Costs and benefits of iodine supplementation for pregnant women in a mildly to moderately iodine-deficient population: a modelling analysis

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Summary

Background Results from previous studies show that the cognitive ability of offspring might be irreversibly damaged as a result of their mother's mild iodine deficiency during pregnancy. A reduced intelligence quotient (IQ) score has broad economic and societal cost implications because intelligence affects wellbeing, income, and education outcomes. Although pregnancy and lactation lead to increased iodine needs, no UK recommendations for iodine supplementation have been issued to pregnant women. We aimed to investigate the cost-effectiveness of iodine supplementation versus no supplementation for pregnant women in a mildly to moderately iodine-deficient population for which a population-based iodine supplementation programme—for example, universal salt iodisation—did not exist.

Methods We systematically searched MEDLINE, Embase, EconLit, and NHS EED for economic studies that linked IQ and income published in all languages until Aug 21, 2014. We took clinical data relating to iodine deficiency in pregnant women and the effect on IQ in their children aged 8–9 years from primary research. A decision tree was developed to compare the treatment strategies of iodine supplementation in tablet form with no iodine supplementation for pregnant women in the UK. Analyses were done from a health service perspective (analysis 1; taking direct health service costs into account) and societal perspective (analysis 2; taking education costs and the value of an IQ point itself into account), and presented in terms of cost (in sterling, relevant to 2013) per IQ point gained in the offspring. We made data-supported assumptions to complete these analyses, but used a conservative approach that limited the benefits of iodine supplementation and overestimated its potential harms.

Findings Our systematic search identified 1361 published articles, of which eight were assessed to calculate the monetary value of an IQ point. A discounted lifetime value of an additional IQ point based on earnings was estimated to be £3297 (study estimates range from £1319 to £11 967) for the offspring cohort. Iodine supplementation was cost saving from both a health service perspective (saving £199 per pregnant woman [sensitivity analysis range −£42 to £229]) and societal perspective (saving £4476 per pregnant woman [sensitivity analysis range £540 to £4495]), with a net gain of 1·22 IQ points in each analysis. Base case results were robust to sensitivity analyses.

Interpretation Iodine supplementation for pregnant women in the UK is potentially cost saving. This finding also has implications for the 1·88 billion people in the 32 countries with iodine deficiency worldwide. Valuation of IQ points should consider non-earnings benefits—eg, health benefits associated with a higher IQ not germane to earnings.

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Introduction

Severe iodine deficiency in pregnancy is linked to impaired neurodevelopment of the unborn child, manifesting in a permanent reduction in intelligence quotient (IQ) and cretinism in some children.[1,2] A systematic review of iodisation programmes and trials in China reported an 8·7 (95% CI 6·3–11·1) IQ point difference in children born to women in severely deficient regions with and without iodine supplementation during pregnancy and after birth.[2] However, strong evidence exists[1,2] that this cognitive impairment is prevented by iodine supplementation in pregnancy. Although the cognitive effects of severe iodine deficiency in pregnant women are established, the effect of mild iodine deficiency is less clear.[3] In two cohort studies in the UK and Australia, 9-year-old children of women who had a urinary iodine concentration suggestive of mild iodine deficiency during their pregnancy had reduced education outcomes[4] and decreased IQ scores[5] compared with children of iodine-replete women. By contrast, a large Spanish cohort study, [6] which undertook cognitive assessment of infants at a median age of 16 months, did not report a significant association between iodine supplementation and cognitive outcomes.

