Body Mass Index and Serum 1,1,1-Trichloro-2,2-Bis(*p*-Chlorophenyl)Ethane in Nulliparous Chinese Women

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Abstract

Background: Basic health indicators, such as body mass index (BMI), have been associated with serum 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane/1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDT/DDE) levels; however, both positive and inverse associations of BMI with serum DDT/DDE have been reported. Given the association of BMI with a number of outcomes, it may confound studies of DDT/DDE-associated health effects. We investigated the relationship of BMI with serum DDT/DDE accounting for other determinants of exposure among women with relatively recent environmental exposures to DDT.

Methods: Serum DDT/DDE was analyzed in 466 nonsmoking, nulliparous women recruited from Anhui province in China between 1996 and 1998 as part of a reproductive health study of textile workers. The women in the sample were born between 1963 and 1977, 8 to 21 years before China's 1984 DDT ban. We used multivariate linear regression to investigate associations of BMI, age, and birth year with serum DDT/DDE.

Results: Mean (SD) serum total DDT concentration was 32 ng/g (17.8 ng/g). Birth year showed an inverse relationship with serum DDT independent of age. Despite limited variability in BMI, there was a consistent inverse relationship between BMI and serum DDT. Specifically, each kg/m^2 increase in BMI was associated with a -1.34 ng/g (95% confidence interval, -2.12 to -0.56 ng/g) decrease in serum total DDT.

Conclusions: There were high total DDT levels in this sample of nulliparous Chinese women relative to Western populations, birth year was more strongly associated with serum DDT than age, and BMI was inversely related to serum DDT in this study. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2433–8)

Introduction

The adverse health consequences of exposure to 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and its primary metabolite, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), remain an important public health concern for several reasons. DDT/DDE are suspected human reproductive toxicants (1) and probable human carcinogens (2). Due to concerns about the potential harmful effects on humans and animals, the Environmental Protection Agency banned the use of DDT in 1972 except in cases of public health emergencies (3). However, because of their chemical stability, lipophilic nature, and propensity to bioaccumulate, DDT/DDE remain ubiquitous contaminants in food, human adipose tissue, and human breast milk (4). Furthermore, DDT is still used today in many countries where malaria is a public health problem (5). For example, 23 countries in Africa, Asia, and Latin America currently use DDT to control disease-carrying insects (6). China banned agricultural use of DDT in 1984, but use of DDT for malaria control continued in some regions after the ban (7). Consistent with this usage history, populations in Africa, Asia, and Latin America generally have higher tissue DDT/DDE levels than in Europe and the United States (8).

Due to its high lipid affinity, DDT is stored in fatty tissues, including most organs (3). DDT enters the circulatory system, is transported via the lipid component in plasma, and can be measured in serum (6). Serum DDT is on average 100 times lower than levels in adipose tissue, and these levels are strongly correlated with each other (9). Serum DDT/DDE levels are commonly used biomarkers of exposure in epidemiologic studies evaluating DDT/DDE health effects (10). Except for a positive correlation with age (11, 12) and regional variability (8), consistent determinants of serum DDT/DDE levels are not well established.

Although diet is a common source of DDT exposure for nonoccupationally exposed populations, specific dietary correlates of DDT/DDE have not been consistently shown (11, 13). Most notably, basic health indicators, such as body mass index (BMI) and weight change, have been variously associated with serum DDT/DDE levels. Given the potential association of such factors with disease, their potential to confound studies of DDT/DDE health effects must be considered.

It is recognized that given a one-time exposure to DDT/DDE of the same magnitude, serum DDT/DDE can vary considerably among individuals due to multiple factors, including variability in metabolism, timing of sample collection relative to exposure, and BMI (14). Metabolism studies investigating weight changes have observed that DDT/DDE concentrations increase in plasma, adipose, liver, heart, brain, or muscle after food restriction in animals previously fed diets containing organochlorines (15). Increases in plasma and adipose tissue organochlorine concentrations have been observed after body weight loss in obese patients (16).

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Epidemiologic studies investigating DDT stores and body weight independent of pregnancy have reported mixed findings. Three U.S. studies (17-19) and one Swedish study (12) have reported a positive association between p,p'-DDE concentrations and BMI, whereas three other U.S. studies (11, 20, 21) have not found an association. The apparent inconsistencies in the observed cross-sectional association of BMI with DDT may, in part, be a function of exposure kinetics. For example, Wolff and Anderson (14) have proposed a model showing that the BMI/organocholorine relationship is dependent on how recent exposure has been and the distribution of BMI in the population. This model predicts that for recent exposures, pharmacodynamic equilibrium results in low BMI being associated with high organochlorine levels. Because excretion rate is inversely proportional to BMI, the Wolff and Anderson model stipulates that eventually this relationship will reverse (14).

