American Society for Nutrition
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Advances in Nutrition
AN INTERNATIONAL REVIEW JOURNAL
journal homepage: www.journals.elsevier.com/advances-in-nutrition

Review

A Scoping Review of Iodine and Fluoride in Pregnancy in Relation to Maternal Thyroid Function and Offspring Neurodevelopment

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A B S T R A C T

Iodine (I), an essential nutrient, is important for thyroid function and therefore growth and development. Fluoride (F), also an essential nutrient, strengthens bones and teeth, and prevents childhood dental caries. Both severe and mild-to-moderate I deficiency and high F exposure during development are associated to decreased intelligence quotient with recent reports associating high levels of F exposure during pregnancy and infancy to low intelligence quotient. Both F and I are halogens, and it has been suggested that F may interfere with the role of I in thyroid function. We provide a scoping review of the literature on I and F exposure dur pregnancy and their individual effects on thyroid function and offspring neurodevelopment. We first discuss I intake and status in pregnancy and the relationship to thyroid function and offspring neurodevelopment. We follow with the F in pregnancy and offspring neurodevelopment. We then review the interaction between I and F on thyroid function. We searched for, and found only one study that assessed both I and F in pregnancy. We conclude more studies are needed.

Keywords: iodine, fluoride, pregnancy, neurodevelopment, thyroid function

Statement of Significance

To our knowledge this is the first article to review the relationship between fluoride and iodine on thyroid function and offspring neurodevelopment during pregnancy. Although little research exists in this area, it is an understudied area which warrants further investigation.

Introduction

Thyroid function is of critical importance in pregnancy and reproduction. Suboptimal thyroid function, such as autoimmune thyroid disease, is associated with infertility, miscarriage, and poor growth and neurodevelopment of the fetus [1,2]. Severe iodine (I) deficiency, or Iodine Deficiency Disorders (IDDs), during pregnancy has devastating consequences to the offspring. Neurologic cretinism is the most severe form of IDD and is characterized by cognitive deficit, deaf mutism, motor spasticity, and squint [3]. Myxedematous cretinism, the less severe form of IDD, has less severe cognitive deficit but is characterized by growth retardation, dry and thick skin, and sparse hair [3]. The effects of mild-to-moderate maternal I deficiency on pregnancy and offspring neurodevelopmental outcomes are less studied; however, mild-to-moderate I deficiency is related to low offspring neurodevelopmental scores and educational attainment [4–10].

Like I, fluoride (F) is a halogen. It is recognized as an important nutrient for its role in strengthening bones and teeth [11]. F decreases the risk of dental caries by increasing the formation of fluorapatite or fluorohydroxyapatite, decreasing acid production by bacteria found in the mouth, and improving

Abbreviations: BSID, Bayley Scales of Infant Development; F, fluoride; IQ, intelligence quotient; I, iodine; IDD, iodine deficiency disorder; NIS, sodium/iodide symporter; T4, thyroxine; T3, triiodothyronine; UFC, urinary fluoride concentration; UIC, urinary iodine concentration; US, United States.

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https://doi.org/10.1016/j.advnut.2023.01.003
Received 16 September 2022; Received in revised form 5 January 2023; Accepted 11 January 2023; Available online xxxx

remineralization after acidogenic challenge [11,12]. Fluoridation of water is deemed one of the most important public health policies of the 20th century for its role in reducing dental caries [12], however, excessive F intake has been reported to adversely affect neurodevelopment [13–15], although other studies do not find an association between F and childhood and adult intelligence quotient (IQ) or learning disabilities [16,17].

Two recent Canadian studies of a population living in a region with an acceptable water F concentration associated low childhood IQ to prenatal (18) and postnatal [19] F exposure. The level of water F of this population was below the recommended 0.7 mg/L [20]; the mean F level for those living in fluoridated and nonfluoridated areas were 0.59 ± 0.07 mg/L and 0.13 ± 0.05 mg/L, respectively [19]. Stimulated by the results of the recent Canadian study, our goal was to review the literature on I and F in pregnancy, including any evidence that F intake during critical periods of neurodevelopment could interfere with the role of I in thyroid function and offspring neurodevelopment. We found some evidence from human and nonclinical studies that F can compete with I to adversely affect the thyroid function [14, 21–24].

Literature search

For this scoping review, the protocol by Arksey and O'Malley [25] which was outlined by Nkangu et al. [26] was used. These steps are as follows: *1)* define the research question; *2)* identify studies; *3)* select studies; *4)* chart the data, and *5)* summarize results. A PRISMA extension for scoping reviews checklist was completed for presenting the results. Articles included in this review were identified from the PubMed database from inception to August 2022. PubMed search terms included: "iodine AND thyroid"; "iodine AND pregnancy"; "iodine AND development"; "fluoride AND thyroid"; "fluoride AND pregnancy"; "fluoride AND development"; "iodine AND fluoride," "iodine AND fluoride AND thyroid"; "iodine AND fluoride AND pregnancy"; and "iodine AND fluoride AND development." As the journal *Fluoride* is not indexed in PubMed, but contains highly relevant studies, this journal was searched using the same search terms. Studies were included if they measured urinary iodine concentration (UIC), urinary fluoride concentration (UFC), thyroid function, or neurodevelopment of offspring. Only articles written in English were included.

Maternal iodine intake, iodine assessment, thyroid function, and child neurodevelopment

Iodine intake, assessment, and status during pregnancy

The *estimated average requirement* and *recommended dietary allowance* for pregnant women are 160 μg/d and 220 μg/d, respectively, compared with 95 μg/d and 150 μg/d for nonpregnant women [27].

I is found in fish and seafood, seaweed, iodized salt, and some dairy and bread products. Erosion, glaciation, and flooding have leeched I from the soil, and plants grown in I deficient soil are not good sources of I [28]. In addition, low intake of seafood [29], use of noniodized salt [30], and variable use of I in the dairy and grain industries [31,32] can contribute to low I intake. Finally, although the bioavailability of I from food is high, it is not believed to be increased by other food components, and I bound to protein has reduced bioavailability [33]. Specific food components called goitrogens, which are found in cabbage and Brussel sprouts among other foods, are known to interfere with the function of I in the thyroid, especially in those who are I insufficient [33]. I intake has not been assessed in the United States women, as the assessment of dietary I intake only became possible after the June 2020 release of the USDA, FDA, and ODS-NIH Database for the Iodine Content of Common Foods [34].

Several health organizations recommend that prenatal supplements provide 150 μg/d of I [35–37]. Currently, 34 of 59 (57.6%) of the best-selling prenatal vitamins in the US contain I, with a median of 150 μg/d and a range of 25–290 μg/d of I [38]. NHANES from 1999–2006 found that 22.3% of US pregnant women consumed a prenatal supplement containing I [39] whereas a report that included data from 2011–2014 NHANES cycles found that 20% of pregnant women consumed a supplement with I with a mean supplemental intake of 116 ± 6 μg/d [40]. An alternative source of I supplementation, encapsulated seaweed has been shown as a viable option, increasing UIC in nonpregnant women, although TSH slightly increased but it remained within the normal range [41]. A prospective pregnancy cohort assessed UIC throughout pregnancy in a group of women living in the US and found UIC to be adequate (UIC ≥150 μg/L), but even with adequate UIC in the population, it was estimated that 23% of the population did not have adequate I intake [42].

To reliably measure individual I status, >10 spot urine samples [43] are required and samples sizes of at least 100–500 are appropriate for use of spot samples to assess the population or subpopulation I adequacy [43]. The WHO classifies I status in populations as insufficient (median UIC <150 μg/L), adequate (150–249 μg/L), above requirements (250–499 μg/L) or excessive (≥500 μg/L) [44]. Gahche et al. [39] reported a median UIC of 148 μg/L for pregnant women in NHANES 1999–2006, indicating a population of mild-to-moderate I deficiency. More recent data from NHANES 2011–2014 found evidence of mild-to-moderate I deficiency with UIC of 110 μg/L [45]. This suggests a possible decline in I status of US pregnant women compared to NHANES 1999–2006 data. The median UIC in pregnant women has been measured in other countries, many of which have been found to have mild-to-moderate UIC insufficiency.

The methods used to analyze UIC vary [46]. They include the Sandell-Kolthoff method with acid or alkaline digestion and mass spectrometry. Use of both UIC and UIC/creatinine are reported in the literature. This makes comparison among studies difficult. Moreover, although UIC is commonly used and recommended by the WHO for the use of assessment of pregnant populations [44], it has been suggested that UIC may overestimate I deficiency due to the effect of urine volume compared with UIC/creatinine [47].

Iodine intake and UIC

We found 2 interventional studies. One supplemented only participants who were I insufficient and compared the results to universal supplementation of a population [48], reporting that targeted supplementation prevented over supplementation. Another supplemented women beginning 3 mo before pregnancy or at 12 wk of gestation compared with no supplementation [49]

and found that those who began supplementation before pregnancy had higher UIC [49].

Observational studies of I intake from foods, iodized salt, and fortification programs have been done in some countries. Pregnant women in Australia ($n = 783$) were studied after mandatory I supplementation of bread products, and the population I status was apparently adequate [50]. The UIC of the group who consumed a supplement with ≥150 μg/d was 221μg/L, higher than those who consumed a supplement with <150 μg/d or no supplement, 163 μg/L and 159 μg/L, respectively [50]. A weak positive association between UIC and I intake from foods and supplements was observed at 28 wk of gestation [50]. Another study of an adequate population completed in Japan included 701 pregnant women, 545 postpartum women, and 722 newborns and reported a median UIC of 219 μg/L with a range from 6 to 16300 μg/L [51]. UIC was higher during pregnancy than during postpartum, but did not differ among trimesters [51]. Iranian women ($n = 1200$) were also found to have adequate UIC (median UIC = 188 μg/L) with high UIC in the first and second trimester and low UIC in the third trimester [52]. Supplementation with the recommended 150 μg/d of I did improve the I intake of this group [52]. Finally, insufficient UIC (77 μg/L) was observed in a sample of pregnant Danish women ($n = 147$) after the introduction of iodized salt in Denmark, even with the common use of I-containing supplements by this sample [53].

