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Women with high plasma levels of PBDE-47 are at increased risk of preterm birth

https://doi.org/10.1515/jpm-2020-0349
Received July 23, 2020; accepted December 10, 2020; published online January 4, 2021

Abstract

Objectives: Nearly 100% of North American women have detectable levels of flame retardants such as polybrominated diphenyl ethers (PBDEs) in their plasma. These molecules have structural homology to thyroid hormones and may function as endocrine disruptors. Thyroid dysfunction has previously been associated with increased risk for preterm birth. Therefore, we conducted a multicenter, case-cohort study to evaluate if high plasma concentrations of a common PBDE congener in the first trimester increases the risk of preterm birth and its subtypes.

Methods: Pregnant women were recruited at the onset of initiation of prenatal care at Kaiser-Permanente Southern California (KPSC)-West Los Angeles and KPSC-San Diego medical centers. Plasma samples from women whose pregnancies ended preterm and random subset of those delivering at term were assayed for PBDE-47 and thyroid-stimulating hormone (TSH) by immunoassay. Quartile cutoffs were calculated for the patients at term and used to determine if women with exposures in the 4th quartile are at increased risk for preterm birth using logistic regression.

Results: We found that high concentrations of PBDE-47 in the first trimester significantly increased the odds of both indicated (adjusted odds ratio, adjOR=2.35, 95% confidence interval [CI]: 1.31, 4.21) and spontaneous (adjOR=1.76, 95% CI: 1.02, 3.03) preterm birth. Regardless of pregnancy outcome, TSH concentrations did not differ between women with high and low concentrations of PBDE-47.

Conclusions: These results suggest that high plasma concentrations of PBDE-47 in the first trimester, increases the risk of indicated and spontaneous preterm birth.

Keywords: endocrine disruptor; environmental toxins; flame retardant; polybrominated diphenyl ether; preterm birth.

Introduction

Preterm birth is a leading cause of perinatal morbidity and mortality in the United States and much of the world. It affects about 15 million (~11%) of pregnancies worldwide and greatly increases the risk of neonatal mortality [1]. Although there is an inverse correlation between gestational length and probability of survival, babies born at later gestational ages are still at significant risk for neonatal morbidities that include: sepsis, hypoglycemia, necrotizing enterocolitis, and respiratory distress syndrome [1]. Infants born preterm are also at greater risk for long-term neurological disorders that include: cerebral palsy [2], autism spectrum disorders [3–7], intellectual disability/mental retardation [2, 4], schizophrenia [8, 9], and learning problems that can extend into adulthood [10]. The cost to society in terms of lost productivity and increased medical and education costs is approximately $26.2 Billion/year [1].

No single causal factor has been identified for preterm birth and it is considered to be a multifactorial condition that can result from genetic (e.g. race-ethnicity [11], obstetric and family history [12, 13], small stature), obstetric (preeclampsia [14], preterm premature rupture of membranes, multiple gestation, teenage pregnancy [14, 15]), and environmental factors such as maternal infection [14, 16] and high ambient temperature [17, 18].

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In recent years there has been increasing concern that exposure to pollution may also increase the risk of preterm birth [19]. Women who live near roadways [20] or in areas of high Nitrogen Dioxides (NO_x), Carbon monoxide (CO) and Particulate Matter 2.5 μm ($PM_{2.5}$; markers of air pollution) have significantly higher preterm birth rates [21, 22]. Chemical pollutants may also increase the risk of preterm birth by increasing inflammation, oxidative stress or by functioning as endocrine disruptors [23]. Persistent organic pollutants (POPs) are of special concern because they are resistant to biodegradation, can be found at sites far away from their source, and can bioaccumulate in tissues of people and animals in the food chain. Among the most prevalent of the POPs are the polybrominated diphenyl ethers (PBDEs) that have been used widely in the United States and Canada as flame retardants. Over time, PBDEs leach out of the products that they were applied to and contaminate dust that, in turn, enters the food chain. They are detectible in nearly 100% of U.S. women and at concentrations of 10 to 100-fold higher than in women in Sweden where their use has been banned [24]. Even with efforts to limit their use in the United States, they are still likely to be a problem for years to come due to their use in infrequently replaced items (e.g. furniture and carpeting) and their continued contamination of the landfills.