The UK is one of a decreasing number of countries that does not have any iodine fortification of food or salt and some of the UK population is now believed to have become mildly iodine deficient.[7] At present, no national guidance for iodine supplementation has been issued to pregnant women, even though pregnancy and lactation lead to increased iodine requirements.[8,9]

A reduced IQ in infancy has broad future economic societal costs because cognitive development has effects on health outcomes, educational attainment, and lifetime earnings. A reduced IQ is associated with an increased

Research in context

Evidence before this study

We searched PubMed, with no restrictions on date or language, with the keywords "iodine", "dietary supplements", "pregnancy", "intelligence", "cognition", "child development", and "costs and cost analysis". We identified no studies reporting the cost-effectiveness of iodine supplementation in pregnancy in a mildly iodine-deficient population. We identified a 2013 systematic review, which focused on mildly to moderately iodine-deficient populations, which concluded that "the impact of maternal iodine supplementation on newborn neurodevelopment remains uncertain due to lack of appropriate controlled intervention trials". One other systematic review of research in mildly to moderately iodine-deficient populations from 2009 reported benefits of maternal iodine supplementation on maternal thyroid indices, but underlined the need for further data for infant neurodevelopment. In two cohort studies in the UK and Australia, 9-year-old children of women who had a urinary iodine concentration suggestive of mild iodine deficiency during their pregnancy had reduced educational outcomes and decreased IQ scores compared with children of iodine-replete mothers.

Added value of this study

To our knowledge, this study is the first model of the cost-effectiveness of iodine supplementation in pregnant women in a mildly to moderately iodine-deficient population. We used an economic model of best available evidence and assumptions that do not favour iodine supplementation and identified that universal iodine supplementation before pregnancy and during pregnancy and lactation increased the child's IQ by 1·22 points, saved the UK NHS £199 and society £4476 per pregnant woman.

Implications of all the available evidence

Available evidence suggests that a policy of iodine supplementation during pregnancy would be benefical. Ideally, a randomised controlled trial would be undertaken to confirm our findings.

rate of mortality,[10] an increased risk of suicide,[11] psychiatric illness,[12,13] and an increased incidence of heart disease.[14,15] An increased IQ is postulated to have a positive effect on an individual's health-improvement behaviour,[16] and those with increased childhood IQ scores are significantly more likely to have higher educational attainment and earnings by the age of 25 years.[17]

Here, we report the results of a model-based economic evaluation using the best available data from the existing published scientific literature, a systematic literature search, and expert clinical input. Because of the need for data-supported assumptions to complete the analysis, we used an approach that limited the benefits of iodine supplementation and overestimated its potential harms as far as possible. We aimed to use economic evaluation to compare the costs and benefits of a strategy of iodine supplementation tablets with a strategy of no iodine supplementation for pregnant women in a mildly to moderately iodine-deficient population.

Methods

Model structure

We developed a decision tree model in TreeAgePro 2014 (TreeAge Software, Williamstown, MA, USA) to represent two alternative strategies—iodine supplementation versus no iodine supplementation. The model pathways (figure) represent the alternative clinical pathways undertaken by pregnant women.

We are interested in the incremental costs and effects of giving universal iodine supplementation to pregnant women. The model pathways represent the alternative (simplified) clinical pathways undertaken by pregnant women. Some of the pregnancies will be unsuccessful and we will not realise any IQ gain related benefits of iodine supplementation. Successful pregnancies without complications due to iodine supplementation intervention whose mothers were iodine deficient presupplementation receive IQ gain related benefits for their newborn baby. Pregnant women who were iodine sufficient without supplementation with normal thyroid function receive no IQ gains for their offspring. We have stacked the cards against iodine supplementation being cost effective with very conservative assumptions. We assumed that some women suffer adverse thyroid dysfunction as a result of iodine supplementation. An increased incidence of pregnancy losses and complications for each type of thyroid dysfunction is caused by iodine supplementation. Pregnancy complications push up the costs from iodine supplementation. Hypothyroidism and isolated hypothyroxinaemia induced by iodine supplementation are assumed to lose IQ points for the offspring. IQ points were subtracted for the children of mothers with adverse thyroid dysfunction from iodine supplementation who were iodine deficient presupplementation.

