Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Screening tools at 6, 18, and 36 months of age and supplemental methods for explorative analyses.

Screening tools with included items at 6, 18 and 36 months

DEVELOPMENT 6 MONTHS OF AGE

1. MOTOR DEVELOPMENT: Ages and stages questionnaire (ASQ)

Alternatives: Yes, often/ Yes, but rarely/ No, not yet

- **Gross motor**
  1. When your child is laying on his/her back, does he/she play with his/her feet?
  2. When your child is laying on his/her tummy, does he/she raise his/her upper body off the ground with straight arms?
  3. Does your child roll over from his/her back onto his/her tummy?

- **Fine motor**
  1. Does your child grab hold of a toy that you give him/her and then put it in his/her mouth or hold it?
  2. When your child is sitting on your lap, does he/she reach out for a toy or other things on the table in front of you?
  3. Does your child hold onto a toy with both hands when he/she is examining it?

2. COMMUNICATION AND SOCIAL DEVELOPMENT: Bailey Scales of Infant Development, Non-Verbal Communication Checklist, and the Ages and Stages Questionnaire

Alternatives: Yes, often/ Yes, but rarely/ No, not yet

1. When you “chat” with your child, does he/she try to “chat” back to you?
2. Does your child babble and make sounds when he/she is lying on his/her own?
3. Can you tell how your child is just by listening to the sounds he/she is making (for example, contented, hungry, angry, in pain)?
4. Do you get a smile from your child when you just smile at him/her (without touching or tickling him/her and without holding up a toy)?
5. When you call your child, does he/she turn towards you one of the first times you say his/her name?

3. TEMPERAMENT: ICQ - INFANT CHARACTERISTICS QUESTIONNAIRE (difficult/fuzzy)

Alternatives 1 to 7 (Likert scale): 1 = totally disagree to 7 = totally agree

1. The child whimpers and cries a lot
2. The child is usually easy to console when he or she cries
3. The child is easily upset and begins to cry
4. The child usually screams angrily and loudly when he or she cries
5. The child demands a lot of attention
6. The child usually plays well alone when left to himself or herself
7. The child is so demanding that he or she would be a considerable problem for most parents
DEVELOPMENT 18 MONTHS OF AGE

1. MOTOR DEVELOPMENT: Ages and Stages questionnaire (ASQ)

Alternatives: Yes, often/ Yes, but rarely/ No, not yet

- **Fine motor**
  1. Does your child throw a small ball or toy with a forward arm motion (if he simply drops the ball, check ‘not yet’ for this item)?
  2. Does your child stack a small block or toy (about 3 cm in size) on top of another?
  3. Does your child turn the pages in a book by himself (he may turn more than one page at the time)?

- **Gross motor**
  1. Does your child move around by walking, rather than by crawling on her hand and knees?
  2. Does your child walk well and seldom fall?
  3. Does your child walk down stairs if you hold onto one of her hands?

2. AUTISTIC TRAITS - Modified Checklist for Autism in Toddlers (M-CHAT)

Alternatives: Yes/No

1. Does your child enjoy being swung, bounced on your knee, etc.?
2. Does your child take interest in other children?
3. Does your child like climbing on things, such as up stairs?
4. Does your child enjoy playing peek-a-boo/hide-and-seek?
5. Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?
6. Does your child ever use his/her index finger to point, to ask for something?
7. Does your child ever use his/her index finger to point, to indicate interest in something?
8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling, or dropping them?
9. Does your child ever bring objects over to you (parent) to show you something?
10. Does your child look you in the eye for more than one second or two?
11. Does your child ever seem oversensitive to noise? (E.g. plugging ears)
12. Does your child smile in response to your face or your smile?
13. Does your child imitate you? (E.g. you make a face – will your child imitate it?)
14. Does your child respond to his/her name when you call?
15. If you point at a toy across the room, does your child look at it?
16. Does your child walk?
17. Does your child look at things you are looking at?
18. Does your child make unusual finger movements near his/her face?
19. Does your child try to attract your attention to his/her own activity?
20. Have you ever wondered if your child is deaf?
21. Does your child understand what people say?
22. Does your child sometimes stare at nothing or wander with no purpose?
23. Does your child look at your face to check your reaction when faced with something unfamiliar?
3. COMMUNICATION: Ages and Stages questionnaire (ASQ)

*Alternatives: Yes, often/ Yes, but rarely/ No, not yet*

1. When you ask him, does your child go into another room to find a familiar toy or object?
2. Does your child say eight or more words in addition to mama and papa?
3. Without showing him first, does your child point to the correct picture when you say, “show me the kitty” or ask, “Where is the dog?”

