

Revisiting suboptimal outcomes of diet-treated PKU patients

G Enns¹, R Koch², V Brumm, E Blakely³, R Suter⁴, E Jurecki⁴

¹Stanford University, Stanford, CA, United States

²University of Southern California/Keck School of Medicine, Los Angeles, CA, United States

³University of Rochester, Rochester, NY, United States,

⁴BioMarin Pharmaceutical Inc., Novato, CA, United States

INTRODUCTION

In the 1960s and 1970s, many countries employed newborn screening programs for phenylketonuria (PKU) in combination with the introduction of a phenylalanine (Phe) restricted therapeutic diet for treatment of infants diagnosed with PKU. Together, these formed the basis of an early-treated PKU management strategy, a standard of PKU care that still exists today. This treatment approach has had remarkable success in ameliorating the most severe clinical manifestations of the disease when implemented within the first few weeks of life. However, PKU treatment strategies evolved over subsequent decades in response to accumulating scientific evidence, which demonstrated that variations in PKU management approaches led to suboptimal patient outcomes. After more than three decades of research, observations, and clinical PKU management experience, national PKU patient management guidelines were published in 2000.¹⁻⁴ The process of guideline development requires the formation of an expert panel to provide evidence-based recommendations following systematic review and dissemination of accumulated scientific literature. Ideally, these recommendations provide health care professionals with management strategies that result in optimized patient outcomes through treatment and diagnosis, as well as the identification of future research needs.¹⁻⁴ Subsequently, studies originating from the scientific and therapeutic community provide further data related to patient outcomes, which may be used to inform the decision process for updating old guidelines or for developing new ones. This latter phase is the point at which PKU research now finds itself: the 2000 NIH PKU Consensus Statement guidance document is currently “provided solely for historical purposes,” and the intervening decade’s worth of new data provides a basis for re-evaluation of these guidelines in light of the current state of medical knowledge. We have used the 2000 NIH Consensus Statement guidance document as a benchmark reference to review the PKU literature published this decade in order to evaluate PKU patient outcomes following institution of these guidelines.⁵

METHODS

An initial search of PubMed, Scopus, and PsychInfo using [PKU or Phenylketonuria] identified non-review articles on PKU published from 2000 to 2009. This data base was subsequently screened for articles containing data on suboptimal patient outcomes in PKU and categorized into the following subtopics: 1) Neuro-Behavioral, 2) Maternal PKU, 3) Growth and Nutrition, 4) Osteoporosis, and 5) Quality of Life.

RESULTS

539 non-review articles were identified with a PKU focus. Of these, 170 reported patient outcomes, of which 162 articles reported suboptimal outcomes and were further categorized based on research focus. The majority of these suboptimal outcomes have been documented in all forms of early-treated PKU. However, Dr. Koch in his 40 plus years of clinical experience frequently observed that many of these suboptimal outcomes in early-treated classical PKU patients were taken off diet therapy.¹⁰ Results of this decade’s literature reveal that a significant burden of illness still exists in the PKU population. The rank order of reported categorized suboptimal outcomes is: Neuro-Behavioral Outcomes (n=89) > Maternal PKU (n=36) > Growth and Nutrition (n=28) > Osteoporosis (n=5) > Quality of Life (n= 4) [Figure 1].