Variables and their respective sources are listed in table 1. Data for the probability of a pregnant woman in the UK being iodine deficient is based on the only UK data available and refers to a selective cohort of women.[5] The proportion of pregnant women in each iodine status category—mild to moderate (median urinary iodine concentration [UIC] of 50–149 μg/L) and severe (UIC <50 μg/L)—and the subsequent effect on a child's IQ were based on a cohort study[5] that examined the association between iodine status during the first trimester of pregnancy and the IQ of their children at age 9 years.

The cost of iodine tablets is based on the cost of local supermarket multivitamin tablets for pregnant women (£3·50 for 30 tablets typically containing 140 μg or 150 μg of iodine).[37] A daily dose of 150 μg of iodine is recommended by the American Thyroid Association[38] and

the European Thyroid Association[39] for euthyroid pregnant and lactating women. Annual incremental health and services costs and public sector costs, including education by a child's IQ category, are taken from a study[40] that looked at the costs associated with neurological impairment when children were aged 11 years old. The incremental childhood cost of preterm birth and the health-care cost associated with stillbirth are taken from published sources.[41,42] We discounted costs at the standard annual rate of 3·5%[24] and updated them to 2013 prices using a subset of the Consumer Price Index, covering price inflation in education, health, and social protection.[43] Public sector costs included in the model consist of health and social services costs, and education costs.

We did an additional systematic search of the scientific literature to establish a monetary value for an IQ point to use in the economic evaluation (appendix p 2). To complete the analysis, some pragmatic assumptions were needed and were informed by the scientific literature and expert opinion. As far as possible, assumptions were conservative. Our model assumptions are listed in panels 1 and 2.

Analyses

We did two separate analyses. In the first analysis (analysis 1), we used a health service perspective in which direct health service costs are taken into account. In the second analysis (analysis 2), we used a societal perspective that additionally takes into account education costs and the value of an IQ point itself.

For both analyses, we assumed that IQ follows the conventional normal distribution with a mean of 100 and a standard deviation of 15. We used Z tables to calculate the reduction in the proportion of children in the lower IQ categories as a result of iodine supplementation (appendix p 9). The present value health and social services costs for the first 16 years of life are calculated for children with a mild neurodevelopmental impairment (IQ scores of 82–92); this is also calculated for children with a moderate or severe neurodevelopmental disability (IQ scores of ≤81), but with an additional cost of special education. These costs savings are then adjusted for survivors by use of UK life tables.[44]

The monetary value of an IQ point (analysis 2 only) was identified by the systematic search done as part of this study (appendix p 2). Analyses 1 and 2 are both presented in terms of their disaggregated cost (in sterling) and outcomes in the form of a cost-consequence analysis, and IQ points gained are reported as natural units.

To investigate the robustness of the base case results, we did a comprehensive sensitivity analysis in which the main motivation was to further disadvantage the effect of iodine supplementation in the model and assess the effect on the results (appendix p 8). Most of the changes explored, for both analyses 1 and 2, were arbitrary where, for example, any gains as a result of iodine supplementation were halved and any detrimental effects as a result of the supplementation were doubled. A probabilistic sensitivity analysis was not appropriate in this case because we were already using estimates for the worst case scenario rather than using central mean estimates. We identified evidence on the benefits of iodine supplementation using systematic reviews and from experts on iodine status and supplementation in pregnant women. We identified three