We explored these associations further in a high DDT/DDE exposure sample of women of childbearing age from China, where DDT/DDE use declined only recently after the agricultural ban in 1984. Specifically, we studied the association of serum DDT/DDE with BMI in a cohort of nulliparous female textile workers for whom potential reproductive health effects of DDT/DDE are being studied. We hypothesized that age would be positively associated with serum DDT/DDE. We also hypothesized that DDT/DDE exposures were recent and this would be evidenced by serum DDT being higher among low BMI women.

Materials and Methods

Study Population. The study population was drawn from participants in a prospective study of reproductive health conducted from 1996 to 1998 among 961 female textile workers in Anhui, China. The women in this parent study were born between 1963 and 1977, 7 to 21 years before agricultural use of DDT was officially banned in China in 1984. The study protocols were approved by the Human Subjects Committee of the affiliated Chinese institutions and by the Institutional Review Boards of the Harvard School of Public Health and the Children's Memorial Hospital. All women provided written informed consent.

Detailed descriptions of the parent study population and data collection methods have been reported previously (22). Briefly, the eligibility criteria for enrollment were as follows: (*a*) full-time employment; (*b*) ages 20 to 34 years; (*c*) newly

married; and (*d*) had obtained state permission to have a child. All of the women were nulliparous. At baseline, each subject completed a physical exam that included measures of weight and height, provided a blood sample, and completed an interview eliciting demographic and lifestyle information. The follow-up portion of the parent study involved providing daily diaries and urine samples to ascertain conception, clinical pregnancy, and pregnancy outcomes. The parent study follow-up was conducted for 12 months or until a pregnancy was clinically confirmed, whichever came first. A total of 961 were enrolled at baseline and 567 completed the follow-up. Baseline serum DDT was measured among women who completed the follow-up portion of the study. One hundred and one women did not have sufficient archived serum available for DDT analysis. This report includes the 466 women who completed the baseline interview and who had serum DDT data available. Demographic and exposure characteristics were compared between the 466 who completed the follow-up and had baseline serum DDT data available and the 495 who either did not complete the follow-up or who did not have DDT data available. Results showed there were no significant differences between the 466 who completed follow-up and the 495 who enrolled at baseline but were not included in our study.

Laboratory Assays. At baseline, each subject provided a nonfasting blood sample. Serum fractions were removed by centrifugation and stored frozen at $-20°C$ until extraction. All serum samples were analyzed by the Harvard School of Public Health Organic Chemistry Laboratory (Boston, MA) for p,p'- and o,p'-isomers of DDT, DDE, and DDD. Total DDT was calculated as the sum of p,p'-DDE, o,p'-DDE, p,p'-DDT, o,p'-DDT, and p,p'-DDD. Full details of the analytic methods and quality control procedures used by our laboratory are reported elsewhere (23). Briefly, primary analyses of serum extracts used gas chromatography with electron capture detection with confirmatory analyses of all samples using a capillary column of different polarity. Quantitation was based on the response factor of each analyte relative to an internal standard. Final concentrations were reported in nanograms of analyte per gram of serum after subtracting the amount of analyte measured in the procedural blank. There was not a sufficient quantity of serum to measure lipids. Among the DDT isomers and metabolites that were measured in this study, p,p'-DDE had the highest concentration and, on average, accounted for 92% of the mass of the DDT isomers and metabolites measured in serum (range 76-98%). p,p'-DDT had the second highest concentration and, on average, accounted for 6% of the mass

Table 1. Characteristics by serum total DDT of the sample of nonsmoking, nulliparous women in Anhui, China, 1996 to 1998

