Dement Neurocogn Disord. 2026 Oct;25(4):195-209
https://doi.org/10.12779/dnd.2026.25.4.195
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Review Article

Check for updates

Fetal Alcohol Spectrum Disorder as a Potential Early-Life Risk Factor for Dementia: A Life-Course Perspective

So-Hee Park

Department of Neurology, Bobath Memorial Hospital, Seongnam, Korea

OPEN ACCESS

Received: Sep 25, 2026
Revised: Oct 7, 2026
Accepted: Oct 8, 2026
Published online: Oct 15, 2026

Correspondence to
So-Hee Park
Department of Neurology, Bobath Memorial Hospital, 155-7 Daewangpangyo-ro, Bundang-gu, Seongnam 13552, Korea.
Email: nrsoheep@naver.com

© 2026 The Author(s). Published by the Korean Dementia Association.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs
So-Hee Park
https://orcid.org/0000-0001-5399-6049

Conflict of Interest
The author has no financial conflicts of interest.

Generative AI Disclosure
Tool and provider: Claude (Anthropic). Model/version: Claude Opus 5. Access dates: 15 September–15 October 2026. Purpose: the author used the tool to assist with structuring the manuscript, drafting initial text, language editing, and generating Fig. 1 from the author's specification. The tool was

ABSTRACT

Current models of modifiable dementia risk span the life course but begin with formal education, leaving the prenatal period unexamined. Prenatal alcohol exposure (PAE) is the leading preventable cause of neurodevelopmental disability; its clinical expression is fetal alcohol spectrum disorder (FASD), of which fetal alcohol syndrome is the most severe form. FASD affects about 0.8% of children worldwide and considerably more in residential and foster care, yet its late-life trajectory is unstudied: the first diagnosed cohort is only now in its sixth decade. This review examines whether PAE may be an early-life dementia risk factor. In rodent models, developmental alcohol exposure produces hippocampal, cholinergic, and epigenetic changes demonstrable in adult animals; the report of Alzheimer-type markers in middle-aged exposed animals rests on a single unreplicated study. In humans, FASD is associated with low cognitive reserve, social adversity, and a high prevalence of adult alcohol use disorder, each an established dementia risk factor. Two hypotheses are distinguished: a pathology hypothesis, in which PAE promotes neurodegenerative change, and a reserve hypothesis, in which lower premorbid reserve brings forward clinical expression at comparable pathological burden. The expected phenotype is more likely mixed than purely Alzheimer-type. No human evidence yet links PAE to incident dementia; the proposition remains a hypothesis, not an established association. Given the mechanistic plausibility, examination is warranted through midlife biomarker studies and record linkage in cohorts with documented exposure; recording PAE in memory clinic history taking and at entry into residential and foster care would supply the data required.

Keywords: Fetal Alcohol Spectrum Disorders; Dementia; Alzheimer Disease; Cognitive Reserve; Prenatal Exposure Delayed Effects; Risk Factors

INTRODUCTION

The Lancet Commission on dementia prevention identified 12 potentially modifiable risk factors in 2020 and 14 in 2024, estimating that their elimination could prevent or delay up to 40% and 45% of dementia cases, respectively.[1,2] The Commission adopted an explicitly

Generated by ximilinkpress

not used to generate, alter, or analyze data. Author responsibility: all references were independently verified against the original sources by the author, who determined the content of Fig. 1, reviewed and edited all content, and takes full responsibility for the accuracy and integrity of the manuscript. No confidential or identifiable material was uploaded to the tool.

life-course framework, yet the only factor it assigned to early life was limited education; prenatal exposures were not considered. The omission is understandable: dementia epidemiology rests on cohorts recruited in midlife or later, and reliable information on the intrauterine environment of a person now in their eighties is seldom available. The omission nonetheless warrants reconsideration, given that the developmental origins of adult cardiovascular and metabolic disease are well established,[3] and that the brain retains the imprint of early insult across the lifespan.

Alcohol is the most prevalent teratogenic exposure in human pregnancy. Prenatal alcohol exposure (PAE) produces a continuum of physical, cognitive, and behavioral outcomes collectively designated fetal alcohol spectrum disorder (FASD), of which fetal alcohol syndrome (FAS), first described by Jones and Smith in 1973,[4] is the most severe and most readily recognized form.[5] Approximately 10% of women worldwide consume alcohol during pregnancy, and FASD affects an estimated 7.7 per 1,000 children globally, with marked regional variation: the World Health Organization European Region has the highest regional estimate at 19.8 per 1,000, and among 187 countries the highest national estimate is 111.1 per 1,000 in South Africa.[6,7] In US communities studied using active case ascertainment, conservative prevalence estimates range from 1.1% to 5.0%.[8] In child welfare, foster care, and residential care settings, the pooled prevalence of FASD is estimated to be 17 to 19 times that in the general population of North America.[9] Three terms used throughout this review are not interchangeable. PAE denotes documented exposure to alcohol in utero, irrespective of outcome, and is the exposure variable in rodent studies and in epidemiological designs based on maternal report. FASD denotes the clinical diagnosis made when exposure is accompanied by pervasive neurodevelopmental impairment. FAS denotes the full phenotype, requiring the sentinel facial features. Where evidence is cited, the term used indicates the ascertainment applied in the source study.

The neurodevelopmental consequences of PAE have been documented for five decades, but their expression in late life remains uncharacterized. Individuals first diagnosed with FAS in the early 1970s are now in their fifties, and the large clinical cohorts assembled during the 1980s and 1990s are in their thirties and forties. No population diagnosed with FASD in childhood has yet reached the age at which dementia becomes common. Consequently, no epidemiological data exist on dementia incidence in FASD, and the possibility that PAE contributes to later risk has received little attention in the dementia literature.

