Mid upper arm circumference: an alternative to BMI for nutritional status assessment in older children p 227

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ORIGINAL RESEARCH Growth curve construction and longitudinal cohort study

A growth reference for mid upper arm circumference for age among school age children and adolescents, and validation for mortality

Mramba L, Ngari M, Mwangome M, et al

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Study question Can mid upper arm circumference (MUAC)-for-age z scores that are compatible with World Health Organization growth references be used in place of body mass index-for-age for assessing mortality risk among school age children and adolescents?

Methods MUAC growth curves were constructed using US population datasets from the Health Examination Survey/National Health and Nutrition Examination Survey, which had been used to construct the 2007 WHO growth references for body mass index in this age group, merged with an imputed dataset matching the distribution of the WHO 2006 growth standards for under 5s and modelling by a Box-Cox Cole Green transformation. Data used for validation were from HIV infected children participating in the Antiretroviral Research for Watoto (ARROW) trial in Uganda and Zimbabwe, and children followed up after discharge from a rural Kenyan hospital. Both cohorts were followed up for survival during one year and analysed using Cox proportional hazards models and receiver operating characteristic curves.

Study answer and limitations The new growth curves transitioned smoothly with WHO growth standards at age 5 years and predicted subsequent mortality at least as well as body mass index-for-age z scores. Limitations included a small number of participants who were older teenagers.

What this study adds The new growth reference for MUAC is a valid predictor of mortality and provides a much simpler alternative to body mass index for assessing nutritional status among school age children and adolescents in clinical practice, emergency settings, and research.

Funding, competing interests, data sharing This study was funded by the Wellcome Trust and the MRC/DfID/Wellcome Trust Joint Global Health Trials Scheme. The authors declare no competing interests. Datasets used to construct MUAC curves are available at www.cdc.gov/nchs/data_access/ftp_data.htm. The modelling code may be requested from LM (Lazarus. Mramba@medicine.ufl.edu). Validation data from Kenya may be requested from the KEMRI/Wellcome Trust Research Programme Data Governance Committee (dgc@kemri-wellcome.org) and from the ARROW trial may be requested through Sarah Walker (rmjlasw@ucl.ac.uk).
Prescribing opioids and psychotropic drugs in pregnancy

**ORiGINAL RESeARCH** Cohort study

**Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications**

Huybrechts KF, Bateman BT, Desai RJ, et al

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**Study question** What impact does in utero co-exposure to psychotropic medications and opioids have on the incidence and severity of neonatal drug withdrawal?

**Methods** Cohort study of sample of 201 275 publicly insured pregnant women nested in the Medicaid Analytic eXtract (2000-10) who filled an opioid prescription during the 45 days before delivery. Psychotropic medications co-filled within the same time window as opioids. Relative risks of neonatal drug withdrawal were estimated with generalised linear models with fine stratification on the propensity score to control for potential confounders.

**Study answer and limitations** The absolute risk for neonatal drug withdrawal ranged from 1.0% (1743/173 841) in infants exposed in utero to prescription opioids alone to 11.4% (57/501) for those exposed to opioids co-prescribed with gabapentin. Among neonates exposed in utero to prescription opioids, the relative risk for drug withdrawal, adjusted for propensity score, was 1.34 (95% confidence interval 1.22 to 1.47) with concomitant exposure to antidepressants, 1.49 (1.35 to 1.63) with benzodiazepines, 1.61 (1.26 to 2.06) with gabapentin, 1.20 (0.95 to 1.51) with antipsychotics, 1.01 (0.88 to 1.15) with Z drugs, and 2.05 (1.77 to 2.37) with exposure to two or more psychotropic medications. This study was unable to distinguish a synergistic effect between opioids and psychotropics from an independent effect of psychotropics. It also relied on data on prescriptions so could not determine compliance.

**What this study adds** The use of psychotropic medications in addition to prescription opioids during pregnancy is common, despite a lack of safety data. The findings suggest that these drugs could further increase the risk and severity of neonatal drug withdrawal.

**COMMENTSARY** Increases in prescribing are a major concern

Over the past two decades, increasing use of opioid pain relievers has led to myriad complications in communities throughout the US. In 2015, every 15 minutes one American died from an opioid related overdose—which is more frequent than deaths from vehicle crashes. Given the rapid rise and scope of the US opioid epidemic, it should not be a surprise that nearly every segment of society has been affected, including pregnant women and their infants.

Infants exposed to opioids are at risk of neonatal opioid withdrawal syndrome, also known as neonatal abstinence syndrome (NAS), which is characterised by difficulty feeding, respiratory problems, irritability, hypertonia, insomnia, and seizures, leading to more complicated and costly hospital admissions. In the US, rates of neonatal abstinence syndrome grew fivefold in the past decade, considered included antidepressants, atypical antipsychotics, benzodiazepines, gabapentin, and non-benzodiazepine hypnotics (Z drugs), co-filled within the same time window as opioids. Relative risks of neonatal drug withdrawal were estimated with generalised linear models with fine stratification on the propensity score to control for potential confounders.

Importantly, not all infants exposed to opioids develop withdrawal, for reasons that remain unclear. In a linked paper, Huybrechts and colleagues find a possible reason for differences in risk—concurrent prescription of psychotropic medications. The authors used a US cohort of 200 000 pregnant women enrolled in the Medicaid programme—a government sponsored programme that pays for healthcare services—all of whom filled a prescription for an opioid. They examined if the risk of NAS was increased among infants whose mothers were co-prescribed a psychotropic medication.

