The effects of iodine on intelligence in children: A meta-analysis of studies conducted in China

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Original Article

The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China

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This study quantifies the effects of iodine on the intellectual development of children using a systematic manual literature search of Chinese publications related to iodine deficiency disorders. The Chinese Medical Reference Database, Medline, and Cochrane library were searched electronically in Chinese and English. Inclusion criteria included: studies conducted in China, comparing children (<16 ys) living in naturally iodine sufficient (IS) with those in severely iodine deficient (ID) areas, or children in ID areas born before and after the introduction of iodine supplementation. Intelligent Quotient (IQ) was measured using Binet or Raven Scales. The iodine sufficient control groups were comparable socially, economically, and educationally with the study groups. Random effects models were used in the meta-analysis. Effect size was the standard deviation IQ point (SIQP), which is equivalent to 15 IQ. Thirty-seven reported studies, total 12,291 children, were analysed. The effect size was an increase of 0.83, 0.82, and 0.32 SIQP respectively, for the children living in IS communities compared with those living in ID areas with no iodine supplementation, with inadequate iodine supplementation, or children who had received iodine during their mothers' pregnancy and after birth. These equal to 12.45, 12.3, 4.8 IQ points. Compared with that of children whose mothers were persistently exposed to ID, the total effect size of the 21 entries was an increase of 0.58 SIQP (8.7 IQ points) in the group receiving iodine supplementation during pregnancy. Furthermore, there was an increase on 1.15 SIQP of Binet or 0.8 SIQP on Raven Scale (17.25 or 12 IQ points) for children born more than 3.5 years after iodine supplementation program was introduced. The level of iodine nutrition plays a crucial role in the intellectual development of children. The intelligence damage of children exposed to severe ID was profound, demonstrated by 12.45 IQ points loss and they recovered 8.7 IQ points with iodine supplementation or IS before and during pregnancy. Iodine supplementation before and during pregnancy to women living in severe ID areas could prevent their children from intelligence deficit. This effect becomes evident in children born 3.5 years after the iodine supplementation program was introduced.

Key Words: iodine, iodine deficiency disorders, intelligence, IQ, children, meta-analysis, China.

Introduction

Iodine is an essential ingredient for the synthesis of thyroid hormones. The development of the brain during pregnancy and the first 3 years after birth is especially sensitive to iodine deficiency.[1] Iodine deficiency (ID) can cause mental retardation in children, one of a series of damages in iodine deficiency disorders (IDD). This is the main reason why 98 countries or regions have enacted legislation requiring salt iodization, or universal salt iodization (USI).[2-4]

How much benefit does iodine contribute to the intelligence of children? A previous meta-analysis of 18 studies found a loss of 13.5 IQ points in children and adults from ID areas.[5] This study, however, failed to include any publications in the Chinese language. In addition, it included outcomes of a mixture of IQ and non-IQ tests.

The success of programs in some countries has been compromised due to the lack of commitment and action from governments, and USI has yet to reach all areas.[6] Evidence from population-based studies to motivate authorities to implement USI is still required. Implementation of USI should be "a simple matter of salt", and indeed, great progress has been made in establishing this program.[2]

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Parts of this work have been previously published in Chinese. Using meta-analysis on 36 published studies[7], ID leads to a 10 point loss in IQ of children living in ID areas; in contrast, an 11.5 IQ point increase was found in children in iodine deficient areas that had been involved in the iodine supplementation program. A similar meta-analysis was published after establishing a database of 128 independent studies from 63 papers.[8] At least a 10 IQ points loss was found in children who lived in ID areas. Effective iodine supplementation plays a remarkable role in protecting brain development and can cause a 12 IQ points increase for children born after IS.[8]

In this communication, we have reviewed more studies from a different perspective, and re-analyzed the data as suggested by the Quality of Reporting of Meta-analyses (QUOROM) statement.[9]

Methods

Searching

Chinese-language journals publsihedand end of 2003 were manually searched. The journals included: Zhong Guo Di Fang Bing Xue Za Zhi (Chinese Journal of Endemic Disease, ISSN1000-4955); Zhong Guo Di Fang Bing Fang Zhi Za Zhi (Chinese Journal for the Prevention of Endemic Disease, ISSN1001-1889); Di Fang Bing Tong Xun (Endemic Disease Bulletin, ISSN1000-3711); conference proceedings; and books related to IDD. Additional reports were identified from reference lists of retrieved reports. Unpublished studies were not included. The Chinese Medical Reference Database (Wei Pu Database 1989 to December 2002) was also searched electronically using the keywords: "iodine" or "intelligence" or "IQ". Medline and the Cochrane Database were searched with free term combinations; the last electronic search was in November 2002. The key words in English were: iodine and/or deficiency, or goiter, or cretinism, or sub-cretinism; child or children; intelligence, or IQ, or cognitive; Binet or Raven.