DEVELOPMENT 36 MONTHS OF AGE

1. AUTISTIC TRAITS - SOCIAL COMMUNICATION QUESTIONNAIRE (SCQ)

*Alternatives: Yes/No*

1. Does he/she talk using short phrases or sentences?
2. Can you now have a to and fro "conversation" with him that involves taking turns or building on what you have said?
3. Has he/she ever used odd phrases or said the same thing over and over in almost exactly the same way? That is, either phrases he/she has heard other people use or the ones he/she has made up?
4. Has he/she ever used socially inappropriate questions or statements? For example, has he/she ever regularly asked personal questions or made personal comments at awkward times?
5. Does he/she ever get his pronouns the wrong way round, (i.e., saying "you" or "he" for "I")?
6. Has he/she ever used words that he/she seems to have invented or made up himself, or ever put things in odd, indirect ways, or metaphorical ways of saying things? For example, saying "hot rain" for "steam"
7. Has he/she ever said the same thing over and over in exactly the same way, or insist on you saying the same things over and over again?
8. Has he/she ever had things that he/she seemed to have to do in a very particular way or order, or rituals that he/she has to you do?
9. Does his/her facial expression usually seem appropriate to the particular situation, as far as you can tell?
10. Has he/she ever used you hand like a tool, or as if it were part of his own body (e.g., pointing with your finger, putting your hand on a doorknob to get you to open the door)?
11. Has he/she ever had any interests that preoccupy him/her and might seem odd to other people (e.g., traffic lights, drainpipes or timetables)?
12. Has he/she ever had any interests that preoccupied him/her and might have seemed odd to other people (e.g. traffic lights, drainpipes or timetables)?
13. Has he/she ever seemed to be more interested in a certain part of a toy (e.g., spinning the wheels of a car) or an object than using the object as it was intended?
14. Has he/she ever had any interests that were unusual in their intensity by otherwise appropriate for his/her age and peer group (e.g., trams, dinosaurs)?
15. Has he/she ever seemed to be unusually interested in the sight, feel, sound, taste or smell of things or people?
16. Has he/she ever had any mannerisms or odd ways of moving his/her hands or fingers, such as flapping or moving his/her fingers in front of his eyes?
17. Has he/she ever had any complicated movements of his whole body, such as spinning or repeatedly bouncing up on an own?
18. Does he/she ever injure him-/herself deliberately, such as by biting his/her arm or banging his/her head?
19. Does he/she ever have any objects (other than a soft toy or comfort blanket) that he/her has to carry around with him/her?
20. Does he/she have any particular friend, or a best friend?
21. Does he/she ever talk with you just to be friendly (rather than to get something)?
22. Does he/she ever spontaneously copy you (or other people), or what you are doing (such as vacuuming, gardening, mending things)?
23. Does he/she ever use gestures, other than pointing or pulling your hand, to let you know what he/she wants?
24. Does he/she nod his head to mean "yes"?
25. Does he/she shake his head to mean "no"?
26. Does he/she usually look at you directly in the face when doing things with you or talking with you?
27. Does he/she smile back if someone smiles at him/her?
28. Does he/she ever show you things that interest him/her to engage your attention?
29. Does he/she ever offer to share things other than food with you?
30. Does he/she ever seem to want you to join in his/her enjoyment of something?
31. Does he/she ever try to comfort you if you were sad or hurt?
32. When he/she wants something or wants help, does he/she look at you and use gestures with sounds or words to get your attention?
33. Does he/she show a normal range of facial expression?
34. Does he/she ever spontaneously join in and try to copy actions in social games—such as The Mulberry Bush or The Farmer's in His Den?
35. Does he/she play any pretend or make-believe games?
36. Does he/she seem interested in other children of approximately the same age whom he/she does not know?
37. Does he/she respond positively when another child approaches him/her?
38. If you came into a room and started talking to him/her without calling his/hers name, does he/she usually look up and pay attention to you?
39. Does he/she ever play imaginative games with another child in such a way that you can tell they understood what each other is pretending?
40. Does he/she play cooperatively in games that need some form of joining in with a group of other children, such as hide and seek or ball games?