Iodine and thyroid function in pregnancy

Quite a few studies have evaluated the effect of I intake and supplementation during pregnancy on UIC, pregnancy outcomes, thyroid physiology, and/or offspring neurodevelopment. Sixteen studies assessed the effect of I supplementation during pregnancy on outcomes related to thyroid function. Some found TSH [54–57], free or total thyroxine (T4) [55,56,58,59], thyroglobulin [54–57, 59–61], thyroid volume [54,56,62,63], and UIC [54,56,59,60, 62–66] to be beneficially affected by I supplementation whereas others found no effect on TSH [59,60,62,63,66], free triiodothyronine (T3) or total T3 [54,55,59,62], free T4 or total T4 [54,57,60, 62,66,67], thyroid volume [59,66], or thyroglobulin [67]. The differences among studies may be related to the I status of the population that was supplemented, although most populations studied are insufficient by WHO standards. Finally, a sample of 125 pregnant women in Puerto Rico were found to be adequate based on UIC (median UIC = 182 μg/L); however, UIC varied based on whether the supplement that the participants consumed was prescribed or not. Those who consumed a prescribed supplement had low UIC compared to those consuming a non-prescription supplement (149 μg/L compared with 250 μg/L) [68].

In addition to maternal outcomes, some studies report positive effects of maternal supplementation on newborn UIC [54–56,66], TSH [58,69], thyroglobulin [55,56], thyroid volume [56], cord blood TSH [55], and free or total T4 [55]. Schulze et al. [67] supplemented pregnant women with 220 μg/d but reported few significant findings on thyroid outcomes although they noted a relationship between T4 early in pregnancy and newborn T4, and a strong relationship between maternal and newborn thyroglobulin [67]. Thyroglobulin was 7 times higher in cord blood than maternal blood [67].

The authors of the study in Japan [51] above did not find a relationship between TSH and free T4 or UIC; however, the mean UIC in the group with a TSH level of ≥2.5 mU/L was higher than in those with a TSH level of <2.5 mU/L in all the 3 trimesters. Those with a UIC level of ≥1000 μg/L had a higher TSH level but not free T4 than those in the <150 μg/L and 150–249 μg/L groups [51]. Newborn TSH and maternal UIC were not related [51].

A study of pregnant women in the United Kingdom ($n = 246$) who had mild-to-moderate I deficiency (median UIC = 135 μg/L) assessed I intake from food and supplements and measured UIC and thyroid function markers. The women were not consuming I at the recommended level from food and few women consumed supplemental I [70]. Moreover, UIC was related to total, dietary, and supplemental I intake and increased by 4% with every 50 μg/d increase in dietary I, whereas thyroglobulin decreased by 4% for every 50 μg/d increase in I intake [70]. Another observational study in China that compared pregnant women in a mild-to-moderate I deficiency area to an I sufficient area ($n = 1461$) found UIC, free T3, and TSH were lower, and free T4 and thyroid dysfunction were higher in women in the mild-to-moderate I deficiency area than those in the I sufficient area [71]. In the I sufficient area, free T3 and T4 increased with higher UIC, but in the mild-to-moderate deficiency area only free T3 increased [71].

A study of 265 pregnant women in an I insufficient population in Turkey found a decrease in UIC from 96 μg/L in the first trimester to 78 μg/L in the second trimester and 60 μg/L in the third trimester [72]. There was a concomitant increase in TSH across trimesters; however, TSH remained within normal limits during all the 3 trimesters [72]. Both free T3 and free T4 decreased throughout pregnancy [72]. A similar decrease in UIC and T3 throughout pregnancy was observed in a study of 215 pregnant women in China, although TSH was found to have a U-shaped curve with gestational age [73]. This is in contrast to a study of South African women ($n = 562$) that found UIC increase in each trimester (133 μg/L, 145 μg/L, and 156 μg/L) [74]. Another study completed in Turkey measured newborn UIC and found 51% of newborns were I deficient [75]. Finally, studies of Swedish women ($n = 604$) [76], Cyprian women ($n = 128$) [77], and Latvian women ($n = 129$) [78] report UICs of 113 μg/L, 105 μg/L, and 147 μg/L, respectively, suggesting mild-to-moderate I insufficiency may occur in these countries.

Three observational studies of I intake during pregnancy were completed in Norway. The first study in Norway assessed dietary I intake, UIC, and thyroid function in a cohort of pregnant women ($n = 1730$) [79] during the 2nd and 3rd trimesters with I insufficiency by both UIC and dietary intake (94 μg/L and 85 μg/L and 202 μg/d and 153 μg/d, respectively) [79]. Among women taking an I-containing supplement before pregnancy and throughout pregnancy, TSH level was lower and T3 and T4 levels were higher than those not taking a supplement [79]. The study suggests that I intake can positively influence thyroid function in populations of pregnant women with mild-to-moderate I deficiency.

A second Norwegian study found that women taking an I supplement during pregnancy had more favorable pregnancy outcomes. Participants in the *Norwegian Mother, Father, and Child Cohort Study* ($n = 73,318$) who chose to consume an I supplement during pregnancy had larger infants and reduced risk of preeclampsia than those who did not had an increased risk of preeclampsia, preterm delivery (gestational age: <37 wk), and

reduced fetal growth [5]. In this group of women, 40% reported taking a supplement with I, and the median I intake from food was 121 μg/d [80]. Those who did not take a supplement containing I had an UIC of 59 μg/L, and those taking a supplement with I had an UIC of 98 μg/L, both considered mild-to-moderate I deficient [80]. An inverse relationship was observed between UIC and free T3 or free T4. I supplementation that began after the 12th wk of pregnancy was associated with significantly low free T4 and a somewhat lower free T3 [80]. This is supported by a study of women in Tehran ($n = 1286$) that found odds of preterm delivery were higher in women with both insufficient UIC and suboptimal thyroid function (UIC <100 μg/L and TSH ≥ 4 μIU/mL) than those with UIC <100 μg/L and TSH <4 μIU/mL [81], and counter to 2 large studies which found mild-to-moderate I insufficiency was not related to worse pregnancy outcomes [82,83]. The final Norwegian study reported a UIC of 79 μg/L and dietary I intake of 140 μg/d, further confirming the I insufficiency of this population [84].

Use of iodized salt has been compared with supplements of 200 μg/d or 300 μg/d of I ($n = 131$) in a cohort in Spain [85]. Participants who reported using iodized salt for 1 y or longer before the study had higher UIC in the 1st and 3rd trimesters and a decrease in thyroid volume in the 3rd trimester than those who had not consumed iodized salt. No differences in TSH, T3, T4, or thyroglobulin were observed [85]. An observational study grouped Italian women ($n = 433$) in 3 categories: those who consumed an I supplement and iodized salt, those who consumed iodized salt, and those who consumed neither [86]. The 3 groups had estimated mean intakes of 200, 125, and 85 μg/d of dietary I, respectively, and all groups were I insufficient with respective mean UICs of 121.2, 76.3, and 52.2 μg/L [86]. Free T4 was higher in those consuming a supplement and iodized salt than in those not consuming a supplement, whereas free T3 was higher in the iodized salt group than in the other groups [86]. The group consuming iodized salt had the lowest TSH concentrations [86].

Findings on the benefits of iodized salt have been contradictory with a cross-sectional study in China with 8518 pregnant women suggesting that iodized salt may not be enough to increase UIC to adequate status [87]. This finding is in agreement with a 2022 review of 61 reports, which found that iodized salt may not be enough to ensure adequate I status during pregnancy [88]. A second study in China ($n = 2144$) found that iodized salt, I-rich food, and an I supplement were all needed to meet I needs in pregnant women [89]. A study of 306 pregnant women in Turkey found higher UIC in users of iodized salt than in those who did not use iodized salt, but they did not achieve adequate status (150 μg/L) [90]; and another study of 139 women in China found the highest I in those consuming *1)* noniodized salt and noniodized supplement followed by; *2)* noniodized salt with a iodized supplement; *3)* iodized salt with iodized supplement; and finally, *4)* iodized salt with a noniodized supplement, although with a small sample size this must be assessed with caution [91]. A study in Spain determined that the use of iodized salt was sufficient in achieving adequate status in pregnant populations [92]. Moreover, finally, a 2022 study of children ($n = 16,445$) and pregnant women ($n = 4848$) in China found that the use of iodized salt in cooking was not related to I status or thyroid function indicators [93], similar to a 2020 systematic review of 37 studies, which found no effect of I supplementation on maternal and infant thyroid hormones, although supplementation reduced maternal thyroglobulin and thyroid volume during pregnancy [94].

Iodine and offspring neurodevelopment

The mechanism by which I during pregnancy influences the cognition of offspring is through thyroid hormone production [28]. If I intake is deficient, thyroid hormone production is inadequate leading to IDD with severe sequelae in the case of severe deficiency and to adverse neurodevelopmental and educational outcomes even in the case of mild-to-moderate deficiency [4–10,95]. Some mother-infant pairs from the Norwegian Mother, Father, and Child Cohort Study ($n = 48,297$) participated in a follow-up study assessing child neurodevelopment [4]. Low intake of I from diet was related to language delay, internalizing and externalizing behavior problems, and decreased fine motor skills but use of an I supplement had no effect on these outcomes; however, there was a U-shaped curve for language with the prevalence of language delay increasing below and above a UIC of 150 μg/L [4].

