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# Mental and psychomotor development in Indonesian infants of mothers supplemented with vitamin A in addition to iron during pregnancy

Marjanka K. Schmidt[1,2], Siti Muslimatun[1,2], Clive E. West[1,3]*, Werner Schultink[4] and Joseph G. A. J. Hautvast[1]

[1]*Division of Human Nutrition and Epidemiology, Wageningen University, The Netherlands*
[2]*SEAMEO TROPMED Regional Centre for Community Nutrition, University of Indonesia, Jakarta, Indonesia*
[3]*UNICEF, New York, USA*
[4]*Department of Gastroenterology, University Medical Centre Nijmegen, The Netherlands*

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Maternal nutrition is important for fetal development, but its impact on the functional outcome of infants is still unclear. The present study investigated the effects of vitamin A and Fe supplementation during gestation on infant mental and psychomotor development. Mothers of infants from five villages in Indonesia were randomly assigned to supervised, double-blind supplementation once per week from approximately 18 weeks of pregnancy until delivery. Supplementation comprised 120 mg Fe + 500 μg folic acid with (*n* 94) or without (*n* 94) 4800 μg retinol in the form of retinyl acetate. Mothers of infants who participated in the national Fe + folic acid supplementation programme, but whose intake of supplements was not supervised, were recruited from four other villages (*n* 88). The mental and psychomotor development of infants was assessed, either at 6 or 12 months of age, using the Bayley Scales of Infant Development (BSID). We found no impact of vitamin A supplementation on mental or psychomotor development of infants. In addition, infants whose mothers had received weekly Fe supplementation had similar mental and psychomotor indices as those whose mothers had participated in the governmental Fe supplementation programme. The study population was moderately Fe and vitamin A deficient. The size of the treatment groups was large enough to detect a mean difference of 10 points on the BSID, which is less than 1 SD (15 points) of the average performance of an infant on the BSID. In conclusion, the present study did not find an impact of weekly supplementation of 4800 RE vitamin A in addition to Fe during gestation on functional development of Indonesian infants. However, smaller improvements in development may be seen if studied in a larger and/or more deficient population.

**Indonesian infants: Mental and psychomotor development: Vitamin A: Iron**

The importance of nutrition, especially Fe, for infant development and subsequent health up to adulthood has been recognised (Lozoff *et al.* 1991; Pollitt *et al.* 1997). Studies in human subjects and animals have shown that poor nutrition during gestation may not only impair fetal growth, but may also have an impact on development during this period (Levitsky & Strupp, 1995; Wauben & Wainwright, 1999). There is evidence that Fe, and possibly also vitamin A, plays a role in brain development (Chen *et al.* 1995; Felt & Lozoff, 1996; Maden, 2000; Zile, 2001). Fe-deficient anaemic infants have been shown to score lower on the mental and psychomotor development indices of the Bayley Scales of Infant Development (BSID; Bayley, 1969, 1993) than Fe-sufficient infants (Lozoff *et al.* 1982). In addition, Fe supplementation improved mental and psychomotor development of Fe-deficient anaemic infants in Indonesia (Idjradinata & Pollitt, 1993). However, not all studies showed a benefit of Fe supplementation (Nokes *et al.* 1998) and little is known about the functional outcomes of supplementation with Fe and other micronutrients during pregnancy (Ramakrishnan *et al.* 1999).

Many Indonesian infants are born to mothers who have suffered from Fe-deficiency anaemia and marginal vitamin A deficiency during gestation (United Nations Administrative Committee on Coordination/Sub-committee on Nutrition, 2000). Although the consequences of this for infant development are still unclear, adverse outcomes of Fe-deficiency anaemia have been established. Fe-deficiency anaemia during pregnancy is not only associated with higher risk of low birth-weight and pre-term delivery (Scholl & Hediger, 1994), but may also reduce fetal and infant Fe stores (Allen, 2000). Vitamin A supplementation, alone or in addition to Fe, has been shown to improve Fe status, besides maintaining the vitamin A status of women

**Abbreviation:** BSID, Bayley Scales of Infant Development.

* **Corresponding author:** Professor Clive E. West, fax +31 317 483342, email Clive.West@wur.nl

during pregnancy (Suharno *et al.* 1993; Muslimatun *et al.* 2001*a*).

