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REVIEW ARTICLE

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# Secondhand smoke exposure and pediatric brain development: resolving the paradox of BDNF dysregulation

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**ABSTRACT**

Prenatal secondhand smoke (SHS) exposure is an increasingly recognized yet mechanistically undercharacterized risk factor for neurodevelopmental impairment. Brain-derived neurotrophic factor (BDNF) is essential for neurogenesis, neuronal survival, and synaptic plasticity, but prior studies report inconsistent findings on its regulation by tobacco-derived toxicants, a discrepancy that has impeded translational progress. This narrative review synthesized 58 sources retrieved from PubMed, Scopus, and Google Scholar (2000–2025), comprising predominantly rodent mechanistic studies together with a smaller set of human post-mortem and observational reports, addressing the differential regulation of the BDNF precursor (proBDNF) and its mature isoform (mBDNF) following tobacco or nicotine exposure. Because isoform-specific human evidence in the context of passive prenatal SHS exposure remains scarce, the mechanistic model proposed here is derived largely from active nicotine or cigarette smoke exposure paradigms and extrapolated to the SHS context, a lower-dose exposure that may differ quantitatively, and possibly qualitatively, in its effects. Within this scope, nicotinic acetylcholine receptor activation and oxidative stress appear to upregulate total BDNF transcription, while the post-translational proteolytic conversion of proBDNF to mBDNF, mediated by furin, matrix metalloproteinases, and the tPA/plasmin system, is concurrently impaired. We propose, as a hypothesis requiring direct empirical testing rather than an established conclusion, that this imbalance redirects neurotrophic signaling from the pro-survival TrkB pathway toward the pro-apoptotic p75NTR cascade, and that it is plausibly associated with the cognitive, attentional, and behavioral difficulties reported in some prenatally exposed children. We further propose that the proBDNF/mBDNF ratio, rather than total BDNF concentration alone, may represent a more functionally relevant candidate biomarker, although its clinical utility remains unproven pending prospective validation and clarification of the peripheral-central BDNF correlation. Collectively, this model offers a testable mechanistic framework, rather than a settled explanation, for the neurodevelopmental consequences of in utero SHS exposure.

**Keywords:** brain-derived neurotrophic factor, nicotine, neurodevelopment, oxidative stress, prenatal exposure, secondhand smoke

## Introduction

Indonesia is among the countries with the highest cigarette consumption rates worldwide, a pattern that imposes a substantial and persistent public health burden. Secondhand smoke (SHS) exposure represents a major preventable health concern, particularly in low- and middle-income countries (LMICs), where household smoking remains pervasive. Maternal exposure to cigarette smoke, whether active or passive, is common in domestic environments, and women in these settings are frequently and repeatedly exposed to SHS [1]. Cigarette smoke contains thousands of toxic chemical compounds, including nicotine, carbon monoxide, and reactive free radicals, each capable of exerting significant biological effects on developing tissues [2–4]. Despite this high prevalence, the neurobiological mechanisms by which such exposure disrupts fetal brain development remain incompletely understood.

Prenatal cigarette smoke exposure constitutes a critical risk factor for neurodevelopmental impairment.

Accumulating evidence links this exposure to structural and functional brain alterations, including reduced cortical thickness, hippocampal abnormalities, disrupted synaptogenesis, and increased neuronal apoptosis, changes that have been associated with long-term cognitive deficits, behavioral disorders, and other adverse neurodevelopmental outcomes in exposed offspring [5–7].

Brain development begins in the prenatal period and continues into early adulthood, with the most rapid and vulnerable phases occurring during fetal life and early childhood. This process is governed by tightly regulated mechanisms, including neuronal proliferation, migration, differentiation, synaptogenesis, and myelination, and disruption during these critical windows can produce irreversible alterations in brain structure and function [8,9].