Two other observational studies found associations between maternal UIC and offspring cognition [96,97], whereas a third found little evidence of an association between maternal UIC and offspring cognition [98]. The first was a secondary analysis of participants of the *Avon Longitudinal Study of Parents and Children Cohort* ($n = 1040$) in England compared maternal I-creatinine ratio to child cognition measured by the *Wechsler Intelligence Scale for Children at age 8* and reading ability at age 9 [96]. The population UIC was found to be mild-to-moderately I insufficient (UIC of 91.1 μg/L) [96]. Verbal IQ and reading accuracy as well as comprehension were more likely to be in the lowest quartile for children who had mothers with I-creatinine ratio <150 μg/g [96]. The second included a cohort of pregnant women in Japan ($n = 75,249$) with UIC considered sufficient (UIC, 158 μg/L) that measured dietary I along with kelp and seaweed intake [97]. Offspring cognition was measured using the Japanese translation of the Ages and Stages Questionnaire, Third Edition [97]. Risk of delay in motor skills and problem solving at 1 y, and communication, fine motor skills, problem solving and personal-social domains at 3 y was more likely in those whose mothers were in the lower quintile for I intake during pregnancy compared with the highest quintile [97]. The final study was completed in a population of I sufficient (UIC of 203 μg/L at 17 wk and 211 μg/L at 34 wk) pregnant women in India ($n = 283$) found no association with social quotient, mental development, and motor development measured by the Social Interaction Score [98]. It must be noted that the studies that found an association with developmental scores were in insufficient [96] or marginally sufficient populations [97], whereas the study that found no effect was in a population considered sufficient [98].

Four randomized trials have assessed neurodevelopment and behavior in the offspring of women assigned to I during pregnancy [8,10,59,85]. In 3, some evidence of cognitive benefit was observed, but one did not find benefits to cognition [59]. Neurodevelopment was assessed with the Brunet-Lezine scale at 18 mo of age in the offspring of women ($n = 440$) supplemented with 200 μg/d of I [8]. Study participants began supplementation during 3 times in pregnancy: 4–6 wk of gestation, 12–14 wk of gestation, or at term [8]. The earliest

supplementation resulted in high offspring neurodevelopmental scores [8]. In a second study, pregnant women supplemented with 300 μg/d of I had children whose behavior was in better agreement with their age regarding performance on the *Behavioral Rating Scale Psychomotor Developmental Index of the Bayley Scales of Infant Development* (BSID) than those who were not supplemented; however, there was no effect of supplementation on the *BSID Mental Development Index* [10]. This study should be interpreted with caution as children of the unsupplemented group were tested at 12.4 mo and the supplemented group at 5.5 mo of age.

Santiago et al. [85] assessed cognition at 12.8 mo in the offspring of pregnant women assigned to consume iodized salt or 200 or 300 μg/d of I supplement. The *BSID Mental and Psychomotor Developmental Scales* were both significantly increased with the consumption of a supplement containing I, but significance was lost after adjusting for variables such as gestational age at birth [85]. I supplementation had no effect on birthweight, thyroid volume, Apgar score, or cord blood TSH levels [85]. On the other hand, an observational study of 6644 women in the United Kingdom found that maternal mild-to-moderate I insufficiency (median UIC = 76 μg/L) was not related to adverse neurodevelopmental outcomes of offspring measured by early years foundation stage (aged 4–5 y), phonic scores (aged 5–6 y), and Key Stage 1 (aged 6–7 y) school assessments [99].

The study which found no benefit to cognition, supplemented pregnant women (n = 832) in Bangalore, India and Bangkok, Thailand with 200 μg/d of I [59]. The population baseline median UIC of 131 μg/L indicated a mild-to-moderate I insufficient group [59]. Improvements in maternal UIC and some thyroid markers were observed [59]. The *Neonatal Behavioral Assessment Scale* assessed at 6 wk, and the BSID assessed at age 1 were not different between groups, except for the expressive language BSID which was low in the I supplementation group [59]. The *Wechsler Preschool and Primary Scale of Intelligence Third Edition* and *Behavior Rating Inventory of Executive Function Preschool Version* assessed at age 5.4 y were not different between groups [59].

Although most studies that have looked at low maternal I exposure suggest that it adversely influences fetal neurodevelopment, 4 studies report this can also happen with high I intake during pregnancy. Abel et al. [4], Murcia et al. [9], and Zhou et al. [6] estimated I intake from foods and supplements and measured infant neurodevelopmental outcomes in Norway, Spain, and Australia, respectively. In the study conducted in Norway, there was a U-shaped curve for language development with the risk for language delay increasing below and above a UIC of 150 μg/L [4]. A supplement intake ≥150 μg/d compared with <100 μg/d in the study conducted in Spain was associated with a 5.2-point *reduction* on the Psychomotor Development Index, and a 1.8-fold increased risk of having a Psychomotor Development Index score <85 that was greater in girls than in boys [9]. In a large study (n = 699), Zhou et al. [6] found that children of mothers in the lowest and highest quartile of maternal dietary I intake had low cognitive, language, and motor scores at 18 mo and greater odds of developmental delay. Furthermore, although I intake was related to offspring neurodevelopment, UIC was not, and smaller total gray matter volume was found to be related to both high and low I status [6]. Finally, a multi-micronutrient supplement containing 150 μg/d of I was compared with 2 supplements containing only folic acid and iron. The study found a trend toward low verbal IQ in children (n = 1530) whose mothers had UIC ≥500 μg/L during pregnancy [100].Together these studies suggest there is a window of I intake in pregnancy that is optimal and outside of which neurodevelopment is less than optimal.

The idea that excessive I intake during pregnancy may have adverse outcomes was further discussed by Lee and Pearce [101] who suggest hypothyroidism could occur in the fetus exposed to excess I after the fetal thyroid gland develops the capacity to produce thyroid hormone. They also suggest excessive I intake during pregnancy may induce the Wolff-Chaikoff, a temporary decrease of thyroid function after exposure to large amounts of I, effect in the fetus [101]. They cite a report by Connelly et al. [102] of 3 cases of neonatal hypothyroidism after maternal consumption of very high doses of I (12.5 mg/d) from prenatal supplement [102]. Excessive I intake has been associated with macrosomia [103], and suggested to induce maternal subclinical hypothyroidism and isolated hypothyroxinemia [101,104]. Shi et al. [104] suggest that a safe upper limit of I intake during pregnancy should be aligned with an UIC that does not exceed 250 μg/L as this UIC was associated with an increased risk of subclinical hypothyroidism. A UIC of >500 μg/L is considered excessive and is related to isolated hypothyroxinemia [104]. The previously stated findings are supported by a systematic review (n = 9 studies) and meta-analysis (n = 8 studies) published in 2022, which found that excessive I status during pregnancy is common and related to maternal hypothyroxinemia, hypothyroidism, and hyperthyroidism along with newborn macrosomia and thyroid dysfunction [105]. Countering this, a study of 349 pregnant women in Korea with median dietary I intake during pregnancy of 459 μg/d found no relationship to maternal thyroid function and neonatal outcomes [106].

I supplementation of 200–300 μg/d during pregnancy benefits offspring cognition in most [8,10,85], but not all studies [59]. Observational research found a U-shaped curved related to language development [4] suggesting both low and high I intake during pregnancy may adversely affect offspring. This is further evidenced by low developmental scores of children of mothers in the lowest and highest quartiles of I intake [6], reductions in developmental scores related to high (150 μg/d compared with 100 μg/d) I supplementation [9], and reduced total gray matter volume with both high and low I [107]. In summary, there are some studies which suggest that I supplementation during pregnancy benefits offspring cognition. The I status of the population appears to be an important factor with greater benefits for the severely I deficient and mixed results for those with mild-to-moderate I deficiency [94]. Table 1 summarizes reports related to I status during pregnancy and thyroid and/or offspring neurodevelopment.

Fluoride in pregnancy and child neurodevelopment

Fluoride exposure during pregnancy

F is found in water, both naturally and artificially, but it is also consumed in seafood and tea. Additional exposure can occur from dental products and procedures. The AI of F during

TABLE 1
Summary of findings related to iodine status and intake and maternal and infant outcomes.

Author	Study design	Country	Level of iodine supplementation or iodine status of the population	Duration of intervention	Outcomes related to development and thyroid function
Tinna et al. [48]	Interventional	Thailand	Targeted supplementation (150 μg/d in those with UIC <150 μg/L or no iodine in those with urinary iodine concentration ≥150 μg/L) compared with universal supplementation (150 μg/d)	Second trimester to delivery.	Targeted supplementation prevents over supplementation compared with universal supplementation.
Young et al. [49]	Interventional	Guatemala, Pakistan, India	Iodine supplementation of 250 μg/d of iodine 3 mo preconception, 12 wk of gestation or no supplementation.	≥3 mo of conception, 12 wk of conception, or no supplementation-delivery.	Supplementation before pregnancy increases UIC.
Condo et al. [50]	Observational	Australia	Fortification of bread with iodine	N/A	Weak association between iodine intake from foods and supplements at 28 wk of gestation.
Fuse et al. [51]	Observational	Japan	Population considered to have adequate iodine status	N/A	Median UIC of 219 μg/L which is considered adequate ranging from 6 to 16,300 μg/L. No difference in UIC between trimesters. Those with UIC ≥1,000 μg/d had higher TSH levels than those in lower UIC groups. No relationship between maternal UIC and newborn TSH
Delshad et al. [52]	Observational	Iran	Population considered to have adequate iodine status	N/A	Median UIC of 188 μg/L. High UIC in the first and second trimester and low in the third. Supplementation of 150 μg/d improved intake.
Censi et al. [54]	Interventional	Italy	225 μg/d potassium iodide tablet compared with placebo	12 wk gestation-8 wk postpartum	Positive effect on maternal TSH, thyroglobulin, thyroid volume, UIC No effect on maternal T3 or T4.
Nohr et al. [55]	Observational	Denmark	150 μg/d from supplements compared with no intake of iodine from a supplement	N/A	Positive effect on maternal TSH, T4, and thyroglobulin. No effect on maternal T3.
Glinoer et al. [56]	Interventional	Belgium	100 μg/d of potassium iodide or 100 μg/d of potassium iodide plus 100 μg/d T4 compared with placebo.	End of first trimester to term.	Positive effect on maternal TSH, T4, thyroglobulin, thyroid volume, and UIC.
Nohr et al. [57]	Interventional	Denmark	Three groups: 1) 150 μg/d iodine during pregnancy and postpartum, 2) 150 μg/d during pregnancy but not postpartum, 3) no iodine supplementation	*1)*11 wk gestation- 3 mo postpartum *2)*Delivery to 3 mo postpartum *3)*No supplementation	Positive effect on maternal TSH and thyroglobulin. No effect on maternal T4.
Guo et al. [58]	Observational	China	Compared women who exclusively took iodine containing supplements with those exclusively not taking iodine containing supplements.	N/A	Positive effect on maternal T4.
Gowachirapant et al. [59]	Interventional	India and Thailand	200-μg/d potassium iodide orally compared with placebo	10 wk of gestation to delivery	Positive effect on maternal T4, thyroglobulin, and UIC. No effect on maternal TSH, T3, or thyroid volume.
Manousou et al. [60]	Interventional	Sweden	150 μg/d of iodine from a multivitamin compared with a multivitamin without iodine	7–12 wk of gestation to delivery	Positive effect on maternal thyroglobulin and UIC. No effect on maternal TSH, or T4.
Schulze et al. [61]	Interventional	India	Compared a multiple micronutrient supplement (220 μg/d iodine) to iron and folic acid only (no iodine)	10 wk of gestation to 12 wk postpartum	Positive effect on maternal thyroglobulin.
Antonangeli et al. [62]	Interventional	Italy	200 μg/d compared with 50 μg/d of iodide	10–16 wk of gestation to 6 mo postpartum	Positive effect on maternal thyroid volume and UIC. No effect on maternal TSH, T3, or T4
Romano et al. [63]	Interventional	Italy	20 mg/kg iodide (120-180 μg/L iodine) compared with a control group	From the first prenatal appointment to delivery	Positive effect on maternal thyroid volume and UIC. No effect on maternal TSH.
Stoutjesdijk et al. [64]	Interventional	The Netherlands	Daily multivitamin with 150 μg/d of iodine	20 wk of gestation to 4 wk postpartum	Positive effect on maternal UIC.

