Shortened version of the title: Prenatal iron status and child neurodevelopment.

Effects of prenatal iron status on child neurodevelopment and behavior: a systematic review.

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ABSTRACT

Background: Iron deficiency and iron-deficiency anemia are the main worldwide nutritional disorders. A good level of prenatal iron is essential for the correct child neurodevelopment but this association has been poorly investigated.

Objective: To gather the scientific evidence on the relation between prenatal iron status and child neurodevelopment. To emphasize the importance of personalize the dose and type of supplementation.

Methods: Wide search strategy was performed in electronic databases for English language articles with no limitations as regards the language or date of publication. Additional studies were selected by hand search. The inclusion criteria were pregnant women without high-risk pregnancy and their children as study population and neurodevelopment as the main outcome.

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Results: 6 RCTs and 13 observational studies were included. The majority concluded that deficit or excess iron during pregnancy injures the mental and psychomotor development of child. Other authors found no association of low iron level with troubles in neurodevelopment, recommended multimicronutrients instead of iron alone and/or showed inconsistent results.

Conclusions: Both iron deficiency as its excess are harmful for the child neurodevelopment. The prenatal iron supplementation should be adjusted for each woman, taking into account the iron stores, some genetic mutation and other health habits.

Keywords: neurodevelopment, mental, psychomotor, supplementation, iron, children.

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INTRODUCTION

Iron deficiency is the most common and widespread nutritional disorder in the world, and the main cause of anemia. Currently, it has been estimated that anemia affects around 800 million children and women world-wide; in the 50% of women and in the 42% of children it is caused by iron deficiency (ID) (World Health Organization 2015). The low-income areas show a high prevalence of anemia (Stevens et al. 2013) but it is also present in developed countries, being the only significantly prevalent nutrient deficiency in industrialized countries (Miller 2013; CDC 2002). Infants, children, adolescents, and women of childbearing age, especially pregnant women, are the main risk population because of their high requirements of iron (Harvey et al. 2013) although women are also susceptible of suffer anemia in the postpartum (Organization 2016). Apart of these, there are other factors may also contribute to the disorder, including overall nutritional status and genetic conditions (Harvey et al. 2013). Several countries have launched supplementation programs as health policy to prevent iron deficiency (Stevens et al. 2013), most of them generalized and routine, which may in general be positive. However, in this regard it is also important to consider that in some cases the iron supplementation may contribute to hemoconcentration if women have a genetic disorder in the “hemochromatosis” (HFE) gene (Arija et al. 2014).

While the maternal nutrient status and micronutrient supplementation can influence fetal development, including birth weight and infant physical development, the evidence for an association between gestational nutrition and brain development has been particularly strong for iron, n-3 fatty acids, and folate. The role of iron in signal controlling in some neurotransmitters and their involvement in the myelination process makes iron necessary for brain development and maturation during the fetal period and infancy (CDC 2002). However, knowledge about this relationship is very limited and there is some controversy regarding the issue of supplementation (Leung 2011).

In this systematic review, we compile evidence that a good prenatal iron status improves the child's mental and psychomotor neurodevelopment, and of the damage caused by either a deficit or excess.

METHODS

Search Strategy

The search strategy selected randomized controlled trials (RCTs) and observational studies in humans, with no limitations as regards the language or date of publication. The Medline/PubMed, Cochrane Library and Scopus electronic literature databases were searched on December 21, 2014. Our search strategy was as follows: ("iron" OR "iron supplementation" OR "hemoglobin" OR "haemoglobin" OR "anemia" OR "anaemia" OR ("Ferritins"[Mesh]) OR ("Hemoglobins"[Mesh]) OR ("Anemia"[Mesh])) AND ("pregnancy" OR "pregnant" OR gesta*) AND ("neurobehavioural" OR "neurobehavioral" OR "neurodevelopmental" OR" behaviour" OR "behavior" OR "birth outcomes" OR "pregnancy outcomes" OR "cognition" OR "offspring outcomes" OR "neurodevelopment" OR "psychomotor development" OR "cognitive" OR "mental" OR "newborn behavioral assessment scale" OR "brazelton" OR "neurophysiological"). Additionally, we identified more studies throughout hand search of references from previous reviews. An updated search was conducted on April 18, 2016 to look for articles published since the first search.

The registration number is CRD42015016541.

Inclusion Criteria

RCTs and observational studies that investigated the effect of prenatal iron status on child neurodevelopment (including mental, psychomotor and behavioral domain) were included. The study population of these investigations was pregnant women without high-risk pregnancy and their offspring. Studies conducted in populations with a disease and/or investigations that reported effects of prenatal iron on pregnancy, birth outcomes, and physical development or growth were excluded.

Data Extraction and Quality Assessment

The information from the studies was summarized in separate tables for RCTs and observational studies, including subject and intervention/observation characteristics, outcomes of interest and psychological tests used. The data are not comparable between different types of study, and as such the results were discussed separately according whether they came from RCTs or from observational studies.

The data were extracted independently and in the case of Lewis et al. (Lewis et al. 2014), we contacted the authors to obtain a better understanding of their statistical methods, but they did not respond to our request.

The quality assessment for RCTs and observational studies was carried out using the revised CONSORT checklist (Schulz et al. 2010) and the STROBE checklist (von Elm et al. 2008), respectively. The articles were rated qualified as follows: “good” if the score was ≥17 items (>80% of the checklist), “average” if the score was 13-16 items (60-79% of the checklist) and “poor” if the score was ≤12 items (<50% of the checklist). The Cochrane Collaboration tool

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(Higgins and Green 2011) was used to evaluate the risk of bias in each study, and the overall percentage of each type of risk.