Brain-derived neurotrophic factor (BDNF) is among the most important neurotrophins regulating brain development, playing a central role in neuronal survival, synaptic plasticity, neurogenesis, and cognitive function. Adequate BDNF signaling is essential for normal brain maturation, and its dysregulation is consistently associated with neurodevelopmental impairment and cognitive dysfunction [10–12].

Current evidence on the effect of prenatal cigarette smoke exposure on BDNF expression remains inconsistent: several studies report decreased BDNF levels following exposure, whereas others report increased expression. This contradiction suggests that total BDNF concentration alone does not adequately capture the underlying neurobiological effects [4,13,14].

Emerging evidence indicates that the functional outcome of BDNF signaling depends critically on the balance between its two principal isoforms, proBDNF and mature BDNF (mBDNF), which exert opposing biological effects on neuronal survival. Disruption of this balance may shift signaling from a neuroprotective toward a pro-apoptotic state, offering a plausible mechanistic explanation for the paradox observed across prior studies.

An important caveat applies to the evidence synthesized in this review: the large majority of mechanistic studies linking cigarette smoke to BDNF dysregulation involve direct, active nicotine or whole-smoke exposure paradigms in animal models, whereas the population of primary interest, namely fetuses and neonates exposed passively through maternal SHS, receives nicotine at systemically lower and more intermittent doses [4,15–18]. Active smoking delivers nicotine to the fetal circulation in bolus concentrations within seconds of inhalation, whereas passive exposure results in lower peak concentrations absorbed more gradually through ambient inhalation, with corresponding differences in receptor saturation and downstream signaling intensity. The mechanistic framework proposed in this review is therefore an extrapolation from active-exposure evidence to the SHS context, and the degree to which the same proBDNF processing defect operates at the substantially lower nicotine doses typical of passive prenatal exposure has not been directly established [4]. This distinction is carried through the remainder of the review and is revisited explicitly in the Limitations section.

Although nicotine exposure during prenatal SHS is substantially lower than that associated with active smoking, several biological characteristics of the maternal–fetal unit support the plausibility that even chronic low-dose exposure may perturb neurodevelopmental signaling. Nicotine readily crosses the placenta and accumulates in fetal tissues, while the immature fetal liver exhibits limited metabolic capacity and slower nicotine clearance than in adults, thereby prolonging fetal exposure despite relatively low maternal concentrations. In addition, SHS exposure typically occurs repeatedly over extended periods in domestic environments, resulting in cumulative rather than acute exposure [19–21]. Such chronic low-level stimulation is biologically plausible to induce repeated activation of nicotinic acetylcholine receptors (nAChRs), promote cumulative oxidative stress, and engage redox-sensitive signaling pathways that regulate BDNF transcription and post-translational processing [22–24]. Although the magnitude of these molecular responses is likely to differ quantitatively from that observed following active smoking or experimental nicotine administration, the underlying biological