Selection

Inclusion criteria

The initial inclusion criteria were (1) studies conducted in China, (2) subjects were less than 16 years old and (3) the degree of ID in the community was severe. The definition of severe ID, however, varied during the time. Criteria employed in those studies to define severe ID included prevalence of endemic goiter (PEG) (i.e in the entire population) ≥10%; goiter rate in 7-14 year olds ≥50%; goiter rate in 8-10 year olds ≥30%; or median urinary iodine ≤25μg/L.[2,10,11] The controls were either from different communities (i.e naturally IS communities), or the same communities, formerly ID and became IS after the introduction of iodine supplementation. Adequate iodine supplementation in severe ID areas was defined as median urinary iodine >100 μg/g Cr with ≤10% of the population having less than 50μg urinary iodine/g Cr and a goiter rate in 7-14 year olds of <20% or PEG ≤8%.[12] Inadequate iodine supplementation in severe ID areas was defined if one of the indicators mentioned above was behind the level of adequate iodine supplementation. The control groups were comparable in terms of social, economic and educational levels to the study groups. The principal outcome is IQ as measured by the Chinese Binet Scale (Binet), or the Combined Raven Test for Rural China (Raven).[13,14]

Exclusion criteria

Studies that met the initial inclusion criteria were then further examined. Studies with duplicate publication, unbalanced matching or incomplete data were excluded. When duplication occurred, the studies reported in conference proceedings, in earlier publications and in lower rank journals were excluded (Fig. 1).

Validity assessment

Original studies were reviewed and checked against the inclusion and exclusion criteria. Studies whose control group comprised of towns or with mild ID areas were excluded as were studies whose intervention group included children receiving inadequate iodine during their mothers' pregnancy. Evidence that a study was duplicated was based on comparing author name, research institute, survey site, time published in journal, and data reported in the paper. We excluded studies without available data published, including sample size, mean, and standard deviation. We have contacted two authors in the attempt to clarify data reported in their studies. We received answer from one, and had no response from the other.

Data abstraction

Two step abstraction was used. Studies were initially abstracted by MQ, and they were checked by YQY.

Study characteristics and groups

We evaluated the effect of ID on intelligence in four groups:

Group I: Different communities: Iodine sufficient vs. iodine deficient without iodine supplementation.

Group II: Different communities: Iodine sufficient vs. iodine deficient with inadequate iodine supplementation.

- *Subgroup II-1:* with inadequate iodine supplementation, Binet.
- *Subgroup II-2:* ID during pregnancy, with inadequate iodine supplementation, Binet.
- *Subgroup II-3:* with inadequate iodine supplementation, Raven.

Group III: Different communities: iodine sufficient vs. iodine deficient with adequate iodine supplementation during pregnancy and after birth.

Group IV: Same community: children born after vs. before iodine supplementation.

- *Subgroup IV-1:* 1-2 years after iodine supplementation, Binet.
- *Subgroup IV-2:* 2.1-3 years after iodine supplementation, Binet.
- *Subgroup IV-3*: >3 years after iodine supplementation, Binet.
- *Subgroup IV-4:* 0.5-2 years after iodine supplementation, Raven.
- *Subgroup IV-5:* >3 years after iodine supplementation, Raven.

The outcomes are the standard deviation IQ point (SIQP). One SIQP, instead of overall effect size, equals to 15 IQ points in a population.

