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Atypical general movements in the general population: Prevalence over the last 15 years and associated factors

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Abstract

Aim: To determine the prevalence of atypical general movements (GMs) in the general population, to examine its time trend and associated factors.

Methods: Participants consisted of 300 infants born in 2016-2018 (current cohort; gestational age 39.4 weeks (27-42); 162 boys), representative of the Dutch population. GMs were assessed at 2-4 months corrected age in terms of GM-complexity (definitely abnormal (DA) or not) and fidgety movements (present or absent). GM-complexity data from a cohort of 455 Dutch infants born in 2001-2002 were used to investigate the time trend.

Results: In the current cohort, 10 infants (3%) showed DA GM-complexity and 8 (3%) absent fidgety movements. Only one infant had both GM-impairments (0.3%). The prevalence of DA GM-complexity did not differ from that in the 2001-2002 cohort (adjusted *odds ratio* (OR) = 1.47 [0.53, 4.06]). DA GM-complexity was associated with maternal smoking (adjusted OR = 3.59 [1.56, 8.28]) and marginally with prematurity (adjusted OR = 2.78 [1.00, 7.74]); absence of fidgety movements was curvilinearly associated with assessment age only (OR = 1.06 [1.01, 1.12]).

Conclusion: In the general population, the prevalence of DA GM-complexity and absent fidgety movements is 3%. The finding that they rarely co-occur and are associated with different factors indicates that GM-assessment needs to address both aspects.

KEYWORDS

general movements, general population, neurological function, prevalence, risk factors

1 | INTRODUCTION

General movements (GMs) are the spontaneous movements involving all parts of the body in the foetus and young infant. Accumulating

evidence suggests that the assessment of the quality of GMs evaluates early neurological function and identifies infants at high risk of developmental problems, including cerebral palsy (CP).^{1,2} The predictive power of GMs assessment (GMA) is particularly high when it is performed at 2 to 5 months corrected age (CA; so-called fidgety

Abbreviations: CA, corrected age; CP, cerebral palsy; CI, confidence interval; DA, definitely abnormal; GM, general movement; GMA, general movements assessment; IMP, infant motor profile; MA, mildly abnormal; OR, odds ratio; SINDA, Standardized Infant NeuroDevelopment Assessment; UMCG, University Medical Center Groningen.

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phase).³ GMA in the fidgety phase focuses on two different but interrelated aspects: (a) the basic parameter of GM-quality typically present at all GM-ages, that is movement complexity and variation (in short: movement complexity) and (b) the age-dependent presence of fidgety movements.¹ The former refers to the spatial and temporal variation of the movements; the latter are tiny movements occurring irregularly over the body. Currently, there are two variants of GMA: Precht's method⁴ and the Hadders-Algra classification.¹ They assess the same construct of GMs, that is movement complexity and fidgety movements, but focus in their description on either of these aspects. Precht's method emphasises the absence of fidgety movements, whereas Hadders-Algra's classification stresses the marked reduction in movement complexity in GMs classified as definitely abnormal (DA).

GMA has been applied extensively in high-risk infants. In these infants, the prevalence of clinically relevant atypical GMs, that is DA GM-complexity and/or absent fidgety movements, is well documented. The prevalence of these atypical GMs in infants born very preterm is 22%-26%^{5,6}; that in infants with a brain lesion 34%-53%.^{7,8} In contrast, relatively little attention has been paid to GMs in typically developing infants. Most studies on low-risk infants reported on small samples (from 21 to 84 infants; 0%-11% atypical)⁹⁻¹² or more or less selective samples: healthy full-terms participating in a study on infant nutrition (0% atypical)¹³; infants born to subfertile couples (1% atypical)¹⁴ and healthy full-terms matched to a cohort of extremely preterm infants (3% atypical).¹⁵ Only the Dutch study of Bouwstra et al¹⁶ studied the prevalence of atypical GMs in the general population born in 2001-2002. The study reported a prevalence of 4%.