This review assembles the evidence bearing on that possibility. It summarizes the neurodevelopmental and neurobiological sequelae of PAE, reviews experimental evidence linking developmental alcohol exposure to neurodegenerative processes, and distinguishes two hypotheses that are often conflated: that PAE promotes neurodegenerative pathology, and that it lowers the reserve against which such pathology is expressed. It describes three pathways through which FASD might increase dementia risk in humans, considers what phenotype would be expected, addresses the objection that dementia cannot be diagnosed in a congenital disorder, and sets out a research agenda with particular reference to Korea. PubMed and Google Scholar were searched between 10 April 2025 and 30 June 2026, without restriction on year of publication, combining terms for PAE and FASD with terms for aging, cognitive decline, neurodegeneration, Alzheimer's disease (AD), and dementia. Reference lists of retrieved articles were hand-searched, and Korean-language government reports were reviewed in the original; publications in English and Korean were eligible. The review is narrative rather than systematic, and formal appraisal of study quality was not undertaken.

DND Dementia and Neurocognitive Disorder

NEURODEVELOPMENTAL CONSEQUENCES OF PAE

Ethanol crosses the placenta freely and disrupts multiple stages of brain development, including progenitor proliferation, neuronal migration, synaptogenesis, myelination, and programmed cell death.[10,11] Timing, dose, and pattern determine the phenotype: binge drinking is the pattern most detrimental to fetal development, and no trimester is without risk, because exposure at any gestational stage can impair brain growth and function.[5,10] Most individuals with FASD lack the full facial phenotype and are classified as partial FAS or alcohol-related neurodevelopmental disorder, diagnoses that require documented exposure and are consequently often missed.[5] Structural imaging in children and adolescents with FASD shows reduced total brain volume, with the corpus callosum, cerebellum, and basal ganglia disproportionately affected, and more variable findings have been reported for the hippocampus.[12] The hippocampus and the cholinergic basal forebrain are among the regions affected earliest in AD, and their developmental compromise, where it occurs, may reduce brain reserve in later life.

The cognitive profile of FASD is characterized by reduced general intelligence, with mean intelligence quotient estimates for FAS of about 68 to 79, and by disproportionate impairment of executive function, working memory, processing speed, and adaptive behavior.[13,14] Intellectual disability is present in only a minority; most affected individuals function in the borderline or low-average range, a point relevant to the conceptual discussion below. Outcomes in adolescence and adulthood have been examined in clinical follow-up studies. In a Seattle clinical sample of 415 individuals with FAS or fetal alcohol effects, lifetime prevalence among adolescents and adults was 61% for disrupted school experience, 60% for trouble with the law, 50% for confinement, and 35% for alcohol or drug problems.[15] The features present in childhood largely endure, although some may diminish or change over time and data beyond adolescence remain limited.[16]

Psychiatric comorbidity is highly prevalent in FASD. Attention-deficit/hyperactivity disorder (ADHD) is present in more than half of affected individuals, and conduct, mood, and substance use disorders are common.[17,18] The diagnostic consequence is that a child with unrecognized FASD is likely to receive a diagnosis of ADHD alone, leaving the prenatal etiology, and its implications for lifelong health, unrecorded.

EXPERIMENTAL EVIDENCE LINKING DEVELOPMENTAL ALCOHOL EXPOSURE TO NEURODEGENERATION

Rodent models of PAE have long been used to investigate neurodevelopmental mechanisms, but only recently have exposed animals been followed beyond young adulthood to determine whether developmental exposure predisposes to neurodegenerative change. The available evidence, summarized in **Table 1**, is limited in volume, and the findings most directly relevant to AD rest on single reports; where several studies exist, as for hippocampal neurogenesis and neuroinflammation, the reported effects are inconsistent. This evidence is presented here as hypothesis-generating rather than as an established mechanism.

Alzheimer-type pathology

Rats of both sexes exposed to alcohol throughout gestation and examined at 12 months of age displayed impaired learning and memory together with elevated acetylcholinesterase

https://doi.org/10.12779/dnd.2026.25.4.195

Table 1. Experimental evidence linking developmental alcohol exposure to neurodegenerative mechanisms

Mechanism	Model and timing of assessment	Principal findings	Relevance to dementia	Ref.
Alzheimer-type pathology	Rat, gestational exposure, assessed at 12 mon	Increased hyperphosphorylated tau, Aβ and Aβ1-42, BACE1, UNC5C, and AChE activity in cortex and hippocampus; impaired learning and memory	Induction of AD-related biochemical changes following prenatal exposure (single study, not replicated)	19
Hippocampal cell loss and neurogenesis	Multiple rodent models, neonatal and gestational exposure	Hippocampal cell loss and altered neuronal morphology; adult neurogenesis altered, with direction and magnitude varying by model, dose and timing	Reduced hippocampal reserve; adult neurogenesis declines further in aging and AD	20
Cholinergic dysfunction	Mouse, postnatal day 7 exposure, assessed in adulthood; rat, gestational exposure	Basal forebrain cholinergic neuron number reduced 34%–42% in adulthood; elevated AChE activity at 12 mon	Cholinergic loss is central to the AD cognitive phenotype	19,21
Neuroinflammation	Rodent, neonatal exposure	Microglial and astrocyte activation and microglial loss; elevated cytokines and chemokines in the developing brain	Microglial priming is a proposed route to accelerated neurodegeneration; persistence into adulthood not established	22,23
Oxidative stress and mitochondrial dysfunction	Rodent and cell models	Increased reactive oxygen species; reduced antioxidant capacity; altered mitochondrial function	Shared mechanism with brain aging and AD	10,11
Epigenetic reprogramming	Rodent models; human FASD cohort	Persistent DNA methylation and histone changes; genome-wide methylation signature in FASD	Molecular route from prenatal exposure to lifelong altered gene expression	24,25
HPA axis dysregulation	Rodent, gestational exposure	Lifelong stress hyper-responsiveness and elevated glucocorticoids	Glucocorticoid excess is hippocampotoxic	26

Aβ: amyloid-β, BACE1: β-site amyloid precursor protein cleaving enzyme 1, UNC5C: unc-5 netrin receptor C, AChE: acetylcholinesterase, AD: Alzheimer's disease, FASD: fetal alcohol spectrum disorder, HPA: hypothalamic-pituitary-adrenal.

activity, hyperphosphorylated tau, amyloid-β (Aβ) including the Aβ1-42 fragment, β-site amyloid precursor protein cleaving enzyme 1, and the netrin receptor unc-5 netrin receptor C in cerebral cortex and hippocampus, a constellation the investigators interpreted as an AD-like phenotype induced by PAE.[19] Whether PAE interacts with genetic risk for AD in aged transgenic models carrying familial AD mutations has not been examined.

