Prenatal alcohol exposure and health at midlife: Self-reported health outcomes in two cohorts

Coles C. D., PhD*,[1,2] Shapiro Z. R., PhD,[1] Kable, J. A., PhD,[1,2] Stoner S. A., PhD,[3] Ritfeld, G. J., MD, PhD,[1,4, 5] Grant T. M., PhD,[3]

[1]Departments of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
[2]Department of Pediatrics, Emory University School of Medicine
[3]Fetal Alcohol and Drug Unit, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington.
[4]Barrow Neurological Institute at Phoenix Children's, Phoenix, Arizona
[5] Department of Child Health, University of Arizona College of Medicine – Phoenix, Phoenix, AZ
*Corresponding author:

12 Executive Park, Rm 212
Department of Psychiatry and Behavioral Sciences
Emory University School of Medicine
Atlanta, GA 30329
Phone: 404-712-9814
Fax: 404-712-9809
ccoles@emory.edu

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Abstract

Background: The Developmental Origins of Health and Disease Hypothesis (DOHaD) suggests prenatal alcohol exposure (PAE) should have implications for adult physical and mental health. Since the health profile of older adults with PAE and diagnoses of FASD is unknown, the current study evaluates self-reported health problems of midlife adults with and without a history of PAE to describe these outcomes.

Methods: Participants (N=357) recruited from longitudinal cohorts in Atlanta and Seattle completed a health survey assessing a range of physical conditions. Initial analysis compared frequency of conditions between alcohol-exposed and nonexposed groups. To identify patterns within groups, ten problem areas were subjected to latent class analysis (LCA). Finally, direct effect of PAE on health outcomes was evaluated using multilevel modeling, controlling for effects of other factors.

Results: Versus unexposed controls, individuals with PAE reported significantly higher frequencies of problems with hearing, dentition, heart, cancer, gastritis, kidney stones, bladder, diabetes, thyroid, skin, and seizures. LCA found Controls yielded 2 classes, with 45% reporting sleep and vision problems, and 55% reporting sleep, vision, cardiovascular, endocrine, immune, and dental problems. The PAE group yielded 3 classes, with 13% endorsing few health problems, 43% reporting sleep, vision, immune, and dental problems, and 43% reporting sleep, vision, cardiovascular, urinary, endocrine, skin, immune, dental, and gastrointestinal problems. With multivariate analysis, controlling for other influences, PAE was associated directly with hearing, urinary, dental, and gastrointestinal problems. A similar pattern was found for alcohol-exposed individuals who did and did not meet criteria for fetal alcohol syndrome (FAS).

Discussion: Patients affected by alcohol may report greater frequency and range of health adversity. That PAE was only uniquely associated with a limited set of problems suggests that many health outcomes in midlife result from an initial vulnerability potentiated by postnatal stress resulting from other associated factors.

Key Words: DOHaD, Prenatal alcohol exposure, health, lifespan, midlife, adult

INTRODUCTION

Alcohol is an established teratogenic agent that produces birth defects, growth retardation and cognitive/behavioral disorders that are observable early in life (Jones et al., 1973; Riley et al., 2011). However, there has been limited examination of the possible effects of prenatal alcohol exposure (PAE) on adult health and development despite an increasing recognition that other prenatal stressors and early life experiences are associated with a greater risk of adult disease and disorder (Barker & Thornburg, 2013). This impact of prenatal events is referred to as "fetal programming" based on the "developmental origins of health and disease (DOHaD) hypothesis" (Barker, 2012). These effects of early experience on emerging health problems have been demonstrated in a number of studies examining stressful events during pregnancy, most notably those of Barker and colleagues who found associations between low birth weight (a marker for stress) and the biological risk of adult disease including coronary heart disease, hypertension, type II diabetes and mental health disorders (Barker, 2012; Hales et al., 1991). This approach to understanding vulnerability to adult disease usually assumes a "dual" strike process that can account for observed effects with prenatal events as the first insult making the organism more vulnerable to subsequent environmental stressors that lead to increased risk later in life (Barker et al., 2012; Liu et al., 2023).

The possibility of alcohol being an agent for fetal programming of later physical and mental health has been raised and investigated in animal models (Nguyen et al., 2019). This was summarized by Lunde and colleagues (Lunde et al., 2016), and explored in both children and animal models (Akison et al., 2019); however, there remains limited research directed at human health outcomes among adults. Given that prenatal stress has been most commonly found associated with cardiovascular, endocrine, particularly metabolic syndrome, musculoskeletal,

and neurobehavioral disorders, these conditions have been the primary focus in the limited research in this area (Arima & Fukuoka, 2020; Cook et al., 2019; Kable et al., 2021; Liu et al., 2023; Parkington et al., 2010). However, recent surveys of self-selected volunteers (Himmelreich et al., 2020) and clinical samples (Reid et al., 2021) have suggested that a broader range of negative consequences may be observed. These and other studies, e.g., (Bodnar et al., 2016; Bodnar et al., 2022; Dylag et al., 2024; Gauthier & Brown, 2017; Kable et al., 2021; Sarkar, 2015), provide reason to believe that PAE may be a factor in the development of health problems in exposed individuals in any organ system. If this is so, it is important to have a wider understanding of the risks associated with this exposure both in order to improve clinical care for affected individuals but also to develop methods for prevention through the identification of areas of significant concern where early intervention may be most effective.

