Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort

Shu-Li Wang¹,², Ph.D.; Pei-Chien Tsai³, Ph.D., Chiu-Yueh Yang³,⁴, Ph.D., Yueliang Leon Guo*, M.D., Ph.D.

¹Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Miaoli, Taiwan; ²Institute of Environmental Medicine, College of Public Health, China Medical University Hospital, Taichung, Taiwan; ³Department of Basic Medical Sciences, National Cheng-Kung University Medical College, Tainan, Taiwan; ⁴Department of Health Business Administration, Hung-Kuang University, Taichung, Taiwan; ⁵Department of Environmental and Occupational Medicine, National Taiwan University (NTU) College of Medicine and NTU Hospital, Taipei, Taiwan.

Corresponding Author:
Yueliang Leon Guo, MD, PhD
E-mail: leonguo@ntu.edu.tw

Running title: Diabetes and persistent organic pollutants

Received 26 December 2007 and accepted 13 May 2008.
**Objective:** Polychlorinated biphenyls and dibenzofurans (PCBs/PCDFs) are important and persistent organic pollutants (POPs) within humans. Recent cross-sectional studies have detected increased concentrations of serum POPs within diabetic patients. We aimed to examine the association between previous high exposures to PCBs/PCDFs and the cumulative incidence of type 2 diabetes and hypertension.

**Research Design and Methods:** During the late 70s, the consumption of rice-bran oil laced with PCBs poisoned thousands of Taiwanese people. Between 1993 and 2003, we examined 1,054 Yucheng (“oil-disease”) victims against neighborhood references, using a protocol blinded for POP exposure. Here we report the results derived from 378 Yucheng subjects and 370 matched references.

**Results:** The diabetic risk to members of the Yucheng cohort relative to their references was significantly increased for women (Odds Ratio=2.1, 1.1-4.5) but not for men, after the considerations of age, body mass index, cigarette smoking and alcohol intake. Yucheng women diagnosed with chloracne had an adjusted OR of 5.5 (95% C.I.: 2.3-13.4) for diabetes and 3.5 (1.7-7.2) for hypertension, as compared to those who were chloracne free.

**Conclusions:** Yucheng women, who had endured previous exposure to PCBs/PCDFs, suffered from increased incidences of diabetes, particularly for those who had retained significant levels of the pollutant, as evident from chloracne. When planning treatments against diabetes, the body burden of PCBs and dioxins should be carefully considered, especially for women.
Type 2 diabetes is becoming more prevalent throughout the world, and although a number of conventional risk factors have already been identified, they can only partly explain such high levels of incidence. Polychlorinated biphenyls (PCBs) and dioxins are persistent organic pollutants (POPs) with long half-lives in the human body, and may act as endocrine disruptors and exhibit endocrine system effects (1). The study of veterans of Operation Ranch Hand reported a higher dioxin level in diabetic patients compared to non-diabetic subjects (2). Longnecker et al. revealed a 30% higher level of total PCBs in diabetic (primarily type 1) pregnant women over non-diabetic subjects recruited in 1959–66 (3). Similar conclusions were drawn from other population studies in Belgium (4), from the National Health and Nutrition Examination Survey (NHANES) (5), in Michigan (6), and in Seveso, Italy (7). These data raised great concerns for public health (8), and promoted etiological research into the biological effects of POPs (9, 10). Recently, the NHANES study in the US threw up striking dose-response relationships between the prevalence of diabetes and serum levels of 6 POPs, including PCB 153, dioxins, and organochlorine pesticides (OCPs) (11). Interestingly, severe obesity (BMI ≥ 30 kg/m²) did not relate to an increased diabetic risk in those with undetectable levels of POPs. The cross-sectional study findings warrant a follow-up cohort study to assess the long-term effects of POPs upon the risk of developing diabetes and hypertension.

A mass poisoning occurred in central Taiwan after a quantity of rice-bran oil was ingested in 1978-1979 that was later found to be contaminated with PCBs and their heat-degraded byproducts (12). By the end of February 1983, there were 2,061 recorded cases of PCBs poisoning, based on the symptoms and pathology of the illness, such as abnormally high levels of blood PCBs. The Yucheng (means “oil disease”) cohort was estimated to have consumed an average of 1g (range: 0.77-1.84 g) of PCBs, and 3.8 mg of PCDFs during an average of nine months exposure to the contaminated oil. Most (83%) of the blood levels ranged from 11 to 150 ppb. The current 24-year follow-up study of the Yucheng cohort provides a good opportunity to examine the hypothesis that raised levels of PCBs/DFs might be associated with an increased risk to diabetes. Though obese people have been encouraged to reduce body weight by calorie restriction, serum levels of total PCBs increased in the 6-9 months following the weight loss program (13). Studying the effects of POPs upon the degree of risk to type 2 diabetes is clearly relevant to managing both diabetes and obesity in modern societies.