Over the years, changes in obstetric and neonatal practices led to decreasing rates in perinatal mortality and morbidity, also in low-risk infants.¹⁷ This may have resulted in a lower prevalence of atypical GMs in present times compared with earlier periods. In addition, previous studies reported the prevalence of atypical GMs either in terms of DA GM-complexity^{5,12,14,16} or by means of absent fidgety movements.^{6-11,15} We know that in high-risk infants DA GM-complexity and absent fidgety movements are highly but not perfectly interrelated. We hypothesise that both characteristics of GM-impairment may be less coupled in low-risk populations, as their underlying neurobiological substrate presumably differs.¹ In addition, information on the prevalence of both GM-impairments in the general population may serve as a reference for studies in high-risk populations.

The aim of this study is threefold, (a) to report the prevalence of atypical GMs both in terms of DA GM-complexity and in terms of absent fidgety movements, in a cohort representative of the general Dutch population; (b) to examine if the prevalence of atypical GMs decreased over the last 15 years; and (c) to investigate which prenatal, perinatal and socio-economic characteristics are associated with atypical GMs. Our representative sample includes infants aged 2 to 4 months. The period of 2 to 4 months covers the age range of the fidgety phase. We did not include infants aged 5 months as 5-month-olds are mostly involved in goal-directed movements and

Key notes

- This study reports the prevalence of atypical features of general movements (GMs) in Dutch infants representative of the general population, therewith providing reference data for high-risk infants.
- Atypical GM-complexity and absent fidgety movements are prevalent in 3% of infants aged 2-4 months, but these impairments rarely co-occur (0.3%).
- Atypical GM-complexity is associated with maternal smoking and marginally with prematurity, whereas absence of fidgety movements is only associated with assessment age.

spend little time with fidgety GMs anymore.¹⁸ We hypothesised that (a) the group of infants with GMs with DA GM-complexity would only partially overlap with the group of infants with GMs lacking fidgety movements, as both phenomenon presumably are based on different pathophysiological mechanisms¹; (b) the prevalence of atypical GMs in the current cohort is lower than that in the cohort of Bouwstra et al¹⁶; and (c) prenatal and perinatal complications, including preterm birth, and low socio-economic status are associated with atypical GMs.

2 | METHODS

2.1 | Participants

This study is based on the IMP-SINDA project, a study performed to collect norm data for the Infant Motor Profile (IMP)¹⁹ and the Standardized Infant NeuroDevelopmental Assessment (SINDA).²⁰ The project aimed to recruit a cross-sectional sample of infants that was representative of the Dutch population in terms of maternal education and ethnicity, with 100 infants per month of age. Inclusion criteria were 2 to 18 months CA, living in the northern part of the Netherlands (ie in the provinces of Groningen, Friesland and Drenthe) and having caregivers with sufficient understanding of the Dutch language to give informed consent. Infants were only excluded if they were too ill to be assessed (eg severe congenital cardiac disorder with insufficient oxygen saturation). Infants were recruited via well-baby clinics and advertisements, between January 2017 and March 2019. The 300 infants aged 2, 3 and 4 months CA were included in the current GM-study. All children were assessed once. The Medical Ethical Committee of the University Medical Center Groningen (UMCG) approved the study design (METc 2016/294), and the study was registered in the Dutch trial register (NL58069.042.16). All caregivers provided written informed consent. Caregivers filled out a standardised questionnaire on prenatal, perinatal and neonatal (in

short: perinatal) and socio-economic history. If the questionnaire revealed complications, medical records from the concerning hospital were consulted.

For the evaluation of a time trend, data of the 455 infants of the cohort of Bouwstra et al.¹⁶ were used. These infants had been born in 2001-2002 and were assessed at 3 months CA as part of their routine health check at one of the well-baby clinics in the northern part of the Netherlands. Infants whose parents had an insufficient understanding of the Dutch language were not eligible for inclusion. The prenatal, perinatal and socio-economic data of participants were collected by means of standardised forms and from medical records. For detailed information see Bouwstra et al.¹⁶

2.2 | GMA

GMs were recorded in a similar way in both cohorts. The infants were placed in supine position on a mattress, dressed in a diaper and a bodysuit. Spontaneous movements in an actively awake state without interacting with other persons or toys were videotaped for at least 3 minutes. The recordings in the IMP-SINDA cohort were based on the first three minutes of the IMP-assessment, which in young infants consists of a recording of spontaneous movements in supine. The recordings were performed at home, at well-baby clinics, or at the baby-laboratory of Developmental Neurology of the UMCG, depending on the parents' preference. GMA scoring was performed offline by MHA, who has worked on GMA for more than 25 years and was masked for the infant's perinatal history and social background.

