,541; 97% of the birth cohort alive and traced) (Järvelin et al., 2004). Participants who responded (n = 8,463) and resided in Northern Finland and in Helsinki area were invited for a clinical examination (n = 6,033) (Akhgari et al., 2003; Al-Gubory, 2014; Kaur and Kaur, 2018). Study participants gave written informed consent for their data usage. All procedures performed were in accordance with the 1964 Helsinki declaration. The Ethics Committee of the Northern Ostrobothnia Hospital District has approved the NFBC1966 study. The flowchart of the study population is shown in **Figure S1**.

2.2. Exposures

Participants invited to the clinical examination at 31 years filled in general health questions on dietary intake, exposure to certain chemicals including solvents, glues etc., before obtaining the blood samples. The question included "How long have you been exposed to the following substances - pesticides and plant protection products in years and in months?" and "What type of pesticide and plant protection products were used". **Table S1** shows the reported pesticides and plant protection products used in NFBC1966. The responses were categorised as pyrethroid, organophosphates, insect repellents, herbicides, fungicides, and plant growth regulators (**Table S2**). Participants who reported no pesticide exposure at all were categorized as "no" (non-exposed) and who reported pesticides exposure up to 12 months (PEM) or for multiple years (PEY) and specific pesticide use (PEU) in **Table S2** were categorized "yes" (exposed). Overall pesticide exposure (OPE) combines all the participants who reported pesticide exposure in months or in years and specific pesticide use. So, the exposures of this study are overall pesticide exposure (OPE), length of pesticide exposure in months (PEM), pesticide exposure in years (PEY) and specific pesticides (PEU). PEM and PEY were explored separately from overall exposure to assess the severity of exposure and PEU also for accuracy of reporting.

2.3. Blood samples measurements for biological markers of health

Blood samples of the NFBC1966 participants were taken after an overnight fasting period from 08 to 11 h, centrifuged immediately and stored first at − 20 °C and later at − 80 °C. Blood samples were analysed in NordLab Oulu (former name Oulu University Hospital, Laboratory), a testing laboratory (T113) accredited by the Finnish Accreditation Service (FINAS) (EN ISO 15189).

2.4. Biological markers of health (outcome variables)

The **online** supplementary material section reports detailed analytical methodology of markers of health: cardiometabolic [systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), fasting glucose, insulin, Homeostatic Model Assessment for insulin resistance (HOMA-IR), ß-cell function (HOMA-ß) and insulin sensitivity (HOMA-S), high sensitivity C-reactive protein (hs-CRP)], haematological parameters [total leukocyte count (WBC), total red blood cell (RBC), haemoglobin (Hb), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), MCH concentration (MCHC), platelets], lung function [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1)], sex hormones [luteinizing hormone (LH), testosterone (TT), sex-hormone binding globulin (SHBG)], liver and kidney function profiles [total protein, albumin, globulin, alkaline phosphatase (ALP), alanine aminotransaminase (ALT), gamma-glutamyl transferase (GGT), urea, creatinine], and vitamin D [the list of abbreviations are given separately upfront and in the footnotes of tables and figures].

2.5. Control for potential confounders

We included sex, body mass index (BMI), socioeconomic position (SEP) and season of pesticide use as reported from previous literature and tested here as potential confounders in the regression analyses (detailed information in the **online** supplementary material).

2.6. Statistical analyses

Descriptive statistics were computed for all explanatory, confounder, and outcome measures. The results are presented as mean (95% CI) for normally distributed variables and median (IQR) for non-parametric distribution and n (%) for categorical variables. The differences between the participants with and without OPE, PEM, PEY and PEU exposure were analysed by chi-square test for categorical variables, independent-sample Student t test for normally distributed data and Wilcoxon–Mann–Whitney U test for nonparametric data. Spearman correlation coefficients were used to assess the relationship between exposures and cardiometabolic, haematological, lung, sex hormones, liver, kidney function profiles, vitamin D and heatmaps were used to present the correlations. The outcome variables (cardiometabolic, haematological, lung, sex hormones, liver, kidney function profiles and vitamin D) were all converted to standardised scores (z-scores) for the regression analyses.

Multivariable regression analyses were performed to assess the independent associations of reported OPE, PEM, PEY and PEU (explanatory variables) with health markers (dependent variables). We examined the associations using five models: model 1: unadjusted, model 2: adjusted for sex, model 3: adjusted for sex and BMI, model 4: model 3 with additional adjustment for SEP, and model 5: model 4 with additional adjustment for season of pesticide use. Further the analyses were stratified by sex: model 1: unadjusted, model 2: adjusted for BMI, model 3: model 2 with additional adjustment for SEP, and model 4: model 3 with additional adjustment for season of pesticide use. Only for PEY with liver function markers (total protein and albumin), further adjustment with alcohol intake was made (**Figure S9**). We did not apply multiple testing correction as the research questions were specified and hypotheses based. Regression coefficients from these associations can be interpreted by the category change (yes/no) change in OPE, PEM, PEY and PEU. All statistical analyses applied 2-sided tests using $P < 0.05$ for significance. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) and R version 3.6.3 (R Project for Statistical Computing).