MATERIALS AND METHODS
Subjects: Beginning in 1992 and using the addresses listed for the 2,061 victims in the Yucheng registry obtained from the Taiwan Provincial Department of Health, we attempted to locate each subject’s record. Out of these, the addresses were wrong for 154 records, which prevented us from tracing those people, and a further 70 records had to be excluded because they belonged to the children of this Yucheng cohort (Figure 1). A total of 83 subjects were deceased (8%), 668 were less than 30 years of age (66%) and 32 had a remote address (3%). Individuals for the background exposed groups were recruited in 1992 and were matched against the subjects in terms of neighborhood (being the same as back in 1979), for gender, for age (no more than 3 years different) and for exposure to POPs, such that none of the control individuals were in the original registration cohort (14). Between 1993 and 2003, we conducted a morbidity follow-up of the exposed subjects and their reference group with trained interviewers blinded to
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exposure status. Medical information on individuals who had been diagnosed or treated by certified medical doctors was acquired by telephone. The current study focused on individuals born before January 1, 1963, to examine the association between the cumulative incidence of type 2 diabetes and postnatal exposure to PCBs/PCDFs. We excluded 38 Yucheng subjects and 46 from their reference groups who were missing data on BMI or cigarette smoking, which are important risk factors for type 2 diabetes and hypertension, respectively. After all exclusions, 378 Yucheng subjects and 370 matched references remained for analysis within the current study. We focused on those over the age of 30 in the current study because type 2 diabetes is a chronic disease prevalent in the middle aged population, and also to prevent including subjects who could have had prenatal exposure to PCBs/PCDFs. Among the 668 subjects less than 30 years of age, there are 90 with a matched reference that could be successfully followed for a separate analysis. However, within this younger group there were no diabetic subject and just one hypertensive patient. We therefore omitted them from our current analysis.

Body burden of dioxins and polychlorinated biphenyls (PCBs): Total PCBs levels were quantitated from serum samples originally collected by the Taiwan Provincial Department of Health in 1979-83 (12). These serum samples ranged from 0.7g to 8.2g in amount (average 4.5g) and were kept frozen at –20°C prior to analysis. Except for initial analyses carried out in Tokyo, all PCBs levels were analysed by the Food and Drug Bureau of the Department of Health Executive, Yuan, Taiwan. A Microtek 200 gas chromatography (GC) system was fitted with an electron capture detector (Ni$^{63}$-ECD) and a glass column (3mm x 2mm) packed with Chromosorb WHP (80/100 mesh) coated with 3% OV-1. The temperatures of the inlet, column, and detector were maintained at 230°C, 200°C, and 280°C, respectively. The Webb-McCall method was adopted to quantify PCBs, with Kanechlor 500 used as a reference standard (15). For the background exposed reference group, serum pooled from 50 subjects was analyzed using a high resolution gas chromatography-high resolution mass spectrometry (HRGC/HRMS) method. Although we studied congener-specific profiles of PCBs/PCDFs in 1994 (16), we utilized information on total PCBs levels measured at the time of the episode for the respective dosages that related to the cumulative incidence of disease.