**Table 1.** Summary of studies on prenatal cigarette smoke exposure and BDNF expression

| Model/Subject | Developmental Stage | Exposure Type & Dose | Method & Brain Region | Findings (Total BDNF vs Isoform; TrkB/p75NTR) | Refs |
|---|---|---|---|---|---|
| Neonatal rats (3 age cohorts: P1–5, P5–10, P10–15) | Early postnatal (neonatal), direct exposure, not gestational | Nicotine 66 µg (fixed dose; bodyweight normalization not stated) vs saline | Immunoassay & Western blot; hippocampus, frontal cortex | Total BDNF and NGF ↓ in all groups vs control; largest expression differences in the 10–15-day and 5–10-day cohorts | [15] |
| ICR mice | Three windows compared: gestational (GD7, maternal exposure) vs early postnatal (PND2, PND21, direct inhalation) | Cigarette smoke, 10 consecutive days, timing varied by window | RT-PCR & Western blot; hippocampus | GD7 exposure → total BDNF/TrkB mRNA ↓ in hippocampus + depression-like behavior; PND21 group showed no significant change | [16] |
| Sprague-Dawley rats, adult offspring (~PND90) | Gestational (GD8–21, IV) | Nicotine 0.05 mg/kg/injection, IV, 3×/day, GD8–21 | ELISA (protein); NAc, dorsal striatum, prefrontal cortex (PFC) | Total BDNF changed in all three regions with complex prenatal-nicotine × methamphetamine interactions; BDNF levels significantly predicted conditioned hyperactivity | [17] |
| Sprague-Dawley rats, adult male offspring (20 wks) | Gestational (early/mid/late/whole pregnancy, waterpipe) | Waterpipe tobacco smoke, 2 h/day, maternal exposure at varying gestational windows | Radial arm water maze + hippocampal BDNF assay; hippocampus | Total BDNF ↓ in hippocampus, associated with short- and long-term memory impairment; no change in oxidative stress biomarkers | [18] |
| Female Sprague-Dawley rats, adolescent offspring | Gestational (in utero) | Gestational nicotine vs saline | Microarray + qRT-PCR; amygdala, prefrontal cortex, nucleus accumbens, periventricular nucleus (PVN), dorsal striatum (CPu) | Total BDNF/growth-factor pathway genes significantly modulated in a brain-region-specific manner; part of a broader cell death/survival gene network shift toward pro-death signaling | [43] |
| Sprague-Dawley rats, adolescent offspring (PND36) | Gestational (GD8–21, IV) | Nicotine 0.05 mg/kg/injection, IV, 3×/day, GD8–21 | ELISA (protein); nucleus accumbens (NAc), dorsal striatum (Str), frontal cortex (FC), hippocampus (Hipp) | Total BDNF ↑ in NAc, Str, and Hipp; ↑ in FC attenuated by adolescent methamphetamine co-exposure | [44] |
| C57BL/6 mice, male offspring (4 wks & 4–6 mo) | Gestational + early postnatal (GD4–parturition) | Mainstream cigarette smoke, 4 h/day, 5 days/wk (maternal plasma cotinine ≈25 ng/mL) | RT-PCR & Western blot; striatum, cortex | Total BDNF mRNA and protein ↓ (males only), accompanied by ↓ striatal/cortical dopamine and serotonin | [45] |
| C57BL/6J mice, young male offspring (PND20) | Gestational + lactational (pre-mating 6 wks → gestation → lactation) | 2 cigarettes twice daily (nicotine <1.2 mg, CO <15 mg per cigarette) | IHC; 7 medullary nuclei + facial (pontine) nucleus | Total BDNF ↓ in hypoglossal (XII) & nucleus of the solitary tract (NTS); TrkB ↑ in XII but ↓ in facial nucleus (region-selective) | [46] |
| Wistar rats, offspring (prenatal + perinatal + 9-wk post-wean; total 15 wks) | Prenatal (GD1 onward) through perinatal/juvenile | Nicotine 10 mg/L + Vitamin E 300 mg/L, drinking water | Biochemical assay (MDA, GSH, TOS, TAS, OSI, Caspase-3); whole brain tissue | Total BDNF ↓, accompanied by ↑ oxidative stress markers (MDA, TOS, OSI) and ↓ antioxidant markers (GSH, TAS); Vitamin E partially protective | [47] |
| Mice, juvenile offspring (PND20) | Gestational + lactational | Nicotine in maternal drinking water, gestation + lactation | Microarray, IHC, confocal microscopy; hippocampus | BDNF co-localized with Iba1+ microglia (M2 polarization state) in hippocampus; total BDNF changes linked to inflammatory/synaptic gene dysregulation | [48] |