Hippocampal integrity and neurogenesis

Developmental alcohol exposure produces lasting hippocampal cell loss and changes in neuronal morphology, and alters adult hippocampal neurogenesis, a process that supports pattern separation and memory throughout life; the direction and magnitude of the neurogenic change vary with the rodent model, the blood alcohol concentration achieved, and the timing and frequency of exposure.[20] Adult neurogenesis declines with aging and has been reported to be further reduced in AD, although its extent in the adult human hippocampus remains debated; diminished neurogenic capacity at the outset of adult life may therefore bring forward the point at which function falls below the clinical threshold.

Cholinergic dysfunction

The basal forebrain cholinergic system is selectively vulnerable to developmental alcohol exposure. In mice exposed on postnatal day 7, a model of late-gestation exposure, basal forebrain cholinergic neuron number was reduced by 34% to 42% when counted in adulthood, whereas brainstem cholinergic, dopaminergic, and serotonergic populations were not significantly affected.[21] Elevated acetylcholinesterase activity was also reported among the Alzheimer-type findings in exposed rats at 12 months.[19] Given the centrality of cholinergic loss to the cognitive phenotype of AD and to its symptomatic treatment, a developmentally compromised cholinergic system is a plausible substrate for earlier or more severe clinical expression.

Neuroinflammation

PAE activates microglia and astrocytes in the developing brain, raising pro-inflammatory cytokine and chemokine expression, and also produces microglial loss. Whether this state

https://doi.org/10.12779/dnd.2026.25.4.195

persists into adulthood is not established, and the few data from adult animals are mixed.[22,23] Chronic neuroinflammation is increasingly regarded as contributing to AD pathogenesis rather than acting only as a secondary response, and early-life microglial priming is one mechanism through which early adversity is thought to accelerate later neurodegeneration.

Oxidative stress and mitochondrial dysfunction

Ethanol metabolism generates reactive oxygen species, and the fetal brain possesses limited antioxidant capacity. PAE alters mitochondrial function and antioxidant defenses,[10,11] processes that are also prominent in brain aging and AD.

Epigenetic reprogramming

PAE induces stable changes in DNA methylation, histone modification, and non-coding RNA expression that persist across the lifespan and, in some models, across generations.[24] A genome-wide DNA methylation signature has been identified in children with FASD,[25] and altered methylation of genes governing neuronal development, immune function, and glucocorticoid signaling provides a molecular route by which a prenatal exposure could shape brain aging decades later.

Hypothalamic-pituitary-adrenal axis dysregulation

PAE reprograms this axis, producing lifelong stress hyper-responsiveness,[26] and sustained glucocorticoid excess is itself hippocampotoxic.

Collectively, these findings do not establish that PAE causes dementia in humans. They indicate that several biological substrates relevant to AD, including hippocampal and cholinergic vulnerability, neuroinflammation, and epigenetic dysregulation, are engaged by developmental alcohol exposure; the hippocampal, cholinergic, and epigenetic changes remain demonstrable in adult animals. Whether amyloid and tau processing is also affected remains undetermined. The proposition that developmental alcohol exposure directly increases amyloid or tau burden should at present be regarded as provisional: it rests on a single rodent study that has not been independently replicated, and no corresponding human biomarker data exist. These models offer one inferential advantage that human studies cannot reproduce: animals are randomized to exposure and reared under standardized conditions, so the smoking, poor maternal nutrition, socioeconomic disadvantage, and childhood adversity that accompany maternal drinking in human populations are absent. That neurodegenerative changes are observed in middle-aged exposed animals in the absence of these co-exposures suggests that the biological exposure may contribute independently of them, although the small number of studies limits how far this inference can be taken. Human studies will nonetheless need to isolate that contribution through multivariable adjustment and prospective cohort design.

PATHWAYS FROM PAE TO DEMENTIA RISK IN HUMANS

The evidence that follows bears on two hypotheses that are conceptually distinct but often conflated. The pathology hypothesis holds that PAE promotes neurodegenerative processes themselves, such that an exposed individual accumulates greater amyloid, tau, neuroinflammatory, or vascular pathology at a given age. The reserve hypothesis holds that pathological burden is unchanged but that lower premorbid cognitive and brain reserve brings forward the age at which a given burden becomes clinically manifest. The two