3. Results

3.1. Descriptive characteristics of the study population

Table 1 **and Table S3** present descriptive characteristics of the overall pesticide exposure, length of pesticide exposure and specific pesticides with demographic, anthropometric, SEP, lifestyle, diet and environmental covariates. OPE, PEM, PEY and PEU differed with regards to sex and SEP. PEY, i.e. longer use, differed by educational status, smoking, alcohol, dietary index, and season of pesticide use. PEY and PEU differed with latitude of residence.

Cardiometabolic markers examined in relation to PEM, PEY and PEU are summarised in **Table S4 and S6.** TC, LDL and HOMA-B values were higher by length of pesticide use (PEM) compared to non-exposed ($P \leq 0.05$). Median TG values were also higher in PEM ($P = 0.02$) or PEY ($P = 0.01$) exposed participants compared with those for non-pesticide users.

Table S5 and S7 shows haematological, lung, sex hormones, kidney and liver function profiles and vitamin D levels in relation to PEM, PEY and PEU. According to bivariate analyses Hb, HCT, GGT and creatinine values differed in relation to either PEM and/or PEY. In all these analyses higher values were observed in the pesticide users. Significant differences on MCV, SHBG and creatinine values were also observed between participants reporting PEM, PEY and PEU exposure with lower values in the pesticide users. To clarify the results, we further stratified by sex which showed median LH and SHBG concentrations were higher in relation to PEM, PEY and PEU exposure when compared to non-exposed in both sexes (**Table S8 and S9**). Median SHBG values were in opposite directions with respect to sex in PEU group (**Table S9**).

Figure S2 presents spearman correlation coefficients between PEM, PEY and PEU with health markers. PEU was highly positively correlated with PEM ($r = 0.488$; $p < 0.0001$) and PEY ($r = 0.415$; $p < 0.0001$).

3.2. Multivariable regression analyses of OPE, PEM, PEY and PEU with cardiometabolic risk markers

Figures 1, S3, S6A, S7A and S8A (men and women, respectively) show results from the multivariable regression analysis of OPE, PEM, PEY and PEU with cardiometabolic markers. Fig. 1 shows graphically the overall picture, β-values, and their CIs with bars while supplementary materials shows values themselves. In the unadjusted model, OPE was positively associated with SBP, TC, LDL, TG, hs-CRP and negatively with HDL. In fully adjusted model 5, the association of OPE, i.e. overall exposure that accounts all exposure groups with LDL (β = 0.14; 95% CI: 0.02, 0.27; p-value = 0.03) remained. PEM was independently positively associated with TC, LDL and TG. The association of PEM with TG attenuated when adjusted for sex, however, the associations remained for TC (β = 0.21; 95% CI: 0.04, 0.39; p-value = 0.017) and LDL (β = 0.19; 95% CI: 0.02, 0.36; p-value = 0.03) with adjustment for all covariates (sex, BMI, SEP and season of pesticide use). In unadjusted analyses, PEY was positively associated with SBP, DBP, TC, LDL, TG and negatively with HDL. However, after further adjustment with sex and other covariates none of the associations remained. Similar pattern was seen between PEU and cardiometabolic markers, however, the positive association between PEU and LDL (β = 0.22; 95% CI: 0.04, 0.39; p-value = 0.014) remained in the final model.

In sex-stratified analyses, OPE, PEM, PEY and PEU were associated positively with TC and LDL; and PEU was negatively associated with HDL (β = -0.30; 95% CI: −0.59, −0.004; p-value = 0.046) in females in final model 4.

3.3. Multivariable regression analyses of OPE, PEM, PEY and PEU with haematological, sex hormones and lung function

Figures 2, S4, S6B, S7B and S8B (men and women, respectively) show results from the multivariable regression analysis of OPE, PEM, PEY and PEU with haematological, lung and sex hormones. Fig. 2 shows

Table 1
Descriptive statistics of the study population in NFBC1966.