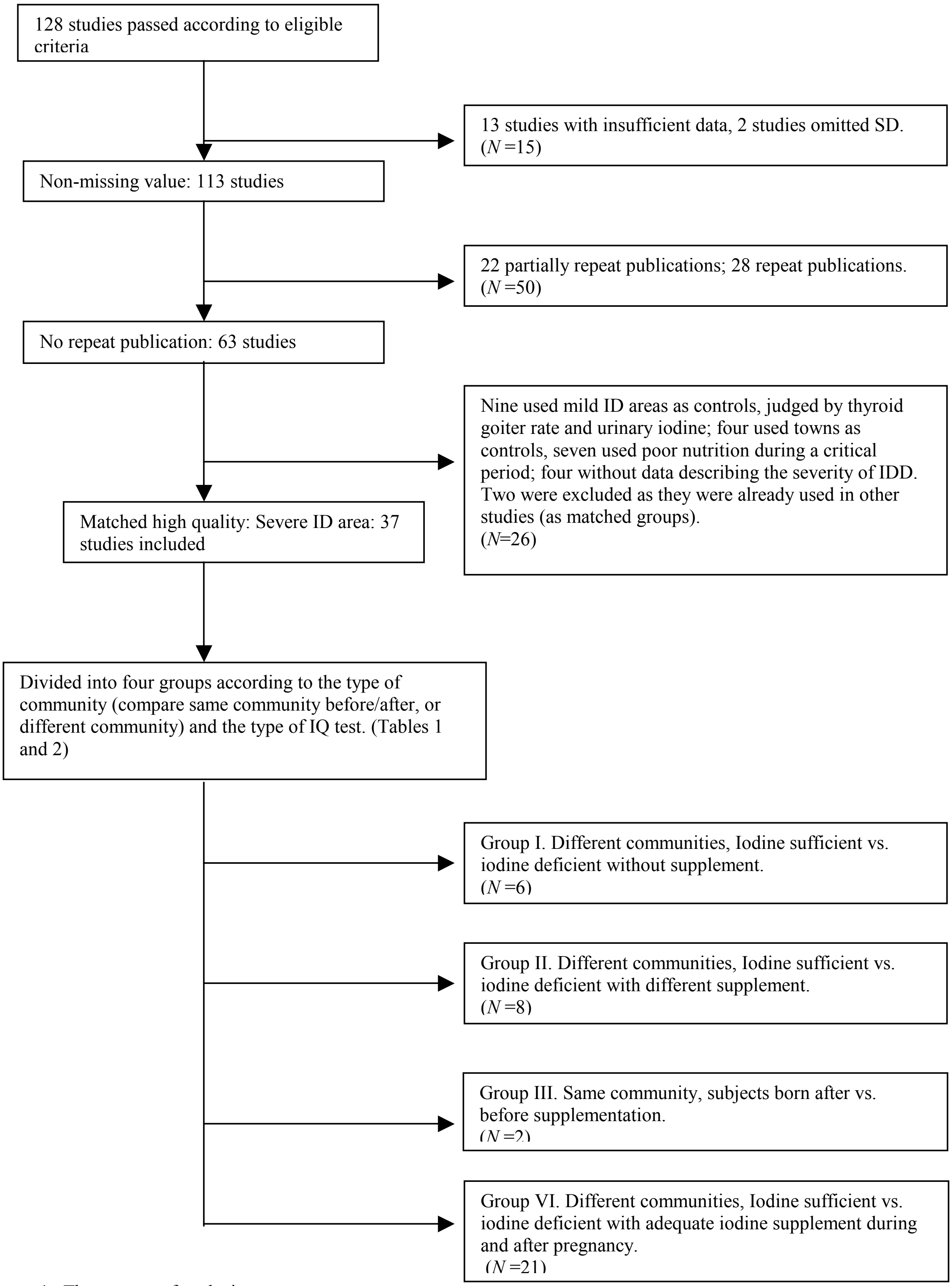

Figure 1. The process of exclusion

Quantitative data synthesis

RevMan 4.1 (available at http://www.cochrane.org/cochrane/revman.htm) was used to analyse the effect sizes and heterogeneity of the data. We calculated the standardized mean difference, the 95% confidence intervals (CI) of IQ with random effect model, and weighed by variance. The subgroup analysis was carried out in order to estimate the effect of different levels of ID and intervention on intelligence scale, and the overall effect size was calculated to estimate the general effect of the group.[15]

Assumptions

Factors known to influence intelligence, other than ID, were similar in both the study and control groups, including socio-economic-cultural background and educational levels.

Results

Trial flow

A total of 128 studies were examined for possible inclusion, including 3 published in English. Of these, 76 studies (59.4%) were published in journals, 15 studies (11.7%) were published in supplements of journals, and 37 studies (28.9%) were found in conference proceedings. Using the inclusion criteria, 37 eligible studies (27 journals, 5 supplements, 5 proceedings) were included in this meta-analysis. Based on the IQ test and the iodine status of the communities, the studies were divided into four groups (Fig. 1).

Study inclusion and characteristics

The 37 eligible studies had 12,614 subjects aged 4.5-15 years, and were conducted in 13 provinces in China. The iodine intervention was iodised salt, except for three communities,[w19,w24] which used iodised oil during pregnancy. The original studies reported iodine concentrations in urine or in drinking water, total goiter rates, and prevalence of endemic goiter was listed in Tables 1 and 2.

Quantitative data syntheses

Group I. These surveys were conducted between 1984 and 1991 when only Binet Scale was used. The effect size of all 6 eligible studies (total 1385 subjects), was an increase of 0.83 SIQP (95% CI: 0.56, 1.10) for the groups living in IS communities comparing with ID. The heterogeneity of these studies was statistically significant ($P<0.05$) (Fig. 2). In order to explore the cause of the heterogeneity, the exclusion approach was applied. After excluding one study (Wang Guyuan-1[w7]), the test for heterogeneity was no longer statistically significant ($P=0.68$). The overall effect size, however, was reduced to 0.68 SIQP for the remaining 1062 subjects. There was no obvious reason to explain this change based on the original reports.