RESULTS

We identified a total of 1,806 articles from the electronic databases search and three more from handsearching, of which 106 were selected for careful reading of the abstract. Finally, 19 studies met the inclusion criteria (6 RCTs and 13 observational studies) and were considered in this systematic review. 87 articles were excluded according to the exclusion criteria (Figure 1). The studies reviewed were published between 1986 and 2015 and varied widely in size, location and intervention and parameters of observation, but they all focused on some feature of child neurodevelopment.

Tables 1 presents the characteristics of the RCTs, which were located as follows: two were conducted in Australia (Zhou et al. 2006; Parsons et al. 2008), a developed country, while the others were conducted in developing countries; two in rural China (Li et al. 2009; Chang et al. 2013), one in Indonesia (Prado et al. 2012) and other in rural Vietnam (Hanieh et al. 2013). For the supplementation, most of the researchers recruited volunteers at between 14 and 20 weeks of gestation, and they administered the micronutrients until delivery. Zhou et al. (2006) randomly assigned the pregnant women into two groups, which received 20 mg of iron or placebo daily. Two years later, Parsons et al. (2008) continued the observation of outcomes, leading to another report. Other researchers, Li et al. (2009) and Chang et al. (2013), allocated the women into three supplementation groups: folic acid (FA) (400 µg/d), folic acid plus iron (IFA) (with 60 mg/d of Fe) and multimicronutrients (MMN) (with 30 mg/d of Fe). Hanieh et al. (2013) wanted to assess

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if the effect was different with daily IFA (with 60 mg of Fe), intermittent IFA or intermittent MMN supplementation (both including 60 mg of Fe twice a week). Prado et al. (2012) did not assess the effect of iron in isolation, but their intervention groups were IFA or MMN (including iron), with 30 mg/d of Fe in both cases.

Table 2 presents the characteristics of the observational studies. Five were conducted in developing areas: Vietnam (Tran et al. 2013; Tran et al. 2014), a poor state of the United States (Vaughn et al. 1986), rural China (Yang et al. 2010) and the Republic of Benin (Mireku et al. 2015). The rest were reported in the United States (Tamura et al. 2002; Schmidt et al. 2014; Wehby and Murray 2008), the United Kingdom (Lewis et al. 2014), Finland (Fararouei et al. 2010), Canada (Rioux FM et al. 2011) and Spain (Hernández-Martínez et al. 2011; Cucó et al. 2005).These investigations focus on maternal iron status throughout pregnancy. Some reports specify whether the women received supplements supplemented and the doses of supplementation, while others lack this information and work with biochemical data.

As regards the point at which the effect of supplementation was evaluated, in the majority of RCTs and observational studies this took place in toddlers and school-age children while in six of them (Li et al. 2009; Hanieh et al. 2013; Tran et al. 2014; Tran et al. 2013; Vaughn et al. 1986; Rioux et al. 2011) the age of the group was less than one year old, while in two others (Cucó et al. 2005; Hernández-Martínez et al. 2011) the assessment was conducted at 2--3 days old and another one (Fararouei et al. 2010) evaluated the effect over 30 years.

Quality of Reporting

The total scores on the CONSORT and STROBE checklist ranged from 14 to 20, with a mean score of 18; as a result, thirteen studies had a “good” quality and six were rated “average.” The

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quality of the studies included was also assessed by using Cochrane tool mentioned above (Higgins and Green 2011). Figures 2 shows the percentage of each type of bias among the studies. In general, the risk of bias is low, most of the researchers present the complete outcome data and they do not incur any reporting bias, but several studies lack information about the blinding of the outcome assessment, so the risk is not clear in these cases. The observational studies have a high probability of selection bias because the sequence is not usually generated from the general population and exposure cannot be controlled by the researchers. The blinding of participants is another factor that is usually uncontrolled in studies of this type, which gives them a high probability of risk of performance bias.

Maternal iron assessment

There are several indicators that complement each other when evaluating the body's iron level. Iron stores are usually measured based on the Serum Ferritin (SF) concentration while the best measure of circulating iron is Transferrin Saturation (TS). Researchers assess the maternal iron status at various points in the pregnancy and most consider iron deficiency (ID) to be if SF<15 µg/L (Tran et al. 2014; Hanieh et al. 2013; Tamura et al. 2002) but SF<12 µg/L may also be found in the literature (Hernández-Martínez et al. 2011; Zhou et al. 2006; Parsons et al. 2008). TS<16% is another indicator of ID but only Hernández-Martínez et al. (2011) used it in our review. A generic diagnosis of anemia requires a hemoglobin (Hb) concentration lower than 110 g/L (Chang et al. 2013; Prado et al. 2012; Vaughn et al. 1986; Yang et al. 2010; Fararouei et al. 2010) but iron-deficiency anemia (IDA) requires one or more ID factors and Hb<110 g/L (Zhou et al. 2006; Parsons et al. 2008; Tran et al. 2013; Hanieh et al. 2013). Furthermore, Yang et al.

(2010) take into account high values of Hb (≥ 124 g/L) when discussing possible adverse effects on maternal and fetal health.

Schmidt et al. (2014), Li et al. (2009) and Lewis et al. (2014) did not take into account maternal iron status, but they established conclusions based on extensive scientific evidence that maternal iron supplementation improves prenatal iron status.