	Serum total DDT				
	Quartile				
	1st	2nd	3rd	4th	Total
Sample size	116	117	117	116	466
Serum total DDT (ng/g)					
Mean (SD)	13.5 (3.6)	23.5 (2.5)	34.0 (4.0)	57.1 (13.9)	32.0 (17.8)
Median	13.9	23.4	33.1	54.0	27.8
Range	5.5-19.2	19.2-27.8	27.8-41.2	41.6-113.3	5.5-113.3
Birth year					
Range	1970-1977	1968-1976	1966-1976	1963-1976	1963-1977
Median	1974	1973	1973	1972	1973
	Mean (SD)				
Age (y), $n = 465$	24.5 (1.3)	24.8 (1.5)	25.0 (1.5)	25.3 (1.9)	24.9 (1.6)
Height (cm), $n = 462$	157.6 (4.6)	157.8 (5.3)	157.4 (5.0)	157.5 (5.4)	157.6 (5.1)
Weight (kg), $n = 462$	50.1 (5.6)	49.2 (5.3)	49.8 (6.2)	47.8 (5.4)	49.2 (5.7)
BMI (kg/m^2), $n = 462$	20.1 (1.9)	19.8 (1.9)	20.1 (2.1)	19.3 (1.8)	19.8 (2.0)

(range 2-19%). Summed together, p,p'-DDE and p,p'-DDT accounted, on average, for 98% of the mass of the DDT isomers and metabolites measured in serum (range 93-100%).

Statistical Methods. The major focus of our analysis was to investigate the relation of BMI with serum DDT/DDE accounting for age and potential temporal trends in exposure expressed as birth year. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meters (m) squared (kg/m^2). Because p,p'-DDE and p,p'-DDT accounted, on average, for 98% of the mass of the DDT isomers and metabolites measured in serum (range 93-100%) and were highly correlated (Pearson correlation coefficient = 0.63), we conducted our analyses using total DDT, calculated as the sum of p,p'-DDE, o,p'-DDE, p,p'-DDT, o,p'-DDT, and p,p'-DDD. We conducted our analyses modeling total serum DDT and p,p'-DDE individually both as continuous variables and in quartiles. We used crude and adjusted linear regression models to estimate the association between BMI, age, birth year (by quartiles), and serum total DDT or p,p'-DDE. We investigated second-order models using BMI squared and age squared to explore nonlinear associations. We investigated potential interactions between birth year quartiles and BMI in relation to serum total DDT or p,p'-DDE by regression models, plots, and graphs. Because the findings were very similar for total DDT and p,p'-DDE, we only present the data for total DDT in this report. Twelve of the women had BMI >24, and upon seeing no differences in results after excluding them, we graphically present BMI, DDT, and birth year data only for lean women with BMI <24.

Results

Table 1 shows characteristics of the subjects in each quartile of serum DDT. The population was composed of generally young (mean age = 24.9 years) and lean (mean BMI = 19.8 kg/m^2) reproductive aged women. Mean serum total DDT concentration was 32.0 ng/g (SD = 17.8 ng/g). Despite a relatively narrow age range (21-34 years), increasing age was associated with higher serum total DDT levels. Subjects in each serum total DDT quartile had similar heights, but higher serum DDT was associated with lower weight and BMI despite limited variability in these measures.

Figure 1 compares the mean and SE of serum p,p'-DDT, p,p'-DDE, and total DDT by the birth date quartiles. It shows (a) a relatively high level of serum total DDT and p,p'-DDE compared with those reported in contemporaneous Western populations; (b) p,p'-DDE as the predominant form of serum total stores; (c) a detectable but low level of p,p'-DDT across the four birth date quartiles; and (d) a decrease in all forms of DDT with later birth year. Furthermore, the ratio of p,p'-DDT to p,p'-DDE did not vary by birth year quartile. By way of serum concentration comparisons, mean p,p'-DDE in this study was 5,940 ng/g lipid (estimated, assuming 0.5% lipid) versus 270 ng/g lipid in 1,027 U.S. women ages ≥12, measured between 1999 and 2000 (24).

Table 2 shows crude and adjusted linear regression β estimates of BMI, age, and birth year by serum total DDT. BMI was inversely associated with serum total DDT independent of adjustment for age or birth year. Specifically, each kg/m^2 increase in BMI was associated with a −1.34 ng/g [95% confidence interval (95% CI), −2.12 to −0.56 ng/g] decrease in serum total DDT after multivariate adjustment. In the unadjusted model, age was positively associated with DDT levels with each year of age associated with 2.51 ng/g higher serum total DDT (95% CI, 1.51-3.51 ng/g). However, in the model that adjusted for birth year, age was no longer significantly associated with serum total DDT. Each year of older age was associated with only 0.08 ng/g higher serum total DDT (95% CI, −1.35-1.51 ng/g). Instead, birth year

showed a strong and consistent inverse dose-response relationship with serum total DDT (i.e., the earlier the year a woman was born, the higher her serum total DDT even after adjustment for age). For example, after adjustment for age at serum collection and BMI, women born between 1963 and 1972 had 15.66 ng/g (95% CI, 9.43-21.89 ng/g) higher serum total DDT levels than women born between 1974 and 1977.

