PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity
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The objective was to determine PON1 status as a predictor for organophosphorus insecticide sensitivity in a cohort of Latina mothers and newborns from the Salinas Valley, California, an area with high levels of organophosphorus insecticide use. PON1 status was established for 130 pregnant Latina women and their newborns using a high-throughput two substrate activity/analysis method which plots rates of diazoxon (DZO) hydrolysis against rates of paraoxon (PO) hydrolysis. Arylesterase activity (AREase) was determined using phenylacetate as a substrate, allowing comparison of PON1 levels across PON1\(^{\text{Q192}}\) genotypes in mothers and children. Phenylacetate hydrolysis is not affected by the Q192R polymorphism. Among newborns, levels of PON1 (AREase) varied by 26-fold (4.3–110.7 U/ml) and among mothers by 14-fold (19.8–281.4 U/ml). On average, children's PON1 levels were four-fold lower than the mothers' PON1 levels (\(P<0.001\)). Average PON1 levels in newborns were comparable with reported hPON1 levels in transgenic mice expressing human PON1\(^{\text{Q192}}\) or PON1\(^{\text{R192}}\), allowing for prediction of relative sensitivity to chlorpyrifos oxon (CPO) and DZO. The predicted range of variability in sensitivity of mothers and children in the same Latino cohort was 65-fold for DZO and 131 to 164-fold for CPO. Overall, these findings indicate that many of the newborns and some of the mothers in this cohort would be more susceptible to the adverse effects of specific organophosphorus pesticide exposure due to their PON1 status. Of particular concern are exposures of pregnant mothers and newborns with low PON1 status. *Pharmacogenetics and Genomics* 16:183–190 © 2006 Lippincott Williams & Wilkins.

Pharmacogenetics and Genomics 2006, 16:183–190

Keywords: children, chlorpyrifos, diazinon, Latino cohort, paraoxonase 1 (PON1), PON1 status, pregnancy

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Sponsorship: This study was supported by 2 P01 ES009605, ES11387, ES09883, P30 ES01896, EPA-R82670901-5, P60 MD00222, and NIEHS ES09601/EPA: RD-83170901. The contents of this paper are solely the responsibility of the authors and do not necessarily represent official views of the NIH, or the EPA.

Received 26 July 2005 Accepted 13 October 2005

Introduction

Recent biological and ambient monitoring data have indicated widespread organophosphate pesticide exposures to the US population, including adults, pregnant women, children and fetuses [1–9]. In some cases, these exposures may exceed health-based reference levels [10–11]. Although many uses, including residential applications, of chlorpyrifos (CPS) and diazinon (DZ) were recently restricted by agreements with registrants [12,13], agricultural uses are still widespread. Organophosphate exposures at high doses have profound effects, primarily on the central nervous system [14], and there is growing evidence in animals and humans to suggest that chronic low level exposure may affect neurodevelopment [5,15–17].

The young of many species are more susceptible to organophosphate toxicity than adults [18–22]. For example, the maximum tolerated dose (MTD) of CPS in 7-day-old (PND7) rats is approximately 7.7% of the MTD in adult animals [22]. One factor contributing to the increased sensitivity in newborns is that levels of paraoxon 1/arylesterase (PON1), a key organophosphate detoxifying enzyme, are three- to four-fold lower than in adults [23–27]. Even among adults, the levels of PON1 can vary by at least 13-fold [28].

Human PON1 enzyme, a high-density lipoprotein-(HDL) associated esterase, is encoded as a 355 amino acid protein by the PON1 gene on chromosome 7q21.3–22.1 [29] with only its initiator methionine residue removed before incorporation into HDL particles [30,31]. In humans, a Q192R polymorphism affects the catalytic efficiency of hydrolysis of some organophosphate substrates [28,32,33], including chlorpyrifos oxon (CPO), the toxic metabolite of CPS [34]. The characterization of all 28 TagSNPs accounts for only 28% of the variance in PON1 levels (G.P. Jarvik, personal communication), much of which is attributable to a C-108T polymorphism in an Sp1 binding site in the 5' regulatory region [35–37].

