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***In Utero* Exposure to Iodine-131 from Chernobyl Fallout and Anthropometric Characteristics in Adolescence**

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Abstract

Prenatal exposure to external radiation has been linked to growth retardation among atomic bomb survivors in adolescence. It is unclear from previous studies whether *in utero* exposure to internal radiation such as iodine-131 (I-131), which concentrates in the thyroid gland, has an effect on physical growth. We examined the associations between estimated thyroid gland dose from prenatal exposure to I-131 and self-reported height and weight in a cohort of 2,460 individuals exposed to radioactive fallout from the 1986 Chernobyl nuclear accident [mean I-131 dose = 72 (mGy)] and screened for thyroid diseases in adolescence. Using multivariable linear regression models, we estimated the mean differences in height, weight and body mass index (BMI) per unit increase in dose (100 mGy) in models adjusted for gender, age at examination, type of residence (rural/urban) and presence of thyroid disease diagnosed at screening. All of the adjustment factors as well as the trimester of exposure were evaluated as potential modifiers of the dose response. Overall, no significant dose response was found for height ($P = 0.29$), weight ($P = 0.14$) or BMI ($P = 0.16$). We found significant modification of the dose response for weight and BMI by presence/absence of thyroid disease ($P = 0.02$ and $P = 0.03$, respectively), but not for other factors. In individuals without thyroid disease ($n = 1,856$), there was a weak, significant association between I-131 thyroid dose and higher weight (210 g per 100 mGy, $P = 0.02$) or BMI (70 g/m² per 100 mGy, $P = 0.02$) that depended on individuals ($n = 52$) exposed to ≥ 500 mGy. In individuals with thyroid disease ($n = 579$, 67.4% with simple diffuse goiter) no significant association with I-131 for weight ($P = 0.14$) or BMI ($P = 0.14$) was found. These results do not support the hypothesis that *in utero* exposure to I-131 at levels experienced by a majority of study subjects may be associated with meaningful differences in adolescent anthropometry. However, additional studies are needed to clarify whether *in utero* exposure to I-131 at levels ≥ 500 mGy may be associated with increases in weight/BMI and to evaluate the confounding or modifying role of thyroid disease, past iodine deficiency, maternal and prenatal/postnatal factors.

INTRODUCTION

Among atomic bomb survivors, exposure to external radiation *in utero* or in early childhood, with largely homogeneous irradiation of all organs, has been linked to reduced head circumference as well as to lower weight and shorter stature in adolescence and adulthood (1–7). The observed dose-dependent growth retardation did not vary statistically with gestational age at exposure (6), although the power to detect such variation was limited. The associations between anthropometric characteristics and *in utero* exposure to internal radiation, such as iodine-131 (I-131), are currently unknown. In this study, we explored these associations in a population exposed prenatally to Chernobyl fallout.

The accident at the Chernobyl nuclear power plant on April 26, 1986, released significant amounts of I-131, that contaminated large portions of northern Ukraine. The main exposure pathway for I-131, which concentrates in the thyroid gland, was through consumption of I-131 in contaminated milk or green leafy vegetables. Exposure to the fetus can result from maternal ingestion since the placenta is freely permeable to iodines. With the onset of thyroid gland function at 10–12 weeks of gestation, the fetal thyroid begins to progressively accumulate I-131 and other iodines from the maternal circulation by the placental iodine pump (8). Due to selective uptake of I-131 by the thyroid gland, exposure to I-131, unlike exposure to external radiation, is heterogeneous, with the thyroid receiving the highest dose of all organs and tissues (9). Throughout gestation, the uptake of I-131 by the fetal thyroid increases faster than thyroid mass and autoregulation of iodine transport to compensate for excess or deficiency in iodine levels does not develop in the fetus until close to term. Thus, the prenatal thyroid dose of I-131 is a function of stage of gestation, with minimal dose in early gestation and maximal dose in the third trimester. *In utero* exposure to I-131 is of particular concern because the small size of the fetal thyroid gland results in higher absorbed doses given similar exposure to I-131 and because fetal thyroid cells undergo rapid cell division potentially increasing susceptibility to carcinogenic and other harmful effects of I-131 (10).

Exposure to I-131 during childhood is a recognized cause of thyroid cancer (11–13) and may also elevate serum levels of thyroid stimulating hormone (TSH) and increase the risk of subclinical hypothyroidism (12, 14). TSH concentrations have been positively correlated with body mass index in childhood (15) and adulthood (16), although the temporal sequence of the TSH/high body mass index relationship is unclear. The thyroid gland is known to play an important role in regulating bone maturation and production of insulin-like growth factor (17). Alterations in thyroid function may lead to detrimental effects on growth. Short stature, for example has been reported as a common consequence of clinical hypothyroidism associated with Hashimoto thyroiditis in children (18).