Child neurodevelopment assessment

Neurodevelopment is a broad concept that includes the maturation of the central nervous system, which may be assessed at early stages using psychological tests of mental and psychomotor development, and behavioral assessment measures. Later, in childhood, neuropsychological and intellectual ability (Intellectual Quotient, IQ) tests and other behavioral-emotional assessment tests may be used.

Mental Development (MD) *assessment*

To assess infant MD, six studies were included --three RCTs (Hanieh et al. 2013; Li et al. 2009; Chang et al. 2013) and three observational studies (Tran et al. 2014; Tran et al. 2013; Rioux et al. 2011)-- using Bayley Scales (in the first (Bayley 1969), second (Bayley 1993) and third edition (Bayley 2006)), which include many aspects of mental development such as language and cognition. Rioux et al (2011) also used the Brunet-Lézine Scale of Psychomotor Development of Early Childhood (Josse 1997) on 6-month-old infants. At the pre-school and school age, the Stanford--Binet Intelligence Scale (Becker 2003) and Wechsler Intelligence Scales for Children (Wechsler 2002; Wechsler 1974) respectively were used to determine IQ (Zhou et al. 2006; Tamura et al. 2002; Yang et al. 2010; Lewis et al. 2014). The Test for Auditory Comprehension

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of Language (Carow-Woolfolk 1998) provided information on the children's auditory acuity in Tamura's research (2002) and the Yale Children's Inventory for Attention and Tractability (Sally et al. 1988) was used to determine if children suffered from attention deficits and learning disabilities. To assess educational achievement over 30 years, Fararouei et al. (2010) used school scores at 14 and 16 years old and the highest level of education at 31 years old. Prado et al. (2012) adapted the following tests to evaluate several cognitive domains in Indonesian children aged 42 months: the Picture Vocabulary Scale (Dunn et al. 1997) and the MacArthur--Bates Communicative Development Inventory--Level III (Fenson et al. 2007) were used to assess language abilities; the Block Design Test of British Ability Scale (Elliot 1996) and the Wechsler Preschool and Primary Scale of Intelligence--III (Wechsler 2012) for assessing visuospatial ability; the Visual Search Test of NEPSY Developmental Neuropsychological Assessment (Korkman and Kirk 1998) for assessing visual attention and the Snack Delay Test (Tracy et al. 2007) and the Windows Test (Russell et al. 1991) were used to determine executive function.

In one study, symptoms of Autistic Spectrum Disorders (ASD) were identified using the Social Communication Questionnaire (Rutter and Lord 2003) and ASD were diagnosed using the Autism Diagnostic Interview--Revised (Lord et al. 1994) and the Autism Diagnostic Observation Schedule--Generic (ADOS) (Lord and Rutter 2000). Schmidt et al. (2014) assessed cognitive function using the Mullen Scales of Early Learning (Mullen 1995), like Mireku et al. (2015) one year later, and adaptive function was established using the Vineland Adaptive Behavior Scales (Sparrow and Balla 1984).

Behavior assessment

The Bayley Scales also evaluate the socio-emotional dimension and adaptive behavior of children, and were the measure used by Vaughn (Vaughn et al. 1986) in addition to the Brazelton Neonatal Behavior Assessment Scale (NBAS) (Als et al. 1977). Other researchers (Cucó et al. 2005; Hernández-Martínez et al. 2011) also used the NBAS to evaluate children's behavior because it enables observation of the best capacities of newborn children. Prado et al. (2012) used the Brief Infant--Toddler Social and Emotional Assessment (Briggs-Gowan 2002) to evaluate the emotional development of children, while another test, the Strength and Difficulties Questionnaire (SDQ) (Goodman 2006) was useful due to being able to report possible emotional and behavioral problems in children (4 to 17 years) based on information from parents and teachers (Zhou et al. 2006; Parsons et al. 2008). Children's temperament also was evaluated in one study (Parsons et al. 2008) using the Short Temperament Scale for Children (Prior and Sanson 2000).

Psychomotor Development (PD) *assessment*

Seven of the studies also evaluated children's psychomotor development. Most of the researchers used the motor score on the Bayley Scale (Li et al. 2009; Chang et al. 2013; Hanieh et al. 2013; Tran et al. 2014; Prado et al. 2012) in addition to the mental domain of BSID. Meanwhile, Tamura et al. (2002) used the Peabody Developmental Motor Scales (Folio and Fewell 2000) to assess the fine and gross motor capacity of children at 5 years old, and Wehby et al. (Wehby and Murray 2008) used the Denver Developmental Screening Test (Frankenburg and Dodds 1967) for the same parameter at 3 years of age. Cucó et al. (Cucó et al. 2005) used the Motor cluster of NBAS, Prado et al. (2012) applied the Ages and Stages Questionnaire (Schaefer et al. 2000) and

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Mireku et al. (2015) used the Mullen Scales of Early Learning (Mullen 1995) to assess PD in children.

DISCUSSION

Maternal iron status

When discussing maternal iron status during pregnancy and its importance for the mother and child's health is necessary to take into account the metabolism of iron and the different factors that may influence it. Apart from the fact that iron absorption depends on several dietary conditions which are even more pronounced in supplemented pregnant women, the storage levels of iron, overall nutritional status, genetic mutations and specific physiological states such as pregnancy and infancy also may modify its absorption (Forrellar et al. 2000; García et al. 2010; Olivares et al. 2010; Harvey et al. 2013). During pregnancy, iron needs increase from 0.8 mg/d in the first trimester to 7.5 mg/d in the third trimester (FAO and WHO 2001; Cao and O'Brien 2013) because the child's development depends on the transfer of iron from the mother. The increased ability to absorb nutrients is directly related to nutritional requirements (Andrews 1999; Hallberg 2001) but the absorption of iron from the diet is known to be insufficient to cover increased iron needs during pregnancy, meaning that the iron balance is dependent on the amount of stored iron. It is therefore important to have good nutritional health before getting pregnant and there is also a need to monitor possible genetic mutations in the HFE gene that causes iron overload.