Among the difficulties in studying the effect of PAE on adult health is that the exigencies of human clinical research make it difficult to discriminate effects of prenatal exposure from the multiple other potential influences that cannot be controlled completely even with the best research designs. The result is often that the contribution of PAE is not identified. In addition to issues associated with retrospective documentation of alcohol exposure, studies can be influenced by research design. For instance, in the surveys cited, individuals who responded were drawn either from clinical samples (Reid et al., 2021) or were self-selected volunteers (Himmelreich et al., 2020), raising the possibility that these groups might have a higher number of medical concerns and thus their responses could potentially overestimate the effects of PAE. In another example, Weeks and colleagues (Weeks et al., 2020) identified hospitalized patients diagnosed with fetal alcohol spectrum disorders (FASD) and carried out a retrospective records review, finding a higher rate of metabolic abnormalities in this high risk group. Such

retrospective studies using medical records typically identify higher rates of illness than do prospective studies of community samples (Euser et al., 2009). The findings from these studies are valuable particularly in identifying areas for further study but, due to the characteristics of the participants, the associations found can exaggerate health problems associated with PAE by sampling those most at risk. Another problem can be difficulties in identifying appropriate contrast groups due to the association of PAE with other types of adversity which themselves have been shown to be associated with later health risks, such as adverse childhood experiences (ACEs) (Felitti et al., 1998). Therefore, to better understand the long-term risk associated with PAE, more research is needed in both clinical and community samples with attention to sampling methods and external factors that may contribute to results. Finally, as many of the health issues of concern, particularly those that are attributed to fetal programming, become problematic during middle age and older, signs and symptoms predictive of these later outcomes may not be recognized earlier in life. Research, therefore, should include obtaining information about health in midlife when many of these chronic health problems begin to become evident. As understanding of these outcomes increases, earlier identification of health issues and their precursors in childhood and adolescence may be possible.

The current study seeks to address the question of the impact of PAE on health in midlife by surveying longitudinally followed adults with known PAE or childhood diagnoses of FASD that imply PAE. We asked about current health status, access to health care and conditions for which they had received diagnoses from health care professionals. The goal was to review a broad range of health problems including both the conditions usually observed in studies of DOHaD, like metabolic syndrome and cardiovascular problems, and to review of other systems that have been reported to be affected in younger individuals or observed in animal studies,

including the visual (Reid et al., 2021; Tsang et al., 2023), auditory (Cheung et al., 2022), immune (Bodnar et al., 2016), gastrointestinal (McMahan et al., 2023), and genitourinary (Dylag et al., 2024) systems and to probe for the incidence of cancer (Mead & Sarkar, 2014) (See Table 1 for a complete list). In addition, it is important to compare responses of exposed individuals with those of an unexposed contrast group of similar age and demographic characteristics to identify conditions that are more commonly reported in the alcohol group while being less frequent in contrast groups. Finally, it is necessary to take into account other factors that also may play a role in increasing risk among these individuals, including socioeconomic status (SES), childhood adversity, and access to health care.

To describe the relationship of PAE to health in midlife, we carried out three different types of analyses with the survey results. First was a simple description of areas reported to reflect the experience of the participants with these health problems. While these frequences do not discriminate the direct effect of PAE from other factors, they do identify the lived experience of reporting individuals as a group. Next, to identify patterns of health issues that may be more common in adults with PAE, Latent Class Analysis (LCA) allowed a person-centered approach to the identification of groupings of individuals based on their health problems. This approach provided insight into the broad range of health problems individuals with (and without) PAE experience. We anticipated group separation based on severity of health problems (low/high or low/medium/high). Finally, we employed a variables-centered approach (multilevel regression) to identify those outcomes that are directly associated with PAE after statistically controlling for demographic and environmental factors.

METHODS

Participants

From 2018 to 2022, 357 individuals were recruited from longitudinal research studies of participants with a history of PAE or who had been diagnosed with FASD as well as contrast groups of unexposed individuals. Of these, 134 were recruited from a cohort consisting of 427 individuals, who were born from 1980 to 1986, to women receiving prenatal care at a large, inner-city hospital in Atlanta that served a low SES, predominantly Black population (Coles et al., 2002; Coles et al., 1985; Lynch et al., 2017). In the original sample, alcohol use was assessed in all women applying for prenatal care between 1980 and 1986. At that time, those who denied drinking any alcohol or reported drinking at least 1 ounce of absolute alcohol per occasion at least once a week were recruited for the study and interviewed to obtain detailed information regarding alcohol consumption. Following delivery, children underwent postpartum assessment of medical, behavioral, and dysmorphic outcomes (Coles et al., 1985; Coles et al., 1987), and were reassessed in childhood (Coles et al., 1997), adolescence (Coles et al., 2002), and in early adulthood (Lynch et al., 2015). During these assessments, information was collected on growth, cognitive ability, and presence of dysmorphic features, allowing participants to be classified as to the extent of the effect of their exposure on physical status and function. (Table 2)

The remaining 222 participants were recruited from a cohort (Streissguth et al., 1991; Streissguth et al., 1996; Streissguth et al., 1985) of 475 individuals who were referred as children to the University of Washington for clinical evaluation between 1973-1995 and later recruited for participation in research studies. Most children were referred due to known or suspected PAE accompanied by cognitive and/or behavioral problems. The cognitive and physical characteristics associated with FASD were assessed in this cohort when the initial referral was made during childhood with members of this cohort diagnosed with either Fetal Alcohol Syndrome (FAS) or as having effects of their exposure but not meeting criteria for FAS (Table

2). (Streissguth et al., 1991; Streissguth et al., 1996; Streissguth et al., 1985), Control group participants were recruited during the same time frame and were chosen to be similar to the PAE participants in age, sex, and race. In some cases, controls who had moved away and were unable to participate were replaced by additional controls recruited from the greater Seattle area.

Study records and commercially available databases were used to identify participants' current contact information and inform them about the study. Informed consent was carried out in person or remotely using REDCap (Research Electronic Data Capture), a HIPAA-compliant secure web application for building and managing online surveys and databases (Harris et al., 2009). Participants who took part in the study completed the health survey online using REDCap or as part of an in-person visit. Forms were read to individuals who were not able to complete forms due to reading or cognitive problems and participants were accompanied by guardians when appropriate. Participants were reimbursed for their time and travel costs. The study protocol was approved by the internal review boards at Emory University School of Medicine and the University of Washington.