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TABLE 1 (*continued*)

Author	Study design	Country	Level of iodine supplementation or iodine status of the population	Duration of intervention	Outcomes related to development and thyroid function
Adu-Afarwuah et al. [65]	Interventional	Ghana	Comparison of a multiple micronutrient (250 μg/d) and an iron folic acid supplement (no iodine)	<20 wk gestation- delivery	Positive effect on maternal UIC.
Liesenkotter et al. [66]	Interventional	Germany	300 μg/d potassium iodide compared with a control group	First prenatal appointment to lactation	Positive effect on maternal UIC No effect on maternal TSH, T4, or thyroid volume
Schulze et al. [67]	Interventional	India	Comparison of a multiple micronutrient (220 μg/d iodine) and an iron folic acid supplement (no iodine)	Participants enrolled at 10 wk gestation- unknown end of supplementation	No effect on maternal T4 or thyroglobulin
Rodriguez-Diaz et al. [68]	Observational	Puerto Rico	Previous to this study there was no data on the iodine status of pregnant women in Puerto Rico	N/A	Adequate UIC at baseline, but varied based on type of supplement (prescription versus nonprescription)
Dandamrongrak et al. [69]	Interventional	Thailand	Iodine supplemented group compared with a non-supplemented group	<18 wk gestation to delivery.	Positive effect of maternal supplementation of newborn TSH
Threapleton et al. [70]	Observational	United Kingdom	Population with mild-to-moderately iodine deficiency	N/A	Median UIC of 101 μg/L while intake was 143 μg/d from supplements and foods and 48% under the United Kingdom recommended intake (140 μg/d) Higher UIC, higher iodine to creatinine ratio, lower thyroglobulin, and lower odds of palpable goiter were associated with total iodine intake.
Chen et al. [71]	Observational	China	Comparison of an iodine sufficient area and a mild-to-moderate deficiency area.	N/A	UIC, free T3, and TSH were lower and free T4, and thyroid dysfunction was higher in the pregnant women in the mild-to-moderate I deficiency area than those in the I sufficient area. In the I sufficient area, free T3 and T4 increased with increase UIC, but in the mild-to-moderate deficiency area only, free T3 increased.
Aktas et al. [72]	Observational	Turkey	Marginally iodine sufficient population.	N/A	Urinary iodine concentration decreased from the first to second trimester to the third trimester. Concomitant increase in TSH throughout pregnancy, although TSH remained within normal limits. T3 and T4 decreased throughout pregnancy.
Wang et al. [73]	Observational	China	Iodine sufficient population	N/A	Decrease in UIC and T3 through pregnancy. U-shaped curve with gestational age.
Siro et al. [74]	Observational	South Africa	Iodized salt fortification program is in use, but salt reduction legislation has decreased intake	N/A	Increased UIC throughout pregnancy.
Vural et al. [75]	Observational	Turkey	Marginally sufficient population	N/A	51% of newborns were found to be iodine deficient.
Stravik et al. [76]	Observational	Sweden	Mild-to-moderate iodine deficient population	N/A	Maternal median UIC of 113 μg/L. Median intake of iodine of 98 μg/d.
Canna et al. [77]	Observational	Cyprus	Mild-to-moderate iodine deficient population	N/A	Maternal median UIC of 105 μg/L.
Veisa et al. [78]	Observational	Latvia	Mild-to-moderate iodine deficient population	N/A	Maternal median UIC 147 μg/L.
Naess et al. [79]	Observational	Norway	Mild-to-moderate iodine deficient population	N/A	Dietary intake and UIC were deficient. Those taking an iodine containing supplement had lower TSH and higher T3 and T4 than non-supplement users.
Abel et al. [5]	Observational	Norway	Mild-to-moderate iodine deficient population	N/A	Low iodine intake was related to higher risk of preeclampsia, preterm delivery, and reduced fetal growth, but not early preterm birth and intrauterine death in those not taking an iodine supplement Use of a supplement was related to reduced risk of preeclampsia and increased fetal growth.
Abel et al. [80]	Observational	Norway	Mild-to-moderate iodine deficient population	N/A	Iodine intake from food and currently using an iodine containing supplement were not related to markers of thyroid function.

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TABLE 1 (*continued*)

Author	Study design	Country	Level of iodine supplementation or iodine status of the population	Duration of intervention	Outcomes related to development and thyroid function
					Beginning iodine supplementation after week 12 of pregnancy was related to lower T4. Urinary iodine concentration was inversely related to T3 and T4.
Nazaropur et al. [81]	Observational	Tehran	Community considered iodine sufficient	N/A	Higher risk of preterm birth in those with deficient UIC and suboptimal thyroid function.
Cui et al. [82]	Observational	China	Mild-to-moderate iodine deficient population	N/A	Urinary iodine concentration was not related to worse infant or pregnancy outcomes.
Torlinska et al. [83]	Observational	United Kingdom	Mild-to-moderate iodine deficient population	N/A	The iodine to creatinine ratio was not related to adverse pregnancy outcomes.
Aakre et al. [84]	Observational	Norway	Mild-to-moderate iodine deficient population	N/A	Urinary iodine concentration was mild-to-moderately deficient (79 μg/L) and intake was below recommendations (140 μg/d).
Santiago et al. [85]	Interventional	Spain	Iodized salt used compared with supplement of 200 μg/d or 300 μg/d	Supplementation beginning at 10 wk gestation	No difference in thyroid markers between groups. Beginning supplementation before pregnancy was related to lower thyroid volume and higher UIC during the first and third trimesters. No relationship found with child neurodevelopment.
Moleti et al. [86]	Observational	Italy	Grouped by: consumption of iodine supplements with iodized salt, only iodized salt, or neither	N/A	T4 was higher in the group consuming iodize salt and a supplement with iodine compared with non-supplement users T3 was higher in the iodized salt group and this group had the lowest TSH.
Wang et al. [87]	Observational	China	Iodine sufficient community	N/A	Iodized salt alone is not enough to increase UIC to adequate level.
Apaydin et al. [90]	Observational	Turkey	Mild-to-moderate iodine deficient population	N/A	Iodized salt users had higher UIC than noniodized salt users.
Huang et al. [91]	Observational	China	Iodine sufficient community	N/A	Highest I in those consuming noniodized salt and noniodized supplement followed by noniodized salt with an iodized supplement, iodized salt with iodized supplement, and finally, iodized salt with a noniodized supplement. Small sample size, assess with caution.
Gonzalez-Martinez et al. [92]	Observational	Spain	Iodine sufficient population	N/A	Iodized salt is sufficient in achieving adequate UIC status.
Cui et al. [93]	Observational	China	Iodine sufficient population	N/A	Iodized salt is not an important source of iodine in children and pregnant women.
Abel et al. [4]	Observational	Norway	Mild-to-moderate iodine deficient population	N/A	Maternal iodine intake was related to offspring language delay, behavioral problems, and fine motor skills at the age of 3 y. No relationship to gross motor skills or walking by 17 mo.
Zhou et al. [6]	Observational	Australia	After mandatory iodine fortification of bread	N/A	Low cognitive, language, and motor skills in children in the lowest and highest quartile of iodine intake. Higher odds of developmental delay in the lowest and highest than in second and third quartiles. No relationship between UIC and cognitive outcomes.
Hynes et al. [7]	Observational	Australia	Before the mandatory iodine fortification of bread	N/A	Low scores on spelling, grammar, and English-literature sections of standardized exams administered at the age of 9 y in those with mothers with UIC <150 μg/L.
Berbel et al. [8]	Interventional	Spain	200 μg/d potassium iodide beginning at 4–6 wk of gestation, 12–14 wk of gestation, or after delivery	First pregnancy appointment-end of lactation	Supplementation increased the mean UIC and the proportion of participants with UIC >150 μg/L of the groups

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TABLE 1 (*continued*)