During the past decade, a number of studies have demonstrated that exposure to PBDEs may increase the risk of adverse pregnancy outcomes [25]. PBDEs have been detected in cord blood [26], fetal membranes [27], amniotic fluid [28] and the placenta [29, 30]. Given that PBDEs have structural similarity to thyroid hormones and can interfere with thyroid hormone receptor signaling [31], much of the research to date has focused on neurodevelopment of the fetus (reviewed in [32]). *In utero* exposure to PBDEs has been correlated with increased disruptive behavior [32], lower IQ [33, 34], and reading difficulties [35, 36] in the offspring.

PBDEs have also been correlated with lower birth weight and reduced fetal growth [25, 37, 38] but their effects on preterm birth are less clear. *In vitro* studies have demonstrated that they increase the production of proinflammatory cytokines associated with preterm birth [39–41]. One study that used archived samples that were collected from women in Tennessee reported that high PBDE-47 concentrations in the maternal plasma at the time of labor significantly increased the odds of delivering preterm birth [42]. However, the findings of this study are limited in that only African-American and Caucasian women were sampled and all blood samples were collected at time of admittance to labor and delivery [42]. How high exposures to PBDE-47 earlier in pregnancy may affect pregnancy outcomes in a more racially and ethnically diverse population is unclear. Although previous studies have demonstrated that hypothyroidism increases the risk of preterm birth [43, 44], it is unclear if PBDEs cause preterm birth by disrupting the biological activities of the thyroid hormones. Therefore, we collected plasma samples from a population of women in California (where PBDEs exposures are known to be especially high) [45] during the first trimester of pregnancy to determine if high maternal plasma concentrations of PBDE-47 correlate with increased risk of preterm birth and changes in plasma thyroid stimulating hormone (TSH) levels.

Materials and methods

Patients

This study was performed with approval and oversight from the Kaiser-Permanente Southern California (KPSC) Institutional Review Board. Data for this study came from Flame Retardants and Adverse Pregnancy Outcomes (FRAPO), a study funded by a grant from the National Institutes of Health (NIH) and National Institute of Environmental Health Sciences (NIEHS). Inclusion criteria for the FRAPO study included: being member patient at the time or before the index pregnancy and initiating prenatal care at Kaiser Permanente San Diego (KP-SD) or KP West Los Angeles (KP-WLA) medical centers. Exclusion criteria included: (1) multiple gestation, (2) plans to relocate outside KPSC center areas before their due date, (3) employer-employee or family relationship with the research staff, (4) currently incarcerated, (5) inability to provide informed consent due to mental impairment or any other reason, and (6) inability to understand and communicate in English or Spanish.

Pregnant women who were prescreened against the inclusion and exclusion criteria were approached by the study coordinator when they initiated prenatal care in the first trimester of pregnancy and told about the study. If agreeable, they were offered an opportunity to participate and asked to provide written informed consent. At the first trimester visit, pregnant women completed a questionnaire to assess behavioral, nutritional and residential history, and provided a blood sample (88 percent [n=3529] of recruited women provided blood). Maternal sociodemographic, medical and obstetrical data were abstracted from study questionnaires and the electronic health records (EHR). Gestational age was largely based on first and early second-trimester ultrasound examination. Additional questionnaires and blood samples were collected at each trimester during the prenatal visits, and plasma was harvested by centrifugation at each study site, aliquoted and transported on dry ice to on-site research biospecimen storage center in sterile tubes where samples were stored at −80 °C until analysis. Outcome was ascertained from the EHRs. Plasma samples from all cases of preterm birth and a random set of term births (selected using the sampling function of the statistical software) were then shipped to New York University-Long Island School of Medicine in New York for the immunoassays to be performed.

Immunoassays

Although there are 209 different PBDE congeners, PBDE-47 is the most frequently detected congener in food [46], dust [46], plasma [47, 48] and breast-milk samples [24]. Quantification of PBDEs in patient

samples using chemical techniques requires extraction of large volumes of plasma followed by analysis with gas chromatography mass-spectroscopy (GC-MS/MS). Previous studies have found that quantification of PBDE-47 using immunoassay techniques correlate well with GC-MS/MS and have the advantage of using smaller samples volumes [49–51]. Therefore, we quantified PBDE-47 using immunoassay reagents purchased from Abraxis Biotech (Westminster, PA) that have previously used to quantify PBDEs in patient plasma [42]. Samples that fell below (n=5) or above (n=11) the quantification range were set to 8 pg/mL and 50 ng/mL (the lower and upper limits of the assay), respectively. Plasma TSH concentrations were ascertained using immunoassay kits purchased from Abcam (Cambridge, MA).