| Model/Subject | Developmental Stage | Exposure Type & Dose | Method & Brain Region | Findings (Total BDNF vs Isoform; TrkB/p75NTR) | Refs |
|---|---|---|---|---|---|
| Swiss mice, adult female offspring | Early postnatal (lactational, P4–P17), not gestational | Nicotine 8 mg/kg/day via osmotic minipump in dam, through breastfeeding | ELISA/Western blot; cerebellum, striatum, brainstem | Total BDNF ↓ in cerebellum & striatum; long-lasting synaptic protein changes (PSD-95, synapsin I) persisting after nicotine-free period | [49] |
| Rats, adult male offspring (19 wks) | Gestational + lactational (days 4–21 of lactation) | E-cigarette aerosol, 1 h/day, gestation + lactation | Radial arm water maze + biomarker assay; hippocampus | No significant change in total BDNF (only ↑ SOD activity); long-term memory impaired despite unchanged BDNF — notable negative/null finding | [50] |
| Wistar rats, fetal offspring (GD20) + H19-7/IGF1R hippocampal cell line | Fetal (in utero, GD9–20) | Nicotine 2 mg/kg·day, s.c., GD9–GD20 | Biochemical/molecular assay + in vitro; fetal hippocampus | Total BDNF pathway ↓, with ↑ hippocampal apoptosis, ↑ glutamate excitotoxicity, and compensatory ↑ GAD67; effects replicated in vitro | [51] |
| Human fetuses/ infants (n=45: 27 fetuses [19 SIUDS + 8 controls] and 18 newborns [10 SIDS + 8 controls]; total 29 SIUDS/SIDS vs 16 controls) | Fetal to infant (25 gestational weeks–6 postnatal months) | Maternal cigarette smoking, >3 cigarettes/ day before and during pregnancy (self-reported history); 13/29 SIUDS/ SIDS mothers vs 3/16 control mothers were active smokers | IHC (BDNF-Index, Class 0–3) + TUNEL (apoptosis) + GFAP (astrogliosis); pontine Kölliker-Fuse nucleus (brainstem) | BDNF-Index Class 0 (negative) in 7/19 SIUDS and 7/10 SIDS vs 0/8 fetal and 6/8 infant controls; KFN hypoplasia/ agenesis in 12/19 (63%) SIUDS and 3/10 (30%) SIDS vs 0/16 controls ($p<0.05$–$p<0.01$); concurrent astrogliosis (GFAP+) in 8/19 SIUDS (42%, $p<0.01$) and apoptosis (TUNEL+) in 8/19 SIUDS and 6/10 SIDS interneurons; abnormalities correlated with maternal smoking (77% of smoker-mother sudden-death cases vs 67% of smoker-mother controls affected, $p<0.01$); proBDNF/mBDNF isoform not distinguished | [55] |
| Human fetuses/ infants (n=45 total: 29 SIUDS/ SIDS [19 fetal SIUDS + 10 infant SIDS] vs 16 controls [8 fetal + 8 infant]) | Fetal to infant (25 gestational weeks–6 postnatal months) | Maternal cigarette smoking, >3 cigarettes/ day (from before pregnancy); validated by maternal history and hair cotinine testing. Smoking-status comparison: 13 SIUDS/ SIDS with smoker mothers vs 29 cases (11 SIUDS + 5 SIDS + 13 controls) with non-smoker mothers | IHC (BDNF-Index, Class 0–3) + TrkB IHC; cerebellar cortex, internal granular layer (IGL), particularly posterior lobule | BDNF (pan-BDNF antibody, isoform not distinguished): 13/13 (100%) smoke-exposed SIUDS/SIDS cases showed no/ light BDNF immunosignaling (Class 0/1), vs only 6/29 (~21%) of non-smoke-exposed cases ($p<0.01$); TrkB co-expressed with BDNF in high-expression cases; no significant difference in apoptosis (TUNEL) between groups | [56] |

*PFC: Prefrontal Cortex; PVN: Paraventricular Nucleus; NAc: Nucleus Accumbens; dSTR: Dorsal Striatum; GD: Gestational Day; IHC: Immunohistochemistry; WB: Western Blot; ADHD: Attention-Deficit/Hyperactivity Disorder. Exposure conditions and dosing were verified against the original publications and standardized for consistency in terminology and units.

pathways are expected to overlap [4,22]. Accordingly, the mechanistic framework proposed in this review should be interpreted as a biologically plausible hypothesis derived from shared molecular pathways rather than as evidence that passive and active exposure produce identical neurodevelopmental effects. Direct validation in experimental models specifically designed to mimic prenatal SHS exposure remains an important priority for future research [4,22].