Adequate maternal vitamin A status during pregnancy is important for the development of the fetus and to attain sufficient levels of vitamin A in breast milk (Underwood, 1994). It has been shown that vitamin A supplementation during pregnancy benefits the vitamin A status of pregnant women and that vitamin A status during the third trimester is associated with vitamin A levels in breast milk (Ortega *et al.* 1997; Muslimatun *et al.* 2001*b*). However, the effect of vitamin A status during gestation on infant development has not yet been explored.

In Indonesia, Fe supplementation during pregnancy is standard practice and thus it is not ethical to conduct a study in which pregnant women are not provided with Fe (Yip, 2000). However, compliance with supplement intake is found to be low, and supervised weekly Fe supplementation may be an alternative method (Schultink & Gross, 1996). Fe-deficiency anaemia during gestation may have impact on infant development; thus, it is important to evaluate any new regimen of Fe supplementation during pregnancy on infant outcome.

The present study investigated whether adding vitamin A supplementation to weekly Fe supplementation during pregnancy improved mental and psychomotor development of infants, and whether weekly Fe supplementation and the ongoing governmental programme performed similarly or not with respect to infant development. In addition, the relationship between maternal vitamin A and Fe status during pregnancy and infant development was explored.

## Materials and methods

### *Study design*

Pregnant women from nine rural villages in Leuwiliang subdistrict, Bogor district, West Java, Indonesia, were enrolled in six rounds from November 1997 until May 1998, and their infants were born from February to November 1998. After birth, all eligible infants were followed up once per month up to at least 12 months of age. Mothers of these infants had been supplemented with Fe + folic acid (with or without vitamin A) during pregnancy or had access to Fe + folic acid tablets through the ongoing government programme. Details of the study design and other outcomes than infant development have been published earlier (Muslimatun *et al.* 2001*a*,*b*; Schmidt *et al.* 2001, 2002). Briefly, women from five villages who were 16–20 weeks pregnant, aged 17–35 years and parity less than six, were randomly assigned on an individual basis to double-blind weekly supplementation until delivery. Supplementation was 120 mg Fe as ferrous sulfate and 500 μg folic acid or the same amounts of Fe and folic acid plus 4800 μg retinol in the form of retinyl acetate. Tablet intake was supervised by volunteer health workers and monitored by field assistants. Health personnel and participants received clear instructions in order to avoid additional Fe tablet intake. The average period of supplementation in these weekly groups was 20 weeks. Women from four other villages, referred to as the 'daily' group, were recruited at the same time. These women had free access to Fe tablets from the healthcare services following government policy that pregnant women should receive 90–120 Fe + folic acid tablets, each containing 60 mg Fe as $FeSO_4$ and 250 μg folic acid. Tablet intake in this group was not supervised, because this was an effectiveness trial comparing the weekly, supervised Fe supplementation with the current programme. Adherence of tablet intake was assessed through interview during a postnatal home visit, which revealed that the median tablet intake was fifty, while only 17 % of the subjects took more than ninety tablets (Muslimatun *et al.* 2001*a*). The purpose and procedures of the study were explained to the women at enrolment and only women who gave written informed consent were enrolled. The Ministry of Health in Indonesia and the Ethical Committees of the Medical Faculty at the University of Indonesia and Wageningen University approved the research proposal.

### *Study population*

Of 366 women recruited at approximately 18 weeks of pregnancy, 318 infants were eligible for follow-up after birth. Subjects dropped out because of withdrawal from supplementation (*n* 18), moving outside the research area (*n* 15), stillbirth (*n* 10) or twins (*n* 3, only one infant survived), or neonatal death (*n* 2) (Muslimatun *et al.* 2001*a*; Schmidt *et al.* 2001). There were no differences among the treatment groups in drop out numbers and no differences between mothers and infants who dropped out and those that were still participating during pregnancy, at birth or during follow-up. However, mothers with complete biochemical data (we used intention to treat analysis) had lower serum transferrin receptor concentrations and higher parity (1·6 *v.* 1·3) than mothers without complete biochemical data (Muslimatun *et al.* 2001*a*). Mothers were interviewed at enrolment for socio-economic background and pregnancy history and at a postnatal visit at home for infant food intake and other variables using pre-coded questionnaires.