https://doi.org/10.12779/dnd.2026.25.4.195

DND Dementia and Neurocognitive Disorder

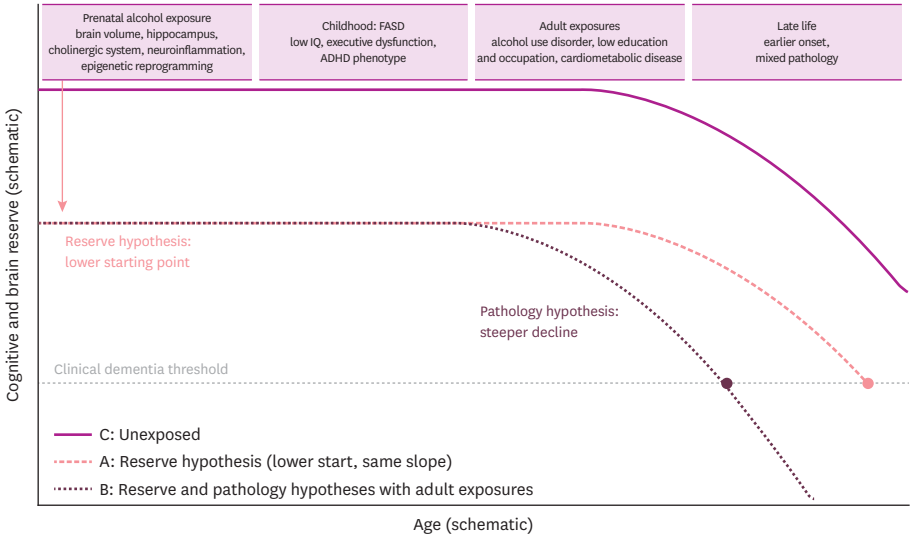


Fig. 1. Life-course multiple-hit model linking prenatal alcohol exposure to dementia risk, showing the two hypotheses separately. Prenatal alcohol exposure produces reduced brain volume, hippocampal and cholinergic vulnerability, neuroinflammation, and epigenetic reprogramming, which manifest in childhood as FASD with reduced general intelligence, executive dysfunction, and a high prevalence of ADHD. Trajectory A illustrates the reserve hypothesis alone: the slope of decline is the same as in an unexposed individual (trajectory C), but the starting point is lower, so the clinical dementia threshold (dotted line) is crossed earlier at a comparable burden of pathology. Trajectory B adds the pathology hypothesis together with additional adult exposures, namely alcohol use disorder, low educational and occupational attainment, and cardiometabolic disease, and therefore declines more steeply as well as starting lower. The two hypotheses are distinguishable in principle: A predicts earlier clinical expression at comparable biomarker levels; B predicts higher biomarker levels at a comparable age. Axes are schematic and do not represent measured values; ages of threshold crossing are illustrative. FASD: fetal alcohol spectrum disorder; ADHD: attention-deficit/hyperactivity disorder.

hypotheses yield distinguishable predictions: the first predicts higher biomarker levels at a comparable age, the second earlier clinical expression at comparable biomarker levels. They are not mutually exclusive; the mechanisms reviewed above bear mainly on the first, the human evidence mainly on the second. In the absence of direct epidemiological data, the case for FASD as a potential human dementia risk factor rests on three consequences of PAE, each independently associated with dementia (**Fig. 1**).

Diminished cognitive and brain reserve

Reserve theory holds that individuals with greater premorbid cognitive ability, education, and brain volume tolerate a greater burden of neuropathology before reaching the threshold of clinical impairment.[27,28] The corollary follows: individuals who enter adulthood with lower brain volume, lower intelligence, and poorer executive function should reach that threshold earlier. Early-life cognitive ability is among the more consistent predictors of late-life dementia. In the Nun Study, low linguistic ability in early adulthood predicted both AD neuropathology and clinical dementia six decades later,[29] and life-course models of dementia etiology assign substantial weight to the developmental period.[30] FASD is characterized by all three: lower brain volume, lower intelligence, and poorer executive function.

Accelerated cardiometabolic aging

Adults with FASD appear to carry an increased burden of physical illness, although the human evidence remains limited. A recent review of whole-body health in FASD cites a self-report survey of adolescents and adults in which cardiovascular problems occurred at 1.5 to 20 times general-population rates, hypertension at twice the general-population rate,

https://doi.org/10.12779/dnd.2026.25.4.195

and autoimmune disease in 35%; findings for type 2 diabetes are inconsistent, and weight is distributed differently by sex rather than shifted simply toward obesity.[31] The concept of alcohol-induced developmental origins of adult-onset disease has been articulated on the basis of both animal and human data.[32] An earlier review of adult outcomes concluded that the health consequences of PAE in human adults are largely unknown, while animal models indicate increased susceptibility to hypertension, diabetes, and immune dysfunction.[16] Beyond physical health, preliminary findings from two North American cohorts assessed at midlife indicate a higher prevalence of depression, anxiety, bipolar disorder, and ADHD, together with greater environmental adversity and lower socioeconomic status,[33] and a Korean nationwide study reported a 25% higher rate of hospitalization and a 33% higher all-cause mortality among individuals with an FASD diagnosis than among those without, with the largest excess in hospitalization for diseases of the nervous system.[34] Midlife hypertension, diabetes, and obesity are each established dementia risk factors,[1,2] and an excess of these conditions in FASD would elevate dementia risk through vascular and metabolic pathways independent of its direct neurodevelopmental effects.

Cumulative exposure across the lifespan

PAE is a marker of a high-risk environment as well as a biological insult. Individuals with FASD more often experience maltreatment, repeated changes of placement, disrupted schooling, and confinement,[15,17] adversities that overlap with the low educational attainment and social isolation identified as modifiable dementia risk factors.[1,2] Of particular relevance, adults with FASD show an elevated prevalence of alcohol use disorder, reflecting genetic liability, familial environment, and the impulsivity that characterizes the condition.[15,17] Heavy alcohol use in adulthood is among the strongest modifiable risk factors for early-onset dementia; in a French nationwide cohort, alcohol use disorders were the strongest such factor and were present in more than half of early-onset cases.[35,36] An individual exposed to alcohol in utero who subsequently develops alcohol use disorder therefore sustains two alcohol-related insults to the same vulnerable structures, an interaction that no human study has yet examined.

PAE seldom occurs in isolation from broader early adversity. The English and Romanian Adoptees study, which followed children exposed to severe institutional deprivation in infancy into young adulthood, demonstrated that deprivation exceeding six months produced neurodevelopmental problems, including inattention and overactivity, that persisted into the third decade despite subsequent placement in supportive families.[37] Early adversity of this kind is now recognized as a determinant of adult brain structure and function,[38] and children with PAE are disproportionately exposed to it. Separating the contribution of the biological exposure from that of the environment in which it typically occurs will be a central methodological challenge, although with respect to dementia risk both would act in the same direction.

The pathways described above make it unlikely that the expected late-life phenotype is pure AD. Several of the mechanisms engaged by developmental alcohol exposure, among them neuronal loss, neuroinflammation, and oxidative injury, are not specific to amyloid and tau pathology, and any cardiometabolic burden in adults with FASD would act principally through cerebrovascular injury. Adult alcohol use disorder, when present, adds a third component through direct neuronal toxicity, thiamine deficiency, and cerebellar and mammillary body damage. The more plausible prediction is therefore mixed pathology, in which vascular cognitive impairment and alcohol-related neuronal damage combine with

https://doi.org/10.12779/dnd.2026.25.4.195

a variable and as yet unquantified degree of Alzheimer-type change, expressed earlier than expected because reserve is low. This has a direct methodological consequence: studies testing the hypothesis should not confine themselves to amyloid and tau biomarkers. White matter hyperintensity burden, covert infarcts, cerebral microbleeds, and measures of cerebellar and mammillary body volume belong in the same assessment, and a negative amyloid result would not refute the hypothesis.