GMA consisted of both the evaluation of GM-complexity and fidgety movements. GM-complexity was classified into four classes: normal-optimal (abundant complexity and fluency), normal-suboptimal (sufficient complexity, no fluency), mildly abnormal (MA, insufficient complexity, no fluency) and definitely abnormal (DA, very limited or absent complexity, no fluency).¹ Fidgety movements were classified according to the following categories: continually present (frequent occurrence in whole body with very short pauses), intermittently present (occurrence in whole body with prolonged pauses), sporadic (isolated occurrence in a few body parts with long pauses) and absent (no fidgety movements).⁴ DA GM-complexity and absent fidgety movements are the clinically relevant forms of atypical GMs, as they are associated with development problems, including CP.^{1,4}

The GMs recordings in the Bouwstra cohort were performed at the well-baby clinics. Two assessors, HB and MHA (inter-rater reliability: kappa = 0.82), performed GMA in terms of GM-complexity.¹⁶ The degree of fidgety movements was not recorded and the old videotapes did not allow for re-assessment.

2.3 | Statistical analyses

The background characteristics of the IMP-SINDA and Bouwstra cohorts were compared using Mann-Whitney tests for continuous

data and Fisher's exact tests for categorical data. The time trend of DA GM-complexity was examined by an univariable logistic analysis and a multivariable logistic analysis with adjustment for the unbalanced background characteristics. To investigate which factors were associated with atypical GMs, the association of individual background characteristic with atypical GMs was first tested with an univariable logistic regression analysis. Significant associated factors ($P < .05$ in univariable analyses) were then entered into a multivariable regression analysis to investigate the major determinants. We ran two separate analyses: one on DA-GM complexity and one on absent fidgety movements. For the former analysis, we pooled the IMP-SINDA and the Bouwstra cohorts; for the latter analysis, we only could use the IMP-SINDA cohort. For the evaluation of the association between the infant's age at GMA and atypical GMs, CA in weeks was used, both for infants born at term and preterm, as it is known that the developmental changes in GMs are stronger associated with CA than with postnatal age.²¹ The strength of associations was presented by the odds ratio (OR) with 95% confidence interval (CI). A P value lower than .05 was considered to be statistically significant. All analyses were conducted with SPSS package version 23 (SPSS Inc.).

3 | RESULTS

3.1 | Cohort characteristics

Table 1 describes the background characteristics of the IMP-SINDA and Bouwstra cohorts. Compared to the Bouwstra cohort, the IMP-SINDA cohort had a younger maternal age ($P < .001$), a higher proportion of non-native Dutch parents (mothers: $P < .001$, fathers: $P = .006$), a lower rate of maternal substance use ($P < .001$) but a higher rate of maternal medication use ($P = .001$) during pregnancy, a lower birthweight ($P = .003$) with a higher percentage of infants small for gestational age ($P = .019$) and a younger assessment age ($P < .001$).

3.2 | Prevalence of atypical GMs and time trend

The assessment in the IMP-SINDA cohort revealed that 10 (3%) infants had DA GM-complexity (Figure 1A) and 8 (3%) showed absent fidgety movements (Figure 1B). Only one infant (0.3%) showed GMs with both impairments. This infant was born preterm, and his cranial ultrasound had shown small cysts in left periventricular area. His GMs had been assessed at 8 weeks CA.

The prevalence of DA GM-complexity seemed slightly lower in the IMP-SINDA cohort (3%) than in the Bouwstra cohort (4%).¹⁶ However, the likelihood of having DA GM-complexity in the two cohorts did not differ significantly when examined without ($OR = 0.89$ [0.40, 1.97], $P = .771$) or with adjustments for the unbalanced background characteristics (adjusted $OR = 1.47$ [0.53, 4.06], $P = .461$).