See Online for appendix

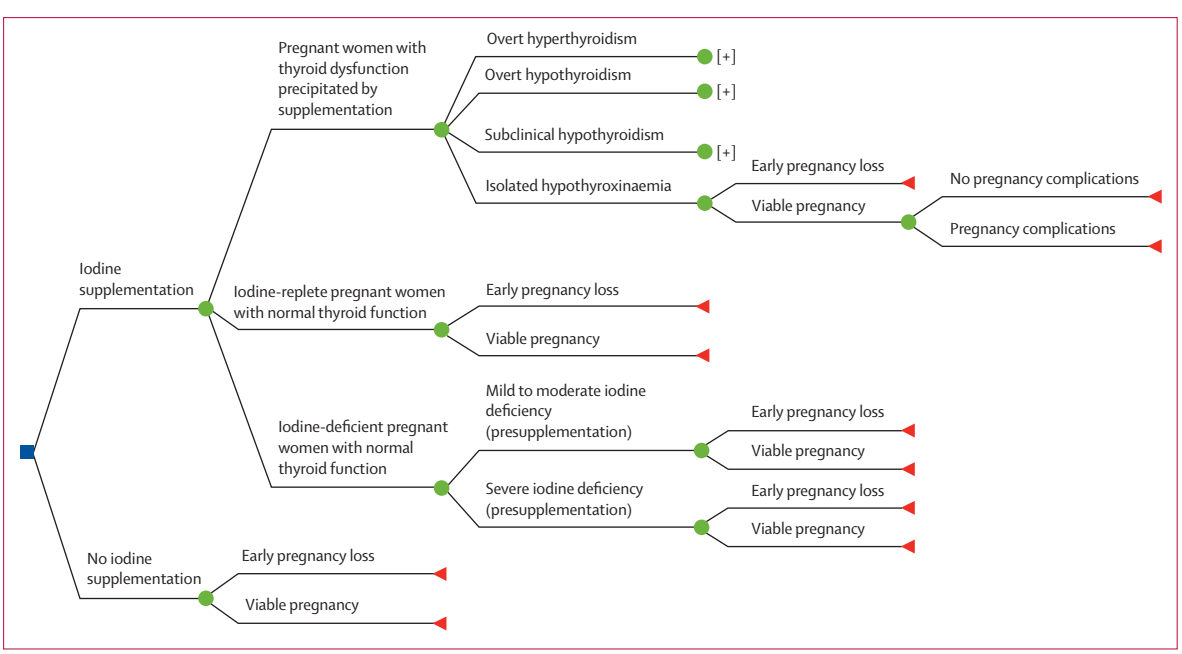

***Figure*: Decision tree representing the alternative clinical pathways taken by pregnant women**
The model is identical at every node ending in [+].

cohort studies of iodine status in pregnancy and IQ or cognitive development in infants and children[4–6] and two trials of iodine supplementation in pregnant women.[45,46]

Role of the funding source

There was no funding source for this study. All authors made the collective decision to submit for publication.

Results

Our systematic search identified 1361 published articles, of which eight studies[47–54] passed quality criteria and were assessed to calculate the monetary value of an IQ point (appendix p 4). The quality criteria were as follows: an individual's IQ is used and is not a proxy; variables are clearly specified; IQ measure follows a conventional