Maternal iron deficit and mental development

The first author to investigate the relationship between maternal iron status and child mental development was Vaughn et al. (1986), who concluded that no maternal biochemical or hematological parameters were related with BSID scores in a study with 115 pregnant women and their babies. He may have reached that conclusion because at that time only the first edition of the BSID had been published, which was not as specific as the following versions, but it also may be due to the sample size being insufficiently representative for an observational study. Later, Tamura et al. (2002) assessed children's auditory comprehension of language and their ability to obey rules and follow general decorum orders, and they concluded that a low cord serum ferritin concentration correlated with worse scores in all tests. In 2008, Wehby et al. (2008) analyzed the effects of some micronutrient supplementation at least 3 days a week during the 3 months prior to becoming aware of the pregnancy, and/or during the following 3 months, on the language skills of children aged 3; they concluded that MMN use was associated with a reduced odds ratio for moderate risk to language but not supplementation with iron alone. Li et al. (2009) subsequently tested the effect of iron in 1,305 women, both alone and in combination with FA, versus MMN supplementation on the MD of children, and found additional effects in the IFA group compared with FA alone; however, the BSID scores were better in the mental development index (MDI) in the MMN group than in the others, consistent with the findings of Wehby et al. (2008) and Prado et al. (2012), who conducted a similar study with 487 pregnant women. Two more recent investigations have been conducted in low income countries, and this may be the reason for the results obtained, because the requirements of micronutrients were so high in malnourished women that iron alone is not sufficient to ameliorate the mother and the child's health. Another case with negative results was the study by Rioux et al. (2011), who evaluated maternal iron status and infants' cognitive performance in 63 Canadian mother-infant dyads; they did not observe any relation between these two variables, which may be due to the small sample size. Fararouei et al. (2010) conducted a cohort study in Finland on 11,656 pregnant women and their offspring at 14, 16 and 31 years old; they aimed to assess the educational achievement of the offspring as related to the maternal Hb level during pregnancy and unlike the authors above, they concluded that there was a direct association between these two parameters, especially in the final stages of pregnancy. These data therefore suggest long-term influences of the prenatal iron status on the cognitive development of offspring, although further research is needed to replicate these results. More recently, Chang et al. (2013) and Hanieh et al. (2013) conducted their respective RCTs in Southeast Asia and both concluded that prenatal iron supplementation led to increased BSID scores in the cognition domain. When Hanieh carried out his study of in 1,258 women, comparing daily and intermittent (twice a week) iron supplementation, he recommended the second option for non-anemic women as well as women of child-bearing age to prevent beginning pregnancy with low iron reserves. However, this recommendation should not be extrapolated to populations with a high prevalence of anemia because intermittent supplementation might be insufficient if women have poor iron reserves. Hanieh's result is supported by the findings of Chang et al., who observed that supplementation is more effective in women beginning pregnancy without ID, and recommend beginning the supplementation before becoming pregnant. Likewise, Tran et al. (Tran et al. 2013) used the third edition of the BSID to evaluate the 378 children in their observational study conducted in Vietnam, and the results showed that ID during the gestational period leads to diminished

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cognitive abilities. Mireku et al. (2015) were more neutral in their conclusions from a study conducted on 636 Beninese children, in which they found no relation between prenatal Hb concentration and the cognitive abilities of infants at 1 year of age.

Maternal iron deficit and behavior

For children's behavioral development, Vaughn (Vaughn et al. 1986) concluded that the mother's iron-binding capacity was significantly related to irritability in children at 3 days of age, according to the NBAS and at 5 months, according to the Bayley Scale. He therefore observed that mothers of more irritable infants had lower levels of circulating iron than mothers of less irritable infants. Zhou et al. (2006) concluded from their RCT of 430 women and their children that SDQ mean scores in behavioral and emotional difficulties did not differ significantly between the supplemented and control group; this was perhaps because the dose of supplementation was too low to notice any significant clinical effect. Two years later, Parsons et al. (2008) continued with observations of 264 children in the study in Australia, and according to their results a better maternal iron status during pregnancy is related with an absence of behavior problems at 4, 6 and 8 years of age. They also evaluated the temperament of children aged 6 and 8, and found no difference between the Fe and placebo groups, so they concluded that routine iron supplementation in pregnancy in a well-nourished population has no clearly beneficial effect on parental reports of child temperament. These observations may be due to the fact that the Australian population had a good baseline nutritional status, but also may be because the iron dose was insufficient. In contrast, when Wehby et al. (2008) conducted a large study (n = 6.774) in the American population, they found that iron use reduced the risk (OR 0.5 [0.35-0.72]) on the personal-social scale of the Denver Test (Frankenburg and Dodds 1967), even when the dose of

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supplementation was ignored. A Spanish longitudinal study carried out by Hernández-Martínez et al. (2011) was also based on well-nourished pregnant women who were supplemented with 40 mg/d of Fe, and the researchers concluded that ID affects children's neurodevelopment differently depending on when it occurs. In specific terms, the autonomous response of the neonate may be altered if ID occurs early in pregnancy, consistent with a worse response of the NBAS. However, when iron levels were assessed in terms of intake and not at the biochemical level, Cucó et al. (Cucó et al. 2005) found no differences in any behavioral cluster.