Statistical analyses

Maternal demographic data between pregnancies ending with term and preterm births were compared using Chi-Square statistics for categorical variables and t-tests for numerical variables. We used the quantile function of R to estimate the empirical distribution to document the range of exposures to PBDEs in our patient population and to estimate the 4th quartile cutoff for PBDE-47 in the term-born infants. Patients whose PBDE-47 concentration exceeded this value for both groups were considered to have high concentrations of PBDE. Odds of preterm birth were then estimated using logistic regression using the GLM procedure of R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Analysis of the deviance of the fit models indicated that no scale parameters were needed. To compare the effects of 4th quartile PBDE levels on risk of indicated and spontaneous preterm birth, models were fit using multinomial models. Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI) before and after adjustment (adjOR) for study site, maternal age, race-ethnicity and smoking during pregnancy. Maternal pre-pregnancy body mass index (BMI, kg/m^2) was not included as a covariate because previous studies have demonstrated that higher levels of PBDEs correlate with increased BMI in women [52–54], possibly by interfering with thyroid hormones. Laboratory studies have also confirmed that PBDEs promote adipocyte differentiation and lipid accumulation *in vitro* [55, 56] suggesting that they may function as environmental obesogens. Higher BMI is a well-established risk factor for both spontaneous [57, 58] and indicated preterm birth [58]. Therefore, it is biologically plausible that any observed effects of PBDEs on preterm birth are mediated through their promotion of higher BMI. Addition of variables that are in the causal pathway that may attenuate or even obscure the true association between exposure and outcome [59, 60] is not warranted.

Results

Patient characteristics

Women in the preterm group tended to be slightly older and have higher BMIs (25.7 ± 5.7 vs. 27.6 ± 6.0; term vs. preterm birth; mean ± standard deviation) and higher rates of preeclampsia than controls (Table 1). There were similar rates of preterm birth for each of the study centers. African-American and Hispanic women were more frequent amongst the subjects whose pregnancies ended in preterm birth (Table 1). Women with indicated preterm births were older than those with spontaneous preterm birth (33.0 ± 6.4 vs. 30.6 ± 5.4 years; mean ± standard deviation, respectively; p=0.009), had greater rates of preeclampsia (25/83, 35% vs. 6/101, 6%; p<0.001) and SGA/IURG (17/83, 20% vs. 10/101, 10%; p=0.070). However, no differences between women whose pregnancies ended in indicated vs. spontaneous preterm births were detected with regard to study site, race-ethnicity, infant sex, parity, BMI, gestational diabetes, smoking during pregnancy or placental abruption.

Effect of high PBDE concentrations on risk for preterm birth

Nearly all samples (363/368, 98.6%) had detectable levels of PBDE-47 in the first trimester plasma samples. Empirical distributions for PBDE-47 levels are shown in Figure 1 and suggest that PBDE concentrations tended to be higher at group-specific quantiles above the 60th percentile. Using the 75th percentile (≥4.425 ng/mL) for the control group as the 4th quartile cut off, we found that patients with levels above the 4th quartile were at significantly increased risk for preterm birth (Table 2) of both indicated and spontaneous subtypes. Results were largely unaffected by confounders (Table 2). No effect of 4th quartile levels was detected on rates of common causes of indicated preterm birth (preeclampsia, placental abruption, or SGA-IUGR) or gestational diabetes. Additional analyses with centered and scaled data suggested that gestation length (in weeks) was inversely correlated with PBDE concentrations (β=−0.57, 95% CI: −91, −0.23)

Effects of PBDE levels on TSH concentrations

Women whose pregnancies ended in spontaneous (p=0.016), but not indicated (p=0.420), preterm birth had significantly lower TSH concentrations than women whose pregnancies ended at term. Having 4th quartile PBDE concentrations did not affect TSH concentrations in women whose pregnancies ended at term (p=0.245), indicated preterm (p=0.936). or spontaneous preterm (p=0.251) birth (Table 3).