### *Mental and psychomotor development of infants*

Infants were assessed for mental and psychomotor development between January and May 1999 using the BSID I (Bayley, 1969). The BSID was administered in a standardised way by two experienced psychologists, who had shown previously that the reproducibility between them was high (L Karyadi, personal communication). The assessment had been translated into Bahasa Indonesia and both psychologists were trilingual (Bahasa Indonesia, Sundanese and English). The psychologists were blinded with regard to which of the three treatment groups the infants belonged. Half of the infants were assessed at 6·0 (range 5·5–6·5) months and half at 12·0 (range 11·5–12·5) months of age. The assessments at 6 months of age were delayed by 7 months in some infants because of logistical problems. If an infant was ill, the mother was asked to return to enable her infant to be assessed at a later session. Assessments were administered on the floor of two separate quiet rooms in a house in one of the participating villages.

The BSID assesses: sensory–perceptual acuity, discrimination and the ability to respond to such discrimination; early acquisition of object constancy, and memory, learning and problem-solving ability; vocalisation and verbal communication; evidence of the ability to generalise and classify (Bayley, 1969). Examples of assessments are the infant's reaction to sound of a bell, dangling a ring, box of blocks, pushing a toy car or saying 'dada' or 'mama'. The BSID provides a measure of the degree of control of the body and the infant's level of maturation in a wide range of gross- and fine-motor movements (Bayley, 1969). Examples of assessments are if the infant is able to role from back to front, sit independently and pick up blocks or small tablets. From the infant's performance on the assessments, aggregate scores were calculated, the 'raw' scores, from which age-adjusted indices of mental and psychomotor development were derived. Three infants, one in each treatment group, had raw mental scores that were too low to be converted to the mental development index. These indices were set to fifty, the lowest score that can be obtained in the mental development index.

*Biochemical measures*

Non-fasting venous blood samples (5 ml) were taken from women at enrolment, near term and approximately 4 months postpartum and from infants at approximately 4 months of age (2 ml) and collected in tubes without anticoagulant between 09.00 and 12.00 hours. It was not possible to obtain blood samples in all cases due to maternal refusal. In some cases the amount of blood obtained was insufficient for all analyses. Hb was determined using the cyanmethaemoglobin method (test 3317; Merck, Darmstadt, Germany) at the Nutrition Research and Development Centre Laboratory, Bogor. For serum ferritin, soluble transferrin receptor and retinol analyses, blood was allowed to clot before it was placed in a cool-box with cooling elements for transport to the laboratory in Bogor. Blood samples were centrifuged at 3000 ***g*** for 10 min at room temperature and serum was distributed among three vials. Serum was kept at −20°C for 1 month and subsequently at −79°C. All analyses were carried out within 1 year of blood collection. The methods used have been described earlier by Schmidt *et al.* (2001).

*Anthropometry*

The weight and length of infants were measured using standardised methods (Jeliffe, 1996). Weight and length of the newborn infant were measured by two of the authors (M. K. S. and S. M.) at the time of the postnatal home visit (Schmidt *et al.* 2001). Thereafter, two pairs of trained field assistants measured the weight and length of infants when their mothers paid the monthly visit to the health-service post (Posyandu) until 1 year of age. Weight was measured to the nearest 50 g by using a baby-weighing scale (Misaki, Osaka, Japan), which was tared each time before use. Calibration with a standard weight (5 kg) at regular intervals showed that all scales were stable and precise. Recumbent length was measured to the nearest 1 mm by using a wooden length-board. Infants were measured with light clothing. All field assistants had received training and were supervised every month by M. K. S. and S. M. (Schmidt *et al.* 2002). At enrolment, near term and approximately 4 months postpartum, body weight of the mothers was measured to the nearest 0·1 kg by using a UNICEF electronic weighing scale (model 890; SECA, Hamburg, Germany), height to the nearest 1 mm using a standing height measurement microtoise and mid-upper-arm circumference to the nearest 1 mm by using a plastic measuring tape.