	Data	Sources
Probability of a pregnant woman being iodine deficient (%)	67%	Bath and colleagues[5]; Vanderpump and colleagues[18] showed a similar proportion of iodine deficiency in 14–15 year old girls in the UK
Iodine deficiency		
Proportion of iodine-deficient women who are mildly to moderately iodine deficient (%; urinary iodine to creatinine ratio [UIC] of 50–149 µg/L)	89%	Bath and colleagues[5]
Proportion of iodine-deficient women who are severely iodine deficient (UIC <50 µg/L)	11%	Bath and colleagues[5]
IQ gain		
IQ gain from supplementation in previously mildly iodine-deficient women	2·20	Bath and colleagues[5]
IQ gain from supplementation in previously severely iodine-deficient women	3·00	Bath and colleagues[5]
Iodine supplementation		
Duration of iodine supplementation with successful pregnancy and lactation (weeks)	78	Model assumption
Duration of iodine supplementation with early pregnancy loss (weeks)	23	Model assumption
Duration of iodine supplementation with late pregnancy loss (weeks)	47	Model assumption
Pregnancy complications		
Baseline pregnancy risk of early pregnancy loss (%)	20%	Royal College of Obstetricians and Gynaecologists[19]
Baseline pregnancy risk of stillbirth (%)	<1% of total births	UK stillbirth rate[20]
Baseline pregnancy risk of preterm birth (%)	7% of livebirths	UK preterm birth rate[21]
Baseline pregnancy risk of pre-eclampsia (%)	8%	Duley[22]
Pre-eclampsia cost per woman	£11 370·00	Meads and colleagues[23]
Discount rate for costs (%)	3·5%	NICE guide to the methods of technology appraisal[24]
For a few women who might develop thyroid dysfunction as a result of iodine supplementation*		
Incremental incidence of thyroid dysfunction from iodine supplementation (%)	<1%	European Commission[25]
IQ loss from overt and subclinical hypothyroidism	7·00	Haddow and colleagues[26]
IQ loss from isolated hypothyroxinaemia	7·00	Model assumption based on equivalent neurodevelopmental test scores in subclinical hypothyroidism and isolated hypothyroxinaemia groups (Li and colleagues[27])
Incidence of early pregnancy loss from overt hyperthyroidism (%)	26%	Momotani and Ito[28]
OR of stillbirth from overt hyperthyroidism†	8·42 (2·01–35·20)	Aggarawal and colleagues[29]
OR of preterm birth from overt hyperthyroidism	16·50 (2·09–130·02)	Millar and colleagues[30]
OR of pre-eclampsia from overt hyperthyroidism†	3·94 (2·47–6·29)	Aggarawal and colleagues[29]
Incidence of early pregnancy loss from overt hypothyroidism (%)	30%	Glinoer[31]
OR for stillbirth from overt hypothyroidism	9·69 (2·92–32·16)	Allan and colleagues[32]
OR for preterm birth from overt hypothyroidism	15·55 (3·62–66·81)	Ajmani and colleagues[33]
Incidence of pre-eclampsia from overt hypothyroidism (%)	44%	Davis and colleagues[34]
OR for early pregnancy loss from subclinical hypothyroidism	1·88 (1·13–3·15)	Wang and colleagues[35]
OR of stillbirth from subclinical hypothyroidism	3·29 (1·32–8·21)	Allan and colleagues[32]
OR for preterm birth from subclinical hypothyroidism	5·60 (2·30–13·58)	Ajmani and colleagues[33]
OR for pre-eclampsia from subclinical hypothyroidism	3·39 (1·40–8·15)	Ajmani and colleagues[33]
OR for preterm birth from isolated hypothyroxinaemia†	2·54 (1·42–4·54)	Korevaar and colleagues[36]

Data are n (%), mean (SD, where available), or OR (95% CI). OR=odds ratio. *Assumption based on non-pregnant population iodine supplementation programmes that include elderly people. †Adjusted OR.

Table 1: **List of variables assuming the worst case scenario (least favourable to iodine supplementation)**

normal distribution with a mean of 100 and standard deviation of 15 or sufficient information is included in the study to allow the IQ measure's distribution to be converted into one (for cross study comparability); and the results reported in currency form have the applicable year stated.

Most of the studies valued an IQ point on the basis of its effect on an individual's income (appendix p 3). The issue of differences in scaling of IQ tests hindered the comparability across studies. The value of an IQ point, derived from the systematic search and applied to the unborn cohort, comes from the lifetime earnings premium of an additional IQ point. This is calculated to be £3297 (study estimates range from £1319 to £11967; after adjustment with life tables).

With the use of base case assumptions, the results of both analyses show that the iodine supplementation strategy was less costly and more effective compared with no supplementation (table 2). From the UK NHS perspective, where only health-related costs were taken into account (analysis 1), iodine supplementation was cost saving, with an expected positive net present value of £199 per pregnant woman (sensitivity analysis range −£42 to £229) and an increase of an average 1·22 IQ points for the unborn infants. From a societal perspective (analysis 2), iodine supplementation was cost saving with an expected positive net present value of £4476 per pregnant woman (sensitivity analysis range £540 to £4495), and an average increase of 1·22 IQ points for the unborn infants.

For the pregnant women for whom thyroid dysfunction was precipitated by iodine supplementation, an average cost of more than £91000 each would have to be incurred to negate the overall benefits arising from the iodine-deficient pregnant women without thyroid dysfunction taking iodine supplementation in the model looking at the NHS perspective alone.