Figure 2 shows distributions of serum total DDT by BMI, stratified by quartiles of birth year for lean women (BMI < 24; n = 454). Consistent with our multivariate linear regression model (Table 2), there was an inverse relationship between serum total DDT and BMI regardless of birth year quartile. However, in the youngest (4th) quartile (birth date 1974-1977), the slope of the serum total DDT versus BMI relationship seemed less steep (β = −1.03, SE = 0.75) than in the oldest (1st) quartile (birth date 1963-1972; β = −2.82, SE = 1.08). Further analysis of the differences between the slopes of these plots showed there was not clear evidence of effect modification of the relationship between BMI and serum DDT by birth year. The estimated coefficient for the interaction term for 1st birth date quartile versus 4th birth date quartile was β = −1.79, with a wide 95% CI that crossed 1.0 (95% CI, −4.38-0.80; data not shown).

Discussion

These analyses showed a robust inverse association of serum total DDT with BMI among young, thin, nulliparous female Chinese textile workers. Despite a narrow age range, we showed a positive association of serum DDT with age consistent with other population-based studies (11-13). However, this age-DDT association was no longer present when birth year was controlled in the models (Table 2). In our study, the year of birth and age at enrollment were highly correlated because enrollment occurred over a 3-year period. Both year of birth and age at enrollment were strongly associated with serum DDT and DDE when modeled individually. However, year of birth was more strongly associated with serum DDT
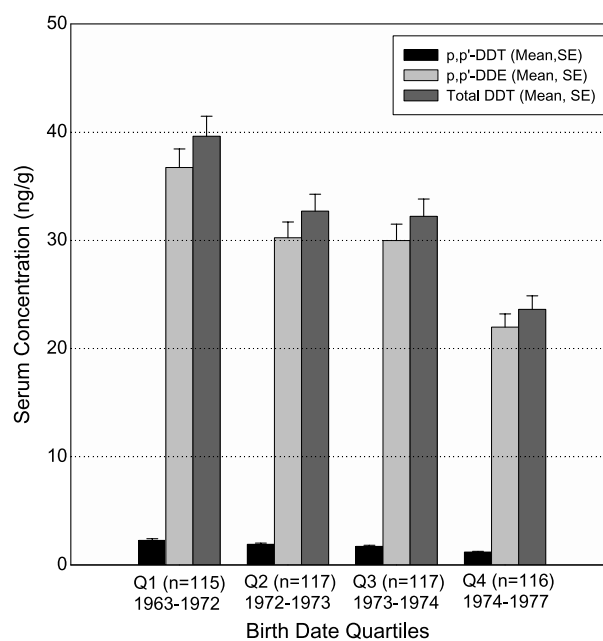
Figure 1. Mean (SE) serum p,p'-DDT, p,p'-DDE and total DDT stratified by birth date quartiles for 465 women of childbearing age, Anhui, China, 1996 to 1998.

Table 2. Regression β estimates of serum total DDT with BMI, age, and birth year in women of childbearing age, Anhui, China, 1996 to 1998

Variable	Total DDT(ng/g)		
	n	Crude	Adjusted
		β (95%CI)	β (95%CI)
BMI (kg/m^2)	462	−1.31 (−2.13 to −0.49)	−1.34 (−2.12 to −0.56)
Age (y)	465	2.51 (1.51-3.51)	0.08 (−1.35-1.51)
Birth year	465		
4th quartile (8/13/1974-7/16/1977)	116	Reference	Reference
3rd quartile (4/6/1973-8/6/1974)	117	8.54 (4.19-12.89)	8.38 (3.91-12.85)
2nd quartile (3/15/1972-4/5/1973)	117	9.01 (4.66-13.36)	8.54 (3.74-13.34)
1st quartile (5/24/1963-3/7/1972)	115	15.92 (11.55-20.29)	15.66 (9.43-21.89)
Birth year test for trend	465	4.82 (3.43-6.21)	4.61 (2.65-6.57)

NOTE: Sample sizes ranged from 461 to 465 because of missing BMI, age, or birth year data.

and DDE concentrations than age at enrollment when we modeled both simultaneously. Both year of birth and age at enrollment are associated with serum DDT and DDE because they measure the period of time over which chronic exposures to DDT and/or DDE occurred, but have different sources of measurement error with regard to the total integrated exposure over time.