The three pathways may operate together, and **Fig. 1** represents them as a multiple-hit model in which a prenatal exposure lowers the starting point of the cognitive trajectory, may steepen its subsequent decline, and increases the probability of additional insults. The model generates testable predictions: individuals with FASD should exhibit earlier onset of cognitive decline, higher dementia prevalence at any given age, and disproportionate representation among early-onset and mixed-etiology dementias.

DIAGNOSIS OF DEMENTIA IN NEURODEVELOPMENTAL DISORDERS

The argument so far presumes that dementia can be diagnosed in an individual whose cognitive function was impaired from birth. Whether that presumption holds is a definitional question. Dementia, or major neurocognitive disorder, requires evidence of significant cognitive decline from a previous level of performance together with substantial impairment on objective testing[39]; if cognitive function was impaired from birth, it may be asked whether decline can be meaningfully identified, and whether the concept of dementia applies at all. The criteria do not, however, exclude individuals whose baseline is developmental. The deficits must represent change rather than a lifelong pattern, and although performance in major neurocognitive disorder typically falls two or more standard deviations below appropriate norms, objective performance is interpreted against the individual's own prior performance, optimally a previous administration of the same test. The manual describes major neurocognitive disorder as frequently co-occurring with neurodevelopmental disorders and identifies clarification of the individual's baseline status as the means of distinguishing them; the only exclusion bearing on this point is that the deficits not be better explained by another mental disorder.[39]

Down syndrome provides the most informative precedent. Adults with Down syndrome have intellectual disability from birth, yet AD-related dementia is diagnosed routinely, its natural history has been characterized using the same biomarker framework as in the general population, and the population is now treated as a genetically determined form of AD suitable for prevention trials.[40-42] The methodological requirements are established: an individual baseline, informant-based instruments and neuropsychological measures calibrated for intellectual disability, and vigilance for diagnostic overshadowing. Prevalence estimates of dementia in intellectual disability vary with the criteria applied,[43] indicating a problem of measurement rather than of principle. Dementia in Down syndrome arises from triplication of the amyloid precursor protein gene, a mechanism without counterpart in FASD; the precedent establishes only that a superimposed neurodegenerative process can be diagnosed in a population with lifelong cognitive impairment.

Three considerations are particularly relevant to FASD. First, most individuals with FASD do not have intellectual disability; cognitive function typically lies in the borderline or

https://doi.org/10.12779/dnd.2026.25.4.195

low-average range, so the ordinary concept of decline from a stable adult baseline applies without modification, provided the baseline is documented. Second, the 2024 revised Alzheimer's Association criteria define the disease biologically, by amyloid and tau pathology detectable through fluid or imaging biomarkers, independent of cognitive status,[44] so whether PAE increases AD pathology can be examined without reference to the clinical definition of dementia. Third, the likely consequence is not that dementia in FASD cannot be diagnosed but that it will be under-diagnosed, as it was in Down syndrome for decades. This consideration strengthens rather than weakens the case for prospective study.

THE KOREAN CONTEXT

Korea combines a high prevalence of PAE, limited clinical recognition of FASD, and a concentrated population of children at elevated risk in residential care. Between 12% and 16% of Korean women report alcohol consumption during pregnancy, and drinking among Korean women of reproductive age has been increasing.[45,46] The estimated prevalence of FAS in Korea, 18 to 51 per 10,000, derives from a single epidemiological survey conducted in 2012 and exceeds the global average for FAS,[45] yet FASD is rarely diagnosed in Korean clinical practice. Diagnostic criteria were developed in populations of European ancestry, Korean norms for palpebral fissure length and the lip-philtrum guide do not exist, and clinician awareness remains limited.

The only systematic study of the FASD phenotype in Korean children screened 307 children and adolescents in seven institutions in Seoul and Gyeonggi Province; of the 113 who screened positive for growth deficiency, 87 underwent dysmorphological evaluation, of whom 13 were classified as FAS, 44 as deferred, and 30 as no FAS. Classification rested on physical features and growth alone because prenatal exposure histories were unavailable; palmar crease abnormalities were more frequent in children classified as FAS, and the investigators suggested that some facial features may differ in Korean children because of ethnic variation.[47] The choice of institutional settings for this study reflects the circumstances in which children enter residential care, namely parental substance use, maltreatment, and family breakdown, which overlap with those that accompany PAE.[9]

A national survey commissioned by the Korean Ministry of Health and Welfare compared ADHD diagnosis and prescribing among all children in residential care with national health insurance claims data for the general child population. In 2019, 9.0% of children in care had been diagnosed with ADHD and 8.4% were receiving ADHD medication, against a reported general-population prescription rate of 0.09%; diagnosis rose from 5.6% in 2016 to 9.0% in 2019, which the investigator attributed to improved access to psychiatric assessment.[48]

Three findings of that report are relevant to the present analysis. First, 88% of the diagnoses were made after admission to the facility, so the diagnostic decision is taken within the child welfare system rather than predating entry to it. Second, the reasons for placement among medicated children—maltreatment in 32.5%, family dissolution in 18.7%, non-marital birth in 18.5%, and poverty or parental unemployment in 16.7%—correspond to the circumstances in which PAE is most likely; 30% of these children had a registered disability, in three-quarters of cases intellectual disability.[48] Third, the report recommends comprehensive assessment at entry, multidisciplinary diagnosis, and periodic review, but makes no reference to prenatal exposure or to FASD. Because FASD is 17 to 19 times more prevalent

https://doi.org/10.12779/dnd.2026.25.4.195

in child welfare settings than in the general population[9] and is accompanied by ADHD in more than half of cases,[17,18] a proportion of these children are likely to have unrecognized FASD, recorded under a diagnosis that does not prompt the lifelong health surveillance the condition warrants.

An identifiable and accessible cohort therefore exists in which the hypothesis could be tested prospectively. The public health implications would also be considerable. Korea has one of the most rapidly aging populations in the world, and national dementia policy has invested substantially in early detection and in managing established modifiable risk factors, but prenatal exposures have not been considered. If even a small fraction of dementia in Korea were attributable to PAE, the absolute number of cases would be appreciable and, unlike cases attributable to most other risk factors, preventable at a single identifiable point.