Measures

To describe the sample and identify potentially confounding factors, participants completed a demographic survey that included self-reported income, occupation, education, race, ethnicity, and marital status. Education, and occupation were recoded into a single variable providing an estimate of social economic status using the Hollingshead Index (Hollingshead, 2011). PAE was identified at initial enrollment and the presence of dysmorphic features and other characteristics used for classification as Alcohol Exposed (PAE) or FAS/Dysmorphic was collected during prior study visits. For the Atlanta sample, PAE was identified through maternal

self-report during pregnancy. For the Seattle sample, PAE was ascertained when children were diagnosed with either FAS or FAE.

Adult Health Questionnaire. To survey their overall health status, participants completed a 190-item health survey that was adapted from modules used in the Behavioral Risk Factor Surveillance System (BRFSS) developed by the Centers for Disease Control and Prevention (CDC) (CDC - BRFSS, June 2023). The number of questions completed depended on the participants' responses as "follow-up" clarification questions were not asked when a particular health issue was not acknowledged. In addition, because some of the areas relevant to the current study were not addressed in the BRFSS, we developed our own modules to ask about the following areas: neurological symptoms, vision, hearing, dental health, gastrointestinal and urinary problems, and immune system disorders. The BRFSS also includes assessment of Adverse Childhood Experiences (ACEs) that have been found to be associated with later health problems and these questions were included in our health survey, as well. Table 1 includes the areas that are addressed in the Health Survey. It is important to emphasize that this self-report survey identified health problems based on the participants' knowledge of their own health and their understanding of diagnoses made by their health care providers. Questions were asked in the following formats: "Do you have any problems with (….);" "Have you ever been told by a doctor, nurse, or other health care professional that you have (…)?" .

Data Analysis

Data used and/or analyzed in the current study are available through the Collaborative Initiative on FASD (CIFASD) consortium (https://cifasd.org/data-sharing/), supported by the National Institute of Alcohol Abuse and Alcoholism (NIAAA). Data from this study are part of Phase 4 (2017-2022).

Missing Data. Across both cohorts, fewer than 5% of participants did not complete the demographic questions and fewer than 1% did not complete the health questionnaire (Table 2). To utilize all available data and reduce bias that can occur from list-wise deletion (Graham, 2009; Graham et al., 2007), we conducted multiple imputation of missing demographic and health variables using with the MICE software package in R (van Buuren & Groothuis-Oudshoorn, 2011).

Frequency of Health Problems. Data were examined at several levels. Initially, we compared the frequency of the reported occurrence of all physical health outcomes endorsed by individuals with prenatal exposure in comparison to those in the contrast group in order to describe the degree to which PAE was associated with these conditions. We also categorized those with alcohol exposure as either exposed (PAE) or as showing physical characteristics of their exposure (FAS/Dysmorphic) for a further analysis. As both these analyses were exploratory, items were analyzed individually and we did not control for listwise error. Only those items related to physical health are included in the current analysis as Mental Health problems were discussed in a previous paper (Coles et al., 2022).

The next level of analysis had two goals, first to identify patterns of outcomes associated with PAE and secondly, to control for other factors that might contribute to these outcomes and identify any outcomes that appeared uniquely impacted by PAE. For these two analyses, we selected 101 stem questions from the areas surveyed covering nine health domains (vision, hearing, cardiovascular, urinary, gastrointestinal, endocrine, immune function, dental, and skin) plus sleep, a frequently reported functional problem (See Supplemental Table S1 for these Questions). Responses were aggregated to create a single binary outcome (yes/no) for each problem area indicating participants' endorsement within that area. Using these data we carried

out Latent Class Analysis (LCA) as well as multivariate analyses that were used to model any health problems uniquely associated with PAE when potentially confounding factors are controlled.

Person-Centered Analyses. LCA is used to divide a population into underlying classes (Collins & Lanza, 2009). A latent class analysis (LCA) was conducted to better understand the different patterns of health problems that may be present in individuals with and without PAE. Within each class, item-response probabilities reflect the probability of endorsing a problem in a particular domain given membership in that class. The membership probability pattern was used to interpret the different classes.

We began by fitting separate models to the PAE and control groups to determine if both groups exhibit an invariant class structure (configural invariance; (Kankaraš et al., 2018). Model selection was guided using the Akaike information criterion (AIC; Akaike, 1974), Bayesian information criterion (BIC; Schwarz, 1978), sample-size adjusted BIC (a-BIC; Sclove, 1987), entropy (Celeux & Soromenho, 1996), and a bootstrapped likelihood ratio test (BLRT; McLachlan, 1987). Lower AIC, BIC, and a-BIC values reflect better model fit; higher entropy suggests improved classification (class separation); significant BLRT values indicate model fit is improved relative to a model with one fewer profile. Model identification was checked with 1000 initial and 100 final stage starts. Models were estimated using Mplus version 8.3. Profile membership was then used to identify class differences in demographic variables, ACEs, dysmorphic features, and BMI using the Bolck-Croon-Hagenaars (BCH; Bakk & Vermunt, 2016) command in Mplus. The BCH approach provides an overall test indicating whether significant differences exist among all latent profiles, and pairwise tests to identify whether differences exist between any two profiles.

Variables-Centered Analyses. To identify those health problems that are most likely to be uniquely associated with PAE while accounting for other factors, we utilized propensity scores and multilevel modeling. Propensity scores (Rosenbaum & Rubin, 1983) are used to quantify the probability of group membership conditional on observed covariates, and represent the likelihood of membership in a particular group (e.g., PAE or control) given each participant's set of demographic covariates. Use of propensity scores allowed us to account for a large number of important covariates while only including a single additional predictor within a regression (Austin, 2011). In the current study, propensity scores were derived by regressing demographic variables on PAE status. We calculated participants' propensity scores within a multilevel framework using the lme4 (Bates, Maechker, Bolker, & Walker, 2015) and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) packages in R (version 4.2.1), to account for the structure of our data, in which participants were nested within sites. As in our prior work (Shapiro et al., 2023), the data supported a model in which intercept, but not slope, varied as a random effect for site, that is Atlanta or Seattle.