Discussion

In this large, racially and ethnically diverse cohort of pregnant women, we determined that high levels of PBDEs

Table 1: Patient characteristics.

Parameter	Term birth (n=184)	Preterm birth (n=184)	p-Value
Maternal age, years	30.9 ± 5.20	31.7 ± 5.96	0.142[a]
Study site			
KP-San Diego Medical Center	78	70	0.457[b]
KP-West Los Angeles Medical Center	106	114	
Race-ethnicity			0.055[c]
Non-Hispanic White	62	44	
Non-Hispanic Black	24	39	
Hispanic	65	77	
Asian/Pacific Islander	26	18	
Multiple/Other	7	6	
Sex of infant			
Male	98	85	0.210[b]
Female	86	99	
Prepregnancy body mass index			0.007[c]
Underweight	3	2	
Normal	99	64	
Overweight	44	62	
Obese	24	30	
Very obese	8	18	
Morbidly obese	6	5	
Parity			0.090[b]
0	101	95	
1	56	46	
2+	27	43	
Median family household income			
<$30,000	18	20	0.185[b]
$30,000–$49,999	49	69	
$50,000–$69,999	53	39	
$70,000–$89,999	40	34	
$90,000+	24	22	
Smoking during pregnancy	5	10	0.292[b]
Self-reported drug use	1	1	1.000[c]
Gestational age at delivery	39.0 ± 1.15	34.1 ± 2.97	<0.001[a]
Preeclampsia/ eclampsia	5	35	<0.001[b]
Placental abruption	1	5	0.215[c]
SGA/IUGR	20	27	0.349[b]
Gestational diabetes	23	30	0.373[b]
PBDE quartile			
Q1–Q3	138	111	0.004[b]
Q4	46	73	

KP, Kaiser Permanente; PBDE, polybrominated diphenyl ethers; Q1–Q4, quartile 1–4; SGA/IUGR, Small for gestational age/intrauterine growth restriction. [a]t-test. [b]χ^2-test, chi-squared test. [c]Fisher's exact test.

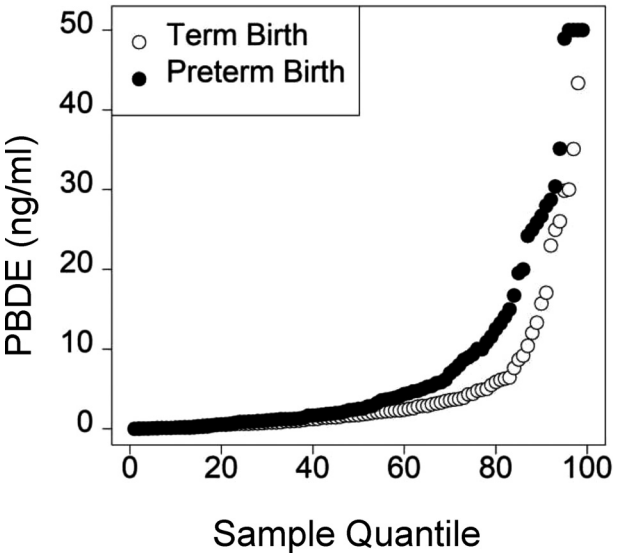

Figure 1: Cumulative empirical distribution of maternal PBDE-47 levels for women having term (n=184) or preterm birth (n=184). Shown are PBDE levels for each patient, ranked into their pregnancy outcome specific quantile (shown on the x-axis).