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Simple biochemical principles dictate that rates of detoxification of substrates are dependent on enzyme levels. Thus, when considering the effects of genetic variability on sensitivity to CPS/CPO exposures, both the quantity (level) of PON1 as well as the quality (Q192 versus R192) of PON1 must be considered. In other cases where the catalytic efficiency of hydrolysis of the two PON1192 alloforms is equivalent [e.g. for diazoxon (DZO) hydrolysis], it is the level of PON1 that is important [34].

Li et al. [38] introduced the term PON1 status to include both PON1 level and functional PON1192 genotype (Q/Q; Q/R; R/R) [38]. In this method, PON1 status is determined with a simple, high-throughput two-substrate assay and analysis where rates of DZO hydrolysis are plotted against rates of PO hydrolysis using serum or non-EDTA preserved plasma samples. This method, validated in adults, provides a functional determination of the PON1192 alloform(s) present in plasma, as well as the level of an individual’s plasma PON1 [39–41], both important in modulating exposures to organophosphorus compounds as well as other risks associated with PON1 status. The lower PON1 levels associated with PON1M55 [42] are primarily attributable to linkage disequilibrium with the inefficient promoter polymorphism T-108 [35].

The development of animal model systems has provided important insights into the role of PON1 in detoxifying specific organophosphorus compounds. Injection of purified rabbit PON1 into rats increased resistance to paraaxon (PO) exposure [43,44] and, more significantly, to CPO exposure [44] because rabbit PON1 hydrolyses CPO very rapidly [45]. These observations were confirmed and extended using mice, which required much less purified PON1 for injections and were more amenable to genetic manipulation [34,38,46]. Injected PON1 protected against CPS/CPO exposures when injected 30 min or 24 h before exposure or up to 3 h post exposure [47]. These experiments provided convincing evidence that high levels of PON1 protected against CPS/CPO exposures. The increase in resistance was most dramatic against CPO exposures [34].

The generation of PON1 knockout mice by Shih et al. [46] provided a model with which to examine the consequence of the absence of plasma PON1 on resistance to organophosphate exposures. The PON1 null mice were found to have dramatically increased sensitivity to CPO [46] and DZO exposure [34], and less noticeably increased sensitivity to the respective parent compounds CPS [46,47] and DZ [34]. It was surprising to find that the PON1 null mice did not have increased sensitivity to PO exposure [34].

Injection of purified human PON1Q192 or PON1R192 reconstituted PON1 activity in the serum of the PON1 null mice allowed for the testing of the efficiency of each human PON1192 alloform in protecting against exposure under physiological conditions without exposing human subjects to these toxic organophosphates [34]. Examination of the catalytic efficiencies of hydrolysis of CPO, DZO and PO showed that it was the catalytic efficiency that determined whether PON1 would protect against exposures. Either hPON1192 alloform protected equally well against DZO exposure, in agreement with the equivalent catalytic efficiency of each alloform for DZO hydrolysis. However, the hPON1R192 alloform provided significantly better protection against CPO exposure, in agreement with the higher catalytic efficiency of PON1R192 for CPO hydrolysis [34]. These observations on CPO exposures have been confirmed in transgenic mice expressing one or the other PON1192 alloform at equivalent levels [48]. The finding that PON1Q192 does not protect as well as PON1R192 against CPO/CPS exposures is important because up to 50% of the general population is homozygous for PON1Q192 [49]. The catalytic efficiency for PO hydrolysis was too low to provide protection against PO exposures [34].

In the present study, we determined the PON1 status of 130 pregnant Latina women and their newborns living in an agricultural community in California [7], a region where approximately 22,727 kg of organophosphates are used annually [50]. We have previously reported that maternal urinary dialkyl phosphate metabolite levels are higher in this population relative to national reference data [8] and were associated with a shorter gestational age [51] and an increased frequency of abnormal reflexes in neonates [16]. The main aims of this study were to assess PON1 status in newborns and mothers and to predict their relative sensitivity to specific organophosphorus insecticides based on recent studies with ‘PON1 humanized transgenic mice’ expressing either human PON1R192 (hPON1192) or PON1Q192 (hPON1Q192) at equivalent levels [48].