Several features of the Korean health system favor such an investigation. Nationwide health insurance claims data, a national dementia registry, and a centrally administered child welfare system with retrievable placement records are seldom available together in one setting. Linkage of FAS diagnostic codes (Q86.0) or documented prenatal exposure with subsequent cognitive outcomes is technically feasible, but no such linkage analysis has yet been reported. Establishing the prevalence of FASD in Korean residential care is a prerequisite for this and for the longitudinal work proposed in the following section.

RESEARCH AGENDA AND CLINICAL IMPLICATIONS

Six approaches could move this proposition from hypothesis to evidence: five research strategies and one immediately implementable change in clinical practice (**Table 2**).

Table 2. Proposed research agenda for FASD and dementia

Approach	Population	Measures	Feasibility and time frame
Midlife biomarker study	Adults with a childhood FASD diagnosis (North American cohorts aged 40–55 yr); adults discharged from Korean residential care, identifiable from facility records	Plasma p-tau217, NfL, GFAP; hippocampal volume; neuropsychological battery; vascular risk profile	High; 2–3 yr; uses existing cohorts
Record linkage	National claims and registry data (Korea, Nordic countries)	FAS diagnosis (Q86.0), maternal alcohol use disorder in pregnancy, or childhood residential care linked to MCI and dementia diagnoses; competing risk of death modeled explicitly	Moderate; constrained by under-diagnosis, cohort youth and premature mortality; repeatable as cohorts age
Prospective documentation at entry into care	Children entering residential and foster care	PAE confirmed by the criteria of the Canadian diagnostic guideline (clinical observation, maternal self-report, collateral report, blood alcohol records, alcohol treatment, or related social, legal or medical problems); sentinel facial features; growth and head circumference	High; immediate clinical value; 88% of ADHD diagnoses in Korean residential care are made after entry, making this the actionable point[48]
Cross-sectional FASD screening in children already treated	Children in residential care currently receiving ADHD medication	Sentinel facial features and prenatal exposure documentation applied retrospectively; proportion never assessed for FASD	Moderate; requires consent and dysmorphology expertise; 1–2 yr; testable within existing facility networks
Experimental models	Aged PAE rodents; PAE in transgenic AD models	Replication of Alzheimer-type marker findings; sex differences; interaction with adult alcohol use; timing of anti-inflammatory and anti-amyloid intervention	High; 2–4 yr
Dementia clinic history taking	Patients with early-onset, low premorbid baseline, or atypical presentations	Birth weight, maternal drinking during pregnancy, developmental milestones, childhood ADHD, history of institutional care	High; no cost; immediately implementable

FASD: fetal alcohol spectrum disorder, p-tau217: tau phosphorylated at threonine 217, NfL: neurofilament light chain, GFAP: glial fibrillary acidic protein, FAS: fetal alcohol syndrome, MCI: mild cognitive impairment, PAE: prenatal alcohol exposure, ADHD: attention-deficit/hyperactivity disorder, AD: Alzheimer's disease.

https://doi.org/10.12779/dnd.2026.25.4.195

Midlife biomarker studies

The North American FASD cohorts now aged 40 to 55 years, and the Korean institutional cohort now in young adulthood, could be assessed with plasma biomarkers of AD and neurodegeneration and with structural imaging. Because current criteria permit a biological diagnosis of AD on the basis of fluid biomarkers alone,[44] preclinical pathology could be detected decades before dementia in a population never examined for it. Such a design would also separate the two hypotheses: at a comparable age, a higher amyloid or tau burden in exposed individuals would favor the pathology hypothesis, whereas a comparable burden accompanied by earlier or more severe cognitive impairment would favor the reserve hypothesis.

Record linkage

National claims and registry data in Korea and the Nordic countries could link FAS diagnoses, maternal alcohol use disorder during pregnancy, or childhood residential care with subsequent diagnoses of mild cognitive impairment and dementia. Such analyses will initially be constrained by under-diagnosis, by the youth of the exposed population, and by premature mortality, which must be modeled as a competing risk, but could be repeated as cohorts age.

Prospective documentation

Prenatal exposure history should be recorded at entry into residential and foster care, and FASD screening incorporated into the health assessment of children in care, as recommended in Canada.[49] The Canadian guideline defines confirmation of exposure operationally, through clinical observation, maternal self-report, collateral report, blood alcohol records, alcohol treatment, or related social, legal, or medical problems,[49] so such information could be obtained at the time of placement. Because 88% of ADHD diagnoses in Korean residential care are made after admission,[48] the entry assessment is the practical point of intervention. A preliminary step is to determine how much relevant information already exists in the records of children placed through child protection investigation, which include more detailed documentation of parental circumstances.

Cross-sectional FASD screening

Children in residential care who are already receiving ADHD medication constitute a defined population in which sentinel facial features could be assessed and prenatal exposure sought retrospectively in placement records. Such a study is feasible within existing facility networks and would establish what proportion of these children have unrecognized PAE.[48]

Experimental models

Aged PAE animals, and PAE in transgenic AD models, should be studied with attention to sex differences, to the interaction of prenatal exposure with adult drinking, and to the timing of anti-inflammatory or anti-amyloid intervention.

Clinical and public health practice

The implications for practice are limited in scope but immediately applicable. History taking in memory clinics rarely extends to birth weight, maternal drinking, or developmental milestones, yet this information is obtainable from patients or relatives in a substantial proportion of cases and may inform the interpretation of an early-onset presentation, a low premorbid baseline, or an atypical neuropsychological profile. FASD should be considered in the differential diagnosis of cognitive impairment in adults with a history of institutional

https://doi.org/10.12779/dnd.2026.25.4.195

care, childhood ADHD, learning difficulties, or facial dysmorphology, particularly when decline begins before 65 years of age. Because adaptive function in FASD is generally reported to plateau in early adulthood, assessment of suspected FASD should establish the individual's own plateau of function and document any departure from it. A structured informant history of the best attained level of independent living, employment, and daily functioning, together with repeated rather than single administration of the same neuropsychological battery, provides the reference against which decline can be judged. School records, disability assessments, and earlier psychological reports often supply the earliest documented level of function. Because the expected phenotype is likely to be mixed, criteria developed for pure AD may not apply directly in this population, and vascular and alcohol-related contributions warrant assessment alongside amyloid and tau. For public health, if the hypothesis is supported, framing abstinence during pregnancy as dementia prevention would extend the prevention message to prospective parents, a group that dementia risk-reduction programs do not currently address.