Author	Study design	Country	Level of iodine supplementation or iodine status of the population	Duration of intervention	Outcomes related to development and thyroid function
					supplemented in pregnancy above those supplemented after delivery. Mean T4 was higher in participants supplemented in pregnancy than those supplemented after delivery. Developmental quotient was higher in those supplemented starting 4–6 wk of gestation than those supplemented at 12–14 wk of gestation and after delivery. The 12–14-wk gestation and after delivery groups were not different.
Murcia et al. [9]	Observational	Spain	Iodine sufficient population	N/A	High intake of iodine from supplements was related to high scores on the *Psychomotor Development Index*.
Velasco et al. [10]	Interventional	Spain	300 μg/d of potassium iodide supplementation compared with a control group.	First trimester of pregnancy to lactation.	UIC was lower in the control group than in the intervention group during the third trimester. TSH, FT3, and FT4 were higher in the control group than in the intervention group during the third trimester. High UIC was related to a low reduction in FT4. *Psychomotor Development Index* was improved in children of mothers in the treatment group, although breastfeeding was a confounding variable *Psychomotor Development Index* correlated with FT4 during the third trimester. Low reduction of FT4 during pregnancy was related to high Psychomotor Development Index score. The intervention group scored higher in reactions to persons, reaction to mother, cooperation, activity, arousal, and making sounds by banging Age of cognitive assessment was 12.44 m in the control group and 5.47 m in the intervention group. This study should be reviewed with caution
Vermiglio et al. [95]	Observational	Undisclosed	Comparison of an iodine deficient area compared with an iodine sufficient area.	N/A	A higher proportion of children in an iodine deficient area were diagnosed with attention deficit disorder than those in an iodine sufficient area. The mean total IQ was lower among those in an iodine deficient area than those in an iodine sufficient area and lower in those with ADHD. Wechsler Intelligence Scales' freedom-from-distraction subscore was also lower in those with ADHD compared with the control. Wechsler Intelligence Scales' verbal subscore was lower in those with attention deficit disorder compared with both the control and those without ADHD. Wechsler Intelligence Scales' performance subscore was lower in those in an iodine deficient area than those in an iodine sufficient area.
Bath et al. [96]	Observational	United Kingdom	Mild-to-moderate iodine deficient population	N/A	Women with iodine to creatine ratio of <150 μg/g were more likely to have a child with IQ in the lowest quartile.
Hisada et al. [97]	Observational	Japan	Iodine sufficient population	N/A	Fine motor delay, problem solving delay, and communication were increased in the low iodine intake quintiles at the age of 1 y.

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TABLE 1 (*continued*)

Author	Study design	Country	Level of iodine supplementation or iodine status of the population	Duration of intervention	Outcomes related to development and thyroid function
					At 3 y of age communication, fine motor skills, problem solving, and personal-social domain delays were increased in the lowest iodine intake quintiles
Lean et al. [98]	Observational	India	Mild-to-moderate iodine deficient population	N/A	No differences in offspring social quotient, mental development, and motor development scores were observed between the lowest and highest maternal urinary iodine quartiles.
Threapleton et al. [99]	Observational	United Kingdom	Mild-to-moderate iodine deficient community	N/A	No relationship between UIC or iodine to creatinine ratio and neurodevelopmental outcomes measured by the *early years foundation stage.*
Mulder et al. [107]	Observational	The Netherlands	Iodine sufficient population	N/A	High and low urinary iodine to creatinine ratio were associated with reduced total gray matter volume, although this finding was not consistent throughout the analysis.
Connelly et al. [102]	Case study	N/A	Maternal ingestion of a supplement containing 12.5 mg/d of iodine (Iodoral)	N/A	Neonatal congenital hypothyroidism.
Dong et al. [103]	Observational	China	Iodine sufficient community	N/A	Maternal UIC ≥250 μg/L was associated with high risk of macrosomia.
Shi et al. [104]	Observational	China	Iodine sufficient community	N/A	UIC of 159–499 μg/L and ≥500 μg/L were related to high risk of subclinical hypothyroidism UIC of ≥500 μg/L was related to increased risk of isolated hypothyroxinemia.
Hu et al. [106]	Observational	Korea	Community at high risk of excessive intake	N/A	Median dietary iodine intake was above the recommended levels, but this was not related to maternal thyroid function or neonatal outcomes.
Sun et al. [89]	Observational	China	Iodine sufficient community	N/A	Iodized salt, iodine rich foods, and iodine supplements are all needed to meet the iodine needs during pregnancy.
Knøsgaard et al. [53]	Observational	Denmark	Iodine deficient community	N/A	UIC of pregnant women in Denmark was insufficient despite iodized salt fortification.
Kampouri et al. [100]	Interventional	India	Comparison of 3 supplements, 2 of which contained only iron and folic acid, and a multiple micronutrient supplement containing 150 μg/d of iodine.	9 wk of gestation compared with 20-wk gestation delivery.	UIC of <150 μg/L during pregnancy was related to low full-scale and verbal IQ scores at the ages of 5 and 10 y. A trend of excessive UIC (≥500 μg/L) to verbal IQ scores was also observed.

IQ, intelligence quotient; N/A, not applicable; T3, Triiodothyronine; T4, Thyroxine; TSH, Thyroid Stimulating Hormone UIC, urinary iodine concentration.
[1]All results reported are significant.
[2]Mild-to-moderate iodine deficiency is defined as urinary iodine concentration of 50-100 μg/L; Iodine sufficient is defined as urinary iodine concentration of 150-249 μg/L.

pregnancy is 3 mg/d, the same as for female adults who are not pregnant [11].

In the US, the public water system is typically fluoridated to a level 0.7 mg/L as recommended by the *US Department of Health and Human Services*, representing a change from the past recommendations of 0.7–1.2 mg/L [20]. F exposure is not believed to be excessive in the US, and a report from the *Environmental Protection Agency* estimates that adult women consume 2.91 mg/d of F [108], slightly < the 3-mg/d AI recommendation from the DRI [11].

It was once believed that the placenta acted as a barrier to F during pregnancy, and it was unknown how the fetus would be affected by maternal exposure to F [109]. F is now known to pass through the placenta [110, 111], although one study suggests that the placenta may be a more effective barrier at increased maternal F exposure [112]. F has been found in the placenta [110], cord blood [109,112,113], and amniotic fluid [109, 113–115].

Contemporary research has been completed to determine the effect of F on the developing fetus and offspring, in both preclinical studies and observational studies of human populations. The previously mentioned recommendations of fluoridation of water to prevent childhood dental caries is regarded as one of the greatest achievements of public health in modern times [12]; however, a systematic review and meta-analysis of 27 studies found that children in areas where environmental exposure to F is high have lower IQ than those in areas of low F exposure [13]. A more recently published meta-analysis of 26 studies and 7258 children also found an inverse relationship between high F exposure and children's IQ [116].

Preclinical studies of fluoride and offspring growth and neurodevelopment

In attempting to explain the relationship between F exposure during pregnancy and IQ, preclinical studies of F exposure during pregnancy have focused on the effects of high levels of F exposure on offspring growth and neurodevelopment. Excessive F exposure decreases the food consumption and weight gain in the mother whereas in the offspring, growth (*in utero* and postnatal) [117], brain weight [15], and hippocampal [15,118–123] as well as cerebellum [124] neurons are adversely affected. Attention, sensory and motor development were also reported to be affected in the study by Bartos et al. but not in the study by Flace et al. [125, 126]. Excessive F was related to increased signaling in T-2 weighted scanning images, indicating brain ventricular edema, and acute degeneration of the ultrastructure in the hippocampal CA1 region, indicating changes in the brain morphology, in addition to decreased glucose utilization and decreased expression of GLUT1 and GFAP proteins [15]. Levels of biomarkers of oxidative stress and biometals (iron, copper, zinc, and manganese) in the CNS were also observed to be altered by F exposure [117]. Oxidant and antioxidant activity were increased, and macromolecules (proteins) were decreased in the CNS with prenatal F exposure in rats [127]. One preclinical study measured thyroid outcomes in Long-Evans hooded rats exposed to F through diet (standard 20.5 ppm F, low 3.24 ppm F) and water (1, 10, and 20 ppm F) starting on gestational day 6 and found no changes in offspring in terms of T3, T4, or TSH levels because of F exposure [128]. In contrast, in a study of 35 communities in Iran (n = 492 infants), birth height and weight were positively correlated with water F levels in communities with low F levels (<0.7 mg/L), but this was not true for those residing in communities with high (>1.5 mg/L) water F levels [129].

Maternal fluoride exposure and child neurodevelopment

In addition to preclinical studies, 8 studies report UFC and offspring neurodevelopment in pregnant women. As with I, F exposure is assessed by measuring the level of F in the urine. The largest studies were in Canada [130], India [131], Mexico [132, 133], and Spain [134]. Several smaller studies in Poland [135], the US [115], China [136], and Mexico [137] had fewer than 100 participants. One study in Mexico (n = 103) measured dietary F intake and toddler developmental outcomes [138].

The study conducted in China (n = 91) measured neonatal neurobehavioral development using the standard neonatal behavioral neurological assessment [136]. Participants were grouped by water F levels, high or 1.7–6.0 mg/L or low 0.5–1.0 mg/L, comparing neurobehavioral outcomes [136]. Those in the high F group were found to have worse outcomes related to neurobehavioral outcomes than the low F group [136]. Although the study reports a significantly higher UFC in the high F group (3.58 ± 1.47 mg/L) than the low F group (1.74 ± 0.96 mg/L), they do not report whether a relationship between UFC during pregnancy and newborn neurobehavioral development was observed [136].

The Canadian sample (n = 2001) compared UFC of pregnant women, living in fluoridated areas (mean 0.7 ± 0.4 mg/L) with those living in nonfluoridated areas (mean 0.34 ± 0.24 mg/L). Women living in fluoridated areas had UFC almost 2 times higher than those living in nonfluoridated areas [130]. UFC increased throughout the pregnancy with higher third trimester levels compared with those of first trimester [130]. There was also a relationship between UFC, and water F levels in the pregnant women [130]. This is the same cohort previously mentioned in relation to the effects of maternal UFC on child cognition, finding low IQ at ages 3–4 y for boys but not girls [18], In a subsequent publication, the authors reported that postnatal F exposure estimated from water F concentration in the postal code of the same cohort was associated with low childhood IQ [19]. The relationship was found in both formerly breast-fed and formula-fed children; however, the adverse relationship with F was large in children previously fed infant formula [19].