**Methods**

**Subjects and recruitment**

A subset of 130 maternal-newborn pairs were randomly selected from the CHAMACOS cohort (Center for the Health Assessment of Mothers and Children of Salinas), a longitudinal birth cohort study (n = 601 enrollees, 528 live births) of the effects of environmental exposures on the health of children living in the Salinas Valley [7]. Women were eligible for enrollment in the CHAMACOS study if they were 18 years or older, less than 20 weeks gestation at enrollment, English- or Spanish-speaking, Medi-Cal eligible, and planning to deliver at the Natividad Medical Center. All women were Latina by ethnicity, including 87% born in Mexico, and the remainder in the USA. Approximately 28% of the women had worked in the fields during the pregnancy and...
another 14% had other jobs in agriculture, including packing shed, nursery and greenhouse work. Overall, 82% of subjects had agricultural workers living in their homes during pregnancy. Additional information about exposure and associations with health outcomes is reported elsewhere [7,8,16,51]. All study protocols were approved by both the University of California, Berkeley and the University of Washington human-subject review processes. Informed consent was obtained for all subjects.

Biological sample collection and processing
Blood was collected from mothers at the time of their glucose tolerance test (26 ± 2.3 weeks’ gestation) and in the hospital immediately before or after delivery. Umbilical cord blood was collected by delivery room staff once the baby was safely delivered. Heparinized whole blood was centrifuged, and divided into plasma, buffy coats and red blood cells, and stored at −80°C. Processed plasma samples were stored at −80°C before being shipped on dry ice to the University of Washington, Seattle, where they were also stored at −80°C until analysis of enzyme activity. We first compared PON1 activities in blood collected at one time point only (26 weeks' gestation). PON1 activities were highly correlated between the two time points for all three gestation and delivery). PON1 activities were measured in 25 mothers at two time points (26 weeks' gestation).

Therefore, in subsequent samples, we measured PON1 activities in blood collected at one time point only (26 weeks' gestation).

Determination of PON1 status
PON1 status (functional PON1192 genotype and plasma level) was determined by the method developed and validated on adult populations by Richter and Furlong [39]. This method provides an accurate determination of functional PON1192 genotype through the use of a two-substrate enzyme kinetic analysis. PON1 enzyme activities in plasma of mothers and children were measured with three different substrates, including paraoxon (POase), diazoxon (DZOase) and phenylacetate (AREase), according to published protocols [39–41,52]. Because phenylacetate hydrolysis is not affected by the Q192R polymorphism and has been shown to correspond with PON1192 functional genotype, both for mothers and newborns; (ii) both groups of homozygotes fall closely to the trend line; and (iii) the heterozygote values vary considerably from the trend line (trend line not shown), consistent with the concept of independent cis regulation of each PON1 allele (Fig. 1).

Results
PON1 status
Figure 1 shows the PON1 status for mothers and newborns (cord blood) as determined by the plot of rates of hydrolysis of DZO versus PO. This plot clearly resolves the three functional PON1192 phenotypes (verified by PCR analysis) for the mothers. However, a number of data points for newborns with lower activity values (22 out of 130 or approximately 17%) were not resolved by this analysis and could only be accurately assigned by genotyping the Q192R polymorphism. However, the PON1 status plot provided relative PON1 levels for each of the 22 subjects. This analysis also shows the effects of independent allelic expression in the heterozygotes (including the newborns) with some individuals expressing more of one PON1192 alloform than the other. Genotyping alone does not provide this information. Several points are worth noting from this analysis: (i) there is a large variability of PON1 activity values within each PON1192 genotype, both for mothers and newborns; (ii) both groups of homozygotes fall closely to the trend line; and (iii) the heterozygote values vary considerably from the trend line (trend line not shown), consistent with the concept of independent cis regulation of each PON1 allele (Fig. 1).

Range of plasma PON1 levels
Figure 2 shows PON1 levels across genotypes for mothers and newborns estimated by the AREase activity. Figure 3 shows the effects of the PON1192 polymorphism on rates of paraoxon hydrolysis across genotypes for mothers and newborns, and provides an excellent example of why substrates whose rates of hydrolysis are affected by the PON1192 polymorphism should not be used to compare levels across position 192 genotypes. Rates of paraoxon hydrolysis are significantly lower for Q/Q homozygotes and heterozygotes than for R/R homozygotes. The AREase activity in mothers ranged from a low of 19.8 U/ml to a high of 281.4 U/ml (14-fold) and, in newborns, from 4.3–110.7 U/ml (26-fold) (Fig. 2). The range of AREase activity (PON1 levels) from the lowest newborn to the highest mother was 4.3–281.4 U/ml (14-fold) and, in newborns, provided an excellent example of why substrates whose rates of hydrolysis are affected by the PON1192 polymorphism should not be used to compare levels across position 192 genotypes.