DISCUSSION

Although the 2000 NIH guidelines presented recommendations that have had a positive impact on PKU outcomes,⁹ the evidence demonstrates that a significant burden of illness still exists in the PKU population and presents in all age ranges analyzed [Figure 2]. This confirms the NIH contention that the current treatment guidelines are inadequate for some patients.⁵ Recent evidence has demonstrated that lower and less variable Phe levels are important for optimal patient outcomes, and nutrient composition of the entire diet (in addition to the protein component) is an important clinical consideration. These results demonstrate that “treatment for life” of elevated Phe levels is clinically important. The suboptimal outcomes related to the PKU population in this decade are at least in part due to a lack of Phe control as the patient ages and relaxes/abandons their diet, demonstrated by composite data from both European and US studies [Figure 3].^{6,7} Suboptimal outcomes may also be attributed to limited awareness that current guideline recommendations can still lead to significant neurocognitive deficits.⁷ Further research will be required to understand the economic impact that these suboptimal outcomes may have on society as the PKU patient ages. Others have recently called for new guidelines⁸ to be developed to address these concerns, and the data presented here support this. Revised guidelines as well as new therapies have the potential to 1) decrease the proportion of individuals whose serum Phe levels are outside the target range, given their present dietary management, and 2) improve outcomes amongst individuals whose Phe levels are within the present guidelines but who have suboptimal outcomes. Additional modalities may further reduce serum Phe levels and possibly improve neurocognitive outcomes. The authors suggest that two specific shortcomings of the NIH guidelines should be addressed. Specifically, we question the relaxation of blood Phe levels up to 900 µmol/L in PKU patients 12 years of age and older and note the lack of routine standardized neurocognitive assessments.

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REFERENCES

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FIGURE 1 SUBOPTIMAL OUTCOMES IN PKU: RESULTS OF LITERATURE SEARCH 2000-2009