Recently, in the United States, Schmidt and his team (Schmidt et al. 2014) conducted an observational study, knowing whether women had received supplements and the amount of dietary iron intake, to assess the effect of these on the risk of ASD of children. They monitored the psychiatric clinical evolution of 866 children and found initial evidence for an association between increased maternal Fe supplementation and a reduced risk of ASD.

Maternal iron deficit and IQ

Tamura et al. (2002) evaluated the IQ score of 278 children aged 5 in an observational study conducted in Alabama, and concluded that there is an association between both the highest and lowest quartile of cord serum ferritin concentration and lower scores on intelligence tests, while the middle two quartiles are associated with better scores. Albeit weakly, maternal and cord ferritin concentration correlates significantly (Rusia et al. 1995; Nemet et al. 1986) which highlights the importance of a good maternal state of iron and demonstrates that low iron status impairs children's neural development during pregnancy. As in the case of behavior, Zhou et al. (Zhou et al. 2006) concluded that routine iron supplementation is not sufficient for favorable

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effects on the IQ of children and similarly, the explanation may be that 20 mg/d of iron may be too low for the most of the pregnant women. Likewise, Prado et al. (2012) observed in Indonesia that maternal MMN intake compared with IFA supplementation can improve the cognitive abilities of children at 3.5 yearsold, especially when the women were undernourished or anemic during pregnancy because the absorption is incremented. As in the other aspects of neurodevelopment, this result may due to the fact that the nutritional requirements involve more than iron in low income areas. In line with previous investigations, Lewis et al. (2014) used a population-based cohort (ALSPAC) in the United Kingdom to assess the effect of the iron status of 11,696 pregnant women on the cognition of their children, and found no evidence that low iron levels in pregnancy have a detrimental effect on the brain of the developing fetus and therefore on IQ in childhood. This observation is inconsistent with most findings, and may be because in the United Kingdom health carers prescribe iron supplements at a very early stage in pregnancy for women with low iron stores, meaning that the researchers were unable to study the effects of low iron levels in late period of pregnancy in this cohort.

Maternal iron deficit and psychomotor development

Hernández-Martínez et al. (2011) found in Spain that the third trimester of pregnancy is a critical period in neonatal motor performance. They demonstrated that ID or anemia in this period may delay the children neuromotor development. Accordingly, the observational study also conducted by Cucó et al. (Cucó et al. 2005) in Spain concluded that an appropriate supply of iron, mainly in the final weeks of gestation, contributes to the maturation of the infant neuromotor system, as reflected in improved NBAS test scores for newborns after 3 days of life. These results reinforce the conclusion of Tamura et al. (2002), who some years previously asserted that children aged 5

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whose cord serum ferritin concentration was low obtained worse scores in motor tests than children with intermediate values of ferritin. The conclusion of Tamura's team has recently been confirmed by the results of Mireku et al. (2015) from an African cohort; their study revealed that there was an inverted U-shaped relationship between prenatal Hb during the first half of pregnancy and infant gross motor function at 1 year of age. This shows that low Hb concentrations may be detrimental to the early motor skills of children. Similarly, Li et al. (2009) aimed to determine what kind of supplementation may benefit infant psychomotor development, and they conducted an interventional study comparing the effect of MMN (with 30 g/d of Fe) and IFA (with 60 g/d of Fe). They found further evidence that micronutrient supplementation, but not IFA in this case, improves PD at 1 year of age. Various micronutrients play a role in children's neural development, which is more evident in regions with low recourses such as rural China, where the effect of IFA seems to be insufficient to improve infants' health, although the dose of Fe is high in this group. Prado et al. (2012) arrived at the same conclusion in Indonesia, due to the similar nutritional status of the population and the equivalent nature of the intervention, and therefore recommended MMN supplementation for undernourished pregnant women to improve the PD of children at 3.5 years old. However, Hanieh et al. (2013), who counterpoised daily IFA, intermittent IFA and intermittent MMN supplementation, concluded that at 6 months of age there was no difference between the twice-weekly supplement groups and the daily group in an area of Southeast Asia with low anemia prevalence. This result was perhaps due to the fact that in a well-nourished population, the effect of the variability of total dose of iron or the combination with other micronutrients is less evident than in needy regions. Several years after the study by Tamura et al. (2002), and following Hernández-Martínez et al. (2011),

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Chang et al. (2013) investigated 850 mother-child pairs in rural China, and they also found that anemia in the third trimester was related with poor development of motor skills among children aged 2. The recent results of Tran et al. (Tran et al. 2014) are consistent with these data, and indicate that anemia (Hb<110 g/L) in late pregnancy is associated with poor infant PD at 6 months of age, but this association with maternal iron deficiency was not evident (SF<15 µg/L). Like the authors mentioned above, Tran et al. also concluded that even if ID and IDA in early pregnancy do not have a direct effect on BSID-Motor scores, both conditions indirectly affected the outcomes, increasing the risk of anemia in late pregnancy. As a result, they suggest that interventions to promote infant development should be performed in early pregnancy and explicitly addressed at these antenatal factors.