Epidemiological data on the health consequences of *in utero* I-131 exposure are limited. Follow-up examinations of 480 children exposed prenatally to fallout from aboveground nuclear testing in Nevada (19) found no thyroid neoplasia; however nodules, thyroiditis, hypothyroidism and goiter were present but not clearly dose related. Children on the Marshall Islands who were exposed to Pacific Ocean nuclear testing also showed some excess of thyroid nodules as well as other abnormalities such as shorter stature in males

(20), but the dose absorbed by the thyroid was most likely from radioisotopes of iodine other than I-131 as well as external irradiation and only a small proportion of children were exposed *in utero*. In a previous study, we investigated the radiation-related risk of thyroid diseases in a cohort of adolescents who were *in utero* at the time of the Chernobyl accident in Ukraine. We found a nonsignificant increase in risk for thyroid cancer, but not for other thyroid diseases, with *in utero* I-131 dose (EOR/Gy = 11.66; $P = 0.12$) (21).

The primary objective of the current study was to examine the associations between estimated thyroid gland dose from prenatal and early postnatal exposure to I-131 and self-reported height, weight and calculated body mass index (BMI) in adolescence in the same *in utero* exposed cohort in Ukraine. Because all cohort members underwent a comprehensive medical screening of the thyroid gland, the cohort provides a unique opportunity not only to investigate the association between I-131 exposure *in utero* and adolescent growth, but also, secondarily, to evaluate whether this association is confounded or modified by the presence of thyroid disease.

METHODS

Study Population and Screening Examination

The cohort is comprised of children born to mothers who had been pregnant within two months after the accident on April 26, 1986 in Ukraine (when I-131 was still present in the environment). Details of the study design, population and recruitment have been reported previously (21) and are described briefly here. Eligible mothers had to be pregnant at some point during the time period April 26, 1986 to June 30, 1986, had a live birth resulting from the pregnancy, and a mailing address in one of three northern oblasts (provinces) of Ukraine that were contaminated as a result of the Chernobyl accident. The exposed group of mothers, from settlements with a Cs-137 deposition $> 37 \text{ kBq/m}^2$, had to receive a direct thyroid radioactivity measurement shortly after the accident or had to live in the same contaminated settlement as women of child-bearing age with measureable thyroid activity such that doses for pregnant women could be estimated (22). For comparison purposes, women were identified who were pregnant during the same period of time but resided in relatively uncontaminated settlements (Cs-137 $< 37 \text{ kBq/m}^2$), mostly in the same oblasts and did not have thyroid radioactivity measurement (comparison subjects). A total of 1,818 exposed and 1,227 comparison subjects born to eligible mothers were invited for screening, and of these 1,498 exposed and 1,089 comparison subjects were screened in adolescence. In the analysis, we excluded 4 exposed subjects and 1 comparison subject because they had a date of birth out of the eligible range. An additional 50 exposed subjects and 72 comparison subjects were excluded because they had missing information on weight or height. Of the remaining 2,460 subjects, 1,444 subjects were exposed, including 678 (47%) born to mothers with a direct radioactivity measurement and 1,016 comparison subjects.

The *in utero* exposed and comparison individuals were screened for thyroid diseases using a standard clinical protocol (21) between 2003 and 2006, when subjects were between the ages of 16 and 20, either by a mobile team or at a clinic in the Institute of Endocrinology and Metabolism in Kyiv. The screening examination included thyroid palpation and ultrasonography, as well as serum assays for thyroid hormones and anti-thyroid antibodies

(21). A detailed description of thyroid disease diagnosis and definition is available elsewhere (21). In brief, presence of diffuse goiter was defined by the screening endocrinologist based on palpation. Grade 1 and 2 goiters according to the WHO classification were combined and compared with grade 0. Presence of thyroid nodules was defined based on ultrasound examination. Hypothyroidism and hyperthyroidism were defined as serum TSH concentration >4 mIU/L or <0.3 mIU/L, respectively. Autoimmune thyroiditis (AIT) was defined based on a combination of laboratory (elevated TSH, antibodies to thyroid peroxidase, or thyroglobulin), ultrasound (hypoechoic gland with heterogeneous/granular structure) and palpatory (firm gland) findings. Follicular neoplasia was defined based on results of cytological (FNA) or pathomorphological (surgery) conclusion. Weight, height and smoking status of study participants were self-reported at the time of screening. A structured questionnaire was administered to mothers to collect information on demographics, residential history, medical history, maternal X-ray exposure during pregnancy and consumption patterns of contaminated foods relevant to dose estimation (22). Information on the child's diet was not collected.