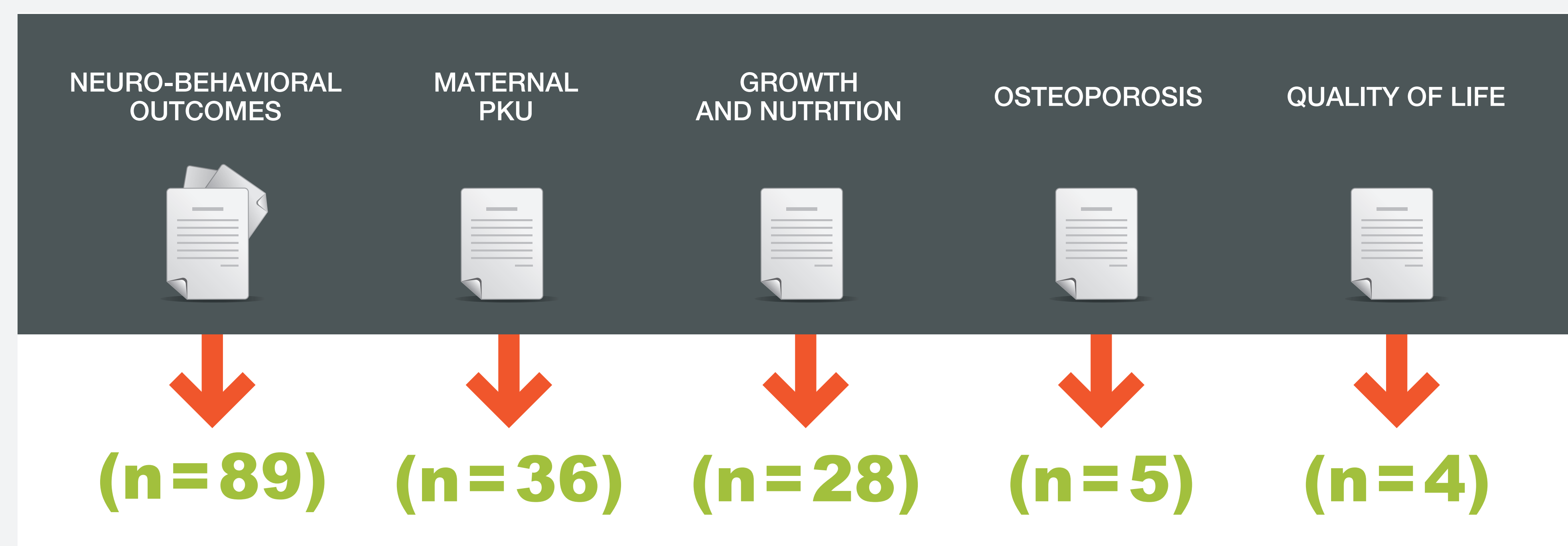


FIGURE 2

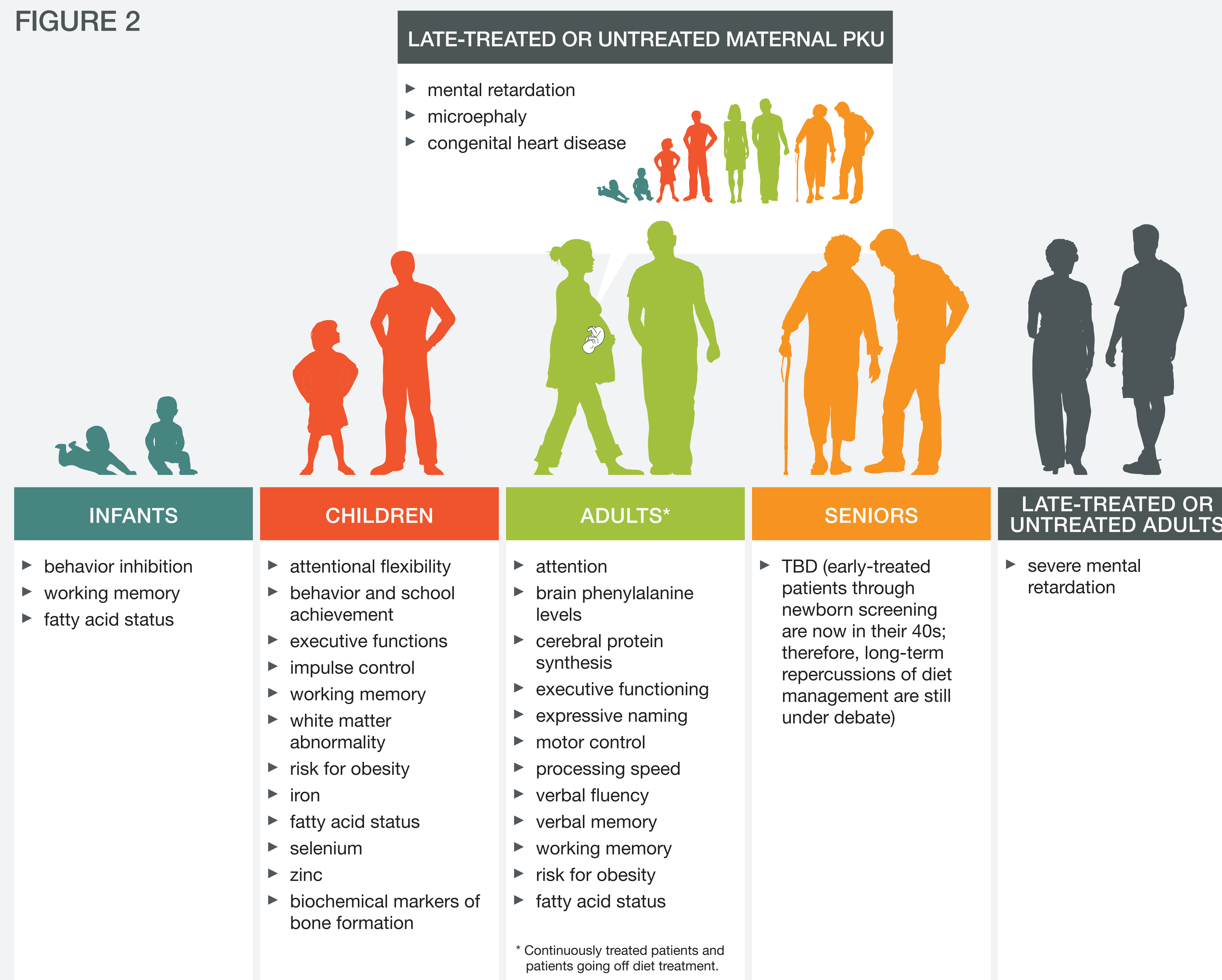