Excessive maternal iron and neurodevelopment

As discussed in the paragraph "*Maternal iron assessment*", some gene mutations can affect iron homeostasis. The HFE gene mutation causes ineffective hepcidin production (Andrews 1999), and a low hepcidin plasma concentration leads to a lack of downregulation of FPN, allowing increased iron uptake (Lewis et al. 2014; Fleming and Ponka 2012; Crownover and Covey 2013; Muñoz and Remacha 2011) which causes hemoconcentration, especially in pregnant women receiving iron supplements (Casanueva et al. 2006; Aranda et al. 2013; Arija et al. 2013). Excess iron damages cells primarily by catalyzing the production of reactive oxygen species (ROS) in quantities that the cellular antioxidant system is unable to delete (Fleming and Ponka 2012). During gestation, the iron overload may increase blood pressure, the risk of eclampsia (Ziaei et al. 2007) and blood viscosity, which can affect the blood flow between the uterus and placenta, diminishing the perfusion of nutrients and increasing the risk of placenta infarction (Aranda et al.

2013). Fetal development may therefore be harmed because the amount of nutrients reaching the fetus is not enough to meet its needs (Yip 2000).

According to the literature, there is some evidence that an elevated concentration of iron may be harmful to children's neurodevelopment. Tamura et al. (2002) were the first to observe this effect and they concluded that a high Hb concentration is related with a lower IQ in children, which shows that a high iron status impairs child neural development in pregnancy, to the same extent as a deficit. Later, Yang et al. (Yang et al. 2010) strengthened this hypothesis, showing the adverse effects on cognitive development produced by excess iron in early pregnancy. Parsons et al. (2008) also contributed by evaluating children's behavior and found that that significantly more children in the Fe group had an abnormal teacher-rated peer problems score than in the placebo group, which suggests that routine Fe supplementation may even have a negative influence on behavior if the mother does not have ID. Further evidence to that effect comes from Hanieh's research (2013), which compared daily and intermittent supplementation with iron and specifically concluded that 40% of women in the daily IFA group had ferritin levels higher than 41 µg/L at 32 weeks of gestation, although this was not associated with hemoconcentration (Hb>130 g/L). It therefore follows that daily IFA supplementation may lead to an excessive increase in maternal SF, which causes adverse outcomes for mother-child health during pregnancy, such as those discussed above. The final evidence for the detrimental effect of excess iron on children's neurodevelopment was provided by Mireku et al. (2015), who noticed that both high and low prenatal Hb concentrations were harmful to children's gross motor development. According to their data, optimal range of maternal Hb seems to be 90-110 g/L.

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In addition to the body's iron stores, physiological state or general nutritional situation, during pregnancy the iron levels may therefore also depend on genetic individualities, meaning that the same iron intake may be beneficial for one woman while for another it may be excessive and lead to a harmful iron overload. For this reason, the scientific evidence points to the need to personalize the supplementation dose in accordance with all these individual characteristics.

Strengths and limitations

We used a wide search strategy, which included observational studies and RCTs, which were selected according to the aim of the study, i.e. children's neurodevelopment after iron supplementation in pregnancy, as well as their iron profile. The year of publication was not a filter in the selection process of the articles included, and as such our systematic review gathers widespread scientific evidence about the effect of a low prenatal iron status and the benefits, but sometimes also the damage, of iron supplementation during pregnancy for children's neurodevelopment. The risk of bias was assessed to take into account the quality of the studies included and to analyze the results more precisely. As mentioned above, the inclusion of observational studies in the review provided more knowledge than if we had only used intervention trials but the high risk of selection and performance bias is nevertheless a limitation. However, we have discussed the results of the studies considering the bias of each one in order to extract wide-ranging and objective knowledge.

CONCLUSION

Although the research on child neurodevelopment related to prenatal iron levels is very limited, the scientific evidence shows an association between ID or IDA during pregnancy and problems

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in MD, behavior and cognitive abilities. PD is also improved by a good maternal iron status during gestation, which is endorsed by all the authors who investigate this outcome. Some research has found evidence that excess iron is also harmful to brain formation and maturation in the fetus and therefore the child's development in the mental and motor domains. However, further investigation is necessary for a better understanding of how a deficit or excessive maternal iron may damage the child's neural development and how to personalize iron supplementation to fit the individual characteristics of each woman in order to avoid ID, IDA and hemoconcentration in pregnancy.

Financial support: This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest: The authors declare that they do not have conflict of interest.

Authors' contributions:

- Lucía Iglesias: searched the articles, conducted its selection process, interpreted them and wrote the manuscript.
- Josefa Canals: contributed in the search of articles, interpreted its information, contributed to the discussion and review the manuscript.
- Victoria Arija: planned the systematic review, interpreted its information, contributed to the discussion and reviewed the manuscript.

All authors read and approved the final manuscript.

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Table 1 Characteristics of randomized controlled trials included in the review.

Reference	**Location**	**n**	**Supplementation**	**Duration**	**Parameters**	**Child Age**	**Outcomes**	**Neurodevelopment Tests**
Zhou, S (2006)	Australia *Adelaide*	430	20 mg/d Fe vs placebo	From 20 wk to delivery	Hb	4 y	IQ	Stanford-Binet Intelligence Scale
					SF		Behavior	Strength and Difficulties Questionnaire (SDQ)
Parsons, A (2008)	Australia *Adelaide*	264	20 mg/d Fe vs placebo	From 20 wk to delivery	Hb	6--8 y	Temperament	Short Temperament Scale for Children
					SF		Behavior	Strength and Difficulties Questionnaire (SDQ)
Li, Q	China	1.3	AF vs IFA (60 g/d Fe)	From 14	-	3, 6,	Mental and	BSID--I