This narrative review was conducted through a systematic search of PubMed, Scopus, and Google Scholar for publications from January 2000 to December 2025, using the keyword combinations

"secondhand smoke AND BDNF," "prenatal nicotine AND neurodevelopment," "proBDNF AND mBDNF AND conversion," "cigarette smoke AND brain development," and "BDNF AND nAChR." Studies were included if they directly examined BDNF expression, isoform distribution, or BDNF-related signaling in the context of prenatal or early postnatal tobacco or nicotine exposure in animal models or human subjects. Studies were excluded if they did not report BDNF-specific outcomes, were non-primary-source reviews, or were non-English publications without an available translation. Reporting of this narrative review was informed by the Scale for the Assessment of Narrative Review Articles (SANRA) framework to improve transparency and reproducibility. A total of 58 references were included in the final synthesis.

Unlike previous reviews that primarily summarized the effects of nicotine exposure on total BDNF signaling, including the comprehensive review by Machaalani and Chen (2018) [4], the present review proposes an integrative mechanistic framework centered on impaired proBDNF-to-mature BDNF conversion as a unifying explanation for the apparent paradox between increased BDNF expression and adverse neurodevelopmental outcomes following prenatal secondhand smoke exposure. Specifically, we synthesize emerging evidence linking oxidative stress-mediated disruption of intracellular (furin) and extracellular (tPA/plasmin- and matrix metalloproteinase [MMP]-mediated) proteolytic processing to a shift from TrkB-dependent neuroprotection toward p75NTR-mediated apoptotic signaling [23–28]. Rather than simply updating previous literature, we propose a hypothesis-driven conceptual model that identifies proBDNF/mBDNF disequilibrium as a potential central mechanism underlying prenatal SHS-induced neurodevelopmental impairment, offering a testable framework to guide future mechanistic, translational, and biomarker-oriented studies while highlighting key knowledge gaps requiring experimental validation.

Despite substantial progress in characterizing the toxic effects of prenatal SHS exposure, a critical gap persists: no prior review has explicitly integrated evidence on BDNF isoform dynamics, specifically the proBDNF/mBDNF ratio, as a mechanistic bridge between contradictory expression data and observed neurodevelopmental outcomes. This review aims to fill that gap by proposing an isoform imbalance framework as a candidate, hypothesis-generating explanation for the BDNF paradox in prenatal smoke exposure, with particular relevance to LMICs, where the burden of SHS-exposed pregnancies remains highest.

## Cigarette smoke exposure as a neurodevelopmental risk factor

Cigarette smoke is a complex mixture of over 7,000 chemical compounds distributed across particulate and gas phases, including nicotine, carbon monoxide, formaldehyde, polycyclic aromatic hydrocarbons, and heavy metals. Beyond these toxic constituents, cigarette smoke constitutes a major exogenous source of reactive oxygen and nitrogen species (ROS and RNS), generated through pyrolysis and subsequent oxidative reactions during combustion [3,29,30]. These reactive species induce oxidative stress by damaging lipids, proteins, and nucleic acids, ultimately leading to neuronal injury. The heavy metals present further exacerbate this redox imbalance by catalyzing the formation of highly reactive hydroxyl radicals via Fenton-type reactions. Together, these convergent mechanisms establish prenatal cigarette smoke exposure as a potent neurotoxic insult, particularly during critical windows of brain development when the fetal nervous system exhibits heightened vulnerability to oxidative damage [31,32].