2. SENTENCE COMPLEXITY

Alternatives:
1. Not yet talking
2. He/she is talking but unintelligible
3. Talking in one-word phrases such as “milk” or “down”
4. Talking in 2 to 3 word phrases, such as “me got ball” or “give doll”
5. Talking in fairly complete sentences, such as “I got ball” or “I have a doll”
6. Talking in long complicated sentences, such as “when I went to the park, I went on the swings” or “I saw a man standing on the corner”

3. ADHD SYMPTOMS: Checklist specific for the MoBa cohort

Alternatives: Not true/ Somewhat or sometimes true/ Very true or often true
1. Can’t concentrate, can’t pay attention for long
2. Can’t sit still, restless or hyperactive
3. Can’t stand waiting, wants everything now
4. Demands must be met immediately
5. Gets into everything
6. Quickly shift from one activity to another
7. Becomes distracted or diverted by outside stimuli (sounds or events)
8. Finds it difficult waiting his/her turn
9. Has problems keeping focused on tasks or activities
10. Is excessively talkative
11. Doesn’t seem to listen when he/she is being spoken to
4. AGGRESSIVE SYMPTOMS: Child behavior Checklist (CBCL)
    - Selected items

Alternatives: Not true/ Somewhat or sometimes true/ Very true or often true

1. Can't stand waiting, wants everything now.
2. Defiant.
3. Demands must be met immediately.
4. Doesn't seem so feel guilty after misbehaving
5. Gets into many fights
6. Hits others
7. Punishment doesn’t" change his/hers behavior

EXPLORATIVE ANALYSES

Choice of confounders was based on a priori considerations. Post-hoc, the effect of each included co-variate in the model was evaluated by comparing crude ORs to adjusted ORs. The risk-estimates and significance levels were negligibly affected by adjustment.

Stratified analyses and Breslow-Day homogeneity tests were performed to assess potential effect-modification. With the exception of breastfeeding, none of the co-variates acted as significant effect-modifiers in the stratified analyses.

To evaluate the effect of baseline differences and treatment selection bias between the exposed group and the reference group, propensity score matching was performed, and risk-estimates for the matched groups were compared to the primary analysis. The predictors in the propensity score model included breastfeeding, maternal age, parity, education, income, single parenting, unplanned pregnancy, folate supplementation, smoking, anxiety/depression, preterm delivery, child congenital malformation and low birth weight. The significant risk-estimates in the drug-exposed group were generally strengthened secondary to propensity score matching (eTables 1 and 2).

Excluding children with major malformations, low birth weight or preterm delivery had minimal effect on the risk-estimates in the different antiepileptic drug-exposed groups.

Only 0.036 % (n=39) of the women in the MoBa-cohort used AEDs during pregnancy for other reasons than epilepsy; including depression, anxiety, pain, cerebral palsy, MS, migraine, or other types of headache. Excluding such pregnancies had no effect on the risk estimates in the epilepsy group.
### eTable 1. Risk of adverse development at 6 months in antiepileptic drug (AED) exposed children compared to propensity score matched controls and all references.

<table>
<thead>
<tr>
<th>Development domain</th>
<th>AED exposed</th>
<th>Matched controls</th>
<th>All references</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adverse score</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Gross motor skills 6 months</td>
<td>13.7% (30/219)</td>
<td>9.4% (83/882)</td>
<td>1.5 (1.0-2.4)</td>
</tr>
<tr>
<td>Fine motor skills 6 months</td>
<td>11.5% (25/217)</td>
<td>4.6% (40/875)</td>
<td>2.7 (1.6-4.6)</td>
</tr>
<tr>
<td>Social skills 6 months</td>
<td>12.7% (28/221)</td>
<td>10.0% (89/888)</td>
<td>1.3 (0.8-2.0)</td>
</tr>
<tr>
<td>Difficult temper 6 months</td>
<td>3.6% (8/220)</td>
<td>5.9% (52/881)</td>
<td>0.6 (0.3-1.3)</td>
</tr>
</tbody>
</table>

1. Each child in the AED-exposed group was matched to four controls with identical or similar propensity score.
2. Unadjusted Odds ratio (OR) with 95% confidence Interval (CI).
3. OR with 95% CI adjusted for maternal age, parity, education, folate use, smoking, depression/anxiety, breastfeeding (months), and child malformation.
**eTable 2.** Risk of adverse development at 6 months in antiepileptic drug (AED) polytherapy exposed children compared to propensity score matched controls and all references.