Statistical methods: Student t, or Mann-Whitney if not normally distributed, and Chi-square tests were used to compare continuous and categorical variables between the exposed and reference groups. A univariate logistic regression model was utilized to calculate odds ratios (ORs) for diabetes prevalence among the exposed, relative to reference subjects, and multivariable logistic regression to evaluate the ORs with adjustments for potential confounding factors. For women we did not carry out further adjustments for cigarette smoking (with only 3 smokers) and alcohol intake (with only 5 drinkers) for deriving a reliable model. We used JMP 5.0.1 software for all the analyses (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows very similar distributions in age, gender, body mass index (BMI), education, life style, and occupation between the Yucheng cohort and the background exposed reference group. Mean PCBs in the Yucheng subjects were about 40–50 fold of those of the reference group. Men appeared to be older than women by around 7 years. We suspected that men less than the age of 35 were too busy working to get registered for special care in 1979-80.
The Yucheng subjects experienced a very high risk of developing chloracne, as compared to the reference group (Table 2). The AOR of diabetes for the Yucheng cohort relative to the reference group remained significant in women (OR=2.1, p<0.05) after adjusting for age and BMI. We found an age-adjusted OR of 6.4 (p<0.05) in women over 65 years of age with diabetes therapy, which rose to 6.6 (p<0.05) after further adjustment for BMI. For both genders there was a slight but non-significant increase in the risk of developing hypertension and cardiovascular disease. We compared the rate at which diabetes developed in subjects that exhibited chloracne with the diabetic rate in subjects who were free of chloracne, and found a highly significant age-adjusted OR of 4.6 (95% C.I.: 1.9-11.4), and AOR of 5.5 (2.3-13.4) in women but not in men (Table 3). The same pattern was found for hypertension (AOR=3.5, 1.7-7.2) and cardiovascular disease (3.0, 1.5-8.6).

DISCUSSION

We found that diabetes was twice as prevalent in Yucheng women who had been exposed to PCBs/PCDFs during the 78-79 poisoning as compared to the reference population in the long-term cohort study. The AOR significantly increased to 2.5 for those requiring therapy for diabetes and to 5.5 for those with chloracne, a condition that is symptomatic for POP poisoning. This correlation between POPs and diabetes is consistent with the findings from cross-sectional studies in Belgium (4) and in the USA (2, 5, 11, 17). In the current study, most excess body burdens of PCBs/PCDFs took place in women with an average age of 25 years, when type 2 diabetes has most likely had yet occurred. The cumulative incidence associated with PCBs/DFs exposure provides the temporality for the exposure having happened prior to the onset of diabetes. However, caution should be exercised in interpreting the data because members of the Yucheng cohort group were accidentally exposed to PCBs/PCDFs for near one year from a diet of contaminated oil. These results might not apply to the background population and further investigations are needed to control for the effects of different PCBs derived from sources other than the 78-79 poisoning. A recent report using the NHANES data showed significant association between non-dioxin-like PCBs and increased risk of insulin resistance in non-diabetic subjects, particularly for those with a larger waist circumference (18). For those in the upper quartile of PCB 170 compared to the non-detectable reference group, the OR increased to 4.1 (p<0.01). In the Yucheng cohort, a total of 33 PCB congener profiles showed that PCB 170 constituted 13 % of all PCB concentrations (16). In addition to PCB 170, PCB 180 (occupied 14% of 33 PCBs), PCB 153 (13%), and PCB 156 (13%) each represented over 12% of the total PCBs. This implies that certain PCB congeners might be associated with an increased risk of diabetes occurrence.

We further report that Yucheng women diagnosed with chloracne have a significantly increased risk of developing hypertension and cardiovascular disease. This increased risk to hypertension may partly result from diabetic complications during cardiovascular disease. Prevalence of increased blood pressure was most strongly correlated with PCDFs, particularly for 1,2,3,4,7,8 HxCDF in non-diabetic subjects in the NHANES study (22). This corresponded to the Yucheng cohort in which 1,2,3,4,7,8-HxCDF (Toxic Equivalent Factor=0.1) and 2,3,4,7,8-PCDF (TEF=0.5) were important congeners, contributing around 20% and 50% of the total dioxins TEQs, respectively (16). This implicates that congeners that contain PCDF or PCDD (dibenzo-dioxins) might be associated with an increased risk towards hypertension.
The current study showed a non-significant association between PCBs/DFs exposure and type 2 diabetes occurrence in men, which is not consistent with previous cross-sectional studies (11, 17). In the Michigan follow-up study of the effects of exposing farming and other households to animal feed contaminated with PCBs, women experienced twice the incidence of self-reported type 2 diabetes when total PCBs exceeded 5 ppb, but there was no increased diabetic risk for men (6). The 20-year follow-up study of the Seveso cohort, highly exposed to TCDD after a factory incident in 1976 in Italy (7), showed that the mortality rate from diabetes had significantly doubled for women residing in the exposure area compared to the reference area; but not for men. It is notable that cigarette-smoking was much more prevalent in the men involved in both our study and in the Michigan study, compared to the women who were investigated. Cigarette smoking has been found to activate the aryl-hydrocarbon receptor (AhR) (19), which might be associated with the accelerated excretion of PCBs. Our study also showed slightly lower mean PCB/PCDF levels in men than in women. Further, women tend to have a greater fat percentage than men, which might result in a longer half-life of these lipophilic compounds. Obesity as a risk factor for diabetes might be attributable partly to the lipophilic compounds’ storage in white adipose tissue (1). Fat tissue was suggested to be a vehicle for increased diabetes risk (8). Women could also be more vulnerable to PCBs/PCDFs exposure due to higher estrogen levels than men. PCDFs, and some PCBs, can induce CYP1A1 and CYP1B1 gene expression by serving as AhR agonists (19). CYP1A1 and CYP1B1 catalyze hydroxylation of the A-ring of estradiol (E2) to form the catechol estrogen 2- or 4-hydroxyestradiol (2-OH-E2 or 4-OH-E2, respectively) that may be altered by exposure to dioxins (20). The metabolism of 4-OH-E2 via redox active compounds generates free radicals, such as reactive semiquinone intermediates. Free radicals are known to cause increased oxidative stress, which has been associated with a range of vascular pathologies, including hypertension and diabetes (21). Further investigations into identifying and dissecting the various POP detoxification pathways are clearly warranted.