We anticipated that reported health outcomes might be affected by recruitment sites and to identify such an effect, we evaluated the unconditional means model, in which we regressed our outcomes on site alone. We then derived the Intraclass Correlation Coefficient (ICC), which provides an estimate of the variance which can be attributed to site for each outcome (See Supplemental Table S2). ICC values for the health domains ranged between 6-19%, suggesting significant cross-site variance in some outcomes.

We included participants' propensity scores in a new series of multilevel regression models predicting health problem domains from PAE status and the propensity scores. Again, we found our data to be consistent with a multilevel regression model with random intercepts, but

not random slopes. We regressed PAE (defined as the presence/absence of any level of PAE) and the propensity score on each of the health domains. In one case, (dental problems), we found the data better supported a simpler linear regression over a multilevel model.

Finally, we also evaluated the possibility that the association between PAE and health outcomes will differ among individuals with and without dysmorphic features, as some outcomes tend to be worse among those with dysmorphic features (Bandoli et al., 2022; Bandoli et al., 2019) suggesting that dysmorphology may be a marker for organ system vulnerability to alcohol effects. We tested this possibility by dividing the alcohol-exposed individuals into groups with (*PAE+*: Yes/No) and without dysmorphology (*PAE-*: Yes/No). We created propensity scores for PAE+ and PAE- and then regressed each of the outcome measures on PAE+, PAE- and both propensity scores. Again, we found dental problems to be best accounted for by a linear regression.

RESULTS

Demographic Characteristics. Table 2 presents the demographic characteristics of the Atlanta and Seattle cohorts. Despite expected site differences, groups were similar within sites suggesting that contrast groups were appropriately chosen. In the Atlanta cohort, participants were predominantly Black, although there was a slightly higher percentage of White individuals in the Contrast group ($F_{(1,129)}$=6.80, p<.05, η^2=.05). Members of the Seattle cohort were predominately White, particularly in the Control group, ($F_{(1,219)}$=85.29, p<.05, η^2=.02), with those in the PAE group more likely to be younger ($F_{(1,208)}$=8.56, p<.01, η^2=.04), have lower SES ($F_{(1,211)}$=135.48, p<.001, η^2=.39), and to be living without a partner ($F_{(1,212)}$=17.53, p<.001, η^2=.08)).

Frequency of Health Problems. Table 3 shows the frequency of endorsement of individual health problems for three groups of participants, those in the control group, those who are designated as alcohol exposed but not meeting criteria for FAS/Dysmorphic and those diagnosed as FAS or Dysmorphic. Data are shown collapsed across both sites for the three groups and with both alcohol groups combined in the final column. Two Chi Square analyses were carried out for each health problem examined, for the three groups and for the PAE vs Contrast groups. Review of these results finds that individuals with alcohol exposure reported significantly higher rates of hearing ($X^2_{(2)}$ =8.75, p =.01) and dental problems ($X^2_{(2)}$ =26.16, p <.001), current "heart" problems ($X^2_{(2)}$ =9.3, p <.01), gastritis ($X^2_{(2)}$ =8.61, p =.014), kidney stones ($X^2_{(2)}$ =7.82, p =.02), bowels problems ($X^2_{(2)}$ =6.85, p =.03), bladder infections ($X^2_{(2)}$ =6.73, p =.035), incontinence ($X^2_{(2)}$ =14,76, p <.001), thyroid disorder ($X^2_{(2)}$ =13.61, p =.001), problems with the skin ($X^2_{(2)}$ =8.76, p =.013), and seizures ($X^2_{(2)}$ =9.96, p =.007). In addition, those with a FAS Diagnosis reported a higher rate of diabetes ($X^2_{(2)}$ =6,38, p =.04) than the other two groups and those who were alcohol-exposed but not dysmorphic, a higher number of cancers ($X^2_{(2)}$ =6.76, p =.034). This information is available for each site individually in Supplemental tables 3a. Atlanta and 3b.Seattle.

Person-Centered Analyses. We began by evaluating the number of latent classes within the PAE and control groups to determine whether unique patterns of health outcomes could be identified in alcohol-exposed individuals and to determine environmental and demographic factors related to these outcomes. Model fits for LCA models with one to four classes in each group were calculated (See Supplemental Tables S4a and S4b). Using the overall pattern of model fit statistics for each, we selected the 2-class model for the control group (Figure 1a) and the 3-class model for the PAE group (Figure 1b). As the PAE and control groups appeared to be

best accounted for by different class structures (configural invariance), we probed the latent class structure separately in each group.

Item response probabilities for the control and PAE groups' classes are presented in Figure 1. Classes in the control group were labeled "Limited Problems" (45%) and "MultiProblem" (55%). Members of the Limited Problems group had a high likelihood of endorsing sleep and vision problems only, while those in the control MultiProblem group were likely to experience sleep, vision, cardiovascular, endocrine, immune, and dental problems. In the PAE group, classes were labeled "Excellent Health" (13%), "Limited Problems" (43%), and "MultiProblem" (43%). Individuals in the Excellent Health group were likely to report only dental problems, those in the Limited Problems group were likely to report sleep, vision, immune, and dental problems. Lastly, members of the PAE MultiProblem group were characterized by a high likelihood of endorsing all domains other than hearing problems.

Tables 4a and 4b present the results from the BCH analyses, examining the relationship between classes and demographics and other variables of interest. Within the control group, we found that relative to the Limited Problems group, the MultiProblem group was older, was composed of more women, fewer black people, more white people, experienced more adverse childhood events, and was more likely to have health insurance. Within the PAE group, compared to both other classes, the MultiProblem group was older, was composed of fewer black people, more white people, and experienced more adverse childhood events. The Excellent Health group tended to exhibit the reverse pattern and was also less likely than members of both other groups to have any form of health insurance.