The sensitivity analysis supported the cost saving indication of base case results (table 2; appendix p 8). Iodine supplementation remained cost saving in all the sensitivity scenarios undertaken with one exception: in analysis 1 (health service perspective) where we assumed zero IQ gain for children of the previously mild to moderately iodine-deficient women, the results suggested an additional cost of £42 per pregnant woman for a gain of 0·17 IQ points for their offspring (table 2).

***Panel 1:* Model assumptions relating to the women**

- Women take daily iodine tablets 13 weeks before pregnancy, throughout pregnancy, and for an additional 26 weeks while breastfeeding. Cessation of iodine tablets occurs at the end of the lactation period or if there is a pregnancy loss event.
- Iodine supplementation will only benefit women who were iodine deficient before supplementation.
- All iodine-deficient women will be iodine replete with supplementation and they adhere to taking the daily supplementation.
- IQ gains will be different depending on the severity of iodine deficiency before supplementation; the presupplementation iodine-deficient women were subclassified into severe and mild or moderate iodine-deficient categories (table 1).
- All pregnancies are singleton.

***Panel 2:* Model assumptions relating to the pregnancy losses and complications**

- Women with early pregnancy losses take daily tablets for 23 weeks on average and women with late pregnancy loss take tablets for 47 weeks on average (these both include the 13 weeks of taking the iodine tablets before pregnancy).
- 0·25%[25] of women of reproductive age have adverse thyroid dysfunction as a result of the iodine supplementation. Without existing evidence, the types of thyroid dysfunction precipitated by the iodine supplementation in the population are split evenly into the four following groups:
  - Overt hyperthyroidism (undetectable thyroid-stimulating hormone [TSH] with raised free T_4 [fT_4])
  - Overt hypothyroidism (increased TSH with low fT_4)
  - Subclinical hypothyroidism (increased TSH with normal fT_4)
  - Isolated hypothyroxinaemia (normal TSH with low fT_4).
- None of the thyroid dysfunctions were diagnosed and treated.
- An increased incidence of pregnancy losses and complications for each type of thyroid dysfunction is caused by iodine supplementation. Only pregnancy complications incurring significant costs (pre-eclampsia, preterm birth before 37 completed weeks of gestation, and stillbirth loss after 24 completed weeks of gestation) are used in the model.
- Although pre-eclampsia and preterm births often occur together, they are separate events in the model.
- The infants whose mothers had overt and subclinical hypothyroidism during pregnancy have losses of cognition of 7 IQ points.[26] On the basis of equivalent neurodevelopmental test scores,[27] this loss is also assumed for infants whose mothers had isolated hypothyroxinaemia during pregnancy. This assumption relates to the hypothyroidism that is induced by iodine supplementation in a few women and in this case is not related to iodine deficiency.
- Children of women with adverse thyroid dysfunction who had iodine supplementation and were iodine deficient before supplementation did not have an increase in IQ after supplementation.

Discussion

To our knowledge, this study is the first to estimate the cost-effectiveness of a policy of iodine supplementation during pregnancy and lactation in a population with mild to moderate iodine deficiency. The analyses showed that iodine supplementation saved money and improved IQ. The results were supported by all the sensitivity analysis scenarios apart from the most extreme scenario, in which supplementation of mildly iodine-deficient pregnant women did not improve IQ. A key strength of the analysis was the use of very conservative assumptions to limit the benefits of iodine supplementation and potentially overestimate adverse outcomes arising from supplementation. In view of the preliminary work for this study showing that iodine in pregnancy was unequivocally cost saving, the aim of our analysis was to explore the robustness of this indication by solely focusing on the worst case possible.