Dioxin-like chemicals relating to diabetes may involve an estrogen dependent Peroxisome Proliferation-Activated Receptor (PPAR) pathway (23). Tetra-chlorinated dibenzo-p-dioxin (TCDD) co-treating estrogens were found to up-regulate Insulin-like Growth Factor Binding Protein-1 (IGFBP-1) in MCF-7 cells by the PPAR pathway (24). These compounds may counter the effects of insulin which down-regulates IGFBP-1. Dioxins or dioxin-like chemicals may therefore disrupt glucose homeostasis.

A hypertriglyceremia state, often coexisting with hyper-triglycerides, might be related to delayed degradation and/or excretion of the lipophilic compounds in diabetic patients. In addition, metabolism of PCBs/DFs related genes, such as cytochrome, CYP1A, CYP1B, and P450 11B (19, 20), may relate to the development of chloracne, and later chronic conditions of hyperglycemia and hypertension. Further study of these genetic polymorphisms related to the effect of susceptibility is suggested.

There might be confounding factors, such as organochlorine pesticides (OCPs) (18), which are often correlated with PCBs/DFs because of a similar exposure route in humans. Nonetheless, levels of DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) were slightly lower in Yucheng women (6,380 ppb, SD=620) as compared to their neighborhood reference (8,700 in pooled serum samples, personal communication with Professor Yueliang Leon Guo). Potential confounding effects from OCPs are therefore unlikely.
The effects of ageing could have influenced this 24-year follow-up study, since members of the exposure group would be expected to die sooner from diabetes and/or cardiovascular disease. This influence might be slight, as we found only one man and six women died form diabetes among all registered Yucheng subjects (25). Besides, the women appeared to be younger than the men by around 7 years. One possibility would be to select a group of younger women; this might reduce the statistical power in women because diabetes and hypertension are generally less prevalent in the younger age group. Nonetheless, we have established the increased risk for women instead of men and thus it is unlikely to have a biased conclusion.

The present study did not include other disease-related lifestyle features, such as exercise and total calorie intake, which might relate to differences in personal socio-economic status and an altered risk to diabetes. We utilized neighborhood reference as a background exposure group. Furthermore, BMI, education, and occupational distribution were similar between the exposed and reference groups. A previous study showed that lipid contents were similar between the two groups (16). We would expect the same conclusion, once differences in lipids, exercise, and total calorie intake have been adjusted for.

In conclusion, an increased cumulative incidence of type 2 diabetes was associated with Yucheng women who had been exposed to PCBs/PCDFs, particularly among those diagnosed with chloracne. In modern societies, the body burden of PCBs and dioxins clearly need to be considered within the framework of diabetes prevention. The effects of female gender and genetic factors warrant further investigations.