The accuracy of the PON1192 functional genotype determination has been verified by polymerase chain reaction (PCR) analysis of more than 2000 adult samples and has been shown to identify individuals with mutations in the PON1 gene [41]. Although this plot suggests that PON1192 homozygotes have lower rates of DZO hydrolysis than heterozygotes and PON1Q192 homozygotes, this is not the case, as the position 192 alloforms have equivalent catalytic efficiencies for DZO hydrolysis [34]. However, the PON1192 alloform is more sensitive to inhibition by the high salt concentration intentionally used in this assay to resolve the three PON1192 phenotypes. The distributions and descriptive statistics of PON1 status and enzyme levels in mothers and their newborns were analysed by STATA 8.0 [54].
U/ml, Q/R = 144 U/ml and R/R = 152 U/ml). The mean PON1 levels were also similar across genotypes in newborns (Q/Q = 31 U/ml, Q/R = 36 U/ml and R/R = 43 U/ml), with the newborn PON1R192 homozygotes having somewhat higher average AREase activity than the PON1Q192 homozygotes and the newborn heterozygotes expressing intermediate levels. However, these AREase activity differences between genotype groups were not statistically significant (P = 0.13). Although newborns had on average four-fold less plasma PON1 than mothers, individual levels in mother-child pairs were modestly correlated (r = 0.47, P = 0.013) (Fig. 4).

**Estimation of the range of sensitivity to organophosphate exposure**

Because both PON192 alloforms hydrolyse DZO with the same catalytic efficiency [34], these data predict a range of sensitivity to DZO exposure of 26-fold in newborns and 14-fold in mothers, with a range of 65-fold from the most sensitive newborn to the most resistant mother. An average four-fold difference in sensitivity to DZO exposure is predicted between mothers and newborns.
Estimation of the range of sensitivity to CPO exposure is more complex, due to the different catalytic efficiencies of the two PON1Q192 alloforms for CPO hydrolysis. However, reasonable estimates of relative sensitivity can be made by taking advantage of data generated in the mouse model system, where the mouse PON1 gene was replaced with either human hPON1Q192 or human hPON1R192 and colonies were established that expressed these alloforms at the same levels in plasma. Transgenic mice expressing hPON1Q192 were found to be 2- to 2.5-fold as sensitive to CPO exposure compared to mice expressing hPON1R192 [48], due to the higher catalytic efficiency of human PON1R192 for hydrolysis of CPO [30]. This two- to 2.5-fold difference in sensitivity, taken together with the 65-fold difference in plasma AREase levels yield an estimated 131–164-fold range in CPO sensitivity between the PON1Q/Q192 homozygous newborn with the lowest PON1 level and the PON1R/R192 homozygous mother with the highest PON1 level.

**Discussion**

To our knowledge, this is the first study where PON1 status [39,41,52] was determined for a large cohort of mothers and their newborns using the two-substrate assay. By plotting rates of DZO hydrolysis against rates of PO hydrolysis, the three Q192R phenotypes were clearly separated in the mothers and provided the relative PON1 levels for each individual in this population. However, we found that for 17% of the newborns, with low PON1 levels, PCR analysis was required to assign position 192 genotypes, although the PON1 status analysis did provide their cord blood PON1 levels. Although some of the earlier studies examined only PON1 status with the two substrate diazoxon/paraoxon assay/analysis, this study included a measurement of rates of phenylacetate hydrolysis (AREase), allowing comparison of PON1 levels across PON1Q192 genotypes. Another study examining the relationship of PON1 levels, exposure and head circumference in a large cohort of 404 births also made use of AREase activity to determine PON1 levels [55], representing a major improvement over the many studies that examined PON1 genotypes alone [49]. They noted a relationship between low PON1 levels, exposure and smaller head circumference.