The finding that year of birth is more strongly associated with serum DDT and DDE is consistent with our belief that environmental exposures to DDT and/or DDE were higher during the period of birth for our cohort (1963-1977) than the period of enrollment in the study (1996-1998). To illustrate, imagine two women who were 30 years old at enrollment, one who was enrolled in 1996, and one enrolled in 1998 (and hence were born in 1966 and 1968, respectively). Although both have the same length of exposure (30 years), the woman who was born in 1966 was exposed during 1966 to 1968 and not during 1996 to 1998, whereas the other woman was exposed during 1996 to 1998, but not during 1966 to 1968.

Thus, these women who have the same age at enrollment have different integrated exposures equal to the difference between the integrated exposure during 1966 to 1968 for the first woman and the integrated exposure during 1996 to 1998 for the second woman. Contrast this with two women who have the same year of birth who were enrolled in 1996 and 1998, respectively. Although both have the same year of birth, they have different integrated exposures equal to the integrated exposure during 1996 to 1998 for the second woman.

In the context of variable enrollment years, our finding that year of birth is more strongly associated with serum DDT and DDE than age might be due to less measurement error when birth year rather than age is used to estimate time of exposure. This is consistent with higher exposure around the years of birth relative to the years of enrollment. Although the study workers did not have jobs involving the production or application of pesticides, in the past, DDT was used extensively in the production of cotton, and cotton textiles
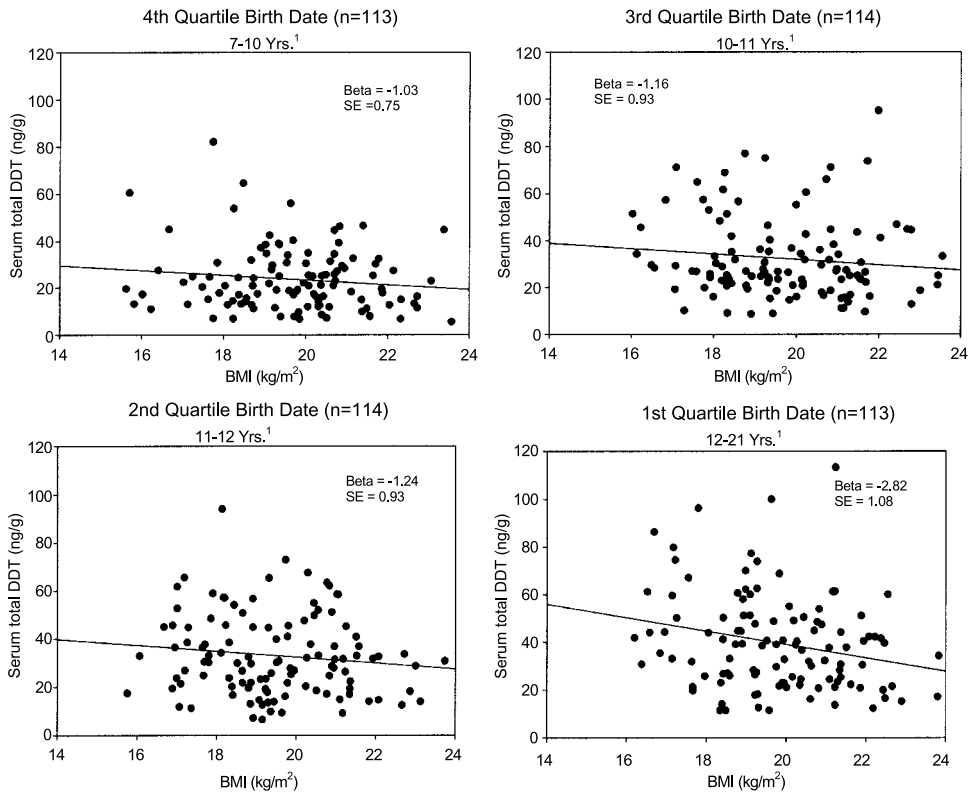

Figure 2. Unadjusted distributions of serum total DDT by BMI stratified by birth date quartiles for 454 lean women of childbearing age, Anhui, China, 1996 to 1998.

[1]Age of women at the time DDT was banned in China in 1984

were produced at the study mill. As an extension of the above argument, birth year may correlate with employment in the mill and, therefore, could be a better proxy than age for indirect occupational exposure.