They found that use of antidepressants (relative risk 1.34, 95% confidence interval 1.22 to 1.47), benzodiazepines (1.49, 1.35 to 1.63), and gabapentin (1.61, 1.26 to 2.06) increased the risk. They also found that exposure to two or more of these medications more than doubled the odds (2.05, 1.77 to 2.37) compared with odds in pregnant women prescribed opioids alone.

In the US, rates of neonatal abstinence syndrome grew fivefold over the past decade, reaching a rate of one affected infant born every 25 minutes.

Prevention and treatment

These data were derived from hospital administrative records, which can be prone to misclassification bias and cannot account for illicit co-exposures (such as cocaine); nevertheless, the data are unique providing the power to detect rare outcomes, and these findings are important in targeting prevention efforts and potentially in tailoring treatment of opioid exposed infants.

Huybrechts and colleagues’ study highlights how the opioid epidemic affects women and infants in the US, where rates of prescribing are nearly four times higher than in Europe. While prescriptions for opioids have declined slightly in the US since 2012, studies of the pregnant women enrolled in Medicaid found that, depending on the state, 9.5% to 41.6% were prescribed at least one opioid in pregnancy. In addition, the growth of use of prescribed opioids has been temporally associated with an increase in opioid use disorder among pregnant women in the US, particularly in rural areas.

Policy approaches to the opioid epidemic must acknowledge that untreated opioid use disorder, anxiety, and depression are harmful for both mother and infant; put simply, healthier mothers have healthier babies.

The large expansion of opioid prescribing and prescribing of psychotropic medications to pregnant women, however, raise major concerns. Most of all medications in use today lack enough information to determine their safety in pregnancy. For instance, gabapentin is categorised as a pregnancy category C medication, with evidence of fetal harm in animal experiments but inadequate controlled studies in humans.

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Treating for two
Use of medications in pregnancy must balance the health of the mother with the potential impact on the developing fetus. These concerns led the US Centers for Disease Control and Prevention to launch an initiative called “Treating for Two,” emphasising the value of better research and reliable guidance that will better inform women’s and clinicians’ decisions about medication use during pregnancy (www.cdc.gov/pregnancy/meds/treatingfortwo/index.html).

For clinicians who provide care for pregnant women and their children, these data have some additional important implications. Given clinical challenges in predicting risk of withdrawal among infants exposed to opioids, the American Academy of Pediatrics suggests that all such infants should be observed for four to seven days after birth to monitor for signs of withdrawal. Huybrechts and colleagues found substantial differences in risk of withdrawal based on exposure to specific psychotropic agents, suggesting opportunities to tailor postnatal monitoring and treatment for the highest risk infants. Lastly, these findings suggest a clear need for a comprehensive, evidence informed strategy regarding opioid use in pregnancy. To be effective, the strategy would specify opportunities for intervention in clinical and public health settings in all time periods related to pre-pregnancy, antepartum/prenatal, peripartum/perinatal, and postpartum/infancy.

There remains a paucity of clinical guidance for obstetricians and pediatricians caring for the mother-child unit; development of a strategy will help to prioritise the development of specific evidence. As the US opioid epidemic accelerates in complexity, there is an urgent need to focus resources on this issue, including expansion of research funding for drug safety in pregnancy and improvement of outcomes for mothers and infants affected by opioid use disorder, more funding for the prevention of the disorder, and an expansion of treatment options for affected mothers and their infants.

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GRIPP2 reporting checklists

Staniszewska S, Brett J, Simera I, et al

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Background While the patient and public involvement (PPI) evidence base has expanded over the past decade, the quality of reporting within papers is often inconsistent, limiting our understanding of how PPI works, in what context, for whom, and why.

Objective To develop international consensus on the key items to report to enhance the quality, transparency, and consistency of the PPI evidence base. To collaboratively involve patients as research partners at all stages in the development of GRIPP2.

Methods The EQUATOR method for developing reporting guidelines was used. The original GRIPP (Guidance for Reporting Involvement of Patients and the Public) checklist was revised, based on updated systematic review evidence. A three round Delphi survey was used to develop consensus on items to be included in the guideline. A subsequent face-to-face meeting produced agreement on items not reaching consensus during the Delphi process.

Results 143 participants agreed to participate in round one, with an 86% (123/143) response for round two and a 78% (112/143) response for round three. The Delphi survey identified the need for long form (LF) and short form (SF) versions. GRIPP2-LF includes 34 items on aims, definitions, concepts and theory, methods, stages and nature of involvement, context, capture or measurement of impact, outcomes, economic assessment, and reflections and is suitable for studies where the main focus is PPI. GRIPP2-SF includes five items on aims, methods, results, outcomes, and critical perspective and is suitable for studies where PPI is a secondary focus.

Conclusions GRIPP2-LF and GRIPP2-SF represent the first international evidence based, consensus informed guidance for reporting patient and public involvement in research. Both versions of GRIPP2 aim to improve the quality, transparency, and consistency of the international PPI evidence base, to ensure PPI practice is based on the best evidence. In order to encourage its wide dissemination this article is freely accessible on The BMJ and Research Involvement and Engagement journal websites.

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**GRIPP2 short form**

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item</th>
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<tbody>
<tr>
<td>Aim</td>
<td>Report the aim of PPI in the study</td>
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<tr>
<td>Methods</td>
<td>Provide a clear description of the methods used for PPI in the study</td>
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<tr>
<td>Study results</td>
<td>Outcomes—Report the results of PPI in the study, including both positive and negative outcomes</td>
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<tr>
<td>Discussion and conclusions</td>
<td>Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects</td>
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<tr>
<td>Reflections/critical perspective</td>
<td>Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience</td>
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PPI=patient and public involvement

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