The study was reviewed and approved by institutional review boards at the National Institutes of Health in the U.S. and the Institute of Endocrinology and Metabolism in Ukraine, and all subjects or accompanying guardians for minors provided informed consent.

Dosimetry

A detailed explanation of the dosimetry methods has been published previously (22). Individual fetal I-131 thyroid doses were estimated for all study participants. The first step in dose reconstruction involved estimation of I-131 activity in the thyroid of the mother over time. It was based on: (1) direct measurement of the radioactivity in the thyroid; (2) personal interview and data on mothers' residential history and dietary habits within two months after the Chernobyl accident; and (3) published information on the behavior of I-131 in the environment and in the body. For mothers with a direct thyroid measurement, the I-131 activity in the thyroid at the time of measurement was derived from the measurement itself. For mothers from contaminated areas who did not have a direct thyroid measurement but who resided in the settlement in which a number of women of child-bearing age had a direct thyroid measurement, the age-specific average value of the available direct thyroid measurements was used to infer the activity of I-131 in the thyroid of the subject's mother at a reference date. For the mothers from uncontaminated areas who did not have a direct thyroid radioactivity measurement and who resided in settlements in which no women of child-bearing age were measured, the activity of I-131 in the thyroid was inferred from the relationship observed between the Cs-137 activity deposited on the ground and the I-131 activity in the thyroid in settlements with available direct thyroid measurements. The relative variation of thyroidal I-131 activity before and after the direct measurement (or reference date for women without measurements) was obtained by means of an ecological model that accounted for the intakes of I-131 by inhalation, ingestion of milk and leafy vegetables, drawing on the mother's residential history and dietary habits acquired during the personal interviews.

The second step of dose reconstruction included calculation of the *in utero* I-131 thyroid dose of the child (given the variation of the I-131 activity in the thyroid of the mother with time) using Berkovski's model, which assumes a continuous increase in dose with increasing gestational age (23–25). For children born within two months after the accident, postnatal thyroid doses of I-131 were also estimated. For the purposes of our study, we used the cumulative I-131 dose, which was a sum of the *in utero* and the postnatal I-131 thyroid dose, the latter accounting for only a small fraction of the cumulative thyroid dose; only 8% of subjects had a postnatal dose and for these the postnatal dose contributed 10% of cumulative dose.

Statistical Methods

We compared the exposed and comparison groups on the distribution of selected characteristics, including age at examination, gender, smoking status, type of residence, specific thyroid diseases, levels of TSH, thyroid volume (based on ultrasound examination) and recent use of thyroid medication. For each group we calculated the mean and median I-131 thyroid doses, overall and by trimester of exposure. We examined the means and standard deviations for height [in centimeters (cm)], weight [in kilograms (kg)] and BMI (kg/m^2) by gender and age at examination (as 16-, 17-, 18- or 19–20 years old), and evaluated whether these outcomes were normally distributed.

We used multivariable linear regression models to estimate the mean differences in height, weight and BMI per unit of increase in cumulative I-131 thyroid dose, which was modeled as a continuous variable, adjusting for relevant confounders. For ease of interpretation, we presented mean differences in height (mm), weight (g) or BMI (g/m^2) at 100 mGy as this dose is close to the mean I-131 thyroid dose received by study participants. We also included I-131 dose as a categorical variable (<10, 10–99, 100–499, 500 mGy). We evaluated as potential confounders the subject's gender, age at examination, smoking status (yes/no), number of cigarettes smoked per day, presence of thyroid disease (yes/no), type of residence (rural/urban), thyroid volume, TSH levels, oblast of residence, recent thyroid hormone use (yes/no) and mother's exposure during pregnancy to radioisotopes (yes/no) or X rays (yes/no). For each of the confounders, we also examined potential interaction with gender. Final dose-response models for weight and BMI were adjusted for gender, age at examination by gender, type of residence, presence of thyroid disease and height, while the final dose-response model for height was adjusted for gender, age at examination, type of residence and presence of thyroid disease. We evaluated modification of I-131 dose-response by gender, age at examination (16–17 years vs. 18–20 years), type of residence, presence of thyroid disease and gestational trimester of exposure by adding an interaction term between I-131 thyroid dose and the effect modifier of interest to the baseline model. We also conducted sensitivity analyses by excluding subjects from the comparison group or those whose mothers had no direct measurement of thyroid radioactivity or were exposed to radioisotope treatment during pregnancy. All statistical tests were two-sided and a *P* value of < 0.05 was used as the criterion for judging statistical significance.