ACKNOWLEDGEMENT

This study is partially supported by the National Taiwan University Hospital Research Grant, and partially supported by the National Science Council grant #96-2314-B-002-100-MY2.
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Figure Legends

Figure 1. Numbers of the Yucheng cohort and their matched reference group during 1979-2003

1979 Yucheng registration (n=2,061)
- Wrong or incomplete address (n=154)
- Children born after episode (n=70)
- Died (n=83)
- Aged < 30 years (n=668)
- Remote address (n=32)

Study in 1993; Age ≥ 30 (n=1,054)
- Matched by age, sex

1790 Yucheng registration (n=1,054)
- Neighborhood Ref. (n=1,045)

Phone interview attempted (n=774)
- Untraceable, incl. deceased in 1993-2003
- Interview refused or unsuccessful

Phone interview attempted (n=843)
- Interview successful (n=457; 54.26%)

Interview successful (n=95; 64.06%)
- Re-match Yucheng and ref. groups (by age < 3 and sex)
- Type 2 diabetes occurrence (n=416; 68 men; 247 women)

Type 2 diabetes occurrence (n=38)
- Missing data on BMI or cigarette smoking

Type 2 diabetes occurrence (n=370)
- 152 men; 218 women
Table 1. General characteristics of the Yucheng cohort and their matched reference group aged ≥ 30 years in 1993

| Characteristics | Men | | | | Women | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|
|                 | Yucheng (n=155) | Ref. group (n=152) | p | Yucheng (n=223) | Ref. group (n=218) | p |
| Age in 2003 (years, ±SD) | | | | | | |
| <55             | 62 (40.0) | 63 (41.5) | ns | 155 (69.5) | 158 (72.5) | ns |
| 55-64           | 37 (23.9) | 40 (26.3) | ns | 29 (13.0) | 26 (11.9) | ns |
| ≥65             | 56 (36.1) | 49 (32.2) | ns | 39 (17.5) | 34 (16.5) | ns |
| BMI (kg/m^2)    | 24.1±3.1 | 24.0±3.1 | ns | 24.3±8.5 | 23.5±3.4 | ns |
| Education (years) | 7.2±4.1 | 7.2±3.7 | ns | 6.6±4.1 | 7.3±4.2 | ns |
| Current smoker (%) | 85 (55.2) | 93 (62.0) | ns | 2 (0.9) | 1 (0.5) | ns |
| Alcohol Drinking (%) | 41 (26.8) | 34 (22.8) | ns | 4 (1.8) | 1 (0.5) | ns |
| Occupation (%)   | | | | | | |
| None            | 70 (45.2) | 59 (38.8) | ns | 111 (49.8) | 92 (42.2) | ns |
| Government      | 6 (3.9) | 4 (2.6) | ns | 7 (3.1) | 8 (3.7) | ns |
| Agriculture     | 12 (7.7) | 13 (15.1) | ns | 5 (2.2) | 6 (2.8) | ns |
| Manufacturing   | 54 (34.8) | 53 (34.9) | ns | 69 (30.9) | 75 (34.4) | ns |
| Commercial      | 13 (8.4) | 13 (8.6) | ns | 31 (13.9) | 37 (17.0) | ns |
| Serum PCBs (ppb)| 73.3±86.3 | 1.67 * | -- | 87.4±151.0 | 1.67 * | -- |

* General population had mean serum PCB levels of 1.67 ppb wet weight as previously reported using pooled sample from 50 reference subjects (16)
Table 2. Prevalence (%) of reported diseases ever diagnosed by a physician in Yucheng and reference groups by gender in Taiwan in 1979-2003