Group II. The effect size of the 8 studies was an increase of 0.82 SIQP (95% CI: 0.56, 1.08), for children who lived in IS areas compared with those who lived in ID areas with inadequate iodine supplementation. The test for heterogeneity was again statistically significant ($P<0.05$). Considering the factors of IQ scales, endemic state in iodine deficient areas, and iodine nutrition at the time of birth in matched groups, the group was further divided into 3 subgroups (Fig. 3).

The effect sizes of subgroup II-1 to 3 were 0.86, 0.90, and 0.67 respectively. After excluding the report of Xie Xinjiang[1 w8] in subgroup II-1, the tests for heterogeneity of each subgroup were no longer statistically significant ($P=0.05$) (Fig. 3). The effect size of subgroup II-1 decreased to 0.63. The data indicates that the severity of ID may be a main contributing factor, because prevalence of endemic goiter reported by Xxie *et al.*,[w8] was 24.5-38.5% when the survey took place.

Group III. The effect size of these 2 studies was 0.32 (total sample = 434), comparing children who lived in IS areas with those who lived in ID areas, but who had received iodine during their mothers' pregnancy and after birth. There was a statistically significant difference in heterogeneity ($P<0.05$), although the values of the 95%CI overlapped each other. After excluding the study by Dong *et al.*,[w11] the tests for heterogeneity of each subgroup were no longer statistically significant ($P=0.05$), and the effect size decreases to 0.12 (Fig. 4). We do not have sufficient information to explain this. Nevertheless, the data from the original papers showed that iodine deficiency was relatively milder in the survey sites with the endemic goiter rate reported as 5.51% or 3.89% respectively (Table 1).

Group IV. The total effect size of the 21 entries was an increase of 0.58 SIQP in the group receiving iodine supplementation during pregnancy and after birth based on 7607 subjects, compared with that of children whose mothers were chronially exposed to ID. The test of heterogeneity was statistically significant ($P <0.05$). We divided them further into 5 subgroups according to the type of IQ test and how long (years) after iodine supplementation the children were born.

Test for heterogeneity was not significant ($P>0.05$) except for subgroup IV-5. The effect sizes of subgroup IV-1 to 3 increased to 0.35, 0.70 and 1.15 SIQP of Binet, and subgroup IV-4 to 5 are 0.23 and 0.80 of Raven respectively (Fig. 5). After excluding the study of He Han,[w23] the effect benefit decreased to 0.67 SIQP in subgroup IV-5, but the test for heterogeneity of each subgroup was no longer statistically significant ($P =0.22$) (Fig. 5). The nationalities of the subjects in He Han's study may be a contributing factor, because the effect size increase was more significant in Han Chinese than Miao and Dong minority groups.[w23]

Discussion

Thirty-seven studies with matched social, economic, educational levels to control villages were selected. Children's intelligence in these studies was measured by either the Binet or the Raven scales. In this communication, we estimated the SIQP of children in four types of iodine nutrition conditions.

The intelligence development of children exposed to severe ID was obviously delayed. The intelligence of children who lived in ID areas with no iodine supplementation had an average of 12.45 IQ points (95%CI: 8.40 to 16.50) lower than that of children who lived in a naturally IS environment (one SIQP is equivalent to 15 IQ points of the population defined above). More importantly, inadequate iodine supplementation couldn't improve children's intellectual development. Children, who lived in IDD areas, either received inadequate iodine intervention or were exposed to ID in utero had on average 12.3 IQ points (95%CI: 8.4 to 16.2) less than children who lived in natural IS areas. The difference in IQ points between the IS group and the group in which children's received adequate iodine during their mothers' pregnancy and after birth was 4.8 IQ points ($P>0.05$), which was not statistically different. In severe ID areas, the intelligence of children receiving iodine supplementation during their