It is important to note that the majority of mechanistic evidence in this area derives from animal models, which differ from human gestational conditions in exposure route, dose, and developmental timing. Human post-mortem studies (see Table 1) are limited by a small sample size (n = 45, drawn from a single underlying cohort of SIUDS/SIDS cases and controls reported across two publications) and retrospective design. These methodological differences partly account for the

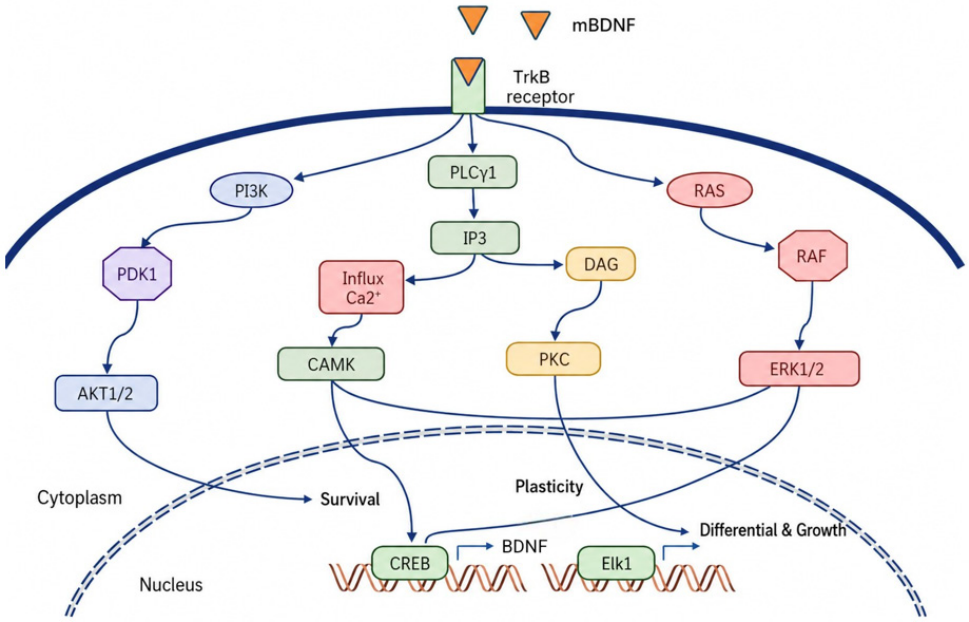


**Figure 1.** BDNF signaling pathways activated via the TrkB receptor. Binding of mature BDNF (mBDNF) to the TrkB receptor activates three major intracellular signaling cascades: (1) the PI3K–PDK1–AKT1/2 pathway, which mediates neuronal survival; (2) the PLCγ1–IP3/DAG–CaMK/PKC pathway, which regulates synaptic plasticity; and (3) the RAS–RAF–ERK1/2 pathway, which governs neuronal differentiation and growth. These three pathways subsequently converge on nuclear transcription factors, including CREB and Elk1, to modulate downstream gene expression. Adapted with modification from Jin (2020) [41].

heterogeneity in reported outcomes across studies, and should be considered when interpreting the mechanistic conclusions of this review.

## Nicotine as a central neurotoxic mediator

Among the constituents of cigarette smoke, nicotine is widely regarded as the principal neuroactive and neurotoxic compound. It acts as an agonist at nicotinic acetylcholine receptors (nAChRs), modulating neuronal excitability and neurotransmitter release during developmental stages when these processes are especially sensitive to perturbation [33–35]. Activation of nAChRs promotes calcium influx and triggers multiple intracellular signaling cascades, including the cAMP/PKA/CREB, CaMK, and MAPK/ERK pathways. Although these cascades may transiently upregulate BDNF transcription, chronic nicotine exposure ultimately disrupts normal neuronal development by inducing apoptosis, reducing neuronal density, and impairing synaptic formation [4,36,37]. Notably, prenatal nicotine exposure has been consistently associated with structural and functional brain alterations, including reduced cortical development and impaired neuronal maturation, findings that underscore its critical contribution to neurodevelopmental toxicity [7,38].