TABLE 1 Basic characteristics of the study populations

	IMP-SINDA cohort (assessed 2017-2019) (n = 300)		Bouwstra cohort (assessed 2001-2002) (n = 455)	
	n of data	median (range) or n (%)	n of data	median (range) or n (%)
Prenatal and perinatal characteristics				
Pre-pregnancy maternal BMI in kg/m ²	298	24.1 (17.4-45.0)		— ^a
Obesity (BMI ≥ 30 kg/m ²), n (%)	298	54 (18%)		
Overweight (25 ≤ BMI ≤ 29.9 kg/m ²)	298	76 (26%)		
Assisted reproduction	297	23 (8%)		— ^a
Maternal smoking	299	35 (12%)	450	61 (14%)
Substance exposure (alcohol or drugs)	299	5 (2%)	452	37 (8%)
Maternal medication ^b	299	33 (11%)	451	20 (4%)
Maternal hypertension	299	38 (13%)		— ^a
Maternal diabetes	299	24 (8%)		— ^a
Maternal thyroid disease	299	9 (3%)		— ^a
Instrumental delivery	300	63 (21%)	447	110 (25%)
Sex: Male	300	162 (54%)	446	214 (48%)
Twin	300	10 (3%)	455	15 (3%)
Birthweight in grams	300	3374 (1120-4875)	447	3500 (850-5432)
Small for gestational age ^c	300	45 (15%)	441	41 (9%)
Gestational age in weeks	300	39.4 (27.3-42.1)	452	40.0 (29.0-42.0)
Preterm birth (<37 wk)	300	26 (8%)	452	32 (7%)
Meconium in amniotic fluid	298	38 (13%)		— ^a
Hyperbilirubinemia requiring phototherapy	298	18 (6%)		— ^a
Socio-economic characteristics				
Maternal age in years	300	30 (16-44)	405	31 (15-46)
Advanced maternal age (Age ≥35 y)	300	48 (16%)	405	86 (21%)
Paternal age in years	293	32 (21-68)	403	33 (16-63)
Advanced paternal age (Age ≥40 y)	293	37 (13%)	403	40 (10%)
Maternal educational level: High ^d	300	119 (40%)	402	146 (36%)
Paternal educational level: High ^d	289	116 (40%)	394	153 (39%)
Maternal ethnicity: Non-native Dutch	300	33 (11%)	407	15 (4%)
Paternal ethnicity: Non-native Dutch	294	27 (9%)	406	16 (4%)
Assessment age in weeks ^e	300	12 (6-20)	449	13 (4-22)

Note: Bold type indicates group difference between the IMP-SINDA and Bouwstra cohort ($P < .05$).

Abbreviation: BMI, body mass index.

^aData were unavailable in the Bouwstra cohort.

^bMaternal medication indicates the use of at least one of the following: insulin, antihypertensive medication, thyroid-stimulating medication, antidepressants/antipsychotics/benzodiazepines, anti-epileptic medication.

^cSmall for gestational age: birth weight for gestational age <10th percentile of Dutch growth curves.

^dHigh educational level: vocational college and university.