The monetary value of an IQ point used was also intentionally conservative and excluded voluntary work and any earnings that happen after the UK retirement age. These factors potentially act to underestimate the true monetary value associated with an additional IQ

	Cost saving analysis 1 from NHS perspective (£)	Cost saving analysis 2 from societal perspective (£)	IQ points gained
Base case results	199	4476	1·22
Sensitivity analysis scenarios			
IQ gain for severe iodine deficiency equal to mild to moderate deficiency	189	4302	1·18
1 IQ point gain from iodine supplementation	46	1900	0·53
No IQ gain for mild to moderate iodine deficiency	–42	540	0·17
Prevalence of iodine deficiency halved	59	2178	0·61
Doubled early pregnancy loss	145	3352	0·92
Doubled cost of iodine tablets	148	4452	1·22
Doubled cost discount rate (from 3·5% to 7%)	144	1608	1·22
No thyroid dysfunction	229	4495	1·23
Health costs savings halved (analysis 1 only)	60	..	1·22
Value of an IQ point halved (analysis 2 only)	..	2409	1·22
No real wage growth (analysis 2 only)	..	3239	1·22
Willingness to pay figure* for an additional IQ point used (analysis 2 only)	..	1832	1·22
Exclusion of public sector costs (analysis 2 only)	..	3953	1·22

*Willingness to pay was used from a US based study[50] that used preference to elicit a figure from parents deciding on chelation therapy for their children.

Table 2: **Summary of base case results and and sensitivity analysis scenarios**

point. The IQ earnings premium used in the model is based on an estimate from a US study[48] in which earnings came from the years 1974 and 1990. In today's technologically driven high skill economy, the earnings benefit from an additional IQ point might be more valuable for a worker than in previous decades.

Health and public sector costs relating to childhood neurological impairment were taken from a study[41] that recorded incremental costs during a 1 year period in mid-childhood (aged 11 years). The model assumed that these annual costs are the same for each year of childhood when in reality they are very likely to vary. Exclusion of these costs in the societal perspective sensitivity analysis did not change the direction of the results. No account has been made of public sector savings resulting from IQ improvement at the upper end of the IQ scale.

For the present value of lifetime earnings, a real wage growth of 1% per year in the future was assumed.[47] However, the sensitivity analysis also took into account a zero real wage growth scenario. This scenario did not prevent the iodine supplementation intervention from remaining cost saving.

This study has several limitations. First, one argument is that if most of the IQ gains will provide an absolute shift in the population IQ distribution, the relative IQ differences remain largely unchanged, negating most of the earnings advantages stemming from the gains in IQ points for workers. A possible response to this is that, generally, economies compete at a worldwide level and the addition of a more intelligent workforce in the future should help with productivity-linked earning gains. Second, some women might already take supplementation, which would mean that the overall modelled benefits might be overstated, but the analysis sought to identify the benefits of iodine supplementation to an individual compared with no supplementation.

We also used the sensitivity analysis to measure a person's willingness to pay for an additional IQ point instead of the monetary value of an IQ point derived from earnings. This analysis was done to allay any issues about using earnings as a basis for the value of an IQ point. However, when the monetary value of an IQ point is excluded (NHS perspective), the result showed that iodine supplementation was still cost saving.

A further possible weakness of our analysis is that iodine status is not identified at the individual level for the pregnant woman and, therefore, some wastage occurs when iodine-sufficient women receive unnecessary supplementation. However, iodine supplementation for iodine-replete pregnant women with normal thyroid function is not likely to cause any harm in most pregnancies. Despite our assumptions of harm in our model, no evidence thus far suggests that iodine supplementation induces thyroid dysfunction in pregnancy. Moreover, iodine is included in some proprietary pregnancy supplements. However, some evidence[25] of induction of thyroid dysfunction in the non-pregnant population does exist. Severe iodine deficiency has been associated with increases in pregnancy loss and complications; rectification of the iodine status of mildly to moderately iodine-deficient women is likely to decrease rather than increase pregnancy loss, although no studies have investigated this thus far. At present, no acceptable test for the assessment of individual iodine status exists; tests for assessment of population iodine status are available, but they require collection of urine from a large sample size, which is both cumbersome and costly. Furthermore, the testing needed for a targeted programme also causes delay, whereas the evidence suggests[45] that the benefits of iodine supplementation are increased with earlier treatment.