RESULTS

Descriptive Characteristics and Dose Distribution

The mean age at examination was 18.4 years and 18.0 years in the exposed and comparison group, respectively (Table 1). Slightly over half of the subjects were female (53.7 and 51.9% in the exposed and comparison group, respectively), and roughly half lived in rural areas [50.2 of the exposed and 49.9% of the comparison group (Table 1)]. The proportion of smokers in both groups was comparable (about 27%). There was a higher proportion of subjects with diffuse goiter and follicular neoplasia and a slightly lower proportion of subjects without any thyroid disease in the exposed group than in the comparison group. Mean TSH level and thyroid volume were comparable in the two groups, as was the proportion of subjects who reported intake of thyroid hormones.

The mean *in utero* and cumulative thyroid doses of I-131 were much higher in the exposed group (110 and 118 mGy) than the comparison group (7 and 10 mGy) (Table 2). Estimates of I-131 thyroid dose for subjects in the comparison group, although small, were above zero because virtually everyone in the area received some I-131 exposure as a result of the Chernobyl accident. For both groups, mean (median) doses from *in utero* exposure to I-131 were higher in subjects exposed in the third trimester than in subjects exposed in the first or second trimester (Table 2). Only a small part of these differences was attributed to postnatal I-131 exposure of subjects initially exposed to I-131 during the third trimester.

Height, weight and BMI were reasonably normally distributed; the gender- and age-specific means and standard deviations of height, weight and BMI are presented in Supplementary Table S1 (<http://dx.doi.org/10.1667/RR13304.1.S1>).

Overall and Gender-Specific Dose-Response Analyses

Irrespective of dose, males were significantly associated with higher height, weight and BMI (Table 3). After stratifying by gender, higher age at examination was significantly associated with taller stature in males ($P = 0.002$), but not in females ($P = 0.14$), suggesting that most females in our study had attained their full adult height (Table 3). Living in a rural residence was significantly associated with higher weight and BMI in females, but not males (Table 3). The presence of thyroid disease (predominantly comprised of simple diffuse goiter, 67.4%) was associated with significantly higher weight and BMI in both males and females and with taller stature in males but not females. The serum levels of TSH were not significantly associated with any of the studied outcomes (not shown) and did not explain the observed associations of these outcomes with thyroid disease.

In linear regression analyses adjusted for the abovementioned confounders, there was no significant association with I-131 thyroid dose for height ($P = 0.29$), weight ($P = 0.14$) or BMI ($P = 0.16$) (Table 3). The dose-response associations were not materially changed by excluding any of the following subjects (data not shown): exclusion of subjects from the comparison group ($n = 1,016$); exclusion of subjects whose mothers had no direct measurement of thyroid radioactivity ($n=766$); exclusion of subjects whose mothers were exposed to radioisotope treatment during pregnancy ($n = 6$).

Dose-Response Analyses by Age at Examination, Place of Residence and Presence of Thyroid Disease

There was no significant interaction between I-131 thyroid dose and age at examination or place of residence for any of the study outcomes (Supplementary Table S2; <http://dx.doi.org/10.1667/RR3304.1.S1>). We did find a statistically significant interaction between I-131 thyroid dose and the presence/absence of any thyroid disease for weight and BMI, but not for height (P for interaction = 0.02, 0.03 and 0.56, respectively) (Table 4). Stratified analyses showed that in subjects without evidence of thyroid disease at screening, I-131 thyroid dose was positively associated with weight (210 g per 100 mGy, $P = 0.02$) and BMI (70 g/m² per 100 mGy, $P = 0.02$), while in subjects with thyroid disease these associations tended to go in the opposite direction and were not statistically significant (−263 g per 100 mGy, $P = 0.14$ for weight and −90 g/m² per 100 mGy, $P = 0.14$ for BMI). Evaluation of dose response for weight and BMI among subjects with specific thyroid diseases (i.e. simple diffuse goiter, nodular goiter, mixed goiter and hypothyroidism) showed associations that were generally consistent with those observed for the overall group (any thyroid disease); although, with the exception of simple diffuse goiter, they were based on small numbers (data not shown).