(2009)		05	vs MMN (30g/d Fe)	wk to delivery		12 m	Psychomotor Development	
Prado, E (2012)	Indonesia *Lombok*	487	IFA (30 mg/d Fe) vs MMN (30 mg/d Fe)	From pregnancy to 3 m after delivery	Hb	3.5 y	Psychomotor	BSID-II
							Development	Ages and Stages Questionnaire
							Language Ability	MacArthur-Bates Communicative Development Inventory--Level III
								The Picture Vocabulary Scale
							Visuospatial	British Ability Scale
							Ability	Wechsler Preschool and Primary Scale of Intelligence--III
							Visual Attention	NEPSY Developmental Neuropsychological Assessment
							Executive	Snack Delay Test

							Function	Windows Test
							Socioemotional Development	Brief Infant--Toddler Social and Emotional Assessment
Hanieh, S (2013)	Vietnam *Ha Nam*	1,258	IFA (60 mg Fe/d) vs IFA (60 mg Fe/2 per wk) vs MMN (60 mg Fe/2 per wk)	From 16 wk to 6 m after delivery	Hb SF	6 m	Mental and Psychomotor Development	BSID--III
Chang, S (2013)	China	850	AF vs IFA (60 g/d Fe) vs MMN (30 g/d Fe)	-	Hb	2 y	Mental and Psychomotor Development	BSID--II

Fe, iron; Hb, hemoglobin; SF, serum ferritin; FA, folic acid; IFA, folic acid plus iron or iron-folic acid; MMN, multimicronutrients; m, months; y, years.

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Table 2 Characteristics of observational studies included in the review.

Reference	Location	n	Duration	Parameters	Offspring Age	Outcomes	Neurodevelopment Tests
Vaughn, J (1986)	USA *New Orleans*	115	-	Hb	3 d	Behavior	Brazelton Neonatal Behavior Assessment Scale
				SF			BSID--I
				Serum Iron	5 m		
				Iron-binding capacity			
Tamura, T (2002)	USA *Alabama*	278	-	SF	5 y	IQ	Wechsler Intelligence Scale for Children--R
						Auditory	
						comprehension	Test for Auditory

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							Comprehension of Language
						Fine and Gross Motor	Peabody Developmental Motor Scales
						Skills	
						Attention	Yale Children's Inventory for attention and tractability
Cucó, G (2005)	Spain *Reus*	66	Before pregnancy to 38 wk	-	3 d	Behavior Psychomotor Development	Brazelton Neonatal Behavior Assessment Scale
Wehby, GL (2008)	USA *Iowa*	6.774	Before pregnancy and/or during the	-	3 y	Fine and Gross Motor Skills	The Denver Developmental Screening Test

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			first 12 wk			Language Ability	
						Personal-social Contact	
Yang, L (2010)	China	3.609	-	Hb	4--6 y	IQ	Chinese-Wechsler Intelligence Scale for Children
Fararouei, M (2010)	Finland	11.656	From 24-28 wk to 31 y after delivery	Hb	14 y	Educational Achievement	*School cores*:
					16 y		Self-reported questionnaires
							School reports
							Self-reported questionnaires
					31 y		Details of university degree
Hernánd	Spain	216	From 13	SF	2--3 d	Behavior	Brazelton

ez-Martínez, C (2011)	*Reus*		wk to delivery	TS			Neonatal Behavior Assessment Scale
Rioux, FM (2011)	Canada	63	-	Blood iron	6 m	Cognition	Brunet-Lézine Scale of Psychomotor Development of Early Childhood
				Hb			BSID-III (Mental Scale)
Tran, T (2013)	Vietnam *Ha Nam*	378	From 12--20 wk to 6 m after delivery	Hb	6 m	Mental Development	BSID--III (Mental Scale)
				SF			
Tran, T (2014)	Vietnam *Ha Nam*	418	From 12--20 wk to 6 m after delivery	Hb	6 m	Psychomotor Development	BSID--III (Motor Scale)
				SF			
Lewis, SJ	United	11.6	-	Hb	8 y	IQ	Wechsler

(2014)	Kingdom *Bristol*	96		HFE, TMPRSS 6 and TF genotype			Intelligence Scale for Children-III
Schmidt, R (2014)	USA *California*	866	From 3 m before pregnancy to breastfeeding	-	2--5 y	ASD	Autism Diagnostic Interview--Revised
							Autism Diagnostic Observation Schedule--Generic (ADOS)
							Social Communication Questionnaire
						Cognition	Mullen Scales of Early Learning
						Adaptive function	Vineland Adaptive

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							Behavior Scales
Mireku, MO (2015)	Republic of Benin *Allanda*	636	Before 29 wk of pregnancy to delivery	Hb	1 y	Cognition	Mullen Scales of Early Learning
						Psychomotor Development	

Hb, hemoglobin; SF, serum ferritin; IQ, intelligence quotient; TS, transferrin saturation; BSID, Bayley Scales of Infant and Toddler Development; ASD, Autistic Spectrum Disorders; m, months; y, years.