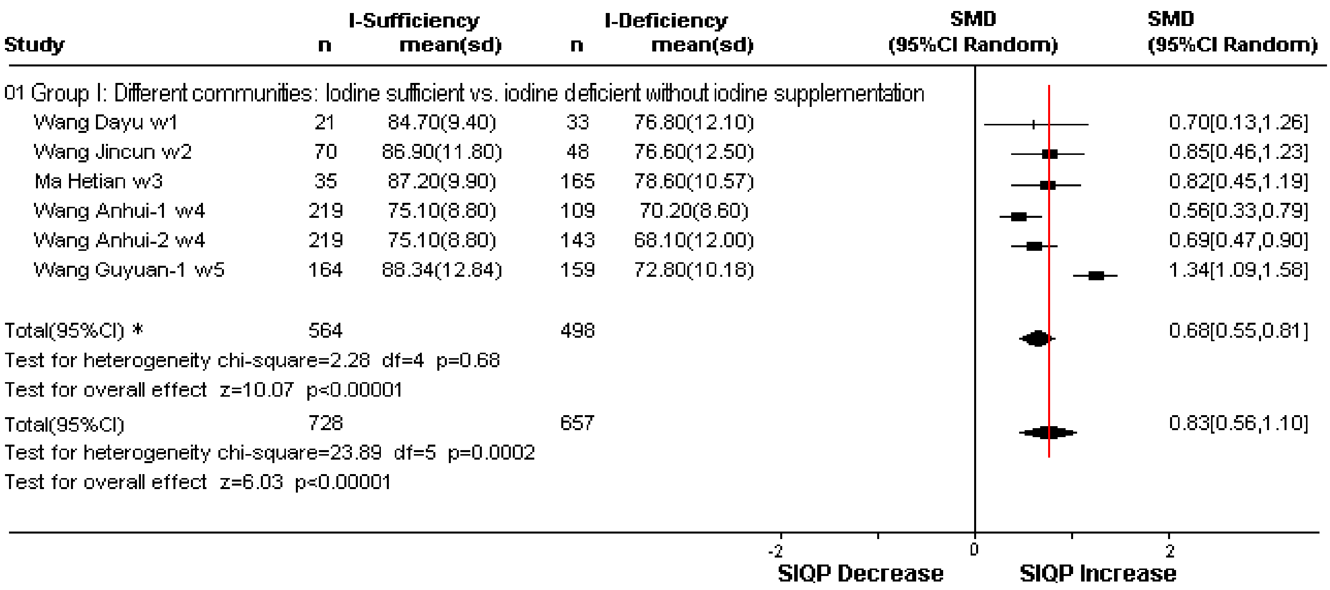

Figure 2. Number of samples, mean (standard deviation of each study), standard deviation of IQ points, 95% confidence interval in Group I: Different communities: Iodine sufficient vs. iodine deficient without iodine supplementation.. Random model was used.
*: Total effect size after excluding Wang Guyuan-1 w5, test of heterogeneity was statistically significant (*P*<0.05).