in the first trimester may increase the risk of both indicated as well as spontaneous preterm birth. Although the etiology of these preterm births subtypes differs substantially, both are associated with placental inflammation and oxidative stress that can be enhanced by PBDEs. Previous studies have demonstrated that PBDEs enhance placental cyclooxygenase-2 (COX-2) and Prostaglandin E_2 (PGE_2) production [41], bacteria-stimulated production of proinflammatory cytokines [41] and oxidative stress [39]-resulting in damage to placental cells [40] and senescence of amniotic epithelial cells [61]. All of these biochemical effects of PBDEs could increase the risk for preterm birth and other adverse pregnancy outcomes. Our findings are consistent with a previous study with a different patient population that used samples collected at time of admission for term or preterm labor [42]; however, the association we found was of much lower magnitude (adjOR=2 vs. adjOR >10). This may be due to several reasons. First, we used prospectively collected samples from a population of women known to have high exposures to PBDEs. The previous study used archived samples from a project designed to explore the biological basis for race disparities in preterm birth [42]. Caucasian women whose pregnancies ended in preterm birth were greatly over-represented in the preterm birth group of that study [42]. Furthermore, all of the samples in the previous study were collected at time of labor and it is possible that the metabolic changes associated with labor that could result in liberation of PBDEs from adipose tissue [62]. Any of these factors could enhance the differences between cases and controls regarding PBDE levels. Our findings also are consistent with another study conducted in Guiyu, China where

Table 2: First Trimester PBDE concentrations in the fourth quartile increases the risk of indicated as well as spontaneous preterm births. Shown are number and % of patients in the fourth quartile, the crude and adjusted OR (95% CI) for preterm birth and its subtypes.

Outcome	$PBDEQ_{1-3}$ n	$PBDEQ_4$ n	%	Odds ratio (95% confidence intervals)	
				Crude	Adjusted
Term birth	138	46	25.0	1.00 (reference)	1.00 (reference)
Preterm birth	111	73	39.7	1.97 (1.27, 3.09)	1.97 (1.24, 3.14)
Indicated preterm birth	47	36	43.4	2.30 (1.33, 3.97)	2.28 (1.29, 4.05)
Spontaneous preterm birth	64	37	36.6	1.73 (1.03, 2.93)	1.75 (1.02, 2.99)

$PBDEQ_{1-3}$, polybrominated diphenyl ethers quartile 1–3; $PBDEQ_4$, polybrominated diphenyl ethers quartile 4

Table 3: Effect of high concentrations of PBDEs on TSH concentrations (pg/mL) in women whose pregnancies ended in term or preterm birth. Shown are least-squares means ± SEM for TSH concentrations for women with PBDEs in the Fourth Quartile ($PBDEQ_4$) compared with the lower three quartiles ($PBDEQ_{1-3}$). No differences were detected between TSH levels for any pregnancy outcome.

Outcome	$PBDEQ_{1-3}$	$PBDEQ_4$
Term birth	74.2 ± 4.9	62.5 ± 8.4
Preterm birth		
Indicated preterm birth	73.9 ± 8.6	82.6 ± 11.4
Spontaneous preterm birth	56.6 ± 7.6	70.3 ± 10.3

PBDE, polybrominated diphenyl ethers; TSH, thyroid stimulating hormone; SEM, standard error of the mean.

umbilical cord concentrations of PBDEs were correlated with adverse outcomes that included low birth weight, stillbirth and preterm birth [25]. A recent study in China reported that concentrations of PBDE-47, PBDE-100 and the sum of the tetra-brominated PBDEs (PBDE-47, –85, –99, and –100) in cord blood correlated with longer gestational length [63]. The reasons for the discrepancy with our study are unclear but it may have to do with higher levels of PBDE exposure and greater rates of preterm birth in our patient population.

Since higher levels of PBDEs were associated with preterm birth during the first trimester, when the fetus is unable to compensate for any deficiency in maternal thyroid hormones, we thought that PBDEs may potentially induce a hypothyroid-like condition that would increase the risk of preterm birth [64]. We found that women whose pregnancies ended in spontaneous preterm birth had lower concentrations of TSH than those that resulted in term or had indicated conditions leading to preterm birth. This is consistent with a previous report that hyperthyroidism as well as hypothyroidism increases the risk for preterm birth [65]. However, we found no correlation between PBDE and TSH levels in women of any of the preterm subtypes. This finding is similar to previous work that reported no correlation between maternal TSH levels and PBDE levels [66] but conflicts with others that found concentrations of PBDE did result in higher [45] or lower [67] maternal TSH levels. It is possible that PBDEs interfere with thyroid hormones through other, more indirect mechanisms or that they affect local levels of thyroid hormones. For example, PBDEs have been shown to interfere with placental thyroid sulfotransferase activity in a sex-specific manner [68]. This could affect local concentrations of thyroid hormones and their transport across the maternal-fetal interface. Recent studies have found that high concentrations of PBDEs correlate with reduced tissue levels of thyroxine [69] in the placenta. Examination of the expression of genes regulated by thyroid hormones in the fetal placental unit (e.g., Brain-derived growth factor, heme oxygenase-1, placental lactogen) may be needed to better ascertain how bioactivity of the thyroid hormones is impacted by PBDE levels. Disruption of local thyroid hormone concentrations in other maternal tissues could also increase the risk of preterm birth through indirect mechanisms. PBDEs have also been shown to promote the differentiation and growth of adipocytes *in vitro* [55, 56] and higher levels of PBDEs correlate with increased BMI and risk of being overweight/obese [52–54]. Although both spontaneous and indicated preterm birth subtypes differ in their etiology, both are associated with placental inflammation and higher BMI.