Variable-Centered Analyses. Our final analysis of the survey results was designed to identify the relationship of PAE with outcomes while controlling for the demographic and

environmental factors that also appear to contribute to the development of problems in health. These results can be found in Table 5. After accounting for potentially confounding variables using propensity scores, PAE was significantly associated with hearing, dental, urinary, and gastrointestinal problems. When we accounted for the presence or absence of dysmorphic features, we found similar patterns in both groups (Table 6). PAE with the presence of dysmorphic features was associated with hearing, dental, and urinary problems, while PAE without dysmorphic features was only associated with dental and urinary problems. There were no additional differences between individuals with and without PAE.

DISCUSSION

The current study is among the first to examine health in midlife in individuals with confirmed alcohol exposure. The results suggest that PAE is associated with significant impact on health, confirming the results reported earlier by Himmelreich et al. (2020). The earlier study, important for its innovation and comprehensiveness, could be criticized as lacking a contrast group and relying on a self-selected sample who may have been experiencing an unusually high level of medical problems. However, in the current study, the report of individuals with PAE is very similar to that of the participants in the Himmerlreich, et al. (2020) study while the age range of the two groups of respondents is similar. Thus, there is convergent data to suggest negative long-term medical consequences of early alcohol exposure.

In carrying out Latent Class Analysis, our goal was to identify those areas where health problems were most commonly observed in individuals with PAE and to determine any uniqueness associated with alcohol exposure. Person-centered analyses suggested the majority of all participants (75%), both in contrast and PAE groups, are likely to belong to a class having problems relating to sleep, vision, immune function (e.g., allergies, rashes), or dental problems. In the

384 contrast group, those with more difficulties also acknowledged cardiovascular and endocrine issues,
385 while the MultiProblem group with PAE exposure has a higher probability of all of the areas
386 queried. Thus, no unique pattern of co-occurrence of health issues was described beyond the overall
387 increase in frequencies associated with PAE. This increased risk suggests that those with PAE
388 should be monitored more closely than unexposed individuals, emphasizing the importance of
389 reliable access to health care for this group.

390 In both contrast and PAE groups, we see that participants' reported health status is also
391 associated with gender, race, age, and number of adverse childhood experiences. Individuals
392 belonging to classes associated with more reported health issues tended to be female, white,
393 older, and have experienced more adverse events in childhood. In addition, having health
394 insurance is also associated with more identified health problems (See Table 2). One possible
395 interpretation is that those without health insurance are less likely to seek routine care and are
396 therefore less aware of problems with their health particularly those conditions that are
397 asymptomatic. The latter explanation is supported, to some extent, by other studies done at the
398 Atlanta site with the same sample (Kable et al., 2021; Kable et al., 2023) in which asymptomatic
399 physical problems were identified that had not been acknowledged by participants in the current
400 study. Indeed, the current study relied on self-report and, for that reason, it is difficult to know if
401 individuals are over reporting, underreporting or completely accurate. There also may be
402 differences in health literacy associated with SES that impact participants perceptions of their
403 health status. The obvious next step in understanding the impact of PAE on later health is to
404 confirm self-report through clinical examination or other objective indicators of health.

405 In the variable-centered analyses when we controlled for other variables that contributed
406 to health outcomes, a slightly different pattern emerged. Although hearing problems did not

emerge as contributing to group classification in our LCA, issues with this area were nonetheless significantly associated with PAE. Likewise, PAE was a significant predictor of urinary and gastrointestinal problems. However, the presence of dysmorphology, often associated with greater severity of neurobehavioral problems identified during childhood, was not strongly associated with a higher number of health problems in adulthood. The overall pattern looked very similar in PAE with and without dysmorphic features, suggesting that lack of physical features was not an indicator of overall physical health with increasing age.

These results, together with our latent class analysis, suggest that PAE alone can be associated with increased prevalence of health problems across multiple health domains. However, as the DOHaD hypothesis would suggest, PAE does not appear to be directly responsible for all such health problems. Instead, we believe PAE produces a greater vulnerability within biological systems, increasing the impact of social determinants of health. Thus, the social correlates of PAE (e.g., low SES) are also associated with negative health outcomes, which may interact with the effects of PAE (e.g., the negative health effects directly attributable to PAE may be exacerbated by poor diet resulting from low SES). In addition, it is possible that some negative health outcomes associated with PAE may also reflect secondary effects of PAE on cognition and adaptive function, which could reduce individuals' ability to maintain their health (e.g., practice self-care, eat a healthy diet, exercise, etc.). Finally, disability status itself may be associated with greater stress (Turk & McDermott, 2018) due to a higher likelihood of lower SES and income. Disability status may also affect individuals' social connections. It is notable, for instance, that those with FASD are less likely to be "partnered" and, thus, experience less social support. Thus, PAE is hypothesized to represent a complex pattern of risk factors that can cumulate in long-term implications for health.

Limitations. There are limitations in the current study that should be considered in interpretation of results. As mentioned above, this is self-report data and, therefore, reflects only the individuals' awareness of their own status, which may not reflect all possible conditions. Many who did not report medical problems, also did not have health insurance or did not seek routine health care. It may be that some of these individuals, in the absence of regular health care, were unaware of potential health problems, specifically asymptomatic problems, like hyperlipidemia or hypertension, while being aware of symptomatic conditions, like gastritis. The obvious next step in understanding the impact of PAE on later health is to confirm self-report through clinical examination. Evaluation of areas identified by participants in greater detail could refine those "problems" into diagnoses. Doing so would provide hypotheses for further research into mechanisms.

Another limitation is the relatively small sample size so that some health issues that have a low prevalence, cannot be identified in this study. This was one of the reasons that broad categories of "disorders" were queried. Finally, the sample of individuals who responded do not represent all individuals exposed to and affect by PAE and therefore the survey should be replicated in other populations. While acknowledging its limitations, the survey adds to the sum of knowledge in this area and suggests potential directions for future research.