		Overall pesticide exposure** (OPE)		P-value
		No (N = 4773)	Yes (N = 264)	
Age		31		
Sex, n %	5037			
Male		2242 (46.97)	180 (68.18)	<0.0001
Female		2531 (53.03)	84 (31.82)	
BMI (kg/m^2), n %	5000			
Normal weight		2857 (60.29)	145 (55.56)	0.129
Overweight and Obese		1882 (39.71)	116 (44.44)	
Educational status, n %	4987			
<9 years of basic school		36 (0.76)	1 (0.38)	0.0003
Basic school		2771 (58.62)	185 (71.15)	
Matriculation examination		1920 (40.62)	74 (28.46)	
Smoking status, n %	4966			
No smoker		2099 (44.57)	110 (42.80)	0.578
Smokers		2610 (55.43)	147 (57.20)	
Alcohol consumption (g/day), n %[a]	4878			
Abstainer		423 (9.15)	38 (14.96)	0.007
Low risk drinker		3934 (85.08)	205 (80.71)	
At-risk drinker		267 (5.77)	11 (4.33)	
Physical activity, n %	4981			
Low		1558 (33.00)	99 (38.08)	0.235
Medium		1626 (34.44)	84 (32.30)	
High		1537 (32.56)	77 (29.62)	
Socioeconomic position, n%	4972			
I + II (Professional)		1175 (24.92)	49 (18.92)	<0.0001
III (Skilled worker)		1474 (31.26)	50 (19.31)	
IV (Unskilled worker)		1202 (25.49)	56 (21.62)	
V (Farmer)		112 (2.38)	68 (26.25)	
VI (Other)[b]		752 (15.95)	36 (13.90)	
Habitual dietary index[c], n %	4982			
0–1		2272 (48.12)	107 (41.15)	0.031
2–3		2390 (50.61)	152 (58.46)	
4–5		60 (1.27)	1 (0.38)	
Season of pesticide use[d], n %	4996			
High pesticide use season		3611 (76.26)	219 (83.91)	0.005
Low pesticide use season		1124 (23.74)	42 (16.09)	
Latitude of residence, n %	5037			
Oulu		925 (19.38)	27 (10.23)	<0.0001
Other provinces of Oulu and Lapland		2998 (62.81)	211 (79.92)	
Helsinki		850 (17.81)	26 (9.85)	

** N varies due to missing data for some of the variables from N = 5037 to N = 4878.
Data are presented as n %.
P-value for differences between overall pesticide exposure with demographic, environmental, anthropometric, socioeconomic position, lifestyle (smoking, physical activity, alcohol consumption), habitual dietary index and season of pesticide use covariates was analyzed by chi-square test and fisher test for categorical variables.
[a]Alcohol classification according to WHO sex-specific classification as abstainer, low risk drinker (≤20 g/day and ≤ 40 g/day for women and men, respectively) or at-risk drinker (>20 g/day and > 40 g/day for women and men, respectively).
[b]Includes students, pensioners, long-term unemployed, or not defined.
[c]Unhealthy diet included daily or frequent consumption of red meat and less frequent consumption of rye or crisp bread, berries or fruit, salads, and vegetables. The score ranged from 0 to 5 and was categorised as 0–1, 2–3, 4–5.
[d]High pesticide use season [summer (1 June–30 August) autumn (1 September–31 October)] and low pesticide use season [winter (1 November–31 March) spring (1 April–31 May)].

graphically the overall picture, β-values, and their CIs with bars while supplementary materials shows values themselves. In model 1, OPE was positively associated with RBC, Hb, HCT, FVC, FEV1 and negatively with SHBG. However, the associations were attenuated in model 2. In fully adjusted model 5, the association of OPE with LH (β = 0.19; 95% CI: 0.05, 0.33; p-value = 0.009) remained. PEM was negatively associated with MCHC (β = -0.19; 95% CI: −0.38, −0.01; p-value = 0.035) and SHBG (β = -0.16; 95% CI: −0.31, −0.01; p-value = 0.035) and positively associated with LH (β = 0.22; 95% CI: 0.02, 0.41; p-value = 0.029) in model 5. PEU was positively associated with RBC (β = 0.16; 95% CI: 0.01, 0.29; p-value = 0.031), platelets (β = 0.21; 95% CI: 0.02, 0.40; p-value = 0.034) and LH (β = 0.24; 95% CI: 0.03, 0.44; p-value = 0.024) and negatively associated with MCH (β = -0.26; 95% CI: −0.45, −0.08; p-value = 0.005) and MCHC (β = -0.19; 95% CI: −0.38, −0.01; p-value = 0.044) in model 5.

In the sex-stratified analyses, PEY were positively associated with LH in males in model 4. OPE and PEM were positively associated with haematocrit in females. In females, PEM was negatively associated with MCHC (β = -0.33; 95% CI: −0.61, −0.05; p-value = 0.022) and SHBG (β = -0.44; 95% CI: −0.78, −0.09; p-value = 0.012) and PEM and PEU were positively associated with LH. PEU was negatively associated with MCH (β = -0.32; 95% CI: −0.53, −0.10; p-value = 0.003) and positively with platelets (β = 0.27; 95% CI: 0.04, 0.49; p-value = 0.023) in males.

3.4. Multivariable regression analyses of OPE, PEM, PEY and PEU with liver and kidney function profiles, and vitamin D

Figures 3, S5, S6C, S7C and S8C (men and women, respectively) show results from the multivariable regression analysis of OPE, PEM, PEY and PEU with liver and kidney function profiles, and vitamin D. Fig. 3 shows graphically the overall picture, β-values, and their CIs with bars while supplementary materials shows values themselves. In model 1, OPE was associated with urea and PEY was positively associated with ALP, GGT and urea. In model 2, the associations were attenuated. In model 5, OPE and PEY were negatively associated with total protein (OPE: β = -0.15; 95% CI: −0.29, −0.02; p-value = 0.024) (PEY: β = -0.19; 95% CI: −0.37, −0.004; p-value = 0.044) and albumin (OPE: β = -0.16; 95% CI: −0.29, −0.04; p-value = 0.013) (PEY: β = -0.30; 95% CI: −0.48, −0.12; p-value = 0.001); PEU with total protein (β = -0.24; 95% CI: −0.43, −0.05; p-value = 0.013) only. OPE, PEM, PEY and PEU were not associated with vitamin D in any of the models.