It is also possible that PBDEs enhance the risk of preterm birth by altering placental growth and physiology. Previous studies have found that PBDEs magnify the production of bacteria-stimulated proinflammatory cytokine [39, 41] and increase oxidative stress in the placenta [70]. Recent studies have also revealed that PBDE-47 inhibits migration and invasion of trophoblasts into the endometrium [71]. Insufficient placental invasiveness and transformation of the spiral arterioles has been previously correlated with preterm birth [72], preeclampsia and fetal growth restriction [73, 74]. Furthermore, umbilical concentrations of higher ordered PBDE congeners were inversely correlated with placental size suggesting effects of PBDEs on placental growth [75].

Strengths of our study include the use of prospectively collected samples from a large, ethnically diverse patient population that is known to have high exposures to PBDEs. Sampling from individual patients and ascertaining their outcomes avoids many of the ecological fallacy problems that are common in environmental epidemiology. Our findings are subject to a few limitations, however. First, we used commercially available immunoassays to quantify PBDE concentrations in our sample population. Although results with this method have previously been comparable to those obtained by GC-MS/MS [49–51], it is possible that the antibody used in the assay has cross reactivity with other environmental toxins. Under most circumstances this would tend to bias the results towards the null but if the cross-reacting substance was itself associated with preterm birth, it could bias results away from the null. Our findings are also limited in that we only examined PBDE-47, the most abundant congener but further studies with PBDE-153 and PBDE-209 may fill the knowledge gap as preterm birth is often a result of placental dysfunction and these two congeners form the bulk of the PBDEs accumulated by the placenta [76, 77] and amniotic fluid [28].

We are also limited by the fact that we are unable to account for other environmental factors such as abuse of recreational drugs and alcohol that could also increase the risk of preterm birth. Consistent with previous studies that reported no effect of smoking on PBDE levels [78], we found no differences in the proportion of smokers amongst pregnant women with 4th quartile PBDE exposures (data not shown). There were only two patients who self-reported illicit drug use in this cohort which may underestimate the level of drug use by the women in this study. While screening instruments can be used to some extent to collect data on the consumption of recreational drugs and alcohol, they vary in effectiveness and none have high sensitivity and specificity [79]. Therefore, laboratory methods are far better for quantifying the impact of this risk factor on the study findings.

In summary, we found that high concentrations of PBDE-47 is associated with increased risk of preterm birth but it does not likely function by inducing a global hypothyroid-like condition in the mother as effects on TSH production were not consistent with a subclinical hypothyroidism. Additional research is needed to exclude the possibility that PBDEs have tissue specific interference of thyroid hormones, to confirm these findings with other populations of women, and to identify other potential mechanisms by which PBDEs induce spontaneous or indicated preterm birth.

Acknowledgments: The authors wish to thank the thousands of pregnant women that generously participated in this study as well as the staff of research assistants, nurses, obstetricians and support personnel at KPSC-San Diego and KPSC-West Los Angeles Medical Centers that helped with the recruitment and data/sample collection. Further thanks are extended to the National Institutes of Health (NIH) and National Institute of Environmental Health Sciences (NIEHS) that provided financial support for this project.

Research funding: The study was supported by NIH/NIEHS 1R01ES023116. The opinions expressed are solely the responsibility of the authors and do not necessarily reflect the official views of the funding agencies.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was performed with approval and oversight from the Kaiser-Permanente Southern California (KPSC) Institutional Review Board.

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