Critically, however, the upregulation of BDNF transcription triggered by nAChR activation does not equate to enhanced neuroprotective signaling. Studies comparing acute and chronic nicotine exposure reveal divergent outcomes: acute exposure may transiently increase mature BDNF through CREB-dependent mechanisms, whereas chronic prenatal exposure is more consistently associated with impaired proBDNF processing and an unfavorable proBDNF/mBDNF ratio [4,14]. This temporal distinction represents an important methodological consideration when interpreting studies that report increased BDNF under nicotine exposure, because brief exposure windows may fail to capture the dominant chronic-exposure phenotype.

## BDNF biology and functional significance

Brain-derived neurotrophic factor (BDNF) is a central regulator of neurodevelopment, governing neurogenesis, neuronal differentiation, synaptic

plasticity, and cell survival [39]. BDNF is synthesized as a precursor, proBDNF, which is subsequently cleaved into mature BDNF (mBDNF) through proteolytic processing mediated principally by furin and matrix metalloproteinases (MMPs) intracellularly and at the cell surface, and by the extracellular tissue plasminogen activator (tPA)/plasmin system, which converts secreted proBDNF to mBDNF and is required for activity-dependent, long-term forms of hippocampal synaptic plasticity [12,28,40,41].

These two isoforms exert opposing biological effects on neuronal fate. ProBDNF preferentially binds to the p75 neurotrophin receptor (p75NTR) to activate apoptotic signaling cascades, whereas mBDNF binds to tropomyosin receptor kinase B (TrkB) to promote neuronal survival and synaptic plasticity [11,12]. The intracellular signaling cascades mediated by mBDNF through TrkB receptors are illustrated in Figure 1. Consequently, the functional outcome of BDNF signaling is determined not solely by its total expression level but, more critically, by the relative balance between proBDNF and mBDNF. Recent evidence further indicates that the proBDNF/mBDNF ratio progressively increases in the context of neurodegeneration [22,25], raising the hypothesis, extended in this review, that analogous disruptions in this balance during early life could serve as indicators of aberrant neurodevelopmental trajectories.

The BDNF paradox in prenatal smoke exposure

Evidence regarding the effect of cigarette smoke exposure on BDNF expression remains inconsistent across the literature. Several studies have reported decreased BDNF levels following acute exposure, whereas others have demonstrated increased expression under conditions of chronic exposure. A summary of key experimental and clinical studies illustrating these discrepant findings is presented in Table 1 [4,42]. It is important to note that most of the studies summarized in Table 1, including the two human post-mortem studies with a smoke-exposed versus non-exposed comparison (references 55 and 56), used a general (pan-BDNF) antibody and quantified overall BDNF immunoreactivity, mRNA, or protein without distinguishing proBDNF from mature BDNF. The only human study identified that used isoform-specific immunolocalization distinguishing proBDNF from mature BDNF (reference 54, Tang et al.) compared infant versus adult brainstem/hippocampus rather than smoke-exposed versus non-exposed cases, and for this reason was excluded from Table 1. Consequently, no currently available human study combines both an isoform-specific readout and a direct prenatal/perinatal smoke-exposure comparison. The proBDNF/mBDNF ratio shift proposed later in this review is therefore inferred indirectly, by combining the altered total BDNF findings in exposed human cohorts with isoform-specific mechanistic evidence from non-exposure contexts, rather than being directly demonstrated by any single study, and should accordingly be regarded as a working hypothesis rather than an established finding.