In the sex-stratified analyses, in final model 4 adjusted for covariates OPE in males and PEY in females was negatively associated with total protein (OPE: β = -0.18; 95% CI: −0.34, −0.009; p-value = 0.038) (PEY: β = -0.41; 95% CI: −0.78, −0.03; p-value = 0.032) and albumin (OPE: β = -0.22; 95% CI: −0.37, −0.06; p-value = 0.007) (PEY: β = -0.50; 95% CI: −0.87, −0.13; p-value = 0.007). PEY was negatively associated with albumin (β = -0.27; 95% CI: −0.47, −0.06; p-value = 0.009) and PEU with total protein (β = -0.28; 95% CI: −0.52, −0.03; p-value = 0.025) in males. Further adjustment for PEY with alcohol intake (**Figure S9**, model 5) did not attenuate the above-mentioned associations.

The results on the associations of overall pesticide exposure, length of pesticide exposure (in months or in years) and specific pesticides with biological markers of health is summarised in Table 2.

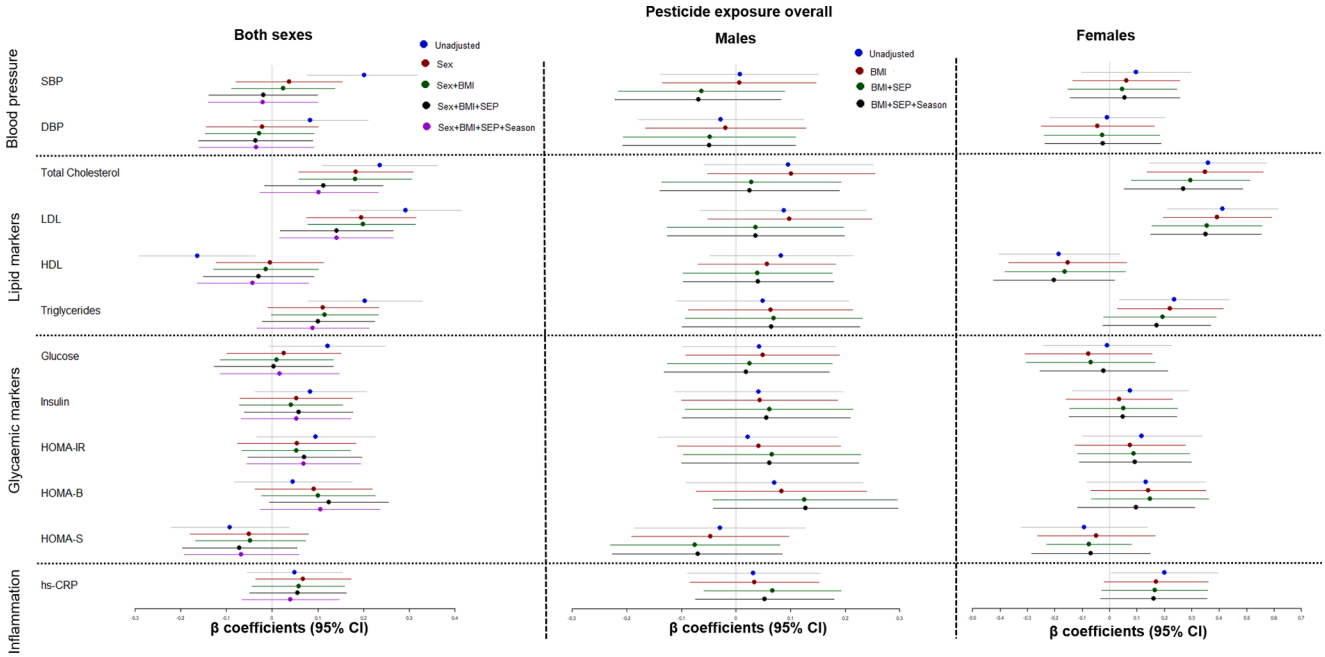

Fig. 1. Multivariable regression analyses of overall pesticide exposure with cardiometabolic risk markers and stratified by sex. Multivariable regression analyses of overall pesticide exposure with cardiometabolic risk factors (outcome) stratified by sex. The results are expressed as β coefficients (95% CI). Model 1 – unadjusted; model 2 – adjusted for sex; model 3 – adjusted for sex and BMI; model 4 – adjusted for sex + BMI + SEP; model 5 – adjusted for model 4 + season of pesticide use in both sexes. Stratified by sex: Model 1 – unadjusted; model 2 – adjusted for BMI; model 3 – adjusted for BMI + SEP; model 4 – adjusted for model 3 + season of pesticide use. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein cholesterol; HDL, High-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HOMA-B, HOMA β-cell function; HOMA-S, Homeostatic Model Assessment of insulin sensitivity; hs-CRP, high-sensitivity c-reactive protein.