The *Early Life Exposures in Mexico to Environmental Toxicants* study was a longitudinal birth cohort study of prenatal and early life exposure to F [132]. This study measured plasma and UFC (n = 872) [137] and childhood IQ (n = 498) [132]. In Mexico, F is fortified in salt and milk [132,137]. Plasma and urine samples were collected at early (13.5 ± 2.3 wk, 0–26 wk), mid (25.3 ± 2.4 wk, 15–37 wk), and late (34.5 ± 2.1 wk, 22–34 wk) gestation [137]. The mean UFC was 0.91 mg/L, and mean plasma F level was 0.0221 mg/L, approximately 40 times lower than UFC [137]. In contrast to other studies, UFC increased until 22–23 wk of gestation, and then decreased until the end of pregnancy [137]. The General Cognitive Index of the McCarthy's Scales of Children's Ability was assessed at age 4 and full-scale IQ from the Wechsler Abbreviated Scale of Intelligence at 6–12 y to assess cognition [132]. For every 0.5 mg/L

increase in UFC, the General Cognitive Index score and full-scale IQ decreased by 3.15 and 2.50 units, respectively [132]. A secondary analysis of this data sought to determine which developmental domains were most adversely affected by maternal F exposure, finding that nonverbal domains (visual--spatial and perceptual reasoning) were more affected [139]. Another study completed in Mexico ($n = 90$) found an inverse relationship between first and second trimester UFC and infant neurodevelopment at a mean of 8 mo (range, 3–15 mo) using the Mental Development Index of the BSID II [133]. A third study in Mexico ($n = 103$) found an inverse relationship between maternal dietary F intake during pregnancy and IQ scores of boys but not in girls at 24 mo of age [138].

In contrast to the studies from Canada [18] and Mexico [132, 133], a study completed in Spain found a positive correlation between maternal UFC during pregnancy, and neurodevelopment measured at 4 y using the McCarthy's scale ($n = 248$) in boys, but not among girls [134]. There was a positive relationship of UFC with the McCarthy's scales on the verbal performance, numeric, and memory domains and the General Cognitive Index for boys [134]. The addition of mercury from cord blood to the model resulted in significance only in the verbal domain and the General Cognitive Index [134]. Although the overall effect of F on developmental scores are in contrast to those found in the studies completed in Canada [18] and Mexico [138], the interaction involving sex on developmental scores was observed in all 3 studies, with boys showing an effect whereas girls were not found to be significant [18,134,138]. Finally, similar to both the Polish and Canadian studies, Spanish maternal UFC was higher in urine samples from later pregnancy than those from earlier in pregnancy [18,130,134,135]. A key difference in these studies is age at neurodevelopmental assessment. The study conducted in Spain assessed development at a mean of 14 mo compared with the other studies that assessed development later in childhood.

IQ is not the only measure of neurodevelopment associated with F exposure during pregnancy. An ecological association study by Malin and Till [140] associated water fluoridation levels in the 1990s with ADHD rates in the early 2000s. The children diagnosed with ADHD in the early 2000s would have been exposed to the 1990s water F levels through pregnancy and infancy, although the actual level of exposure is not reported. Another study found higher scores on tests measuring ADHD behaviors related to maternal UFC during pregnancy in children aged 6–12 y [141].

UFC during pregnancy at levels of water fluoridation considered safe has been related to low offspring developmental scores [18,132] and ADHD [140,141]. At high environmental F exposure, poor pregnancy outcomes were observed [131]. One study does contradict previous findings with a positive relationship between maternal UFC and childhood cognition [134], indicating the need for more research in this area.

Although a study of pregnant women in India ($n = 600$) did not measure outcomes related to child development, it is included here because the authors found a mean UFC of 2.65 mg/L with a range of 1.0–4.3 mg/L, and water analysis showed that all sources of water were above the 1.5 mg/L recommended by the WHO [131]. The primary outcomes reported in this article associated the elevated UFC during pregnancy to miscarriage and still birth [131].

Fluoride from drinking water and childhood intelligence

Additional studies have investigated water fluoridation levels in relation to childhood intelligence. Two very similar studies [142,143] investigated the intelligence of 320 [142] and 160 [143] children age 7–14 y, conceived and raised in high water F areas (4.55 mg/L [142] and 4.12 mg/L [143]) of China and compared with those raised in low water F areas (0.89 mg/L [142] and 0.91 mg/L [143]) of the same country with similar cultural and sociodemographic factors. The IQ of the children living in the high water F areas had lower IQ than those in the low water F areas [142,143]. Chen et al. [142] also report dental and skeletal fluorosis in the higher water F area. They both report parental employment as a confounder of IQ, and Chen et al. [142] also report education as a confounder [143]. Similar findings have also been observed in Iran [144] and India [145]. In Sudan, school performance of 775 children was negatively correlated with F levels in drinking water [146]. Finally, in an area classified as having endemic fluorosis ($n = 720$) by the Chinese Geological Office, primary school children were found to have lower IQ than those in a low F area ($n = 236$) [147]. The endemic fluorosis area also had more children classified as having a low IQ (IQ<69) [147]. Table 2 summarizes the reports related to F and pregnancy and/or offspring neurodevelopment.

I and F and thyroid function

The interaction between I and F exposure during pregnancy and thyroid function has been studied in preclinical models. F can reduce sodium/iodide symporter (NIS) gene expression, and inhibit the sodium/potassium ATPase, which is required for proper functioning of the NIS [148]. Additionally, the NIS exclusively transports monovalent anions, such as F, and it can be postulated that the NIS transports F. Moreover, it can be questioned whether the NIS preferentially transports F over I, although mechanistic studies are needed [149]. Rats exposed to various levels of F and I had effects of both excessive I and F on thyroid morphology and function, with excessive I leading to the most damage, although some negative effects to the thyroid, such as damage to the follicular epithelial cells, were evident with excessive exposure to both [14]. In contrast, low I paired with high F in a study by Ge et al. [150] found severe damage to the thyroid itself, and to thyroid DNA from exposure to low I and high F. When both parents were raised on an I deficient diet with excessive F, a diet that their offspring consumed after birth, the offspring had changes in the brain protein expression related to cellular signaling, energy metabolism, and protein metabolism [24]. A study by Wang et al. [151] found less protein, worse memory and changes in cholinesterase in rats exposed to low I and high F. Another preclinical model found that both excessive I and excessive F negatively affected the thyroid cells, with increases in reactive oxygen species and apoptosis, and decreased thyroid cell viability [22].

At least 3 observational studies suggest that F may compete with I to adversely affect thyroid function. Children and adolescents who are I sufficient but living in areas with high concentrations of water F had higher rates of endemic goiter than those living in areas with low concentrations of water F [23].

Table 2
Summary of findings related to fluoride status and intake and maternal and infant outcomes

Author	Study design	Country	Level of fluoride Exposure	Duration of intervention	Outcomes related to fluoride exposure
Narayanaswamy and Piler [117]	Animal (Wistar rat) study	N/A	100 or 200 ppm fluoride in water and a tap water control	Third day of gestation- twenty first postnatal day	Decreased maternal food consumption and weight gain. Changes in level of antioxidants and minerals in offspring brain leading to oxidative stress.
Jiang et al. [15]	Animal (Sprague-dawley rat) study	N/A	25, 50, 100 mg/L fluoride in water and a tap water control.	Female and male rats were exposed 10 d before pregnancy and offspring were exposed until 2 mo of age.	Decreased brain weight. Impaired learning and memory in offspring. Neuronal degeneration. Decreased glucose utilization and protein expression of glucose transporter 1. Increased brain-derived neurotrophic factor. Changes in hippocampus structure.
Bartos et al. [118]	Animal (Wistar rat) model	N/A	5 mg/L fluoride or 10 mg/L of fluoride and a tap water control	Gestational day 0–postnatal day 21	Decreases in memory were observed in both treatment groups along with decreased catalase and glutamate transaminases, signs of oxidative stress.
Bartos et al. [119]	Animal (Wistar rat) model	N/A	5 mg/L or 10 mg/L of fluoride exposure compared with a control group	Gestational day 0–postnatal day 21	Decreased memory. Decrease α-7 nAChR subunit mRNA catalase in the hippocampus.
Bera et al. [120]	Animal (Wistar rat) model	N/A	2.5 mg/kg/mL and 5.0 mg/kg/L of fluoride treatment groups compared with a control group.	Gestational days 0–9 after birth.	High dose of fluoride was associated with poor outcomes in learning, memory, motor coordination, and blood pressure. An interaction with sex was observed with male pups having worse behavioral outcomes than female pups.
Sun et al. [121]	Animal (mouse) model	N/A	25, 50, or 100 mg/L fluoride	Gestational day 0 to end of lactation.	Increased errors in the radial arm maze test along with reductions in some types of glutamate receptor mRNA suggesting decreased learning and memory ability.
Ferreira et al. [122]	Animal (Wistar rat) model	N/A	10 mg/L of fluoride or 50 mg/L of fluoride compared with a control group	Day 1 of pregnancy to 21 d of lactation.	Increased bioavailability of fluoride in plasma. Redox imbalance measured by assessing antioxidant capacity again against pro-oxidation molecules in the hippocampus. Changes in the hippocampus proteome.
Flace et al. [125]	Animal (Wistar rat) model	N/A	2.5 mg/kg/mL and 5.0 mg/kg/L of fluoride treatment groups compared with a control group	Through all of pregnancy to 9th day of lactation.	Increased reactivity in newborn pups.
Bartos et al. [126]	Animal (Wistar rat) model	N/A	Low levels of fluoride of 5 mg/L or 10 mg/L compared with a control group	Pregnancy-lactation	Both levels showed dysfunction in the CNS mechanisms related to motor development.
Basha et al. [127]	Animal (Wistar rat) model	N/A	50 ppm or 150 ppm exposure to fluoride compared with a control group	1st day of pregnancy to postnatal day 21	Fluoride exposure increased markers of oxidative stress in the developing CNS.
McPherson et al. [128]	Animal (Long-Evans hooded rats) model	N/A	Standard diet of 20.5 ppm fluoride, or low diet of 3.24 ppm fluoride and drinking water exposure of 0, 10, or 20 ppm of fluoride.	Gestational day 6 to adulthood.	No effect on development observed.
Aghaei et al. [129]	Observational (human subjects)	Iran	35 regions of Iran with varying levels of water F ranging from <0.7 to >1.5 mg/L	N/A	In areas with low water fluoridation (<0.7 mg/L) birthweight and length were positively correlated with water F, but this was not true of those living in areas high (>1.5 mg/L) water fluoridation.
Souza-Monteiro et al. [124]	Animal (Wistar rat) model	N/A	Pregnant rats were divided into 3 groups, 10 mg/L fluoride, 50 mg/L fluoride, and a control group for 21 d prenatally and day 21 postpartum. Male offspring were evaluated at day 21 d postpartum.	21 d of gestation and 21 d of lactation.	Exposure of 50 mg/L of fluoride prenatally and through lactation promoted oxidative stress and caused morphological changes of the cerebellum, suggesting motor impairment.
Li et al. [123]	Animal (mice) model	N/A	Pregnant rats exposed to 100 mg/L of fluoride from gestational day 1–20 with outcomes measured in the male offspring.	Gestational day 1 to gestational day 20	Impaired learning and memory. Changes in the hippocampal neurons.