The AREase values provided an estimate of the relative sensitivity to organophosphorus compounds whose in-vivo catalytic efficiencies of hydrolysis are not affected by the PON1Q192 polymorphism (e.g. DZO). The range of AREase values in the mothers was very similar to the range observed in another study of Hispanic farm workers in Washington State where a 13-fold variability was observed [28]. The large range of AREase values observed in this study in the newborns (26-fold) predicts a broad variability in sensitivity to organophosphate exposure even among newborns. Surprisingly, some of the newborns had higher PON1 levels than some of the adults. Thus, the individuals predicted to be highly sensitive to organophosphate exposure include most of the newborns as well as some of the mothers. The studies reported here confirm earlier observations of lower PON1 activities in neonates compared to adults [23–27,56] and are also consistent with a recent report where neonates had 2.6–4.6-fold lower PON1 levels, as assessed by the AREase assay, compared to mothers, in three ethnic groups in New York City [23].

Among the many activities of the multifunctional HDL-associated enzyme PON1, hydrolysis of DZO and CPO is important in providing protection against exposure to DZ/DZO and CPS/CPO. Organophosphate exposures are appropriately considered as mixed exposures to the parent compounds and their oxon forms because most, if not all, exposures include oxon residues [57,58]. Because the rate of cholinesterase inactivation by CPO is at least three orders of magnitude higher than that of its parent compound (CPS) [59], a very small percentage of oxon form in an exposure is significant.

To date, most of the animal model studies with genetically modified mice have examined CPO/CPS exposures [34,38,46–48,60], although some recent studies were carried out on DZ/DZO exposures in PON1 null mice and PON1 null mice injected with each of the purified human PON1Q192 alloforms [34]. The results obtained in these earlier studies have provided important insights and predictions with respect to individual variability in sensitivity to CPO/CPS and DZ/DZO exposures. Li et al. [34] examined the relative in-vivo catalytic efficiencies of hPON1Q192 and hPON1R192 in PON1 null mice reconstituted with purified human PON1R192 or PON1Q192. They found that under in-vivo physiological conditions, injection of either PON1R192 alloform provided equivalent protection against DZO exposure, whereas injected human PON1R192 provided significantly better protection against CPO exposure than did PON1Q192.

A more recent study by Cole et al. [48], using transgenic strains of mice that expressed either PON1Q192 or PON1R192 at nearly identical levels, verified the results of Li et al. [34] from the enzyme injection studies in the PON1 null mice. The mice expressing PON1R192 were approximately two- to 2.5-fold more resistant to CPO exposure than were the PON1 null mice. Mice expressing PON1Q192 were nearly as sensitive as the PON1 null mice to CPO exposures. The IC50 value (exposure level for 50% inhibition) for CPO inhibition in the hPON1Q192 transgenic mice was approximately 1.1 mg/kg dermal exposure versus approximately 2.2 mg/kg in the hPON1R192 mice. The levels of PON1 in the ‘hPON1 humanized’ transgenic mice are relevant to the studies reported here. The transgenic mice expressed levels of
hPON1 of 30–45 U/ml AREase (corrected for baseline AREase activity in PON1 null mice) [48], which are comparable to the average levels of PON1 in the Latino newborns described in the present study.

Cole et al. [24] examined the time course of appearance of PON1 in the plasma of individual children and also in mice expressing the two human PON1192 alloforms under control of the human 5' and 3' regulatory sequences. In children, PON1 reached plateau levels at 6–24 months of age whereas expression of human hPON1 in mice under control of the human PON1 5' regulatory region followed the mouse time course of PON1 appearance, peaking at PND21. Moser et al. [62] observed that, although AREase activity in rats peaked at 3–4 weeks of age as observed by Li et al. [61], resistance to CPS exposure continued to increase up to at least 90 days, corresponding to a continued increase in plasma carboxylesterase activity. Although there is very little carboxylesterase activity in human serum, individual variation in carboxylesterase levels in human liver microsomes has been reported [63].