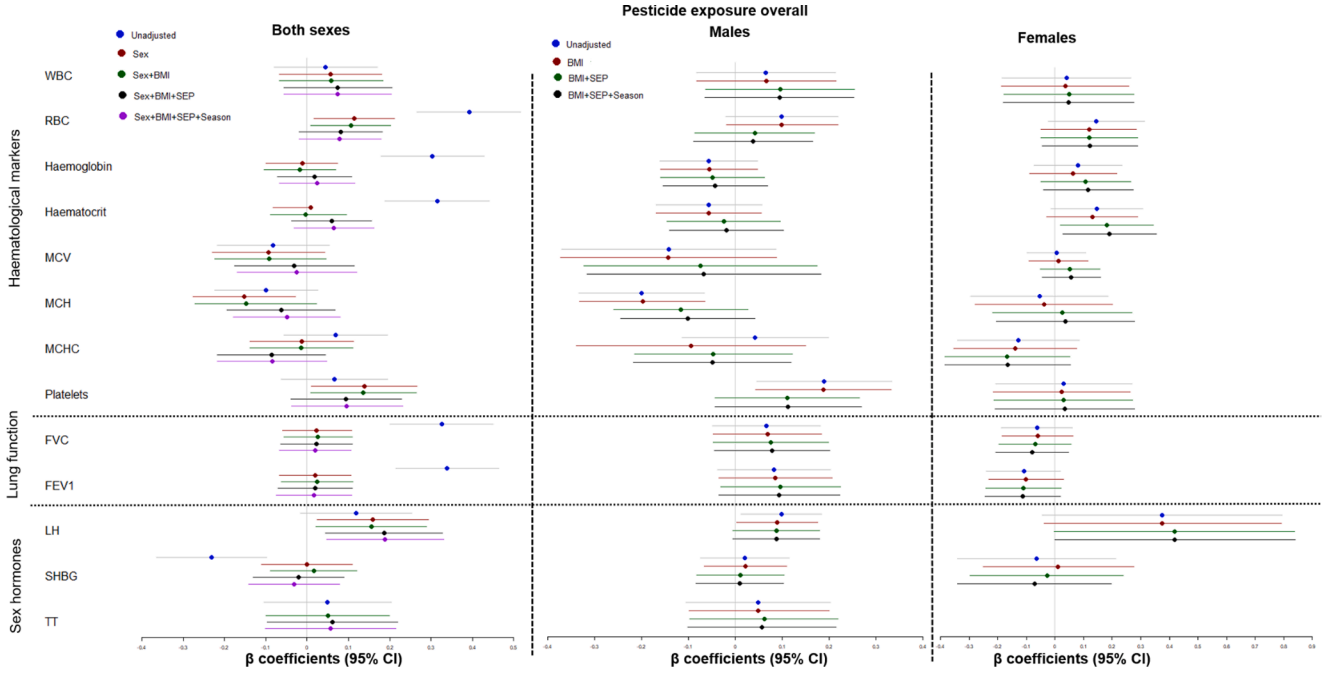

Fig. 2. Multivariable regression analyses of overall pesticide exposure with haematological, lung function and sex hormones and stratified by sex. Multivariable regression analysis of overall pesticide exposure with haematological, lung function and sex hormones (outcome) stratified by sex. The results are expressed as β coefficients (95% CI). Model 1 – unadjusted; model 2 – adjusted for sex; model 3 – adjusted for sex and BMI; model 4 – adjusted for sex + BMI + SEP; model 5 – adjusted for model 4 + season of pesticide use. Stratified by sex: Model 1 – unadjusted; model 2 – adjusted for BMI; model 3 – adjusted for BMI + SEP; model 4 – adjusted for model 3 + season of pesticide use. WBC, total leukocyte count; RBC, total red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; FVC, forced vital capacity; FEV1, Forced expiratory volume in 1 s; LH, Luteinizing hormone; SHBG, sex-hormone binding globulin; TT, total testosterone; (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