*Data analysis*

To analyse the results for the treatment groups, the weekly vitamin A + Fe group was compared with the weekly Fe group to evaluate the effect of vitamin A supplementation, while the weekly Fe group was compared with the 'daily' group to evaluate the different Fe supplementation regimens. Comparisons of continuous, normally distributed data between groups were done using the *t* test; all data were normally distributed besides transferrin receptor and serum ferritin concentrations, which were logarithmically transformed. Comparisons of categorical data between groups (Table 1) were done using the $\chi^2$ test, while associations were evaluated using Pearson's correlation. The relationship between maternal vitamin A and Fe status during pregnancy and infant development was explored using linear regression. For this analysis, the weekly Fe and 'daily' groups were pooled, and treatment group was defined as having received vitamin A supplementation or not (weekly vitamin A + Fe group, 1; weekly Fe group and 'daily' Fe group, 0). We considered this justified because these groups did not differ with respect to anthropometric and biochemical variables of mothers and infants or infant development, and using dummy variables (for the three groups) instead did not change the results. For the association of biochemical variables at enrolment and near term, the following variables associated with infant development were included: age of infant at time of assessment (dichotomous variable), consultation during pregnancy (one to four times or more than four times) as a proxy of health-conscious behaviour (dichotomous variable) and maternal age. For the association of biochemical variables at near term, but not those at enrolment, the treatment variable was included. Statistical analysis was carried out with the SPSS software package (Windows, version 10.0.5; SPSS Inc., Chicago, IL, USA).

## Results

Of the 318 newborn infants initially eligible (see p. 280), sixteen infants moved outside the research area and twelve infants died during the follow-up period from birth to 1 year of age. In addition, fourteen infants did not attend the assessment because they were sick, or their mothers refused or were not present. Data are presented from the 276 infants who participated in assessment of the BSID. More infants were assessed at 6 months ($n$ 166) than at 12 months ($n$ 110) of age; however, infants from the two age groups were evenly distributed over the three treatment groups (weekly vitamin A + Fe, weekly

**Table 1.** General characteristics of infants, assessed for mental and psychomotor development on the Bayley Scales of Infant Development, in the weekly vitamin A + iron-supplemented group, weekly iron-supplemented group and 'daily' group†‡

(Mean values, standard errors and proportions)

| | Weekly vitamin A + Fe | | Weekly Fe | | 'Daily'‖ | |
|---|---|---|---|---|---|---|
| Supplement. . .§ | Mean | SE | Mean | SE | Mean | SE |
| Infant characteristics | | | | | | |
| Birth order | 1·4 | 0·1 | 1·5 | 0·1 | 1·7 | 0·2 |
| Neonatal weight (kg) | 3·2 | 0·1 | 3·2 | 0·1 | 3·3 | 0·1 |
| Neonatal length (cm) | 49·5 | 0·2 | 49·7 | 0·2 | 49·8 | 0·3 |
| Gestational age (weeks) | 37·9 | 0·3 | 38·5 | 0·3 | 37·3* | 0·3 |
| Maternal and other characteristics | | | | | | |
| Age at enrolment (years) | 24·2 | 0·5 | 24·1 | 0·5 | 24·9 | 0·5 |
| Weight at enrolment (kg) | 49·2 | 0·8 | 48·4 | 0·6 | 49·1 | 0·8 |
| Height at enrolment (m) | 1·491 | 0·006 | 1·491 | 0·005 | 1·490 | 0·005 |
| Education beyond elementary school (%) | 26 | | 30 | | 22 | |
| More than four consultations during pregnancy (%) | 61 | | 63 | | 65 | |
| Delivery assisted by traditional birth attendant (%) | 82 | | 85 | | 74 | |
| Occupation of father (%) | | | | | | |
| Daily worker (labourer, farmer, driver) | 47 | | 50 | | 46 | |
| Monthly worker (government or private employee, retired) | 31 | | 36 | | 33 | |
| Trader | 22 | | 14 | | 22 | |
| House with brick wall, tile roof and cemented floor (%) | 67 | | 65 | | 70 | |

Mean value was significantly different from that of the weekly Fe group (*t* test): $*P<0.01$.
† For details of supplements and procedures, see pp. 280–281.
‡ For details of the Bayley scales of Infant Development, see Bayley (1969) and p. 281.
§ Weekly Vitamin A + Fe: forty-one boys and fifty-three girls; Weekly Fe: thirty-eight boys and fifty-six girls; 'Daily', forty-nine boys and thirty-nine girls.
‖ Mothers had free access to Fe tablets from the Indonesian Governmental Health Services.