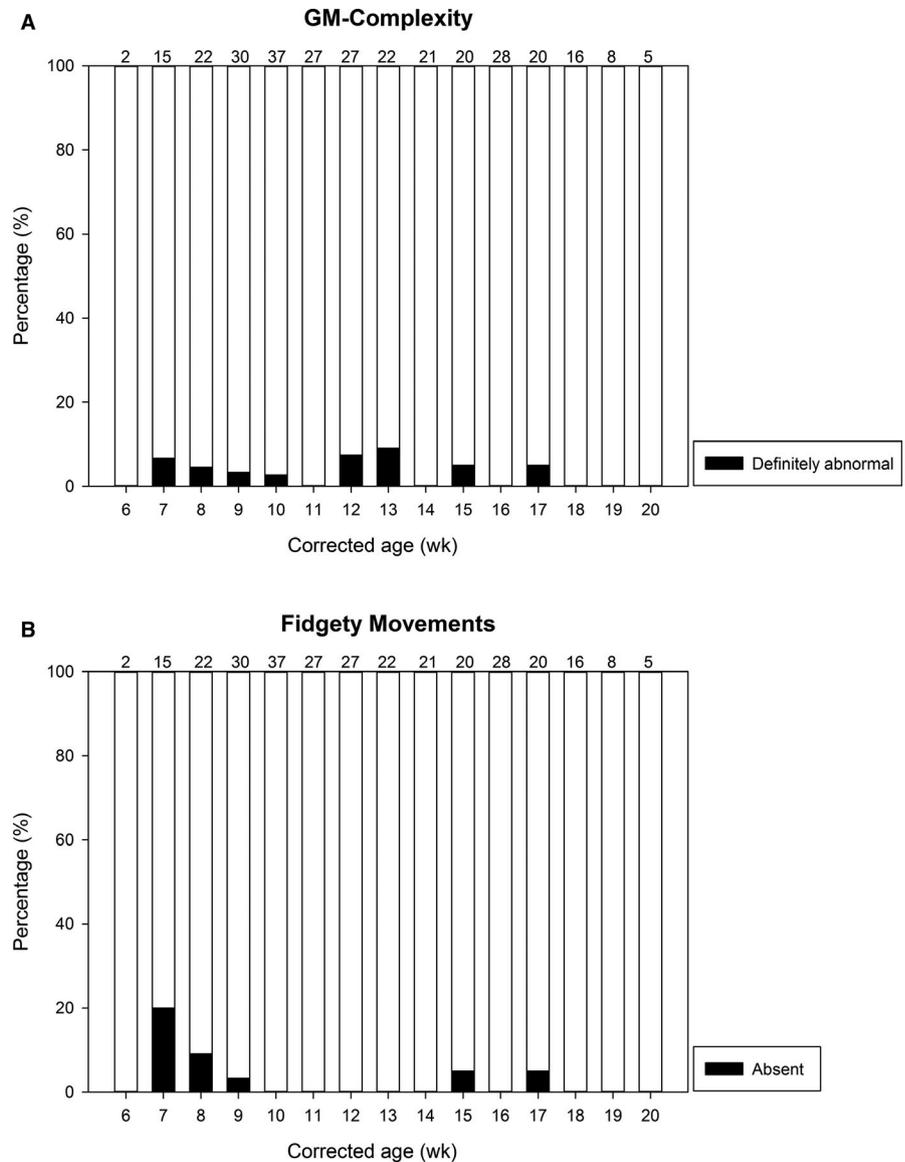
^eCorrected age is used in all infants, estimated from the expected birth date (term age) and assessment date, rounded down to weeks.

3.3 | Factors associated with atypical GMs

Univariable analysis indicated that maternal smoking (OR = 3.65 [1.59, 8.38], $P = .002$) and prematurity (OR = 2.88 [1.05, 7.92], $P = .04$) were

associated with DA GM-complexity (Table 2). Multivariable analysis revealed that DA GM-complexity was significantly associated with maternal smoking (adjusted OR = 3.59 [1.56, 8.28], $P = .003$) and marginally with prematurity (adjusted OR = 2.78 [1.00, 7.74], $P = .051$).

FIGURE 1 Prevalence of atypical general movements (GMs) in the current cohort. Percentage of atypical GMs in terms of (A) GM-complexity and (B) fidgety movements in the IMP-SINDA cohort at various corrected ages (CA) in weeks. Typical GM-complexity includes the classifications of GM-complexity as normal optimal, normal suboptimal, and mildly abnormal. Present fidgety movements include the categories of continually present, intermittently present, and sporadic fidgety movements. The numbers above the bars indicate the numbers of infants assessed at each week CA



Absent fidgety movements were only associated with assessment age in weeks CA (quadratic logistic regression analyses: age-square, OR = 1.06 [1.01, 1.12], $P = .034$) (Table 2), indicating an U-shaped relationship (Figure 1B).

4 | DISCUSSION

The current prevalence of atypical GMs, either in terms of very limited movement complexity or in terms of absent fidgety movements, was 3% in 2 to 4 months old infants representative of the general Dutch population. The prevalence had not changed significantly over the last 15 years. However, in this low-risk population impairment in movement complexity did not automatically imply impairment in fidgety movements and vice versa. Only one infant (0.3%) showed impairments in both GM-features. The results reinforce the notion that movement complexity and fidgety movements are two dimensions of GMs based on different neurobiological mechanisms.