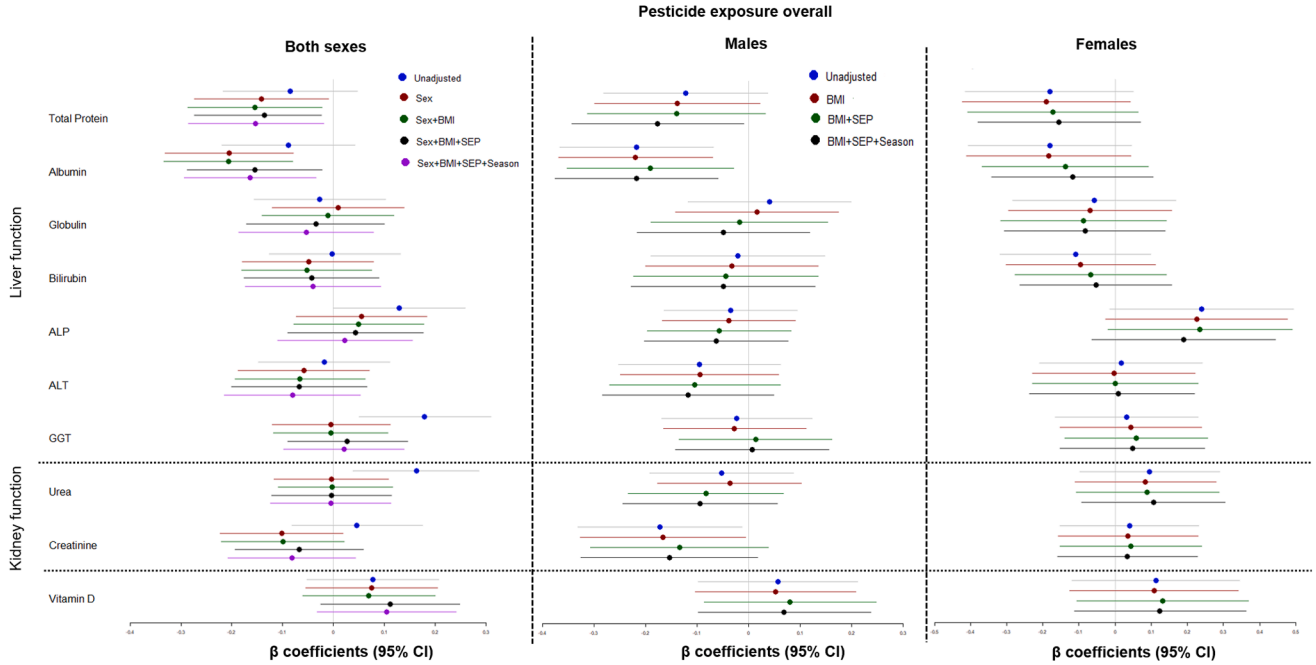

Fig. 3. Multivariable regression analyses of overall pesticide exposure with liver, kidney function profiles and vitamin D and stratified by sex. Multivariable regression analysis of overall pesticide exposure with liver, kidney function profiles and vitamin D (outcome) stratified by sex. The results are expressed as β coefficients (95% CI). Model 1 – unadjusted; model 2 – adjusted for sex; model 3 – adjusted for sex and BMI; model 4 – adjusted for sex + BMI + SEP; model 5 – adjusted for model 4 + season of pesticide use. Stratified by sex: Model 1 – unadjusted; model 2 – adjusted for BMI; model 3 – adjusted for BMI + SEP; model 4 – adjusted for model 3 + season of pesticide use. ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase.

Table 2
Summary results on the associations of overall pesticide exposure, length of pesticide exposure (in months or in years) and specific pesticides with biological markers of health.

Exposure (both sexes)	Males	Females
Overall pesticide exposure (OPE)		
LDL (+)	Total protein (-)	Total cholesterol (+)
LH (+)	Albumin (-)	LDL (+)
Total protein (-)		Haematocrit (+)
Albumin (-)		
Pesticide exposure in months (PEM)		
Exposure (both sexes)	**Males**	**Females**
Total cholesterol (+)	HDL (+)	Total cholesterol (+)
LDL (+)		LDL (+)
MCHC (-)		Haematocrit (+)
LH (+)		MCHC (-)
SHBG (-)		LH (+)
		SHBG (-)
Pesticide exposure in years (PEY)		
Exposure (both sexes)	**Males**	**Females**
Total protein (-)	LH (+)	Total cholesterol (+)
Albumin (-)	Albumin (-)	LDL (+)
		SHBG (+)
		Total protein (-)
		Albumin (-)
Specific pesticides (PEU)		
Exposure (both sexes)	**Males**	**Females**
LDL (+)	MCH (-)	Total cholesterol (+)
RBC (+)	Platelets (+)	LDL (+)
MCH (-)	Total protein (-)	HDL (-)
MCHC (-)		LH (+)
Platelets (+)		
LH (+)		
Total protein (-)		

LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; RBC, total red blood cell; MCH, mean corpuscular haemoglobin; MCHC, MCH concentration; LH, luteinizing hormone; SHBG, sex-hormone binding globulin.

4. Discussion

The present study was conducted to examine the adverse effects of reported non-occupational exposure to pesticides overall and their length of use (in months or in years) and specific pesticides use in relation to biological markers in the Finnish young adults. This is the first study to report on associations of these pesticide exposures with 35 biological markers of health with adjustment for potential confounders BMI, socioeconomic position, and season of pesticide use. In addition, our study analyses were stratified by sex in relation to non-occupational pesticide exposure and health markers.