Fe, 'daily'). Infants who were assessed did not differ with respect to gender, birth order, neonatal weight and length, and maternal age, weight, height, biochemical variables, education and housing from those (*n* 42) that were not assessed (results not shown). However, mothers of infants who were assessed for BSID had higher serum retinol concentrations at enrolment than mothers of infants who were not assessed (1·00 (SEM 0·02) *v*. 0·90 (SEM 0·04) μmol/l, $P<0.05$).

General characteristics of the vitamin A + Fe group and the Fe group were similar, as were the characteristics of the Fe group, compared with the 'daily' group (Table 1). Vitamin A deficiency near term was less prevalent in mothers in the vitamin A + Fe group than in the other two groups (Fig. 1) (Muslimatun *et al.* 2001*a*). Infants in the weekly vitamin A + Fe group had similar mental and psychomotor development indices as infants in the weekly Fe group (Table 2), while the infants in the weekly Fe group did not differ from infants in the 'daily' group. Mental and psychomotor development indices of the BSID did not differ between psychologists (results not shown). The mental development index could not be administered to one infant.

Mental and psychomotor development indices were associated in both age groups (age 6 months *r* 0·669, age 12 months *r* 0·565; $P<0.01$), although this association did not differ significantly between age groups or treatment groups. However, infants scored slightly higher on the

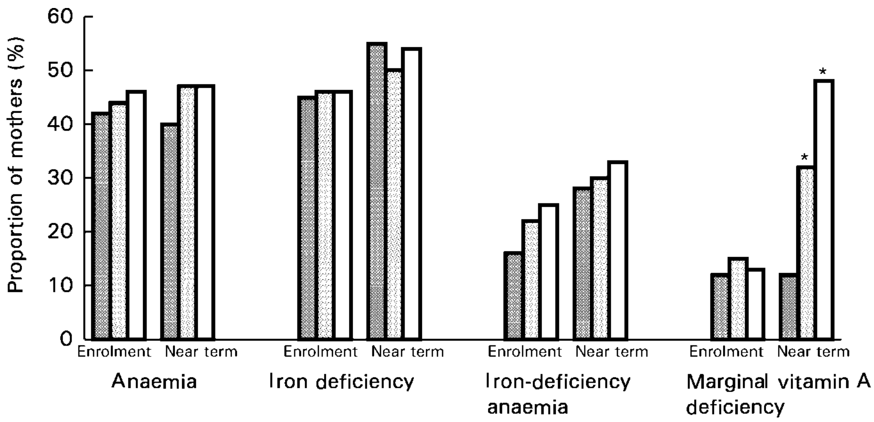


**Fig. 1.** Proportion of women who were anaemic (Hb <110 g/l), iron deficient (serum ferritin <12 μg/l), or both, or marginally vitamin A deficient (serum retinol <0·70 μmol/l) at enrolment (about 18 weeks of gestation) and near term (about 35 weeks of gestation) in the three treatment groups: weekly vitamin A + iron (▩), weekly iron (▨) and 'daily' (□), i.e. mothers who had free access to iron tablets from the Indonesian governmental health services. For details of subjects, supplements and procedures, see Table 1 and pp. 280–281. Mean values were significantly different from those of the weekly vitamin A + iron group ($\chi^2$ test): $*P<0.01$.

**Table 2.** Mental and psychomotor development, assessed by the Bayley Scales of Infant Development in Indonesian infants at 6 or 12 months of age, whose mothers had been supplemented with vitamin A + iron or with iron alone or participated in the national iron supplementation programme, i.e. 'daily' group‡ §