In conclusion, the current study presents evidence that PAE is associated with an increase in poorer health outcomes in midlife. There appear to be certain problems that are more directly related to alcohol exposure, including hearing issues, urinary and gastrointestinal problems, while many other issues may be the result of a "dual" strike phenomenon in which the prenatal exposure leads to vulnerabilities that are potentiated by other environmental factors like adverse childhood experiences or perhaps the increased stress associated with having a behavioral

disability such as Fetal Alcohol Spectrum Disorder (FASD). Our results are of relevance to service providers who might be interested in knowing the likely health profile of patients with a history of PAE, as well as researchers interested in knowing which health systems are likely (and unlikely) to be impacted by PAE rather than factors associated with PAE.

There is much more work to be done to identify and understand the medical issues that occur in individuals with PAE and FASD. The current study is simply a description of areas that should be explored more thoroughly in the future both to identify specific disorders and to begin the process of understanding the mechanisms that produce them. Nevertheless, by identifying these risks, this study does provide the clinician with reason to comprehensively evaluate vulnerable patients to ensure that they receive the necessary care. It should also alert caregivers and others who work with affected individuals of the need for intervention and preventive care since PAE has placed them at a higher risk for the early onset of physical health problems.

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659 Figure Legend

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661 Figure 1. Probability of Health Problem Class Inclusion in Control (top) and PAE (bottom)

662 Classes

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Table 1: Adult Health Questionnaire: Areas Queried

Overall Physical and Mental Health (10 items)

Health Care Access (9 items)

Chronic Health Problems
- Weight (5 items)
- Sleep (9 items)
- Vision (7 items)*
- Hearing (7 items)*
- Dental (5 items)*

Cardiovascular Health (Heart and Blood) (6 items)
- Hypertension Awareness (4 items)
- Cholesterol Awareness (5 items)
- Other Cardiovascular Problems (3 items)

Cancer (3 items)

Stomach, Digestion, Kidney, Bladder and Bowel Problems (13 items)*

Endocrine Disorders
- Diabetes (8 items)
- Thyroid and parathyroid Disorders (5 items)

Immune and Autoimmune Disorders (5items)
- Allergies (4 items)
- Asthma (6 items)
- Autoimmune Disorders (4 items)*
- Arthritis (7 items)

Mental Health and Neurology
- Seizure Disorders (10 items)*
- Mental Health (14 items)
- Symptoms of Anxiety/Depression (23 items)

Adverse Childhood Experiences (ACES) (11 items)

- **Items not included in BRFSS (CDC) Questionnaires and added by the authors*

Table 2. Demographic variables – Atlanta and Seattle cohorts.

	Atlanta					Seattle				
	Mean (SD) or %	**Control** (n=61)	**PAE** (n=74)	***2 Group p***	***% Missing***	**Mean (SD) or %**	**Control** (n=72)	**PAE** (n=150)	***2 Group p***	***% Missing***
Age (Yr)	36.22 (1.77)	36.43 (1.79)	36.06 (1.74)	*ns*	2.96	40.68 (8.3)	43.37 (0.05)	39.38 (7.61)	*<.001*	2.25
Sex (% female)	65%	64%	66%	*ns*	1.48	55%	58%	53%	*ns*	0.90
Hollingshead Index (SES)*	29.60 (12.3)	31.92 (13.25)	28.16 (11.29)	*ns*	2.22	34.72 (15.51)	48.01 (12.44)	28.25 (12.44)	*<.001*	.90
Health Insurance (% Yes)	63.9%	65.6%	55.8%	*ns*	5.6	91.6%	95.38%	89.9%	*ns*	3.6
Insurance Type% Private/HMO	35.5%	40.6%	31.2%	*ns*	41.1	40.3%	72.3%	28.2%	*<.001*	9
Medicaid/IHS[+]	23.4%	25.0%	22.1%			45.2%	18.5%	59.1%		
Race % American Indian	0	0	0		1.48	13%	8%	15%	*ns*	0.45
Pacific Islander	0	0	0			1%	0	1%	*ns*	
Black	90%	81%	97%	*<.01*		5%	6%	4%	*ns*	
White	8%	15%	3%	*<.01*		67%	78%	62%	*<.05*	
Multiracial	2%	3%	0	*ns*		14%	8%	17%	*ns*	
Hispanic / Latino %	0	0	0		2.22	7%	8%	7%	*ns*	5.87
Married / Living with Partner %	36%	39%	33%	*ns*	2.22	44%	56.1%	36%	*<.001*	0.45
FAS / Dysmorphic Features %	26%	0	47%	*<.001*	0	26%	0	39%	*<.001*	0
PAE (ozAA/wk)[#]		0	10.38 (11.18)		0					100

*SES-Socioeconomic Status ;[#]ozAA/wk= Ounces of absolute alcohol per week during pregnancy; [+]IHS=Indian Health Service

Table 3. Frequency of Individual Health Problem Endorsed (Percent "Yes) collapsed across sites. The fourth column (4) combines both alcohol groups.