<table>
<thead>
<tr>
<th>Development domain</th>
<th>AED polytherapy</th>
<th>Matched controls</th>
<th>All references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse score</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td>Gross motor skills 6 months</td>
<td>23.1% (9/39)</td>
<td>8.6% (14/163)</td>
<td>3.2 (1.3-8.0)</td>
</tr>
<tr>
<td>Fine motor skills 6 months</td>
<td>25.0% (10/40)</td>
<td>3.8% (6/159)</td>
<td>8.5 (2.9-25.2)</td>
</tr>
<tr>
<td>Social skills 6 months</td>
<td>22.5% (9/40)</td>
<td>11.1% (18/162)</td>
<td>2.3 (1.0-5.7)</td>
</tr>
<tr>
<td>Difficult temper 6 months</td>
<td>4.9% (2/41)</td>
<td>5.5% (9/163)</td>
<td>0.9 (0.2-4.2)</td>
</tr>
</tbody>
</table>

1. Each child in the polytherapy-exposed group was matched to four controls with identical or similar propensity score.
2. Unadjusted Odds ratio (OR) with 95% confidence Interval (CI).
3. OR with 95% CI adjusted for maternal age, parity, education, folate use, smoking, depression/anxiety, breastfeeding (months), and child malformation.
eTable 3. Breastfeeding 0-6 months \(^1\) in children of women using antiepileptic drugs (AEDs) compared to the reference group.

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference group</th>
<th></th>
<th>Maternal AED use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breastfeeding ²</td>
<td>Mixed ³</td>
<td>Bottle feeding ⁴</td>
<td>Breastfeeding</td>
</tr>
<tr>
<td>1 month</td>
<td>83% (59 168)</td>
<td>13% (9369)</td>
<td>3.6% (2534)</td>
<td>72% (147)</td>
</tr>
<tr>
<td>2 months</td>
<td>78% (55 571)</td>
<td>16% (11 414)</td>
<td>6.0% (4285)</td>
<td>62% (125)</td>
</tr>
<tr>
<td>3 months</td>
<td>72% (51 604)</td>
<td>19% (13 209)</td>
<td>9.2% (6594)</td>
<td>57% (116)</td>
</tr>
<tr>
<td>4 months</td>
<td>66% (47 316)</td>
<td>21% (14 903)</td>
<td>13% (9262)</td>
<td>53% (106)</td>
</tr>
<tr>
<td>5 months</td>
<td>61% (43 997)</td>
<td>23% (16 260)</td>
<td>16% (11 457)</td>
<td>48% (97)</td>
</tr>
<tr>
<td>6 months ⁵</td>
<td>56% (43 373)</td>
<td>25% (19 590)</td>
<td>19% (14 353)</td>
<td>46% (102)</td>
</tr>
</tbody>
</table>

1. Data on breastfeeding and bottle feeding was available for 92 % of the cohort at 0-5 months and for 99 % of the cohort at 6 months.
2. Exclusive breastfeeding (no supplemental bottle feeding).
4. Exclusive bottle feeding (no supplemental breastfeeding).
5. For women breastfeeding at 6 months, 99 % in the reference group and 98 % in the AED-use group breastfed at least once a day.
**eTable 4.** Adverse development at 6 months in children of breastfeeding mothers using antiepileptic drugs compared to the reference group.

<table>
<thead>
<tr>
<th>Child Group</th>
<th>Fine Motor Impairment</th>
<th>Gross Motor Impairment</th>
<th>Social Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (No.)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>77,770</td>
<td>4.8 (3648)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td><strong>Antiepileptic drugs in total</strong></td>
<td>148</td>
<td>8.3 (12)</td>
<td>1.7 (0.9-3.1)</td>
</tr>
<tr>
<td><strong>Monotherapies in total</strong></td>
<td>127</td>
<td>7.3 (9)</td>
<td>1.4 (0.7-2.9)</td>
</tr>
<tr>
<td><strong>Lamotrigine monotherapy</strong></td>
<td>46</td>
<td>6.7 (3)</td>
<td>1.3 (0.4-4.2)</td>
</tr>
<tr>
<td><strong>Carbamazepine monotherapy</strong></td>
<td>40</td>
<td>10.3 (4)</td>
<td>2.1 (0.8-6.1)</td>
</tr>
<tr>
<td><strong>Valproate monotherapy</strong></td>
<td>18</td>
<td>11.1 (2)</td>
<td>2.3 (0.5-10.1)</td>
</tr>
<tr>
<td><strong>Polytherapy</strong></td>
<td>21</td>
<td>15.0 (3)</td>
<td>3.3 (1.0-11.5)</td>
</tr>
</tbody>
</table>

1. Odds ratios with corresponding 95% confidence intervals adjusted for maternal age, parity, education, folate supplementation, smoking, depression/anxiety, and child malformation.
2. Continuous breastfeeding (≥ 6 months).

*P value ≤ 0.05.*