In subjects without thyroid disease, modeling dose as a categorical variable showed that the significant association between continuous I-131 thyroid dose and weight or BMI was largely attributable to subjects exposed to at least 500 mGy ($n = 52$) (Table 4), who had an estimated 2,780 g higher weight (95% CI: 686, 4,874; $P = 0.01$) and 957 g/m² higher BMI (95% CI: 236, 1,679; $P = 0.01$) than subjects exposed to less than 10 mGy. When individuals exposed to 500 mGy or more were excluded from analyses, the dose-response associations with I-131 were no longer significant ($P = 0.83$ for weight and $P = 0.91$ for BMI).

Dose-Response Analyses by Trimester of Exposure

I-131 dose-response associations for any of the outcomes did not vary significantly according to the trimester of exposure (Table 5). In general, the dose coefficients associated with I-131 exposure during the first trimester were imprecise, as evidenced by very wide confidence intervals. For subjects exposed during the third trimester, we found borderline significant associations between I-131 thyroid dose and weight or BMI (180 g per 100 mGy, $P = 0.06$ for weight and 61 g/m² per 100 mGy, $P = 0.06$ for BMI) that reached statistical significance ($P = 0.02$ for weight and $P = 0.02$ for BMI) once analyses were limited to subjects without thyroid disease.

DISCUSSION

To our knowledge, our study is among the first to examine the association between *in utero* dose of I-131 to the thyroid gland and measures of adolescent growth. Since atomic bomb survivors exposed to external radiation *in utero* showed dose-related decrements in physical growth at adolescence (4–7), it was of interest to explore the potential effects of internal I-131 radiation *in utero*, particularly because I-131 concentrates in the thyroid, a gland with a critical role in metabolism and bone maturation (17). In our large cohort exposed to I-131

prenatally and screened in adolescence, we found no overall association of I-131 thyroid dose with adolescent height, weight or BMI. We did find a significant modification of the dose response for weight and BMI by presence of thyroid disease. Somewhat unexpectedly, we found that subjects free of thyroid disease showed a weak but significant association of I-131 exposure with higher weight and BMI, but subjects with thyroid disease did not show this association. The significance of these associations depended on a small number of individuals who received I-131 thyroid doses of 500 mGy. No significant associations between *in utero* exposure to I-131 and adolescent height were observed in groups with or without thyroid disease.

There is scant literature on radiation exposure *in utero* and anthropometric characteristics during childhood or adolescence. One study of atomic bomb survivors, who were exposed to gamma and neutron radiation of all organs while *in utero*, revealed an increase in severe mental retardation and small head size with increasing uterine dose (26). Other studies of atomic bomb survivors looked at a variety of anthropometric characteristics measured repeatedly between 10–18 years of age (5–7). No significant dose response was observed for BMI. For all other outcomes the estimate of the dose response was negative in relationship to the uterine absorbed dose. Associations did not differ significantly by gestation at exposure. The investigators concluded that the inverse associations observed for multiple measurements of anthropometry over time pointed to radiation-related growth retardation (4, 6).

Only one previous study has attempted to evaluate the association between exposure to internal radiation, including I-131 and growth in children, namely the follow-up of 38 children (4 *in utero*) exposed to radioactive fallout from thermonuclear testing carried out in the Marshall Islands and 67 unexposed children (27). Data were collected only up to 8 years after the initial exposure, prior to adolescence for most of the subjects. The authors found a suggestive association for shorter stature in males, but not in females and no associations with weight or head circumference. However, interpretation of the data is complicated by small study size and by the fact that subjects were exposed to a combination of external radiation, short-lived and long-lived radionuclides.

There are two other cohorts exposed to a combination of external and internal radiation. One cohort is comprised of approximately 4,000 individuals exposed *in utero* as a result of their mothers' employment at the Mayak nuclear facility in Russia. The second cohort is comprised of 3,000 individuals with exposure from residence in the nearby Techa River area (28). However, only limited data are available on physical growth in childhood or adolescence among members of these cohorts (29).

Our findings of no overall significant association between I-131 and anthropometric characteristics and of a significant positive association for weight/BMI in subjects without thyroid disease are not consistent with the findings of shorter stature at higher radiation doses in the atomic bomb survivors and the Marshallese, and of lighter weight in the atomic bomb survivors. However, a positive association between radiation exposure and body weight, such as we observed, has been reported for adult survivors of childhood cancer treated with cranial radiation (30–33). However, these patients typically receive much higher

doses of radiation (>10 Gy) and the dose is delivered both to the brain (including pituitary gland) and the thyroid. To what extent such inconsistent findings are attributed to different types of radiation, underlying biological mechanisms or uncontrolled confounding/modifying factors remains unclear.