(Mean values with their standard errors)

| | Weekly vitamin A + Fe (*n* 94)‖ | | Weekly Fe (*n* 94)¶ | | 'Daily' (*n* 88)** | | All infants (*n* 276)†† | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Mental development index | 94·7* | 1·7 | 94·5* | 1·7 | 92·7* | 2·0 | 94·0* | 1·0 |
| Mental development index at 6 months | 85·9† | 1·7 | 87·8† | 1·5 | 84·1† | 1·9 | 85·9† | 1·0 |
| Mental development index at 12 months | 105·4 | 2·3 | 104·0 | 2·8 | 109·8 | 2·5 | 106·1 | 1·5 |
| Psychomotor development index | 101·3 | 1·9 | 102·8 | 1·9 | 103·7 | 2·1 | 102·6 | 1·1 |
| Psychomotor development index at 6 months | 103·7 | 2·2 | 103·2 | 1·8 | 101·4 | 2·2 | 102·7 | 1·2 |
| Psychomotor development index at 12 months | 98·3 | 3·3 | 102·3 | 3·8 | 108·5 | 4·4 | 102·4 | 2·2 |

Mean values were significantly different from the psychomotor development index in each of the three treatment groups (*t* test): *$P<0·01$.
Mean values were significantly different from the mental development index at 12 months of age in each of the three treatment groups (*t* test): †$P<0·01$.
‡ For details of subjects, supplements and procedures, see Table 1 and pp. 280–281.
§ For details of the Bayley Scales of Infant Development, see Bayley (1969) and p. 281.
‖ Number of infants assessed at 6 and 12 months: fifty-two and forty-two respectively.
¶ Number of infants assessed at 6 and 12 months: fifty-five and thirty-nine respectively.
** Number of infants assessed at 6 and 12 months: fifty-nine and twenty-nine (one value missing for mental development index) respectively.
†† Number of infants assessed at 6 and 12 months: 166 and 110 (one value missing for mental development index) respectively.

psychomotor development than on the mental development index (Table 2). Mental development indices were higher at 12 months of age than at 6 months of age, whereas psychomotor development indices did not differ between both age groups (Table 2). Three infants, one in each in each treatment group, had scores too low to be converted into the mental development index (indices were set to 50); however, excluding or including these infants in our data did not change the results.

Mental and psychomotor development indices did not differ between genders. Both indices were inversely correlated with age (d) at the 6 months assessment ($r$ −0·346 and $r$ −0·260 respectively, $P<0·01$) and positively correlated with age at the 12 months assessment ($r$ 0·273 and $r$ 0·200 respectively, $P<0·05$). Indirect measurements of socio-economic status, such as education and nutritional status of women and occupation of both men and women (94 % of the women were housewives) (Table 1) were not predictive of infant development. The infants' nutritional status was moderate, as indicated by height-for-age and weight-for-age z-scores of −0·8 (SD 0·8) and −0·5 (SD 0·9) at 6 months of age, and −1·4 (SD 0·8) and −1·6 (SD 0·8) at 12 months of age respectively. The mean Hb concentration in the infants, measured at approximately 4 months of age, was 105·5 (SD 9·1). Mental and psychomotor development indices were not associated with growth or nutritional status during the first year of life (results not shown).

In the linear regression model (see p. 281), serum retinol concentrations of mothers at enrolment (1·00 (SD 0·27), *n* 245) and near term (0·89 (SD 0·32), *n* 194) showed a positive association with indices of infant mental development (ß 0·123 (*B* 7·6 (SE 3·3), $P<0·05$) and ß 0·115 (*B* 5·9 (SE 3·1), $P=0·06$) respectively) and psychomotor development (ß 0·144 (*B* 9·5 (SE 4·4), $P<0·05$) and ß 0·150 (*B* 8·6 (SE 4·2), $P<0·05$) respectively). Fe status or anaemia of mothers during pregnancy was not significantly associated with infant development.

## Discussion

As far as we know, this is the first study to examine the impact of maternal vitamin A and Fe supplementation on infant development. It has been shown that I deficiency *in utero* negatively affects pregnancy outcome and infant development, and there is some evidence for an effect of protein–energy malnutrition as well (Grantham-McGregor *et al.* 2000). However, we did not find any impact of Fe and vitamin A supplementation during gestation on mental and psychomotor BSID.

The BSID is widely used to assess the development of infants (Nokes *et al.* 1998). Although its predictive value for later development is small (Pollitt, 2001), the BSID can detect differences in development due to supplementary feeding in infants (Husaini *et al.* 1991; Idjradinata & Pollitt, 1993) and children (Humphrey *et al.* 1998). We assured the appropriate use of the BSID by employing two experienced Indonesian psychologists. There was no evidence for observer bias in the BSID indices of the studied infants. In addition, the development indices of the infants studied were in accordance with those in earlier studies in Indonesia and Bangladesh (Husaini *et al.* 1991; Idjradinata & Pollitt, 1993; Humphrey *et al.* 1998; Hamadani *et al.* 2001).