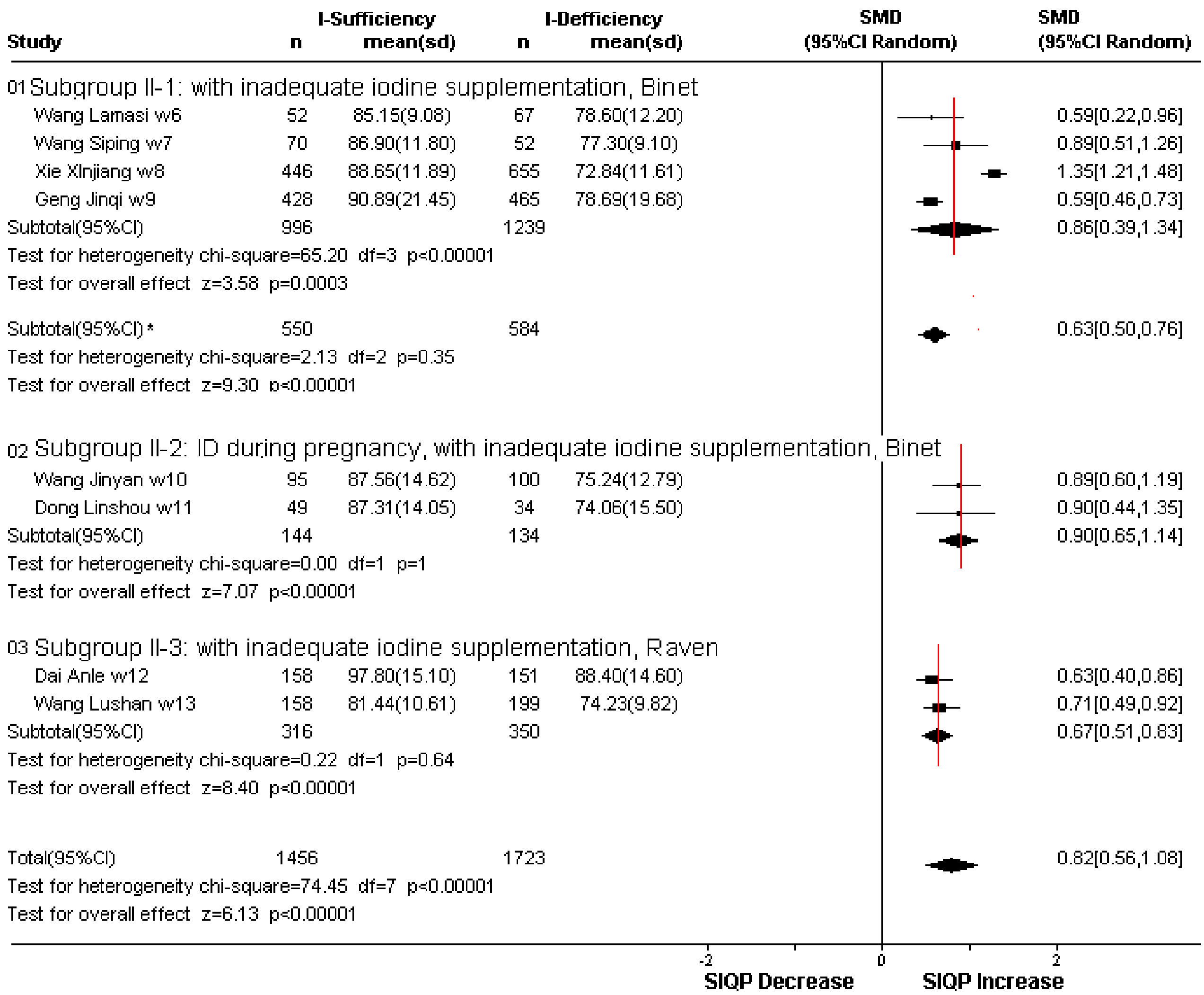

Figure 3. Number of samples, mean (standard deviation of each study), standard deviation of IQ points, 95% confidence interval in Group II: Different communities: Iodine sufficient vs. iodine deficient with inadequate iodine supplementation, which was divided into 3 subgroups. Random model was used.

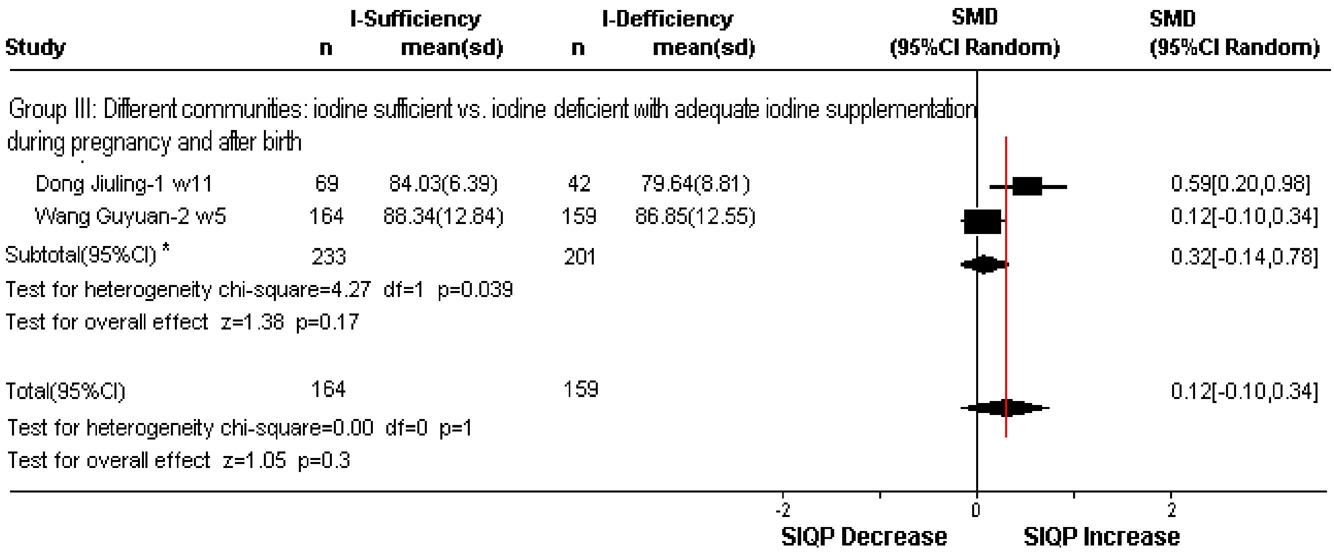

Figure 4. Number of samples, mean (standard deviation of each study), standard deviation of IQ points, 95% confidence interval in Group III: Different communities: iodine sufficient vs. iodine deficient with adequate iodine supplementation during pregnancy and after birth. *: Total effect size after excluding Dong Jiuling-1 w11, test of heterogeneity was statistically significant (*P*<0.05).

Table 2. Characteristics of study Group IV: Children's age, duration of iodine, supplementation (DIS), water iodine concentration (WIC), urinary iodine excretion (UIE), total goiter rate (TGR), and prevalence of endemic goiter (PEG).