| Disease     | Men                  | Women                 |
|-------------|----------------------|-----------------------|
|             | Yucheng (n=155)     | Ref. group (n=152)   | Yucheng (n=223) | Ref. group (n=218) | OR* (95% CI) | AOR†   | OR* (95% CI) | AOR† |
| Chloracne   | 66 (42.9)            | 1 (0.7)               | 117.0§ (25.1-2087) | 111.5§ (23.9-1985) | 51 (23.0) | 0 (0.0) | -            | -    |
|             | 25 (11.3)            | 12 (5.6)              | 2.2‡ (1.1-4.7)     | 2.1‡ (1.1-4.5)     |             |        |             |      |
| Type 2 Diabetes | 22 (14.4)        | 22 (14.7)             | 1.0 (0.5-1.8)      | 1.0 (0.5-1.9)      | 17 (7.7)  | 7 (4.5) | 1.0 (0.3-3.1) | 1.0 (0.3-3.1) |
| <55         | 3 (4.8)              | 7 (11.3)              | 0.4 (0.1-1.5)      | 0.5 (0.1-1.9)      | 7 (4.6)   | 7 (4.5) | 1.0 (0.3-3.1) | 1.0 (0.3-3.1) |
| 55-64       | 9 (25.0)             | 5 (12.5)              | 2.3 (0.7-8.3)      | 3.7 (0.9-17.6)     | 6 (20.7)  | 0 (0.0) | -            | -    |
| ≥65         | 10 (18.2)            | 10 (20.8)             | 0.8 (0.3-2.2)      | 0.8 (0.3-2.3)      | 12 (30.8) | 5 (14.7) | 2.6 (0.8-9.1) | 2.6 (0.9-9.3) |
| -on therapy | 22 (14.3)            | 17 (11.3)             | 1.3 (0.6-2.6)      | 1.3 (0.7-2.7)      | 17 (7.7)  | 7 (3.2) | 2.5 (1.0-6.7) | 2.5‡ (1.0-6.5) |
| <55         | 3 (4.8)              | 3 (4.8)               | 1.0 (0.2-5.7)      | 1.3 (0.2-7.5)      | 3 (2.0)   | 5 (3.2) | 0.6 (0.1-2.5) | 0.6 (0.1-2.5) |
| 55-64       | 9 (25.0)             | 5 (12.5)              | 2.3 (0.7-8.3)      | 3.7 (0.9-17.7)     | 3 (10.3)  | 0 (0.0) | -            | -    |
| ≥65         | 10 (17.9)            | 9 (18.8)              | 0.9 (0.3-2.5)      | 0.9 (0.3-2.6)      | 11 (28.2) | 2 (5.9) | 6.4‡ (1.5-43.9) | 6.6‡ (1.6-45.4) |
| Hypertension| 46 (30.0)            | 39 (26.0)             | 1.2 (0.7-2.0)      | 1.2 (0.7-2.0)      | 41 (18.5) | 31 (14.4) | 1.3 (0.8-2.3) | 1.3 (0.8-2.2) |
| -on therapy | 40 (26.0)            | 31 (20.7)             | 1.3 (0.7-2.4)      | 1.3 (0.8-2.4)      | 29 (13.1) | 21 (9.7) | 1.4 (0.7-2.7) | 1.4 (0.8-2.5) |
| CVD         | 22 (14.2)            | 17 (11.2)             | 1.3 (0.6-2.6)      | 1.3 (0.7-2.6)      | 30 (11.6) | 21 (9.6) | 1.4 (0.8-2.6) | 1.5 (0.8-2.7) |

*OR: age adjusted odds ratio. †AOR: Adjusted for age and BMI in women, and further adjusted for cigarette smoking and alcohol drinking in men. ‡: p <0.05, §: p <0.001
Table 3. Lifetime prevalence of medical conditions (%) in Yucheng individuals without (-) or with (+) reported chloracne aged ≥ 30 years by gender in 2003

| Conditions | Men | | | | Women | | | |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|
|            | Negative (n=95) | Positive (n=72) | p | OR* (95% CI) | AOR† | Negative (n=186) | Positive (n=58) | p | OR* (95% CI) | AOR† |
| Age (mean ± SD) | 61.6±11.6 | 58.7±11.5 | 0.2 | - | - | 52.3±11.4 | 56.9±9.7 | 0.006 | - | - |
| BMI (mean ± SD) | 24.2±3.0 | 24.2±3.2 | 1.0 | - | - | 24.2±9.5 | 24.6±3.3 | 0.7 | - | - |
| Diabetes (%) | 11 (11.6) | 12 (16.9) | 0.2 | 1.7 (0.7-4.3) | 1.7 (0.7-4.6) | 11 (5.9) | 14 (24.1) | 0.0006 | 4.6§ (1.9-11.4) | 5.5 § (2.3-13.4) |
| Hypertension (%) | 34 (35.8) | 19 (26.4) | 0.1 | 0.7 (0.4-1.5) | 0.6 (0.3-1.1) | 27 (14.4) | 22 (37.9) | 0.0009 | 3.3 § (1.6-6.8) | 3.5 § (1.7-7.2) |
| CVD (%) | 14 (14.7) | 12 (16.7) | 0.8 | 1.3 (0.6-3.2) | 0.9 (0.4-2.2) | 22 (11.8) | 15 (25.9) | 0.0035 | 2.3 § (1.1-4.8) | 3.0 § (1.5-8.6) |
| PCBs (ppb) (mean±SD) | 53.9±53.2 | 94.4±106.9 | 0.004 | - | - | 72.6±114.7 | 121.4±202.8 | 0.04 | - | - |

*OR: age adjusted odds ratio. †AOR: Adjusted for age and BMI in women, and further adjusted for cigarette smoking and alcohol drinking in men.

‡: p<0.05, §: p<0.001