Levels of PON1 activities reported in other studies provide insights into the range of sensitivities expected. The hydrolytic activities in plasma of the wild-type C57Bl/6j mice used in our earlier studies were approximately 1800 U/l for chlorpyrifos oxonase (CPOase) and approximately 3500 U/l for diazoxonase (DZOase) [60]. These activities are in the low range relative to those reported for human populations. The ranges of reported activities in another adult Hispanic population were 2145–13 540 U/l for CPOase and 2174–23 316 U/l for DZOase [28]. It is worth noting that PON1 null mice are approximately ten-fold more sensitive to DZO [34] and CPO [46] exposure than wild-type mice. Based on what is known about the catalytic efficiencies of organophosphate hydrolysis and the large variability of PON1 levels observed in this and other populations, mothers and newborns homozygous for PON1192 with very low plasma levels of this alloform are predicted to be a subpopulation uniquely vulnerable to adverse effects from DZ/DZO exposures and especially CPS/CPO [46]. Exposure to CPS/CPO is a particular concern would be exposure of a mother with very low PON1 status carrying a fetus that had not yet developed the capacity for self-protection against organophosphate exposure. PON1192 homozygous mothers with very low PON1 status are also predicted to be unable to pass on to their offspring a PON1 allele that would be protective against exposure. The father of course would contribute one PON1 allele to the child; however, it would need to be a high expressing allele and would take from 6 months to 2 years following birth to be fully protective.

Although the usual precautions need to be observed in extrapolating data generated in an animal model system to predict outcomes in human exposures, genetically manipulating a single gene in an inbred strain of mice is nonetheless informative. PON1 appears to be the only major enzyme in the plasma of both mice and humans that hydrolyzes chlorpyrifos oxon and diazoxon, as can be seen from the colinearity of the plots of rates of hydrolysis of one substrate against others in human populations [28] and from the dramatic consequences of deleting this gene in mice [34,46]. Replacing the mouse PON1 gene with each of the human PON1192 alleles provides a better means of extrapolating between the two species, even though other pathways may contribute somewhat to the detoxication. Even among humans, there is variability in levels and efficiencies of other contributory detoxication enzymes, such as carboxylesterases and cytochromes P450.

Several factors are likely to contribute to the risk of adverse health effects due to exposures to CPS/CPO and DZ/DZO: (i) the level of exposure; (ii) the percentage of oxon residue or other toxic derivatives in the exposure; (iii) the level of enzyme (measured by AREase assay); (iv) the catalytic efficiency of an individual’s PON1 to detoxify organophosphate metabolites (determined by the Q192R polymorphism); and (v) the as yet uncharacterized genetic variability of the cytochromes P450, carboxylesterases and other enzymes that participate significantly in the detoxication of these organophosphorus compounds.

Additional research is needed to determine the relative contributions of PON1, cis- and trans-acting factors that modulate PON1 levels, cytochromes P450 and other enzymes, as well as the genetic and environmental factors that modulate the levels of enzymes involved in detoxication of parent compounds and their respective oxons. A recently reported method of haplotyping using emulsion PCR should be useful in understanding cis factors involved in regulation of protein levels [64]. Research is also needed to determine the exposure levels of specific residues (trichlorophenol, CPS, CPO, diethylphosphate and other toxic metabolites) required for modelling [48,65] the effect of PON1 status on the consequences of exposures.

Evaluation of PON1 status is not only important for determining risk of organophosphate exposure, but also for understanding the role of PON1 in modulating other risks associated with the variability of normal physiological functions of PON1, as well as the role of PON1 in the metabolism of other xenobiotics, including drugs [66]. Multiple results indicating a prominent role for PON1 status in risk for vascular disease have been published previously [40,46,67,68]. More recently, PON1 has been shown to inactivate the quorum sensing signal secreted by Pseudomonads [66,69]; however, data demonstrating the
in-vivo importance of this activity have not yet been reported.

In summary, the range of variability of PON1 status observed in this study, taken together with data from ‘humanized mice’ expressing hPON1Q192 or hPON1R192 in place of mouse PON1, predict a 65-fold variability in CPO exposure in this population, with an average four- to ten-fold variability in sensitivity to CPO between groups of mothers and their newborns. These data predict that most, if not all, newborns, as well as a subpopulation of adults, will exhibit significantly increased sensitivity to organophosphate exposure. These findings highlight the significance of understanding the susceptibility of young children to organophosphate exposure and developing science-based risk standards for pesticide regulation as required by the 1996 Food Protection Act.

Acknowledgements

We gratefully acknowledge CHAMACOS staff, students and community partners, and especially the CHAMACOS participants and their families, without whom this study would not have been possible. We thank Katie Kogut and Erin Weltzien for their help with statistical analyses and Dr Toby Cole for helpful comments and suggestions.

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