LIMITATIONS OF THE CURRENT EVIDENCE

The hypothesis presented here rests on inference rather than on direct evidence. No human study has examined the association between PAE and dementia, and the animal literature is small and heterogeneous: the central observation of Alzheimer-type markers in middle-aged exposed rodents rests on a single study that has not been independently replicated, and the exposure paradigms and time points examined remain limited. Confounding will be a major concern in any future human study: maternal drinking during pregnancy is associated with smoking, poor nutrition, low socioeconomic status, and adverse childhood experiences, each of which independently affects cognitive aging, and isolating the specific contribution of alcohol will require careful design. Under-diagnosis of FASD in adults means that registry-based studies will identify only the most severe and clinically apparent cases. Sex is a further and largely unexamined source of variation: animal studies indicate sex-specific effects of PAE on the stress axis, immune function, and hippocampal outcomes,[26] and women carry a higher lifetime risk of AD, whereas men with FASD may more often develop alcohol use disorder. FASD varies widely in exposure pattern, phenotype, and life course, so dementia risk is unlikely to be evenly distributed across the spectrum. A final consideration operates in the opposite direction. Adults with FASD experience premature mortality, with one Canadian population-based estimate placing mean life expectancy in FAS at 34 years,[50] and competing risk of death will reduce the number of individuals surviving to the age at which dementia becomes common. Crude dementia incidence in this population may therefore understate the underlying susceptibility, and future analyses will need to account for competing risk rather than treat observed incidence as the outcome of interest.

CONCLUSION

FASD is a common, lifelong, and preventable neurodevelopmental condition whose consequences in late life have not been systematically examined. Experimental work in rodents indicates that developmental alcohol exposure engages several mechanisms relevant to neurodegeneration and leaves the adult brain with diminished structural and functional reserve; the further proposition that it directly increases amyloid or tau burden rests on a single unreplicated study and should be treated as provisional. Human data

https://doi.org/10.12779/dnd.2026.25.4.195

show that adults with FASD carry a substantial burden of social adversity and alcohol use disorder, each an established dementia risk factor, while evidence on their cardiometabolic health remains limited. The convergence of these factors in a single population constitutes grounds for investigation rather than evidence that an association exists; the question has not been examined epidemiologically, and the expected phenotype is more likely mixed than purely Alzheimer-type. The objection that dementia cannot be diagnosed in a congenital disorder is addressed by the diagnostic criteria themselves, by experience in Down syndrome, and by the biological definition of AD. As the first diagnosed cohorts approach the age of dementia onset, the hypothesis can be tested prospectively rather than left to retrospective recognition. Korea, where the relevant health and child welfare records already exist in linkable form, is one setting in which such studies could begin. If supported, the hypothesis would extend the life-course model of dementia prevention to the prenatal period, where the exposure itself is preventable.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-446. PUBMED | CROSSREF
2. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet 2024;404:572-628. PUBMED | CROSSREF
3. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr 2004;23:588S-595S. PUBMED | CROSSREF
4. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet 1973;302:999-1001. PUBMED | CROSSREF
5. Hoyme HE, Kalberg WO, Elliott AJ, Blankenship J, Buckley D, Marais AS, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. Pediatrics 2016;138:e20154256. PUBMED | CROSSREF
6. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. Lancet Glob Health 2017;5:e290-e299. PUBMED | CROSSREF
7. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S. Global prevalence of fetal alcohol spectrum disorder among children and youth: a systematic review and meta-analysis. JAMA Pediatr 2017;171:948-956. PUBMED | CROSSREF
8. May PA, Chambers CD, Kalberg WO, Zellner J, Feldman H, Buckley D, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. JAMA 2018;319:474-482. PUBMED | CROSSREF
9. Lange S, Shield K, Rehm J, Popova S. Prevalence of fetal alcohol spectrum disorders in child care settings: a meta-analysis. Pediatrics 2013;132:e980-e995. PUBMED | CROSSREF
10. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol Rev 2011;21:73-80. PUBMED | CROSSREF
11. Goodlett CR, Horn KH, Zhou FC. Alcohol teratogenesis: mechanisms of damage and strategies for intervention. Exp Biol Med (Maywood) 2005;230:394-406. PUBMED | CROSSREF
12. Lebel C, Roussotte F, Sowell ER. Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. Neuropsychol Rev 2011;21:102-118. PUBMED | CROSSREF
13. Mattson SN, Bernes GA, Doyle LR. Fetal alcohol spectrum disorders: a review of the neurobehavioral deficits associated with prenatal alcohol exposure. Alcohol Clin Exp Res 2019;43:1046-1062. PUBMED | CROSSREF
14. Kodituwakku PW. Neurocognitive profile in children with fetal alcohol spectrum disorders. Dev Disabil Res Rev 2009;15:218-224. PUBMED | CROSSREF
15. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 2004;25:228-238. PUBMED | CROSSREF