Given that the thyroid gland plays an important role in regulation of metabolism/resting energy expenditure and bone maturation (34, 35), and that in our study population, this organ received the highest doses, we were interested in whether some potential effects of I-131 on anthropometric characteristics could be mediated or modified by the presence of thyroid disease detected at screening. When I-131 dose estimates and thyroid disease were included into the model simultaneously, the regression coefficients were similar to those when each factor was evaluated individually. However, the I-131 dose response for weight and BMI significantly varied by presence/absence of thyroid disease suggesting that the association with I-131 might not be statistically independent from the association with thyroid disease. Interestingly, the positive associations between thyroid disease and weight or BMI (adjusted for I-131 dose) could not be explained by serum levels of TSH, the best single indicator of thyroid function. In fact, we found no significant association between serum TSH and weight or BMI (data not shown), although the number of individuals with elevated TSH and weight or BMI in the study cohort was small. It also should be noted that we found no significant association between *in utero* I-131 dose and serum TSH level or presence of subclinical hypothyroidism in our earlier study in this cohort (21). Further, we found that TSH did not exhibit a significant effect modification on dose-response associations for weight or BMI (data not shown). Therefore, our results suggest that the effect modification of I-131 dose response for weight or BMI by the presence/absence of thyroid disease does not occur through an influence on TSH levels measured at the time of screening. Because the most common type of thyroid disease in the study population was simple diffuse goiter, a marker of past iodine deficiency, the modifying effect of thyroid disease may point to the importance of stable iodine intake. There is accumulating evidence that past iodine deficiency could increase the I-131-related risk of thyroid cancer (36, 37). However, whether and how it may influence the associations between *in utero* I-131 exposure and anthropometric parameters in adolescence is unknown.

The positive dose-response associations for weight and BMI we observed in the group free of thyroid disease are counter to our *a priori* hypothesis that the I-131 associations with anthropometric parameters might be mediated through thyroid disease, particularly through TSH levels. The magnitude of the associations in the thyroid disease-free group was small and their significance depended on a few individuals with I-131 thyroid doses of 500 mGy. In addition, we cannot rule out the role of unmeasured factors, including parental stature and fatness, birth weight, maternal and birth levels of TSH and iodine deficiency, exposure to other diseases in early life, nutrition, physical activity or other behaviors. Therefore, the findings of our study need to be interpreted cautiously.

Our study has both strengths and limitations. We have estimated individual *in utero* I-131 doses to the thyroid gland based on a combination of radioactivity measurements, personal interview data and ecologic and biokinetic models (21). We had interview data from the mothers on other sources of radiation exposure during pregnancy, and the proportion of

women with such exposures was low. Study sample size compares favorably with previous studies. Moreover, because all subjects underwent a thorough clinical screening for a variety of thyroid diseases, we have detailed information on thyroid gland structure and function. This allowed us to evaluate whether the suggestive association between I-131 thyroid dose estimates and weight or BMI was independent of thyroid disease.

Limitations of the study include considerable uncertainties associated with estimated fetal I-131 thyroid doses (22). Although we know the main sources of these uncertainties, they are very difficult to quantify (21) and so were not accounted for in the analyses. Another notable limitation is that the data on height and weight were self-reported rather than measured. The use of self-reported weight and height could result in measurement error, although the accuracy of adolescent self-reports of height and weight has been evaluated in a number of studies and found to be acceptable (38). Self-reported height, weight and BMI are highly correlated with their measured values. On average, reported height is overestimated and weight is underestimated, particularly in convenience-based samples; in population-based samples such as ours, the differences observed with measured values have been fairly minimal (36). We should note that in our study the associations between gender, age, presence of thyroid disease and anthropometric characteristics (adjusted for dose) as well as the mean anthropometric gender-age specific values agree well with referent values one might expect in nonirradiated populations based on the measurements (<http://www.who.int/growthref/en/>). In addition, inaccuracies in weight and height are unlikely to be related to I-131 thyroid dose estimates, and thus, our estimates of dose-response parameters may in fact underestimate the true ones. BMI calculated from height and weight, which is our proxy measure for total body fat, is a limited measure of adiposity since it provides no information on body fat distribution. Due to the cross-sectional nature of the study, we could not evaluate the effect of *in utero* I-131 exposure on growth trajectories. The cross-sectional design also meant that anthropometric characteristics and thyroid disease were measured at the same time so that one could not entirely rule out the possibility of radiation effects on the thyroid in the past. As mentioned above, we did not have information on several potential confounders or effect modifiers that might affect adolescent weight and BMI, including childhood diabetes and other diseases, parental anthropometry, birth weight, maternal or birth levels of TSH and thyroid hormones, and intake of stable iodine, although to confound the dose-response these factors have to be associated with dose. Finally, despite the relatively large sample size, statistical power was limited to detect interactions. Also, we cannot exclude the possibility that our findings might be due to chance.