Previous research on the DDT and BMI relationship has yielded inconsistent findings. Wolff and Anderson (14) have proposed a pharmacokinetic model to explain the interaction between BMI, time since exposure termination, and organochlorine concentrations in adipose tissue. Where recent exposures are substantial, total absorption of exogenous contaminants (e.g., DDT) exceeds elimination. Their model posits that serum organochlorines are in passive pharmacodynamic equilibrium with an individual's adipose stores. High BMI individuals should have larger adipose stores and therefore lower serum levels compared with low BMI individuals. However, this direction of association has not been observed in most prior epidemiologic studies. The Wolff and Anderson model posits that the rate of elimination of DDT/DDE from adipose stores is faster for those with low BMI relative to those with high BMI. Therefore, after exposure ends the relationship would eventually invert, to a positive association of DDT with BMI as a reflection of the cumulative effect of faster elimination among low BMI individuals. It is, therefore, possible that the inverse BMI/DDT association observed in this study is a consequence of the distribution and elimination kinetics characteristic of more recent peak DDT exposures and generally low BMI.

However, the actual timing of exposure in our population was not clear in this study. Mean DDT levels were higher in earlier birth year quartiles. Given the cross-sectional design of our study, it was not possible to determine whether this was a cumulative age effect, a temporal effect, and/or an effect of related factors such as weight change. Comparing DDE to total DDT did not give a clear indication of exposure timing. We saw a high ratio of DDE to total DDT independent of birth year, suggesting, (a) most of the parent DDT had been metabolized into DDE by the time serum DDT was measured in 1996 to 1998 and/or (b) environmental exposure to DDE and bioaccumulation was ongoing (25) in 1996 to 1998, such as from food, air, water, and soil sources.

There was a consistent inverse relationship between BMI and DDT across birth year strata independent of exposure levels. The magnitude of this relationship could be influenced by the timing of peak exposure relative to one's stage of physical development. The BMI/DDT slope seemed steeper in women who were between 12 and 21 years at the time of the DDT ban, suggesting that DDT exposure after age 12 may enhance the relationship (Fig. 2). However, a comparison of slope differences for the earliest and latest birth year quartiles showed a wide 95% CI overlapping 1.0, indicating we could not show with precision an appreciable difference between the slopes across birth year strata.

Some study design limitations need consideration in interpreting these findings. This study only had a single point analysis of serum total DDT and, thus, prevented an evaluation of how DDT exposure and BMI affected each other temporally. Whereas the literature reviewed here suggests that preexisting anthropomorphic characteristics influence how individuals absorb and release organochlorines in serum, it remains possible that DDT exposure precipitated weight loss or retarded weight gain and, therefore, lowered BMI. Alternatively, greater weight gain among younger women may have contributed to dilutional declines in serum DDT. Information on percent body fat was not available from study participants and, therefore, it was not possible to evaluate whether this influenced the BMI and DDT relationship observed.

It is uncertain what impact lack of adjustment for serum lipids may have had on our findings. In general, serum DDT levels will be relatively overestimated in individuals with higher, compared with lower, serum lipid levels when concentrations are expressed on a wet weight basis. If serum lipids were positively associated with BMI, for example, this would be a source of null bias. That is, we would have underestimated the inverse association of DDT with BMI. However, it is unlikely that fasted status at blood draw (a potentially important source of serum lipid variability in this setting) would correlate with BMI.

However, there are a number of strengths unique to our study population and design. Our sample was relatively homogeneous in terms of age, weight, BMI, and reproductive history. It is known that organochlorine compounds can be released from adipose tissue during fat mobilization such as during weight loss (16, 26) and it has been shown that increased lactation decreases DDT levels in mothers' breast milk (27). Our sample was nulliparous and had no prior history of lactation. Also, the DDT-BMI association was strong although BMI variability in our sample was small (mean BMI = 19.8, SD = 2.0).

Conclusions

A number of studies have reported associations (both positive and negative) between BMI and serum DDT. In our analysis, BMI was consistently inversely associated with serum total DDT. In epidemiologic studies evaluating the health effects of organochlorines, statistical approaches that capture these relationships need to be considered particularly where BMI may be a potential confounder of the association under study. Similarly, pharmacokinetic models (e.g., ref. 14) seeking to quantify the interdependent effects of BMI, exposure timing, and elimination rate on organochlorine biomarkers need further development and testing. Lastly, our results support the importance of birth year as a contributor to apparent age-related increases in serum DDT, particularly among populations where DDT has been in use relatively recently or where population exposures to DDT are rapidly declining.

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