Our study shows that pesticide exposure is positively associated with TC and LDL in both sexes either measured by OPE, PEM, PEY or PEU. In females, all exposure categories were associated positively with TC and LDL; and PEU in particular was negatively associated with HDL. Free radicals produced by pesticides are suggested to play a role in lipid peroxidation contributing to cardiovascular disease risk (Aminov et al., 2013; Kalender et al., 2010; Prakasam and Sethupathy, 2001). Few experimental investigations have examined the associations of exposure to pesticides and lipid profiles (Aminov et al., 2013; Kalender et al., 2010; Prakasam and Sethupathy, 2001). These studies have reported alterations in TC and lipoprotein fractions in the pesticides exposed group (Garí et al., 2018; Hernández et al., 2006; Kongtip et al., 2020; Remor et al., 2009). In addition, epidemiological studies with occupational pesticides exposure have reported consistent results showing higher concentrations of lipid compounds associated with pesticide handling and application (Mecdad et al., 2011). Furthermore, a reduction in antioxidant defense enzymes and total antioxidant capacity has been found in a study of pesticide-sprayers and oxidative stress enzymes (Fareed et al., 2013; Hassanin et al., 2018; Hu et al., 2015; Piccoli et al., 2019). Finally, our results indicate that whatever the exposure may be, either overall, length and/or specific pesticides use alters the TC and LDL concentrations, suggesting females may be at an elevated risk for metabolic diseases even in conditions of low levels of pesticide exposure.

In the present study, reported specified pesticide exposure (PEU) was

positively associated with RBC, platelet count and negatively with MCH. In addition, years of pesticide exposure (PEY) and specific pesticides used were negatively associated with MCHC. In males, PEU was negatively associated with MCH and positively with platelets. Few epidemiological studies which investigated occupational pesticide exposure in relation to haematological markers have reported minor differences in mean values between controls and cases (Aroonvilairat et al., 2015; Gaikwad et al., 2015; Piccoli et al., 2019). In our study, Hb and HCT values were increased with pesticide exposures. In contrast, MCV, MCH and MCHC values decreased in participants exposed to pesticides compared to non-exposed. Our observations were consistent with a few previous epidemiological studies which reported altered levels of haematological markers; however, the associations were attenuated in the multivariate analyses with adjustment for confounders (Fleming and Timmeny, 1993; Jamil et al., 2005; Ündeğer and Başaran, 2005). Our results point out that participants exposed to longer duration (years) and for some pesticides may have disrupted haematopoiesis. These epidemiological results agree with experimental studies which examined non-persistent pesticides for genotoxicity on human peripheral blood lymphocytes (Aguilar-Garduño et al., 2013; Recio et al., 2005).

In our study, pesticide exposures (PEM, PEY, PEU) were positively associated with LH concentrations. Pesticide exposure in months was negatively associated with SHBG concentrations. These associations of pesticide exposures with reproductive hormones were stronger in males than in females and direction of the associations was similar. A small increase in median values of LH concentrations in the individuals exposed to pesticides was observed. Few previous epidemiological and experimental investigations have reported an increase in LH concentrations in individuals exposed to pesticides (Bretveld et al., 2006). However, the direct effects of pesticides on SHBG have not been reported yet in the general population.

Steroid hormones in the bloodstream are usually bound to carrier proteins such as albumin and SHBG. Free hormones can be biologically active, and this influences the SHBG concentrations in blood (Crisp et al., 1998; Pfaff and Keiner, 1973). Estrogens are suggested to increase SHBG synthesis in liver and thus directly influencing SHBG concentration in the bloodstream which contrasts with androgens in decreasing the concentrations (Bretveld et al., 2006; Vinggaard et al., 2000). Chemicals present in pesticides are considered to possess endocrine disrupting potential *in vitro* and may have the capacity to affect/alter sex hormone levels and or block/activate hormone receptors (Chen et al., 2002; McCarthy et al., 2006; Okubo et al., 2004; Trösken et al., 2004). The pesticides used in the studied population (cypermethrin, deltamethrin, dichlorvos, glyphosate, malathion, permethrin, triadimefon) are suggested to have estrogenic effect (Raun Andersen et al., 2002), weak estrogenic activity (Raun Andersen et al., 2002), weak androgen-receptor antagonist activity (Okubo et al., 2004; Richard et al., 2005; Trösken et al., 2004), disruption/inhibition of the aromatase activity (Richard et al., 2005), preventing the production of estrogens (Cocco, 2002; Ishihara et al., 2003), inhibition of catecholamine secretion (Cocco, 2002; Ishihara et al., 2003), binding to thyroid hormone receptors (Kim et al., 2004; McCarthy et al., 2006) and inhibition of estrogen-sensitive cells proliferation (Okubo et al., 2004; Trösken et al., 2004) thereby influencing sex hormone concentrations.