It has been hypothesised that GM-complexity is brought about by activity in cortical-subcortical networks, in which initially the subplate plays a central role and—at fidgety GM-age—the cortical plate of the primary sensorimotor cortices. The fidgety GMs are the result of general maturational processes in the cortical networks.¹

The idea of two different neurobiological mechanisms was further supported by the finding that atypical GM-complexity and atypical fidgety movements were associated with different background factors. Maternal smoking and—marginally—preterm birth were risk factors of DA GM-complexity, whereas assessment age was associated specifically with absent fidgety movements. The association between maternal smoking during pregnancy and DA GM-complexity has been reported previously.¹⁶ Interestingly, Chang et al²² showed that prenatal tobacco exposure is associated with altered microstructures in the thalamus and internal capsule in early infancy, alterations which also are associated with reduced movement complexity.²³ We found just a modest association between preterm birth and atypical GM-complexity and no association between preterm birth and absent

TABLE 2 Associations of background characteristics with atypical GMs

Factor in univariable analysis	Outcome	
	GM-complexity: Definitely abnormal	Fidgety movements: Absent
Prenatal and perinatal characteristics		
Maternal overweight or obesity	OR = 0.86 [0.24, 3.10] ^a	OR = 1.30 [0.32-5.31] ^a
Assisted reproduction	OR = 1.34 [0.16, 11.05] ^a	— ^b
Maternal smoking	OR = 3.65 [1.59, 8.38]	— ^b
Substance exposure	OR = 1.37 [0.31, 5.98]	— ^b
Maternal medication	OR = 1.68 [0.49, 5.78]	— ^b
Maternal hypertension	OR = 1.76 [0.36, 8.60] ^a	OR = 0.98 [0.12, 8.20] ^a
Maternal diabetes	— ^b	— ^b
Maternal thyroid disease	— ^b	— ^b
Instrumental delivery	OR = 1.50 [0.64, 3.51]	OR = 2.32 [0.54, 9.98] ^a
Sex: Male	OR = 0.81 [0.37, 1.75]	OR = 0.70 [0.16, 2.97] ^a
Twin	OR = 1.13 [0.15, 8.66]	— ^b
Small for gestational age	OR = 2.51 [0.97, 6.47]	OR = 0.81 [0.10, 6.71] ^a
Prematurity	OR = 2.88 [1.05, 7.92]	OR = 1.53 [0.18, 12.90] ^a
Meconium in amniotic fluid	OR = 1.75 [0.36, 8.57] ^a	OR = 0.98 [0.12, 8.17] ^a
Jaundice requiring phototherapy	OR = 1.77 [0.21, 14.81] ^a	OR = 2.30 [0.27, 19.80] ^a
Socio-economic characteristics		
Advanced maternal age	OR = 1.63 [0.62, 4.24]	— ^b
Advanced paternal age	OR = 2.46 [0.88, 6.87]	— ^b
Maternal educational level: High	OR = 0.61 [0.24, 1.58]	OR = 0.50 [0.10, 2.51] ^a
Paternal educational level: High	OR = 0.77 [0.29, 1.77]	OR = 0.24 [0.03, 2.04] ^a
Maternal ethnicity: non-native Dutch	OR = 0.65 [0.09, 4.91]	OR = 1.16 [0.14, 9.74] ^a
Paternal ethnicity: non-native Dutch	OR = 0.72 [0.10, 5.49]	— ^b
Assessment age		
Corrected age (quadratic function)	OR = 1.00 [0.97, 1.04]	OR = 1.06 [1.01, 1.12]^a

Note: Data are presented as odds ratio (OR) and 95% confidence interval in brackets. Bold type indicates a significant association ($P < .05$).

^aThe OR was based on the IMP-SINDA cohort only, as data were unavailable in the CB cohort.

^bOR cannot be estimated because the prevalence in study sample was low (2%-13%) and it did not occur in infants with DA GM-complexity ($n = 10$) or infants with absent fidgety movements ($n = 8$).

fidgety movements, whereas it is well known that preterm infants, especially very preterm infants, are at high risk of DA GM-complexity⁵ and absent fidgety movements.⁴ Our findings reflect the low-risk nature of our group in which only a few infants were born very preterm (<32 weeks, $n = 6$).