16. Moore EM, Riley EP. What happens when children with fetal alcohol spectrum disorders become adults? Curr Dev Disord Rep 2015;2:219-227. PUBMED | CROSSREF
17. Popova S, Lange S, Shield K, Mihic A, Chudley AE, Mukherjee RAS, et al. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. Lancet 2016;387:978-987. PUBMED | CROSSREF
18. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics 2007;119:e733-e741. PUBMED | CROSSREF
19. Chaudhary S, Sarkar DK. Fetal alcohol exposure impairs learning and memory functions and elevates levels of various biochemical markers of Alzheimer's disease in the brain of 12-month-old rats. Alcohol Clin Exp Res (Hoboken) 2023;47:882-892. PUBMED | CROSSREF
20. Gil-Mohapel J, Boehme F, Kainer L, Christie BR. Hippocampal cell loss and neurogenesis after fetal alcohol exposure: insights from different rodent models. Brain Res Rev 2010;64:283-303. PUBMED | CROSSREF
21. Smiley JF, Bleiwas C, Canals-Baker S, Williams SZ, Sears R, Teixeira CM, et al. Neonatal ethanol causes profound reduction of cholinergic cell number in the basal forebrain of adult animals. Alcohol 2021;97:1-11. PUBMED | CROSSREF
22. Drew PD, Kane CJ. Fetal alcohol spectrum disorders and neuroimmune changes. Int Rev Neurobiol 2014;118:41-80. PUBMED | CROSSREF
23. Kane CJM, Drew PD. Neuroinflammatory contribution of microglia and astrocytes in fetal alcohol spectrum disorders. J Neurosci Res 2021;99:1973-1985. PUBMED | CROSSREF
24. Lussier AA, Weinberg J, Kobor MS. Epigenetics studies of fetal alcohol spectrum disorder: where are we now? Epigenomics 2017;9:291-311. PUBMED | CROSSREF
25. Portales-Casamar E, Lussier AA, Jones MJ, MacIsaac JL, Edgar RD, Mah SM, et al. DNA methylation signature of human fetal alcohol spectrum disorder. Epigenetics Chromatin 2016;9:25. PUBMED | CROSSREF
26. Weinberg J, Sliwowska JH, Lan N, Hellemans KG. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J Neuroendocrinol 2008;20:470-488. PUBMED | CROSSREF
27. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 2012;11:1006-1012. PUBMED | CROSSREF
28. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chételat G, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement 2020;16:1305-1311. PUBMED | CROSSREF
29. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. JAMA 1996;275:528-532. PUBMED | CROSSREF
30. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 2006;5:87-96. PUBMED | CROSSREF
31. Vanderpeet C, Akison L, Moritz K, Hayes N, Reid N. Beyond the brain: the physical health and whole-body impact of fetal alcohol spectrum disorders. Alcohol Res 2025;45:05. PUBMED | CROSSREF
32. Lunde ER, Washburn SE, Golding MC, Bake S, Miranda RC, Ramadoss J. Alcohol-induced developmental origins of adult-onset diseases. Alcohol Clin Exp Res 2016;40:1403-1414. PUBMED | CROSSREF
33. Coles CD, Grant TM, Kable JA, Stoner SA, Perez A; Collaborative Initiative on Fetal Alcohol Spectrum Disorders. Prenatal alcohol exposure and mental health at midlife: a preliminary report on two longitudinal cohorts. Alcohol Clin Exp Res 2022;46:232-242. PUBMED | CROSSREF
34. Oh SS, Kim YJ, Jang SI, Park S, Nam CM, Park EC. Hospitalizations and mortality among patients with fetal alcohol spectrum disorders: a prospective study. Sci Rep 2020;10:19512. PUBMED | CROSSREF
35. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. Alzheimers Res Ther 2019;11:1. PUBMED | CROSSREF
36. Schwarzinger M, Pollock BG, Hasan OSM, Dufouil C, Rehm J; QalyDays Study Group. Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective cohort study. Lancet Public Health 2018;3:e124-e132. PUBMED | CROSSREF
37. Sonuga-Barke EJS, Kennedy M, Kumsta R, Knights N, Golm D, Rutter M, et al. Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: the young adult follow-up of the longitudinal English and Romanian Adoptees study. Lancet 2017;389:1539-1548. PUBMED | CROSSREF
38. Miguel PM, Pereira LO, Silveira PP, Meaney MJ. Early environmental influences on the development of children's brain structure and function. Dev Med Child Neurol 2019;61:1127-1133. PUBMED | CROSSREF

39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed., text revision. Washington, DC: American Psychiatric Association Publishing; 2022.
40. Zigman WB, Lott IT. Alzheimer's disease in Down syndrome: neurobiology and risk. Ment Retard Dev Disabil Res Rev 2007;13:237-246. PUBMED | CROSSREF
41. Strydom A, Coppus A, Blesa R, Danek A, Fortea J, Hardy J, et al. Alzheimer's disease in Down syndrome: an overlooked population for prevention trials. Alzheimers Dement (N Y) 2018;4:703-713. PUBMED | CROSSREF
42. Fortea J, Vilaplana E, Carmona-Iragui M, Benejam B, Videla L, Barroeta I, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet 2020;395:1988-1997. PUBMED | CROSSREF
43. Strydom A, Livingston G, King M, Hassiotis A. Prevalence of dementia in intellectual disability using different diagnostic criteria. Br J Psychiatry 2007;191:150-157. PUBMED | CROSSREF
44. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024;20:5143-5169. PUBMED | CROSSREF
45. Hur YM, Choi J, Park S, Oh SS, Kim YJ. Prenatal maternal alcohol exposure: diagnosis and prevention of fetal alcohol syndrome. Obstet Gynecol Sci 2022;65:385-394. PUBMED | CROSSREF
46. Oh SS, Park S, You YA, Jee Y, Ansari A, Kim SM, et al. Prenatal exposure to alcohol, tobacco, and coffee: associated congenital complications and adverse birth outcomes. Int J Environ Res Public Health 2021;18:3140. PUBMED | CROSSREF
47. Lee HS, Jones KL, Lee HK, Chambers CD. Fetal alcohol spectrum disorders: Clinical phenotype among a high-risk group of children and adolescents in Korea. Am J Med Genet A 2016;170A:19-23. PUBMED | CROSSREF
48. Hong M. *Investigation on Children Taking Anti-ADHD Medications in Child Custody Facilities*. Sejong: Ministry of Health and Welfare; 2019.
49. Cook JL, Green CR, Lilley CM, Anderson SM, Baldwin ME, Chudley AE, et al. Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan. CMAJ 2016;188:191-197. PUBMED | CROSSREF
50. Thanh NX, Jonsson E. Life expectancy of people with fetal alcohol syndrome. J Popul Ther Clin Pharmacol 2016;23:e53-e59. PUBMED