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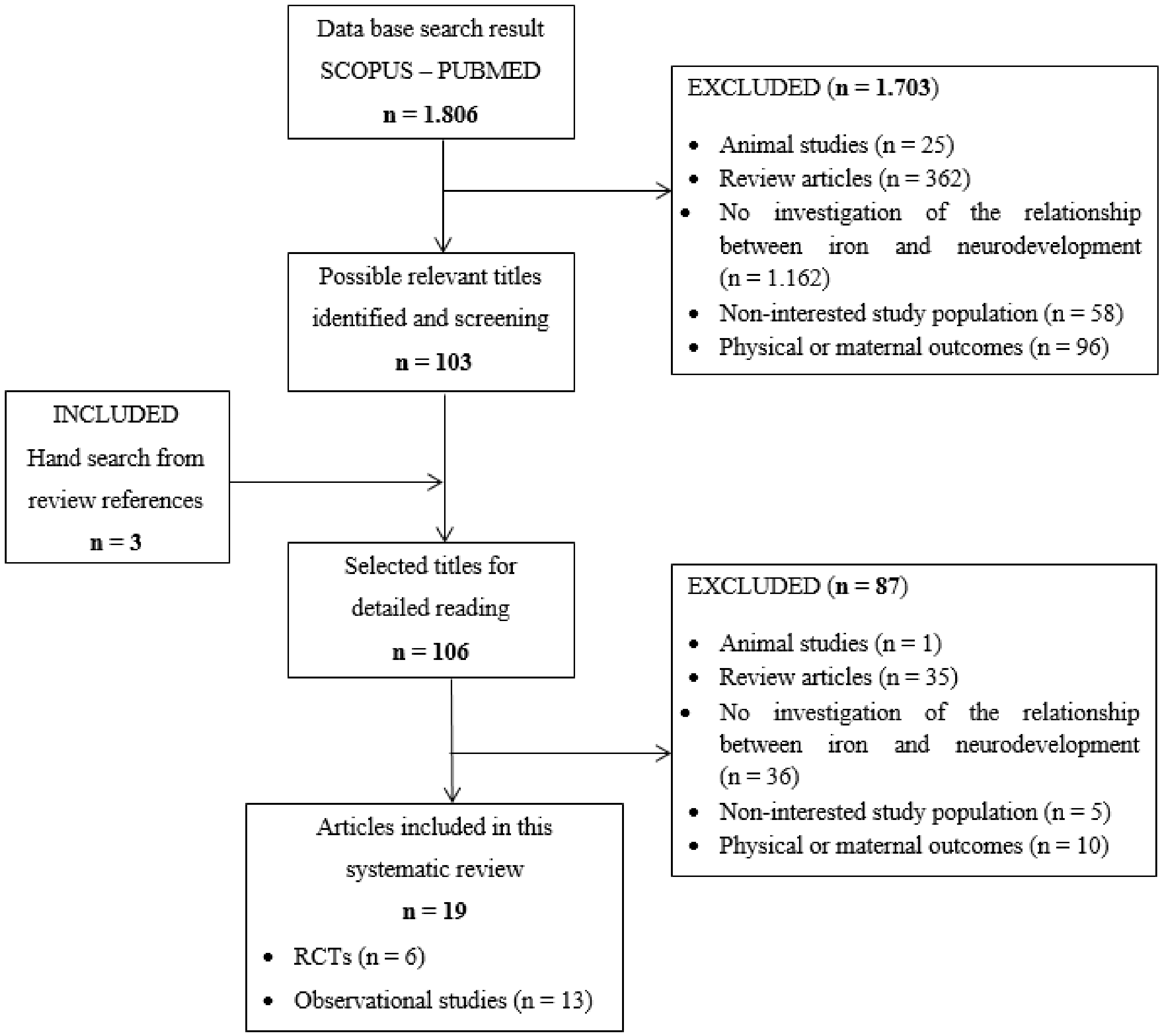

Figure 1 Flowchart of selection process of included articles in systematic review.

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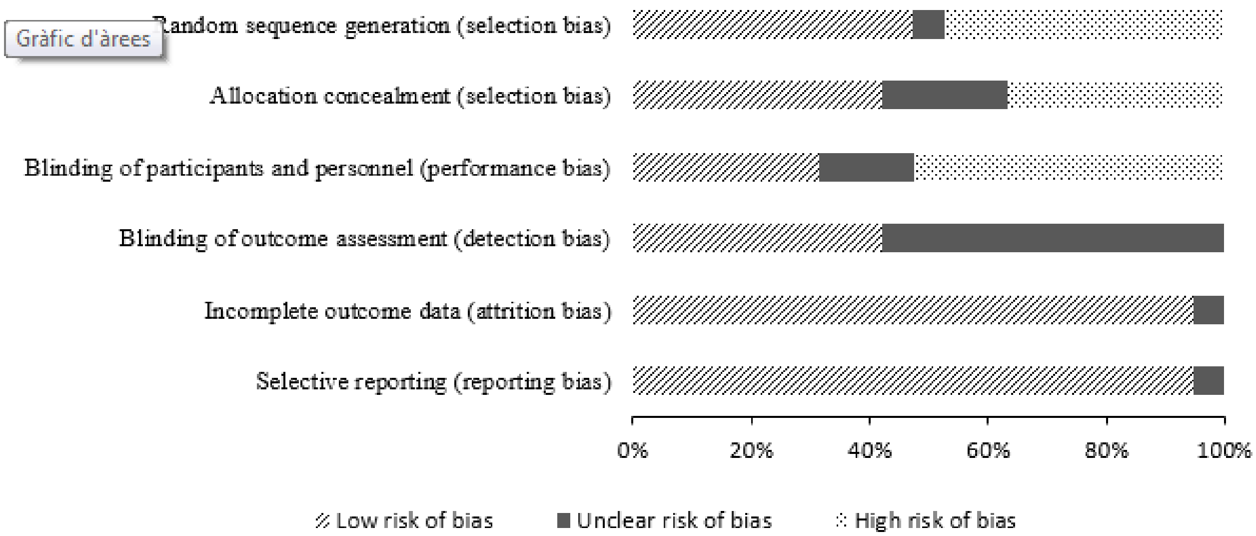

Figure 2 Percentage of bias types among studies.