		Study group: children born after prevention				Control group: children born before prevention			
Author, site, reference	WI (μg/L)	age	DIS (years)	UIE (μg/g Cr)	PEG (%)	age	UIE (μg/g Cr)	TGR (%)	PEG (%)
Subgroup IV-1: 1-2 years of supplementation, Binet									
Shu Shijia w14		6-8	2	>100		10-15	SIDD*		
Zeng Heba1 w15	1.5	9-10	1.5	117.5		11-13	14.5		31.5
Zuo Gugui1 w16	0.9	8,9	2	91.88μg/L		13,14		69.5	
Zhu Han1 w17	0.9	9,10	2	96.6		11,12			39.01
Subgroup IV-2: 2.1-3 years of supplementation, Binet									
Zeng Heba2 w15	1.5	7-8	3.5	117.5		11,12	14.5		31.5
Shen Xinzhou w18	1.27	6-9	2.5	182.5		10-14			16.2
Dong Jiuling2 w11	<0.01	7-9	3	210.66	3.89	11-13			28
Li Jixian w19#	1.09	5-8	3	342.6		9-14	34.26		33.21
Subgroup IV-3: >3 years of supplementation, Binet									
Wang Ninwu w20		5-7	4.5		2.32	14-15			33.84
Fu Longchuan w21	0.75	4,5	3.5	129.35	7.4	10-11		50.5	29.7
Zhu Han2 w17	0.9	7,8	4	96.6		11,12			39.01
Zuo Gugui2 w16	1.6	6,7	5.5	91.88μg/L		13,14		4.4	
Subgroup IV-4: 0.5-2 years of supplementation, Raven									
Chen ShanHui w22		5-15	>1			5-15		>30	20-33
He Han1 w23	0.84-2.06	7,8	1.5	119		12-14	23.3-55.1		13.5
He Miao1 w23	0.84-2.06	7,8	1.5	119		12-14	23.3-55.1		13.5
He Dong1 w23	0.84-2.06	7,8	1.5	119		12-14	23.3-55.1		13.5
O'Donnell XJ1 w24#	1.2	6,7	0.5			5.8-6.8		54	2
O'Donnell XJ2 w24#	1.2	6,7	0.75			5.9-6.9		54	2
Subgroup IV-5: >3 years of supplementation, Raven									
He Han2 w23	0.84-2.06	9-11	3.5	119		12-14	23.3-55.1		13.5
He Miao2 w23	0.84-2.06	9-11	3.5	119		12-14	23.3-55.1		13.5
He Dong2 w23	0.84-2.06	9-11	3.5	119		12-14	23.3-55.1		13.5

Binet: China Binet Scale. Raven: Combined Raven Test for Rural in China. *: SIDD: severe iodine deficient disorders.
#: used oral iodised oil as intervention