Health Problem	1.Control (n=136)	2. Alcohol Exposed (n=128)	3.FASD/Dysmorphic (n=94)	Group Differences and Significance	4. All Alcohol (n=222)	Group Differences and Significance
Sleep	56.1%	63.5%	46.2%	3<1&2, p<.05	56.6%	NS
Apnea	18%	25.2%	19.3%	NS	22.5%	NS
Vision	48.5%	60.5%	52.7%	NS	57.1%	NS
Hearing	18%	29.6%	31.5%	1<2&3,p<.05	30.6%	1<4, p<.01
Dental	30.1%	58.1%	56.0%	1<2&3,p<.01	57.1%	1<4, p<.01
Heart Surgery	0.8%	4.8%	4.3%	NS	4.6%	NS
Heart Problems Now	4.6%	14.8%	14.9%	1<2&3,p<.01	14.7%	1<4, p<.01
High Blood Pressure	22.7%	27.4%	28.2%	NS	27.5%	NS
High Cholesterol	25.2%	19.7%	24.1%	NS	21.8%	NS
Heart Attack	0	2.4%	3.3%	NS	2.7%	NS
Stroke	1.5%	3.2%	2.2%	NS	2.7%	NS
Cancer	2.3%	7.2%	1.1.%	1&3<2,p<.05	4.6%	NS
Gastritis	24.1%	38.4%	40.7%	1<2&3,p<.01	39%	1<4, p<.01
Bowel Problems	12.8%	22.6%	24.2%	1<2&3,p<.05	23%	1<4, p<.05
Kidney Stones	3.8%	12.7%	11.1%	1&3<2,p<.05	12.4%	1<4, p<.05
Bladder Infections	21.1%	36.1%	28.9%	1&3<2,p<.05	33.2%	1<4, p<.05
Incontinence	4.5%	15.3%	22.8%	1<2&3,p<.001	18.3%	1<4,p<.001
Prediabetic	8.4%	12.8%	15.6%	NS	14.3%	NS
Diabetes	6.8%	6.4%	15.4%	1&2<3,p<.05	10.1%	NS
Thyroid Disease	3.0%	14.4%	16.9%	1<2&3,p<.001	15.3%	1<4,p<.001
Autoimmune Disease	13.7%	19.4%	17.2%	NS	18.3%	NS
Allergies	42.9%	54.4%	50.5%	NS	53.2%	NS
Skin Problems	15%	27.4%	28.3%	1<2&3,p<.05	28%	1<4, p<.01
Asthma	27.8%	29.8%	32.6%	NS	30.7%	NS
Arthritis	9.2%	12.4%	11.4%	NS	11.8%	NS
Seizures	4.6%	12%	17.8%	1<2&3, p<.001	14.3%	1<4, p<.05
HIV Infection	0.8%	2.4%	0	NS	1.4%	NS
Hepatitis C	0.8%	2.4%	1.1%	NS	1.9%	NS

Table 4a. Within profile means of health covariates – control classes.

Mean/Percent	MultiProblem (n=70; 55%)	Limited Problems (n=56; 45%)	$\chi 2$	Group Differences and Significance
Site (% Seattle)	.72 (.06)	.33 (.07)	13.24	MP>LP***
Age	41.77 (1.16)	38.13 (.08)	5.37	MP>LP*
Sex (% female)	.71 (.06)	.49 (.08)	3.87	MP>LP*
SES (Hollingshead)	43.38 (1.93)	36.96 (2.32)	3.67	*ns*
American Indian (%)	.06 (.03)	.03 (.03)	.33	*ns*
Black (%)	.21 (.06)	.63 (.08)	15.20	LP>MP***
White (%)	.64 (.07)	.32 (.07)	8.95	MP>LP**
Multiracial (%)	.09 (.04)	.03 (.03)	1.43	*ns*
Hispanic (%)	.02 (.02)	.07 (.04)	1.17	*ns*
Partnered (% Married or living w/ someone)	.58 (.07)	.42 (.08)	2.15	*ns*
ACES	2.70 (.29)	1.18 (.30)	10.87	MP>LP**
Any health insurance (%)	.96 (.04)	.66 (.07)	12.69	MP>LP***
Private health insurance	.58 (.07)	.48 (.08)	.77	*ns*
BMI	23.97 (4.51)	30.92 (1.17)	1.76	*ns*

*Note: *p<.05, **p<.01, **p<.001. MP = MultiProblem, = LP= Limited Problems, ACEs = Adverse Childhood Events Survey, BMI = Body Mass Index*

Table 4b. Within profile means of health covariates – PAE Classes.

Mean/Percent (SD)	MultiProblem (n=96; 43%)	Limited Problems (n=96; 43%)	Excellent Health (n=29; 13%)	$\chi 2$	Group Differences and Significance
Site (% Seattle)	.88 (.05)	.66 (.06)	.06 (.07)	92.87	MP>LP**; MP>E***; LP>E***
Age	41.13 (1.01)	36.03 (.53)	37.39 (.77)	16.49	MP>LP***; MP>E**
Sex (% female)	.74 (.06)	.43 (.06)	.58 (.10)	12.01	MP>L**
SES (Hollingshead)	27.93 (1.49)	28.46 (1.40)	26.73 (2.46)	.34	*ns*
American Indian (%)	.09 (.04)	.14 (.04)	.02 (.04)	4.45	*ns*
Pacific Islander (%)	.00 (.00)	.02 (.02)	.00 (.00)	2.04	*ns*
Black (%)	.14 (.05)	.37 (.06)	.93 (.07)	85.49	LP>MP**; E>LP***; E>MP***
White (%)	.62 (.06)	.38 (.06)	.00 (.04)	89.91	MP>LP*; MP>E***; LP>E***
Multiracial (%)	.16 (.04)	.08 (.03)	.06 (.05)	2.37	*ns*
Hispanic (%)	.07	.04	.03	.73	*ns*
Partnered (% Married or living w/ someone)	.39 (.06)	.36 (.06)	.33 (.10)	.06	*ns*
Dysmorphic Features (%)	.40 (.06)	.43 (.06)	.43 (.10)	.12	*ns*
ACES	5.00 (.34)	3.56 (.35)	2.20 (.56)	20.30	MP>LP**; MP>E***
Any health insurance (%)	.86 (.04)	.83 (.05)	.57 (.10)	6.75	MP>E*; LP>E*
Private health insurance	.24 (.05)	.36 (.06)	.26 (.09)	1.80	*ns*
BMI	31.67 (3.13)	20.83 (4.50)	26.83 (1.34)	3.52	*ns*

*Note: *p<.05, **p<.01, **p<.001. MP=MultiProblem, LP = Limited Problems, E = Excellent Health, ACES = Adverse Childhood Events Survey, BMI = Body mass index*

Table 5. Association of PAE with health outcomes controlling for associated factors using propensity scores