The limitations in our analysis relate to the limitations in the evidence. Although the evidence for the benefit of iodine supplementation in populations who are severely iodine deficient is clear,[1,2] the evidence of benefit in mildly iodine-deficient populations has not been established.[3] Two of the three prospective studies[45,46] of iodine supplementation in women from mildly iodine-deficient areas have shown improvements in child cognition, but these are limited by not being randomised studies, risk of bias, and small sample sizes. A large cohort study, with a short follow-up, provides evidence of potential harm.[6] Maternal consumption of 150 µg per day or more of iodine from supplements was related to a 1·7 (95% CI 0·9–3·0) times higher risk of a child's mental scale score being less than 85 (derived from the Bayley Scales of Infant Development test), but this was not statistically significant. This study was not included in the model because the association was not statistically significant, the

assessments were done at the age of 16 months, which is less robust than the later ages used in Bath and Hynes' study, and a third of the population used iodised salt. We based the IQ gains on an observational study, which was a cohort study comprising highly educated older women,[5] which was a major limitation, but is the most robust information available in the absence of high quality experimental evidence. Although systematic reviews exist, [2,3,55,56] none of them provides an IQ change in a mildly iodine-deficient non-supplemented population.

The use of different IQ tests across studies raises the question of the comparability of findings. Bath and colleagues[5] used the abbreviated form of the Wechsler Intelligence Scale for Children. Our base case estimate, taken from the study by Zax and Rees,[48] used the Henmon-Nelson Test of Mental Ability. Because these two intelligence tests are not perfectly correlated, an individual might get a slightly different IQ score from each test. We explored this possibility in the sensitivity analysis by modification of IQ gains and the results remained cost saving with one exception, which was based on an extreme scenario.

In the absence of randomised controlled trial evidence, our model results strengthen the case for universal iodine supplementation pre-conception and during pregnancy and lactation in mildly to moderately iodine-deficient populations. In our study, we only took into account iodine supplementation in tablet form. Fortification of food with iodine is another way of attaining iodine sufficiency; however, food fortification alone might not be enough to achieve iodine sufficiency for pregnant women.[57]

Our findings have important implications worldwide. 32 countries have mild or moderate iodine deficiency identified from surveys of the iodine status of school-age children.[58] These countries have a population of 1·88 billion people and 241 million school-age children, so the potential effects of introduction of iodine supplementation for pregnant women could be substantial. The use of urinary iodine of school-age children to estimate the iodine status of pregnant women is likely to underestimate the prevalence of iodine deficiency during pregnancy.[59,60] Reduced urinary iodine concentrations have been identified in pregnant women compared with school aged children, possibly because of an increased consumption of milk in children.[59] Additionally, pregnant women have an increased iodine requirement.[61]

A randomised controlled trial would provide the most robust evidence on which to base policy; however, such a study would need costly child developmental assessments. A randomised controlled trial with iodine-deficient pregnant women taking placebo iodine tablets has been described as unethical[9] because iodine supplementation in pregnancy is already recommended by many national and international bodies, including WHO.[8] On the basis of the best available evidence, this study emphasises the cost-effectiveness of an iodine supplementation strategy for pregnant women in the UK. Our findings are applicable to any country which is mildly to moderately iodine deficient, but has no universal salt or other iodisation programme.

Contributors

TER and KJ conceived and designed the study. KJ was responsible for the groundwork that led to the study being planned. KJ, KB, and SC provided clinical data used in the model-based analysis and clinical interpretation. MM did the scientific literature review, the model-based analysis, and interpreted the results under the supervision of TER. PB provided advice on use of data and modelling techniques. MM and TER wrote the first draft of the report. All authors provided input on the manuscript draft. TER is the guarantor for the study.

Declaration of interests

KJ is a member of the UK Iodine Group. All other authors declare no competing interests.

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