In summary, our findings do not provide support for the hypothesis that *in utero* exposure to I-131 at levels experienced by a majority of study subjects may be associated with meaningful differences in adolescent anthropometry. However, we found a significant modification of I-131 dose-response associations for adolescent weight and BMI by the presence/absence of thyroid disease (primarily simple diffuse goiter). If not due to chance or confounding factors, our results may suggest that *in utero* exposure of the thyroid to I-131, particularly at doses equal to or greater than 500 mGy, could influence differences in body weight in individuals without clinically detectable thyroid disease. Additional cohort studies are needed to clarify whether *in utero* exposure to I-131 at higher levels is associated with

increase in weight/BMI in adolescence and to evaluate the confounding or modifying role of thyroid disease, past iodine deficiency, maternal and pre-/postnatal factors in this association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Selected Characteristics of Subjects Exposed *In Utero* to Iodine-131 from Chernobyl Fallout, by Exposure Status

Characteristic	Exposed N = 1,444	Comparison N = 1,016
Age at exam (years) – Mean (SD)	18.4 (1.2)	18.0 (0.5)
Gender – N (%)		
Male	668 (46.3)	489 (48.1)
Female	776 (53.7)	527 (51.9)
Rural (vs. urban) residence – N (%)	725 (50.2)	507 (49.9)
Smoking status – N (%)		
No	1048 (72.6)	737 (72.5)
Yes	392 (27.1)	270 (26.6)
Unknown	4 (0.3)	9 (0.9)
Thyroid disease – N (%)		
Simple diffuse goiter	258 (17.9)	158 (15.6)
Nodular goiter	35 (2.4)	22 (2.2)
Mixed goiter	22 (1.5)	11 (1.1)
Hypothyroidism	47 (3.3)	38 (3.7)
Thyroiditis	5 (0.4)	11 (1.1)
Follicular neoplasia	7 (0.5)	1 (0.1)
Hyperthyroidism	0 (0.0)	3 (0.3)
None	1075 (74.4)	781 (76.9)
TSH (mIU/L) – Mean (SD) ^a	1.8 (1.0)	1.8 (1.0)
Thyroid volume (cm ³) – Mean (SD)	10.8 (4.1)	10.6 (4.4)
Took thyroid hormones in the past year – N (%)	5 (0.4)	7 (0.7)

^aNine subjects had missing TSH measurements (5 exposed, 4 unexposed).

TABLE 2

Iodine-131 Thyroid Dose Estimates by Study Group and Trimester of Exposure

Trimester ATA ^a	N	<u>In utero I-131 thyroid dose (mGy)</u>			<u>Cumulative I-131 thyroid dose (mGy)</u>		
		Mean	Median ^b		Mean	Median ^b	
Exposed							
1	400	3.7	0.0		3.7	0.0	
2	575	104.5	43.4		104.5	43.4	
3	469	206.5	99.5		231.6	115.7	
Comparison							
1	321	0.3	0.0		0.3	0.0	
2	276	7.2	4.2		7.2	4.2	
3	419	13.1	8.2		19.5	12.8	

^a ATA = at time of accident.

^b Median values for first trimester are 0.0 mGy because I-131 dose estimates of less than 0.05 mGy in 433 subjects were rounded to 0.0 mGy.

TABLE 3

Associations between Cumulative Iodine-131 Thyroid Dose (per 100 mGy) and Selected Predictors for Height, Weight and Body Mass Index (BMI) in Adolescents Exposed *In Utero* to Iodine-131 after the Chernobyl Accident