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Table 2 (*continued*)

Author	Study design	Country	Level of fluoride Exposure	Duration of intervention	Outcomes related to fluoride exposure
Li et al. [136]	Observational (human participants)	China	Newborns infants of women in either a high fluoride area (1.7–6.0 mg/L fluoride in water) or low fluoride area (0.5–1.0 mg/L fluoride in water)	N/A	Newborns of women living in the high fluoride area had worse neurobehavioral outcomes than newborns of women in the low fluoride area.
Till et al. [130]	Observational (human participants)	Canada	High water fluoridation exposure (mean 0.7 ± 0.4 mg/L) and low water fluoridation exposure (0.34 ± 0.24 mg/L) were compared. Both levels of exposure are considered safe.	N/A	UFC was almost 2 times higher in areas of high exposure than in areas with low exposure. Positive association between UFC and water fluoride levels.
Goyal et al. [131]	Observational (human participants)	India	Mean of 2.65 mg/L from drinking water. This level is above the level considered safe.	N/A	Elevated UFC was associated with miscarriage and still birth.
Bashash et al. [132]	Observational (human participants)	Mexico	Fluoride exposure in Mexico comes from fluoridated salt and milk.	N/A	Inverse relationship between maternal UFC and offspring IQ.
Valdez-Jimenez et al. [133]	Observational (human participants)	Mexico	Fluoride exposure in Mexico comes from fluoridated salt and milk.	N/A	Inverse relationship between maternal UFC and offspring IQ.
Ibarluzea et al. [134]	Observational (human participants)	Spain	Community water fluoridation level considered safe.	N/A	Positive association between maternal UFC and offspring neurodevelopment (in boys, not girls).
Opydo-Szymaczek et al. [135]	Observational (human participants)	Poland	Community water fluoridation levels considered safe	N/A	Reported UFC in the 28th (0.635 mg/L) and 33rd (0.838 mg/L) wk of pregnancy compared with UFC (1.3 mg/L) in a nonpregnant control group.
Abduweli Uyghurturk et al. [115]	Observational (human participants)	The United States	High community water fluoridation level (>0.3 mg/L) and low community water fluoridation level (≤0.3 mg/L). Both of which are considered safe.	N/A	0.46 mg/L (0.47 mg/L adjusted for specific gravity) in the low community water fluoridation group. 0.72 mg/L (0.74 mg/L adjusted for specific gravity) in the high community water fluoridation group.
Thomas et al. [137]	Observational (human participants)	Mexico	Fluoride exposure in Mexico comes from salt and milk.	N/A	UFC of 0.83 mg/L in early, 0.90 mg/L in mid, and 0.80 mg/L in late pregnancy UFC adjusted for creatinine of 0.92 mg/L during early pregnancy, and 0.95 mg/L during mid and 0.87 mg/L during late pregnancy.
Cantoral et al. [138]	Observational (human participants)	Mexico	Dietary fluoride intake	N/A	No association with cognitive, language. Or motor development. Interaction with child sex. Increasing maternal dietary fluoride was associated with decreasing cognitive outcomes in boys but not in girls.
Green et al. [18]	Observational (human participants)	Canada	Community water fluoridation levels considered safe.	N/A	Inverse relationship between UFC and offspring (boys, not girls) IQ.
Till et al. [19]	Observational (human participants)	Canada	Community water fluoridation levels considered safe.	N/A	Association between postnatal fluoride exposure (water fluoridation of participant zip code) and childhood IQ Larger relationship in formula-fed than in breast-fed children.
Malin et al. [140]	Ecological association study (human participants)	The United States	Community water fluoride at levels considered safe; community water levels of fluoride were assessed for ADHD rates.	N/A	Areas of higher water fluoridation had higher rates of ADHD
Bashash et al. [141]	Observational (human participants)	Mexico	Fluoridated salt; related maternal UFC to ADHD	N/A	High scores observed for ADHD assessments.
Goodman et al. [139]	Observational (human participants)	Mexico	Fluoridated salt.	N/A	Decreases in IQ were found to be specifically related to nonverbal intelligence which indicates visual-spatial and perceptual reason were more impacted.
Chen et al. [142]	Observational (human participants)	China	An area of high water fluoride (4.55 mg/L) compared with an area of low water fluoride (0.89 mg/L)	N/A	For the high water fluoride area, lower IQ and higher dental and skeletal fluorosis were reported than those the low fluoride area. Parental employment and education were confounders of IQ.

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Table 2 (*continued*)

Author	Study design	Country	Level of fluoride Exposure	Duration of intervention	Outcomes related to fluoride exposure
Zhao et al. [143]	Observational (human participants)	China	An area of high water fluoride (4.12 mg/L) compared with an area of low water fluoride (0.91 mg/L)	N/A	The residents of high water fluoride area had lower IQ than those residing in low water fluoride area. Parental education was a confounder of IQ.
Karimzade et al. [144]	Observational (human participants)	Iran	An area of high water fluoride (3.94 mg/L) compared with a low water fluoride area (0.25 mg/L)	N/A	Children in the high water fluoride area had lower IQ than those in the low water fluoride area.
Mustafa et al. [146]	Observational (human participants)	Sudan	Water fluoride ranged from 0.14 to 2.07 mg/L	N/A	School performance in 5/8 subjects was negatively associated with water fluoride levels.
Trivedi et al. [145]	Observational (human participants)	India	Water fluoride ranging from 1.9-3.42 mg/L	N/A	The IQ of school children in the higher fluoride groundwater areas had lower IQ than those in the low fluoride groundwater areas.
Li et al. [147]	Observational (human participants)	China	An area of high fluoride exposure (classified as an endemic fluorosis area by the *Chinese Geological Office*) to an area of low fluoride exposure	N/A	The IQ of children was low in the endemic fluorosis area. A high proportion of children in the endemic fluorosis area had low IQ (IQ <69)

Abbreviations: IQ, intelligence quotient; N/A, not applicable; UFC, urinary fluoride concentration.
All reported findings are significant.
Water fluoridation levels under 4 mg/L are considered safe. Water fluoridation levels less than 0.7 mg/L are recommended.

Another recent study found smaller thyroid volume in children with high UIC than those with low UIC who were living in a high environmental F area of China [152]. Thyroid volume increased with increasing UFC with a greater change observed in boys than in girls [152]. Total T3 was negatively associated with UFC in those with UIC $\leq$300 μg/L [152].

The most compelling evidence that F can adversely influence thyroid status by competing with I comes from an observational study of 1000 nonpregnant Canadian adults [21]. The study found that I deficient individuals had a 0.35 mIU/L increase in TSH levels for every 1 mg/L increase in UFC in a population with a range of F exposure not previously considered to be too high [21].

Iodine, fluoride, thyroid function, and child neurodevelopment

One Canadian cohort study (n = 366) measured both maternal UIC and UFC and neurodevelopment in offspring [153]. I status modified the relationship between maternal UFC and full-scale IQ (3–4 y of age by Wechsler Preschool and Primary Scales of Intelligence-III) in boys [153]. An interaction between UIC, UFC, and sex was observed with boys but girls remained unaffected [153]. In boys whose mothers had insufficient UIC during pregnancy, a 0.5-mg/g increase in maternal UFC was related to a 4.65-point decrease in full-scale IQ, whereas in boys whose mothers had adequate UIC during pregnancy, a 0.5 mg/g increase in maternal UFC was related to a 2.95-point decrease in full-scale IQ [153]. This study supports the theory that maternal I and F intake interact in their effect on offspring cognition. Table 3 summarizes the articles related to the interaction of I, F, and thyroid function, and/or offspring neurodevelopment.

Discussion

From the review of published studies, supplementing populations with mild-to-moderate I deficiency can improve I status and have favorable effects on thyroid function and offspring neurodevelopment. However, findings from Murcia et al. [9], Abel et al. [4], and Zhou et al. [6] suggest that too much I supplementation may adversely affect neurodevelopment. Excessive I status is also associated to maternal thyroid function with Shi et al. [104] suggesting UIC of 250 μg/L as a safe upper limit and 500 μg/L considered excessive because of increased risk of subclinical hypothyroidism and isolated hypothyroxinemia, respectively. The changes in maternal thyroid function shown by Shi et al. [104] and the evidence provided in the review by Lee and Pearce [101] citing the possible induction of the Wolff-Chaikoff effect in the fetus could be related to an adverse effect of excessive I exposure during neurodevelopment.