PEY and PEU were negatively associated with total protein and PEY was negatively associated with albumin (marker) only. OPE in males and PEY in females was negatively associated with total protein and albumin. In males, PEU was negatively associated with total protein and PEY with albumin. These results show alteration of liver function markers with all the exposure categories in both men and women. Total protein is made up of albumin which is synthesized by the liver together with globulin. Albumin has been suggested as a potential biomarker to bio monitor relatively low exposure levels to pesticides (Tarhoni et al., 2008). The level of albumin in the serum is dependent on multitude of factors including nutritional, liver function, urinary and gastrointestinal clearance (Aroonvilairat et al., 2015; Hassanin et al., 2018). Lower albumin levels have importantly been associated with higher risk of ischemic heart disease (Arques, 2018; Ronit et al., 2020). The kidney function indicators (blood urea) and liver function enzymes (AST, ALT) did not differ between the participants and were within normal reference ranges. However, total protein, albumin and globulin levels were lower in participants who reported exposure to pesticides which is in line with previous findings (Hassanin et al., 2018; Mostafalou and Abdollahi, 2013). These results may reflect impairments in protein metabolism as a result of pesticide exposure. In addition, pesticides may alter serum protein concentrations by interference with hepatocytes in impairing protein synthesis and disturbance of kidney function (Johnson et al., 2019; Valcke et al., 2017).

OPE, PEM and PEY were observed to increase GGT and creatinine concentrations. Creatinine, a by-product of cellular functions, is normally filtered from the blood and excreted in the urine. Increased concentrations of creatinine in response to pesticide exposure may indicate impaired glomerular function and kidney damage (Johnson et al., 2019; Valcke et al., 2017). In addition, liver and kidney functions are closely adhered with each other and creatinine increase may result in an increased loss of albumin via the kidney or decreased albumin production by the liver as a result of liver cell damage (Johnson et al., 2019; Valcke et al., 2017).

4.1. Strengths and Limitations

To our knowledge, this is the first study that has explored the exposure to pesticides overall and their length of use and specific pesticides use in relation to comprehensive set of biological markers of health in general adult population of Finland. Further, we investigated and reported gender-specific associations with the pesticide exposures. The data were not accurate enough to analyse actual number of months or years because the length is reported as a use of pesticides for months or years the latter indicating>12 months use. PEU, i.e. reporting the actual product, is used here also for quality control purposes. In addition, PEU strongly correlated with PEM and PEY which shows the reliability of data reporting. In this study, the analyses of pesticide exposure with health markers adjusted for confounders of BMI, socioeconomic position and season of pesticide use. Although, we have included multiple confounders, we cannot rule out that other underlying factors such as a healthier lifestyle among young adults who reported pesticide exposure which may have resulted in unobserved negative confounding, i.e. dilutions of the associations. In addition, we were not able to adjust for factors that link pesticide exposures with activity patterns which may have resulted in further residual confounding.

The design is observational which limits causal inference on the relationship between pesticide exposure and biological markers. We were not able to perform separate statistical analyses for the different groups of pesticides because of the small number of observations. However, we grouped them together as exposure PEU in our study which allowed us to assess the current and cumulative PEU and its effects on multiple biological markers that may have similar mechanistic actions. In addition, the participants may be exposed to multiple pesticides during a lifetime, and multiple pesticides are used during the same season/time. We were able to assess the length of exposure (PEM, PEY) and quantify the interaction of multiple pesticides simultaneously on large number of biological markers of health. The circulating health markers fluctuate over time and this study provides an instantaneous snapshot of the associations between low dose pesticide exposures and comprehensive list of health markers in general population. We should be aware that the measured circulating health markers may not necessarily reflect intercellular processes. However, there is only limited understanding of the complex dynamics underlying relationships between non-occupational pesticide exposure and health markers. This study provides information on how a general population setting could be utilised to examine the associations between pesticide exposure and health markers. In addition, our study participants are young and may

not have been exposed to multiple pesticides by the 31 years and the effects may be more pronounced or decreased with age which could be examined using NFBC data at middle age in the future.

5. Conclusions

The present study reports novel findings in relation to non-occupational pesticide exposure in Finnish young adult population. We report: i) Lipid profile: All the exposures were positively associated with TC and LDL in females, ii) Haematological markers: OPE and PEM were positively associated with haematocrit and PEM negatively with MCHC in females; PEU was positively associated with platelets and negatively with MCH in males; iii) Hormones: PEM was positively associated with LH in males and negatively with SHBG in females, iv) Liver function: OPE was negatively associated with total protein and albumin in males. PEU was negatively associated with total protein and PEY with albumin in males. Overall, this study reports exposure to pesticides to be associated with multiple biological markers of health and the results show differential metabolic effects to exposure to pesticides by sex. The biological markers seem to be indicative of adverse effects of pesticides and warrants for further studies to replicate the findings and determine the underlying mechanisms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

The authors' responsibilities were as follows—SP, KA, JOG, AR, M-RJ: concept and design; SP, M-RJ: data acquisition; SP: statistical analysis; SP, KA, JOG, AR, M-RJ: interpretation of data; SP: drafting of the first version of the manuscript; SP, KA, JR, JOG, JOO, AR, M-RJ: critical revision of the manuscript; and all authors: approved the final version.

Data sharing

Data are available from the Northern Finland Birth Cohort (NFBC) for researchers who meet the criteria for accessing confidential data. Please contact NFBC project centre (NFBCprojectcenter@oulu.fi) and visit the cohort website (www.oulu.fi/nfbc) for more information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106766.

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