DA GM-complexity and absent fidgety movements were both prevalent in 3% of the general population. In high-risk infants, atypical GMs in either format are clearly associated with later diagnosis of CP,¹ but in low-risk infants the isolated presence of very limited GM-complexity or absent fidgety movements is especially associated

with milder forms of neurological dysfunction.¹² Follow-up of the Bouwstra cohort at 3 years and 9 months revealed that DA GM-complexity was also associated with an increased risk of major neurodevelopmental disability, including CP.²⁴ However, predictive values were lower than those reported in groups of high-risk infants (Bouwstra cohort: sensitivity to predict CP 67%, specificity 97%). The relatively low sensitivity for CP was brought about by the fact that one of the three children who had developed CP, had shown GMs with typical complexity and typical fidgety movements. He was diagnosed with a unilateral spastic CP.²⁴

In high-risk infants, the combination of DA GM-complexity and no fidgety movements is associated with the highest risk of CP. Hamer et al²⁵ reported that half of the infants with the combination of these two GM-impairments were later diagnosed with CP. In our study, the prevalence of the combination of DA GM-complexity and absent fidgety movements was 0.3%, a prevalence which is twice the prevalence of CP in the general European population (0.18%).²⁶ This finding and the data of Hamer et al²⁵ may imply that low-risk infants with the combination of the two GM-impairments are at a similar high risk of CP as high-risk infants with DA GM-complexity and no fidgety movements. Future studies are needed to further determine the clinical utility of GMA in the general population. For the IMP-SINDA cohort, follow-up at the age of 4-5 years is planned.

The major strength of this study is the representativeness of the study cohort. Apart from maternal education and ethnicity, which were the selection criteria to achieve a representative sample, perinatal and socio-economic characteristics were comparable to those in Dutch national data (IMP-SINDA cohort vs national data): maternal overweight or obesity (44% vs 37%), assisted reproduction (8% vs 7%), instrumental delivery (21% vs 24%), male (54% vs 52%), twin (3% vs 3%), preterm birth (8% vs 7%), small for gestational age (15% vs 11%), maternal age (30 vs 31 years), paternal age (32 vs 34 years) and high paternal educational level (40% vs 40%).^{27,28} The representativeness allows generalisation of our results to the general population and other low-risk populations in high-income countries, that is populations with similar prevalence of CP, the Netherlands, 0.2%,²⁹ Europe in general (0.18%),²⁶ the United States (0.18%)³⁰ and Australia (0.20%).³¹ Another strength of our study is that the GMAs in both the IMP-SINDA and Bouwstra cohorts were mostly conducted by one experienced assessor. On the other hand, relying on mainly one assessor could also function as a disadvantage, as Gima et al showed that scoring GM-details in a low-risk population was associated with substantial interrater variation.³² The presence of the same assessor for both cohorts supported the reliability of the time trend analysis. The study's major limitation is the single assessment of GMs. As seen in Figure 1B, atypical fidgety movements were observed at 7 to 9 weeks and 15 to 17 weeks CA. We do not know whether the absence of fidgety movements in these children was due to deviant neurological development or typical developmental trends or both. Longitudinal studies in low-risk infants indicated that the absence of fidgety movements is age-related; it occurs in particular at the age margins of the fidgety period.^{9,20} Practically this may

imply that the presence or absence of fidgety movements should be assessed longitudinally in the fidgety phase or—when relying on a single assessment—it should be performed in the restricted time window of 10 to 14 weeks CA.

5 | CONCLUSION

In the general population, the prevalence of atypical GMs was 3%, which has been stable over the last 15 years. However, the two dimensions of atypical GMs were associated with different risk factors: DA GM-complexity with maternal smoking and prematurity; absent fidgety movement with not any of the perinatal and social risk factors. The absence of fidgety movement was only associated with the infant's assessment age in weeks CA. Both GM-impairments infrequently co-occurred. Our results support the idea that GM-complexity and fidgety movements are two important aspects of GMs and both need to be assessed.

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CONFLICT OF INTEREST

Prof. dr Mijna Hadders-Algra has provided courses on the assessment of GMs since 1993. The honorarium of the courses flows into the Research Fund of Developmental Neurology. She did not get a honorarium, grant or other form of payment to produce the manuscript. Other authors declare no conflict of interest.

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