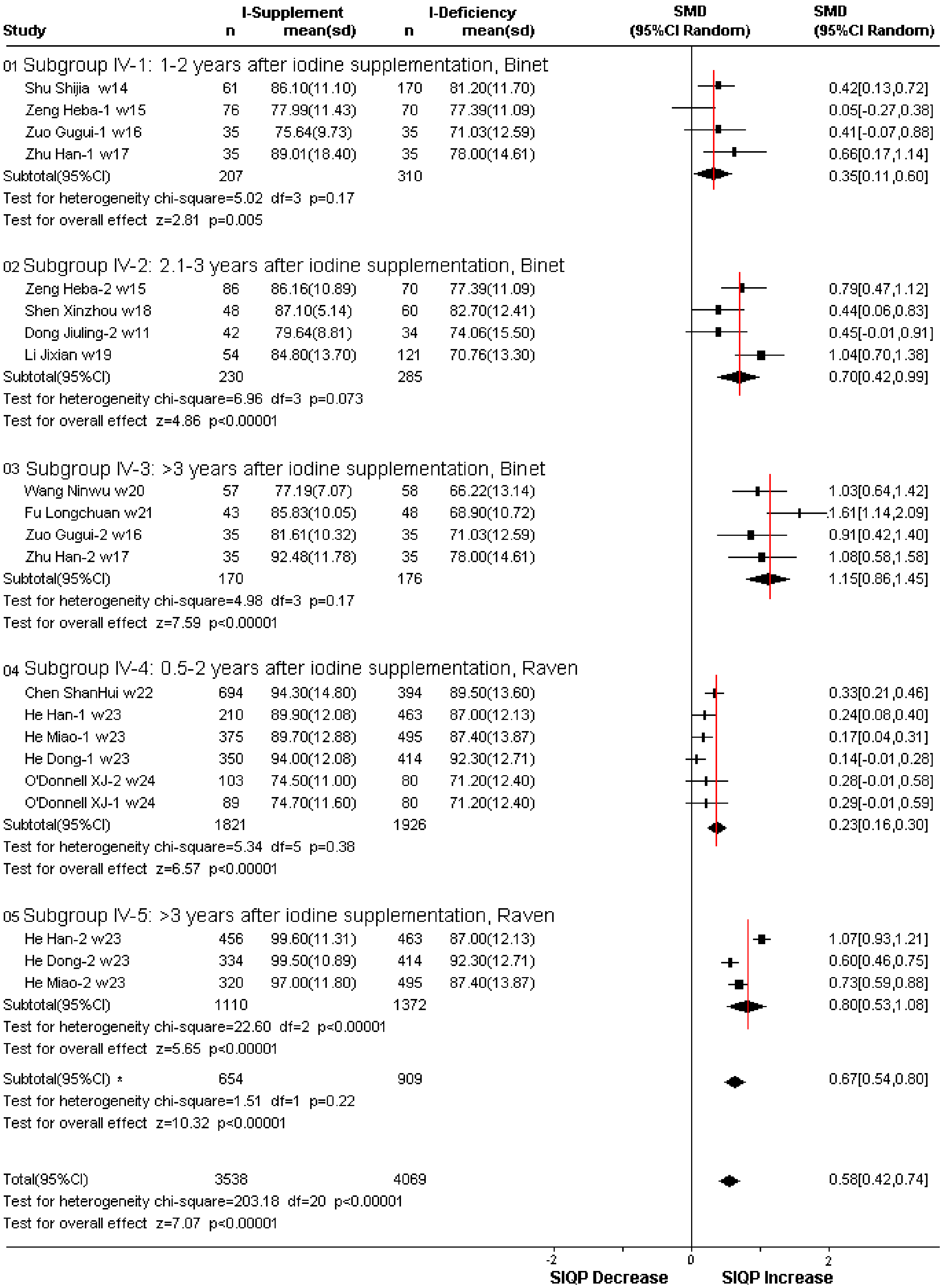

Figure 5. Number of samples, mean (standard deviation of each study), standard deviation of IQ points, 95% confidence interval in Group IV: Same community: children born after vs. before iodine supplementation, divided into 5 groups. Random model was used. *: Total effect size after excluding He Hanw23, test of heterogeneity was statistically significant *(P*<0.05).

mothers' pregnancy and after birth, had an average increase of 8.7 IQ points (95%CI: 6.3 to 11.1) compared with children whose mothers were chronically exposed to ID.

The results of our meta-analysis demonstrates that the positive impact of iodine supplementation on IQ is mainly ob-served in children born 3.5 years after the iodine supplementation program was introduced. There was an increase of 12 Raven points or 17.25 Binet IQ points, depending upon the type of IQ test useed. The intelligence of children born 1-2 years after iodine intervention, however, showed a modest increase of 3.45 to 5.25 points, respectively. This may be because the iodine supplementation program had not reached all infants, pregnant women and people living in IDD areas. Furthermore, iodised salt may not be the best method and cannot provide enough iodine nutrition at the beginning stage of the IDD prevention program.

We tried to control the study quality using the inclusion and exclusion criteria, and by reviewing the original papers by experts in the field of IDD. We excluded duplicate studies and identified poorly matched groups. Different types of publications were searched, such as meeting proceedings, books and studies published in journals. However, we still may not have identified all relevant studies. In addition, bias could have arisen from our review process which was not conducted blindly and the search of published studies was incomplete (despite our efforts to identify all the published studies). Due to the lack of randomized controlled trial data, using observational studies to estimate the benefit of iodine supplementation in ID areas was the only method available.[16,17]

The results of the Binet Scale reflect multiple dimensions of cognitive ability,[13] whilst the Raven Scale is regarded as a cross-cultural, Spearman's "g factor", non-verbal scales.[18] Therefore, the Binet Scale measures multiple abilities and was more likely to be affected by cultural aspects than the Raven Scale. For the purpose of public health, we have combined the results from both methods. The 21 studies reviewed by Bleichrodt[5] were sourced and 18 of these were included in the meta-analysis.[5] Of the four Chinese studies examined by Bleichrodt, we could only locate one (Lin[19]), which did not contain sufficient data (means and standard deviation) to warrant its inclusion in our analysis.

In conclusion, from a population viewpoint, our results show that iodine nutrition plays a crucial role in the intellectual development of children, who either lived in naturally iodine sufficient environments, or received sufficient iodine supplementation in severe ID areas. The intelligence development of children exposed to severe ID was obviously delayed. Inadequate iodine supplementation could not improve children's intellectual development. Adequate iodine supplementation before and during pregnancy to women living in severe ID areas could prevent their children from intelligence deficit, especially for those born 3.5 years after the iodine supplementation program was introduced. In the future, we will search more studies conducted in the world, add them to our database to reanalyse using meta-analysis. Moreover, we will explore the dose response effect of the status of iodine nutrition on intelligence development of children.

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