FIGURE 3A⁶

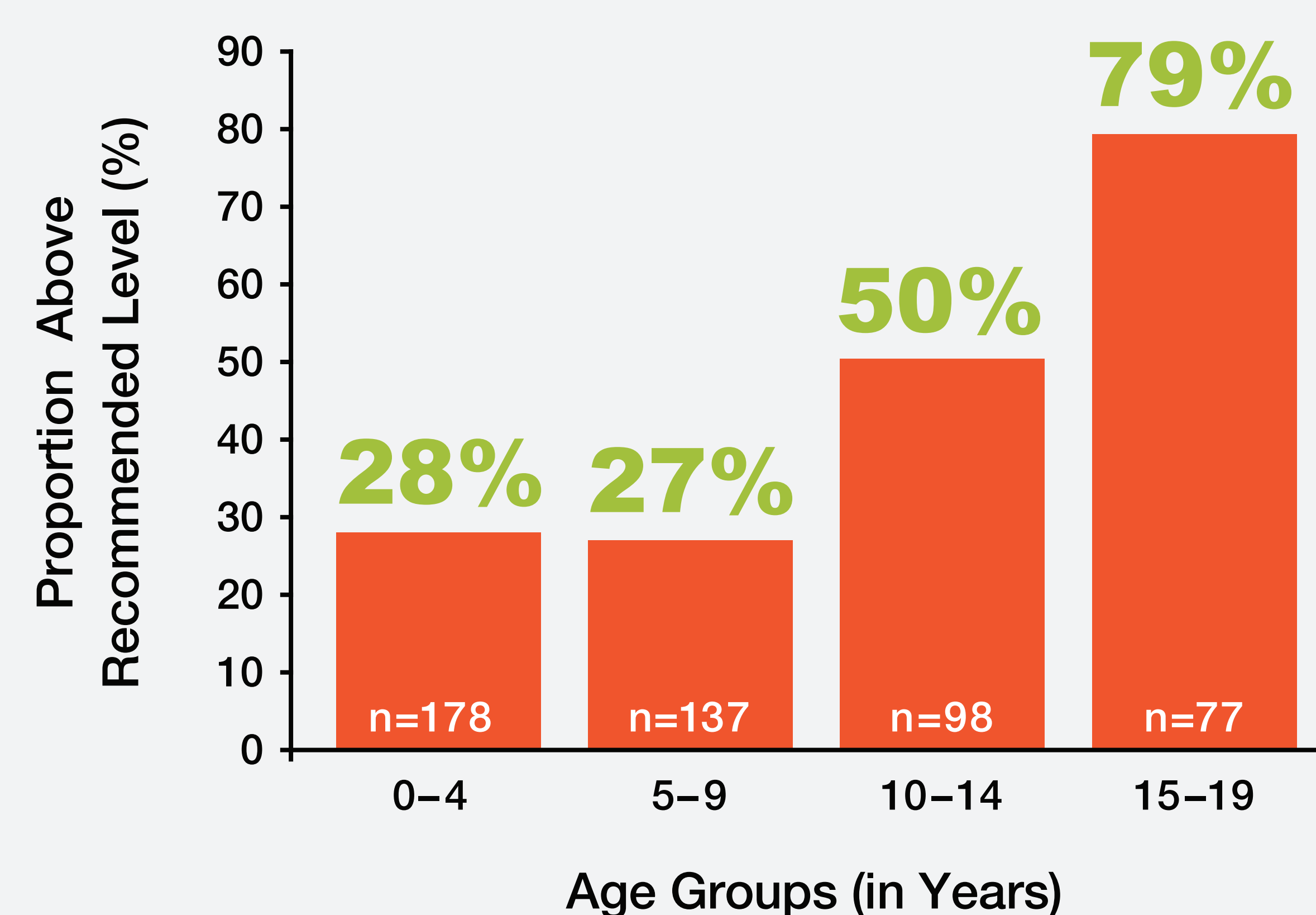


FIGURE 3B⁷