To calculate whether the lack of impact we found was partly due to a small number of subjects, we did a power calculation with the data from our present study. Using the formula of Hassard (1991):

$$n = (Z_{\alpha/2} + Z_{\beta})^2 \times 2(\mathrm{SD}/d)^2,$$

with the difference between groups d = 10, SD 18 (the SD of the BSID in the studied population and slightly higher than the expected SD 15 (Bayley, 1993)), α 0·05 and power (1 − β) 0·9, we found that sixty-eight infants per group would have been enough to pick up a difference of 10 points. To detect a difference of 5 points, 272 infants per group would have been needed. This means that with our sample size, we had a power of at least 90 % to pick up a difference of 10 points between the treatment groups, which is < 1SD (15 points) of the average performance of an infant on the BSID (Bayley, 1993). For example, Fe-deficient anaemic Indonesian infants were found to score 20 points higher on the BSID after Fe supplementation (Idjradinata & Pollitt, 1993). Hence, although weekly supplementation of 4800 RE vitamin A in addition to Fe during gestation was not enough to significantly improve functional development of Indonesian infants by 10 points of the BSID, we did not have enough power to detect a smaller improvement.

Another explanation for the lack of impact could be that the studied population suffered only from moderate degrees of Fe deficiency (Muslimatun *et al.* 2001*a*), which may not be reflected in differences in infant development (Schmidt *et al.* 2002). In addition, development scores of these infants were actually in range of the Bayley classification (Bayley, 1993); thus, it might be that the window for improvement was too small. We do not think that drop-out can be an explanation, because drop-outs did not differ from the participants, except that mothers of infants that did not participate in the BSID assessment had higher serum retinol levels at enrolment than those included, which would have led to attenuation of an impact.

The contrasting finding that maternal vitamin A status during pregnancy was associated with better mental and psychomotor development in infants could be a confirmation of the biological evidence that there is indeed a relationship or a chance finding. Animal studies have shown that retinoic acid is important in embryonic development and that highest concentrations are found in the neural tube, which is to be developed into the spinal cord and the brain (Maden, 2000). A study in vitamin A-deficient pregnant rats showed that vitamin A injection during pregnancy increased brain weight relative to body weight compared with those that did not receive vitamin A (Antipatis *et al.* 2000). In addition, a growth spurt in the human brain occurs in the last trimester of pregnancy (Wauben & Wainwright, 1999). One study of human subjects reported a small impact of supplementation of infants with vitamin A (52 μmol retinyl palmitate) at birth on their Bayley indices at 3 years of age (Humphrey *et al.* 1998). Hence, it might be that we would have seen a small impact of the supplementation if the cohort studied had been larger or more vitamin A deficient, or we had a longer follow-up.

On the other hand, the association found between the vitamin A status of mothers and infant development could be explained, for example, by better caring-capacity of mothers with better nutritional status (Adair & Pollitt, 1985) or be due to chance; it should be mentioned that we could have missed other confounding factors in our present model. Although we did not observe an association between maternal education, housing characteristics and infant development, factors such as low socio-economic status, poor maternal education and lack of stimulation in the home are associated both with anaemia and poor cognitive development (Grantham-McGregor & Ani, 2001).

The different Fe treatment regimens, supervised weekly Fe supplementation or participation in the governmental programme, did not lead to differences in mental or psychomotor development. This is not surprising considering that Fe status of infants in both groups at approximately 4 months of age was comparable, and that although one-third of the infants studied were anaemic, only three were Fe deficient (Schmidt *et al.* 2001). Apparently, at least until 4 months of age, infants had sufficient Fe stores or were protected by Fe supply from breast milk (Anderson *et al.* 1999; Siimes *et al.* 1984).

In conclusion, the present study did not find an impact of weekly supplementation of 4800 RE vitamin A in addition to Fe during gestation on functional development of Indonesian infants. Smaller improvements in development may however be seen if studied in a larger and/or more deficient population.

## Acknowledgements

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