	Height (mm) ^a			Weight (g) ^b			BMI (g/m ²) ^b		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
All									
Age at exam (per year)	5.0	2.0, 8.0	0.001	1,242	914, 1,569	<0.001	411	298, 524	<0.001
Females vs. male	-106.4	-112.0, 100.8	<0.001	-2,410	-3,179, 1,642	<0.001	-795	-1,060, 531	<0.001
Rural vs. urban	-19.6	-25.4, 13.9	<0.001	805	169, 1,441	0.01	293	74, 512	0.01
Height (per 10 mm)				604	561, 648	<0.001	-44	-59, 28	<0.001
Thyroid disease	6.3	-0.3, 13.0	0.06	2,492	1,763, 3,221	<0.001	844	593, 1,095	<0.001
Dose (per 100 mGy)	0.8	-0.6, 2.2	0.29	114	-39, 267	0.14	37	-15, 90	0.16
Males (n = 1,157)									
Age at exam (per year)	7.4	2.7, 12.2	0.002	1,670	1,195, 2,146	<0.001	531	378, 684	<0.001
Rural vs. urban	-25.7	-34.8, 16.7	<0.001	296	-625, 1,216	0.53	83	-213, 379	0.58
Height (per 10 mm)				667	609, 726	<0.001	-25	-44, 7	0.01
Thyroid disease	12.0	2.0, 22.1	0.02	2,923	1,913, 3,933	<0.001	960	635, 1,285	<0.001
Dose (per 100 mGy)	0.1	-2.2, 2.5	0.91	56	-178, 290	0.64	16	-59, 92	0.67
Females (n = 1,303)									
Age at exam (per year)	2.9	-0.9, 6.7	0.14	852	403, 1,301	<0.001	303	140, 466	<0.001
Rural vs. urban	-14.2	-21.6, 6.9	<0.001	1,270	395, 2,146	0.004	481	163, 799	0.003
Height (per 10 mm)				519	454, 584	<0.001	-69	-92, 45	<0.001
Thyroid disease	0.5	-8.3, 9.2	0.92	1,970	925, 3,016	<0.001	703	324, 1,083	<0.001
Dose (per 100 mGy)	1.1	-0.6, 2.9	0.19	158	-44, 360	0.12	53	-20, 126	0.15

Note. There was no statistically significant interaction between gender and dose for height, weight or BMI.

^aLinear regression models adjusted for age at exam, gender, type of residence, and thyroid disease.

^bLinear regression models adjusted for age at exam by gender, height, type of residence, and thyroid disease.

TABLE 4
Association between Cumulative Dose (Per 100 mGy) and Height, Weight and BMI, Stratified by Presence of Thyroid Disease

	Height (mm) ^a			Weight (g) ^b			BMI (g/m ²) ^b		
	β^c	95% CI	P	β^c	95% CI	P	β^c	95% CI	P
Subjects without thyroid disease (n = 1,856)	0.6	-1.0-2.2	0.48	210	39-380	0.02	70	11-129	0.02
Subjects with thyroid disease (n = 579)	1.1	-1.8-4.1	0.45	-263	-611-85	0.14	-90	-209-30	0.14
P interaction			0.56			0.02			0.03
Subjects without thyroid disease (dose in categories) ^d									
<10 mGy (n = 900)	0	-		0	-		0	-	
10-100 mGy (n = 668)	2.7	-4.5-9.8	0.46	52	-713-818	0.89	6	-257-270	0.96
100-500 mGy (n = 236)	3.1	-7.1-13.4	0.55	409	-692-1,509	0.47	105	-274-485	0.59
500 mGy (n = 52)	0.6	-19.1-20.3	0.95	2,780	686-4,874	0.01	957	236-1,679	0.01
P trend			0.52			0.06			0.09

^aLinear regression models adjusted for age at exam, gender and type of residence.
^bLinear regression models adjusted for age at exam by gender, type of residence and height.
^cDose coefficient per 100 mGy.
^dCoefficient represents the average differences in height, weight, or BMI for a given dose category compared to the referent dose category of < 10 mGy.

Associations between Cumulative Iodine-131 Thyroid Dose and Measures of Height, Weight and BMI in Adolescence by Trimester of I-131 Exposure

TABLE 5

Trimester of exposure	Height (mm) ^a			Weight (g) ^b			BMI (g/m ²) ^b		
	β^c	95% CI	P	β^c	95% CI	P	β^c	95% CI	P
All									
First (n = 721)	28.8	-26.1–83.6	0.30	-102	-5,900–5,696	0.97	50	-1,945–2,046	0.96
Second (n = 851)	-1.3	-4.4–1.7	0.38	-27	-364–309	0.87	-12	-129–104	0.83
Third (n = 888)	1.1	-0.6–2.8	0.21	180	-6–366	0.06	61	-3–124	0.06
Subjects without thyroid disease									
First (n = 554)	5.2	-62.9–73.4	0.88	117	-6,941–7,175	0.97	163	-2,249–2,576	0.89
Second (n = 665)	-1.4	-5.0–2.2	0.44	69	-322–459	0.73	20	-116–156	0.78
Third (n = 662)	0.9	-1.0–2.8	0.35	246	43–450	0.02	83	13–153	0.02

^aLinear regression models adjusted for age at exam, gender, type of residence and thyroid disease.

^bLinear regression models adjusted for age at exam by gender, height, type of residence and thyroid disease.

^cDose coefficient per 100 mGy.