Although the possible excessive intake of I during pregnancy deserves more investigation, the more common concern is I deficiency during pregnancy. The UIC data from NHANES studies suggest that US women have mild-to-moderate I deficiency [39,45]. Studies of dietary I intake among pregnant women in the US are now possible thanks to the recent publication of the Iodine Content of Common Foods [34]. An assessment of dietary and supplement intake will allow for a better understanding and more evidence-based recommendations on

Table 3
Summary of papers related to fluoride and iodine status and intake and maternal and infant outcomes

Author	Study design	Country	Level of iodine and fluoride exposure	Duration	Outcomes
Jiang et al. [14]	Animal (rat) model	N/A	Total groups: 8 Three excessive fluoride groups (15, 30, 60 ppm fluoride) One excessive iodine group (1200 μg/L) Three excessive fluoride and iodine groups (all given 1200 μg/L along with 15, 30, or 60 ppm fluoride) One control group	75 or 150 d	Excessive iodine and fluoride affected thyroid morphology and function
Ge et al. [24]	Animal (rat) model	N/A	Iodine deficient, excessive fluoride diet	Male and female rats exposed 3 mo before pregnancy and offspring were exposed until 20 d after birth	Changes in offspring brain protein expression, cellular signaling, energy metabolism, and protein metabolism.
Wang et al. [151]	Animal (rat) model	N/A	One high fluoride group (100 mg NaF/L) One low iodine group (0.0855 mg/kg chow) One group with both high fluoride (100 mg NaF/L) and low iodine (0.0855 mg/kg) One control group	Female rats were exposed 3 mo before pregnancy, and their offspring consumed the same diet through the study (90th day of life).	Learning and memory were worse in the high fluoride, low iodine group. Brain protein was lower in the low iodine group, and then even lower in the high fluoride low iodine group Cholinesterase in the brain was affected by high fluoride, and then even more affected by high fluoride, low iodine.
Ge et al. [150]	Animal (rat) model	N/A	One high fluoride group (100 mg NaF/L [45 mg F–/L] in their drinking water), One low iodine group (0.0855 mg I/kg diet), One high fluoride and low iodine treatment combined group One control group	From 1 mo of age to 20 mo of age	The low iodine, high fluoride, and the combine low iodine and high fluoride groups had more DNA damage and had increased severe thyroid cell damage than the control group.
Liu et al. [22]	Thyroid cell line (Nthy-ori 3-1)	N/A	Excessive iodine and fluoride.	N/A	Negatively affected thyroid cells, increased reactive oxygen species, apoptosis, and decreased thyroid cell viability was observed with excessive exposure to both iodine and fluoride.
Jooste et al. [23]	Observational (human participants)	South Africa	Iodine sufficient population living in an area of high fluoride exposure.	N/A	Increased rates of endemic goiter in children and adolescents.
Du et al. [152]	Observational (human participants)	China	Community with a high environmental fluoride exposure.	N/A	Smaller thyroid size in children with high UIC than in those with low UIC. Increasing thyroid volume with increasing UFC. This change was greater in boys than in girls. Negative association between T3 and urinary fluoride concentration in those with UIC $\leq$300 μg/L.
Malin et al. [21]	Observational (human participants)	Canada	Community water fluoridation level considered safe.	N/A	For every 1 mg/L increase in UFC, TSH levels decreased by 0.35 mIU/L.
Goodman et al. [153]	Observational (human participants)	Canada	Community water fluoridation level considered safe.	N/A	Iodine status during pregnancy was found to modify the relationship between urinary iodine, urinary fluoride, and IQ scores. There was an interaction with sex with boys in particular showing an affect.

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Table 3 (*continued*)

Author	Study design	Country	Level of iodine and fluoride exposure	Duration	Outcomes
					Every 0.5 mg/g increase in maternal UFC was related to a 4.65-point decrease on the full-scale IQ test in boys whose mothers had insufficient iodine status during pregnancy For every 0.5 mg/g increase in maternal UFC, there was a 2.95-point decrease in full-scale IQ test in boys whose mothers had adequate iodine status during pregnancy.

Abbreviations: IQ, intelligence quotient; N/A, not applicable; NaF/L, sodium fluoride per liter; UFC, urinary fluoride concentration; UIC, urinary iodine concentration.
[1]All reported findings are significant.
[2]T3, Triiodothyronine.
[3]Water fluoridation under 4 mg/L is considered safe. Water fluoridation levels less than 0.7 mg/L are recommended.

this topic. The *American Academy of Pediatrics* [35], the *Endocrine Society* [37], and the *American Thyroid Association* [36] currently recommend pregnant women consume a supplement containing 150 μg/d of I, although many prenatal supplements do not contain I, or contain varying amounts of I [38] and evidence indicating only about 20% of pregnant women in the US consume a prenatal supplement containing I [39, 40].

As for F, the benefits of F on reducing dental caries are well known [11,154,155], and the *US Health and Human Services department* has recommended water fluoridation of 0.7 mg/L in the US to reduce risk of childhood dental caries [20]. Recently, the effect of F exposure on the developing brain has been of high interest with studies showing negative relationships between F exposure during fetal and early life and childhood cognition and reveal an interaction of sex on timing of exposure with fetal life for males and infancy for females being time periods of adverse influence of F in neurodevelopment [18,19,132,133,137,138]. These studies were conducted in areas where most exposure comes from water fluoridation, or fortification of salt or milk, and they suggest that the negative effects of F exposure during pregnancy may be observed in individuals consuming water concentrations of F believed to be safe and that are commonly added to water. These studies outnumber a single study that found a positive relationship between UFC and childhood cognition [134]. Finally, there are limitations in the body of literature on F exposure. As soil, and therefore groundwater, may be contaminated with F along with other neurotoxic elements, such as lead or arsenic, it is difficult to distinguish the cause of adverse developmental outcomes in areas of high environmental F exposure. None of the studies in this review have accounted for this. As for methodological limitations, the biomarkers of F exposure (UFC) and iodine status (UIC) are determined in the urine samples in which urine dilution may influence the level of the biomarker. To account for urine dilution, adjustment is typically done by correcting for specific gravity or creatinine. Not all studies reported using this adjustment. Finally, as development is multifactorial, more complex statistical models are required to properly account for the confounding variables, and not all studies in this review used proper statistical models. To improve the understanding of the neurotoxicity of F: *1)* studies accounting for other environmental exposure which adversely influence neurodevelopment; *2)* studies properly adjusting for urine dilution using specific gravity or creatinine; and *3)* studies using multivariable regression models to account for confounding variables of neurodevelopment are needed.

I and F have been shown independently to influence pregnancy, growth, and development [4,5,8–10,18,19,132,133,140,141]; however, only 2 studies, 1 in nonpregnant adults [21] and 1 in pregnant women [153] measured both UIC and UFC. The first study associated high UFC with high TSH levels in I deficient adults in areas with water fluoridation meeting recommendations of <0.7 mg/L [21], whereas the second study found that I status during pregnancy modified the relationship between maternal UFC and IQ in boys aged 3–4 y [153].

The literature on the topic of this review is limited. Preclinical studies are the best evidence that I and F status can interact in ways that have an adverse effect on neurodevelopment and provide possible mechanisms for such an interaction. The only evidence for an interaction in humans comes from a single large

study that measured UIC and UFC and associated high F exposure with high TSH levels in those with low I exposure [21]. Studies that determine both exposures in pregnancy are needed and could help determine if these halogens interact to influence maternal or fetal thyroid function and infant or child neurodevelopment as well as pregnancy outcomes. One possible mechanism might be that F influences the transport of I into the thyroid, leading to thyroid dysfunction [148]. In addition to the limited literature on this topic, there are limitations to the scoping review process. This is not a systematic review of the literature; it is an overview of the evidence available. Owing to this, a risk of bias assessment cannot be complete, and we cannot report implications or recommendations for clinical practice [156].

Conclusion

I intake has not been measured in US women. Median UICs are used to assess I status in populations. Most populations studied, including women in the US are considered mild-to-moderately deficient. Both I and F have effects on the maternal and offspring health. The role of I deficiency in maternal thyroid function and offspring neurodevelopment is well known; however, quite a few studies associate marginal I deficiency with adverse effects on offspring neurodevelopment. Although high exposure to F during fetal development also adversely affects offspring neurodevelopment, 2 large studies conducted in regions with acceptable water F concentration associate lower childhood IQ and maternal UFC during pregnancy [15] and predicted postnatal F exposure through water fluoridation [16]. The findings could simply be because water F standards are higher than desirable for consumption in pregnancy; however, because both F and I are halogens, F intake might interfere with I status and thereby adversely affect thyroid function during a critical intrauterine period of brain development.

Both preclinical and observational studies suggest a relationship among F, I, and thyroid function is plausible. We found a single study that measured both UIC and UFC as well as TSH levels in an I deficient adult population. That study associated high UFC with high TSH levels [115]. We found only one study that measured both UIC and UFC in a cohort of pregnant women. This study found that I status modified the relationship between maternal UFC and male offspring cognition.

We conclude that research is needed to inform recommendations for I intake and F exposure for pregnant women. Studies that measure both UIC and UFC during pregnancy with indicators of thyroid function, such as TSH, and infant development, in addition to mechanistic animal studies could further our understanding of these nutrients and their possible interactions during pregnancy and development.

Author Contributions

The authors' responsibilities were as follows – AKGT, SEC, SS, DKS, DC, HH, and LCH: designed research; AKGT and SS: conducted research; SEC and DKS: provided essential reagents, or provided essential materials; AKGT: wrote paper, SEC and AKGT: had primary responsibility for final content. All authors have read and approved the final manuscript.

Funding

This study was supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development R01 HD083292 and the National Institute of Health Office of Dietary Supplements.

Conflicts of interest

The authors report no conflicts of interest.

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