Problem Domain	Predictor	Estimate	SE	*df*	*t*	*p*
Sleep	Intercept	.74	.15	1.44	4.98	.07
	PAE	-.02	.06	352.00	-.44	.66
	PAE Propensity	-.04	.11	352.81	-.33	.75
Vision	Intercept	-.76	.11	2.18	6.72	.02
	PAE	-.05	.06	352.00	-.80	0.42
	PAE Propensity	-.09	.12	352.87	-.74	.46
Hearing	Intercept	.21	.12	1.89	1.80	.22
	PAE	**.14**	**.05**	**352.00**	**2.51**	**0.01***
	PAE Propensity	-.08	.11	352.99	-.067	.50
Cardiovascular	Intercept	.44	.12	2.21	3.67	.06
	PAE	.03	.06	352,00	.47	0.63
	PAE Propensity	-.02	.13	352.84	-.12	.91
Urinary	Intercept	.30	.15	1.92	.24	.24
	PAE	**.22**	**.06**	**352.00**	**3.75**	**.000*****
	PAE Propensity	-.14	.12	352.83	-1.20	.23
Endocrine	Intercept	.48	.17	1.40	2.80	.16
	PAE	-.02	.06	352.00	-.29	.77
	PAE Propensity	-.02	.13	352.77	-.19	.85
Skin	Intercept	.28	.17	1.40	1.65	.29
	PAE	.09	.06	352.00	1.51	0.13
	PAE Propensity	.06	.12	352.77	.47	.64
Immune	Intercept	.67	.14	1.45	4.86	.07
	PAE	.01	.05	352.00	.14	.89
	PAE Propensity	.11	.11	352.82	.99	.32
Dental [a]	**Intercept**	**.40**	**.07**	**3**	**5.67**	**.000*****

	PAE	**.21**	**.06**	**353**	**3.60**	**.000*** **
	PAE Propensity	.14	.12	353	1.13	.26
Gastrointestinal	Intercept	.30	.14	1.69	2.13	.19
	PAE	**.12**	**.06**	**352**	**1.99**	**0.047***
	PAE Propensity	.08	.13	352.98	.63	.53

[a] linear regression (single-level) mode

Table 6. Association of PAE with and without dysmorphia with health outcomes controlling for associated factors using propensity scores.

Outcome (Measure / Domain)	Predictor	Estimate	SE	*df*	*t*	*p*
Sleep	Intercept	.72	.15	1.82	4.65	.052
	PAE+	-.07	.07	350.01	-1.09	.28
	PAE-	.00	.06	350.01	-.03	0.98
	PAE+ Propensity	-.01	.19	349.87	-.04	.96
	PAE- Propensity	.01	.29	330.15	.02	.98
Vision	**Intercept**	**.80**	**.14**	**2.49**	**5.83**	**.02***
	PAE+	-.05	.07	350.02	-.74	0.46
	PAE-	-.05	.06	350.02	-.75	0.45
	PAE+ Propensity	.06	.21	344.79	.27	.79
	PAE- Propensity	-.31	.30	287.76	-1.04	.30
Hearing	Intercept	.24	.14	2.20	1.73	.21
	PAE+	**.16**	**.07**	**350.02**	**2.42**	**0.02***
	PAE-	.11	.06	350.02	1.89	.06
	PAE+ Propensity	.05	.20	347.39	.26	.79
	PAE- Propensity	-.25	.29	307.21	-.87	.39
Cardiovascular	**Intercept**	**.44**	**.14**	**3.02**	**3.22**	**.048***
	PAE+	.05	.08	350.03	.65	0.51
	PAE-	.01	.07	350.03	.19	0.85
	PAE+ Propensity	-.01	.22	338.56	-.05	.96
	PAE- Propensity	-.01	.33	250.70	-.04	.97
Urinary	Intercept	.36	.18	1.60	1.98	.22
	PAE+	**.24**	**.07**	**350.01**	**3.49**	**0.001****
	PAE-	**.19**	**.06**	**350.01**	**3.15**	**0.002****
	PAE+ Propensity	.02	.21	350.68	.12	.90
	PAE- Propensity	-.46	.31	340.36	-1.49	.14

Endocrine	Intercept	.49	.19	1.66	2.64	.14
	PAE+	.03	.07	350.01	.40	0.69
	PAE-	-.05	.07	350.01	-.74	0.46
	PAE+ Propensity	-.02	.22	350.50	-.11	.91
	PAE- Propensity	-.06	.32	337.76	-.19	.85
Skin	Intercept	.31	.19	1.61	1.65	.27
	PAE+	.06	.07	350.01	.82	.41
	PAE-	.11	.06	350.01	1.72	.09
	PAE+ Propensity	.16	.21	350.66	.77	.44
	PAE- Propensity	-.11	.31	340.06	-.35	.73
Immune	Intercept	.72	.16	1.59	4.42	.07
	PAE+	-.01	.06	350.01	-.22	0.82
	PAE-	.02	.05	350.01	.29	0.77
	PAE+ Propensity	.29	.18	350.70	1.58	.12
	PAE- Propensity	-.16	.27	340.69	-.61	.54
Dental [a]	**Intercept**	**.39**	**.08**	**5**	**4.68**	**.000*** **
	PAE+	**.17**	**.07**	**351**	**2.40**	**.02***
	PAE-	**.23**	**.06**	**351**	**3.60**	**.000*** **
	PAE+ Propensity	.21	.20	351	1.03	.30
	PAE- Propensity	.12	.25	351	.45	.65
Gastrointestinal	Intercept	.44	.19	1.60	2.28	.18
	PAE+	.11	.07	350.01	1.53	.13
	PAE-	.12	.06	350.01	1.85	.06
	PAE+ Propensity	**.51**	**.22**	**350.68**	**2.36**	**.02***
	PAE- Propensity	**-.63**	**.32**	**340.38**	**-1.98**	**.048***

[a] linear regression (single-level) model; PAE+= Having dysmorphic features associated with alcohol exposure; PAE-=No dysmorphic features.