This paradox may be partly reconciled by distinguishing total BDNF expression from the relative abundance of its functionally opposing isoforms. Although total BDNF levels may increase as a compensatory response to cellular stress, cigarette smoke exposure could concurrently impair the proteolytic conversion of proBDNF to mBDNF, a shift that, if confirmed, would elevate the proBDNF/mBDNF ratio and redirect downstream signaling toward a pro-apoptotic state [10,22]. The molecular mechanisms proposed to underlie this isoform-level imbalance, and the extent to which each is currently supported by direct evidence, are examined in detail in the sections that follow [25,52,53].

## Nicotine-mediated mechanisms

Nicotine readily crosses the placental barrier and accumulates in the fetal brain, where it activates nicotinic acetylcholine receptors (nAChRs) and their downstream signaling cascades, thereby enhancing BDNF transcription through CREB-mediated pathways, as illustrated in Figure 2 [23]. Chronic stimulation, however, dysregulates this signaling and impairs post-translational processing of BDNF, such

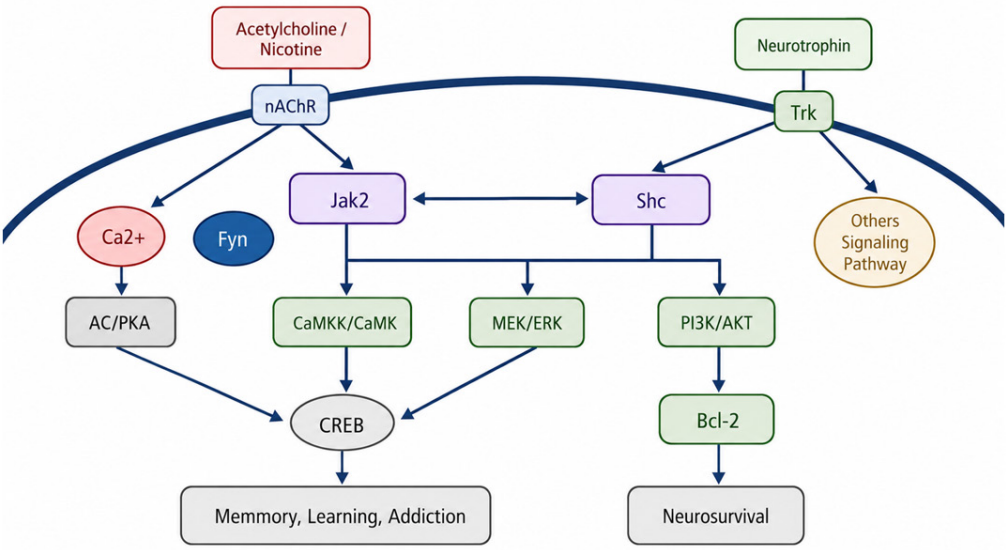


**Figure 2. Convergent signaling between nAChR and Trk/neurotrophin pathways**. Activation of nicotinic acetylcholine receptors (nAChR) by acetylcholine or nicotine triggers $Ca^{2+}$ influx and recruits the non-receptor kinases Jak2 and Fyn, which subsequently engage downstream cascades, including AC/PKA, CaMKK/CaMK, and MEK/ERK, ultimately converging on CREB phosphorylation to regulate memory, learning, and addiction-related processes. In parallel, neurotrophin binding to Trk receptors activates the Shc–PI3K/AKT–Bcl-2 axis to promote neuronal survival. The two pathways intersect at shared downstream effectors, enabling coordinated regulation of neuronal plasticity and survival. Adapted with modification from Kume et al. (2018) [23], who described this convergent signaling in the context of nAChR-mediated neuroprotection; the present review repurposes the same pathway diagram to illustrate how chronic, dysregulated activation of this convergence, rather than its physiological activation, is proposed to impair proBDNF processing, and the figure should be interpreted with this difference in framing in mind. Although adapted from studies illustrating physiological neuroprotective nAChR signaling, the present figure is intended to depict how chronic prenatal secondhand smoke exposure may dysregulate these same pathways through persistent nicotine stimulation and oxidative stress. Thus, the figure illustrates disruption of normal signaling rather than the physiological neuroprotective role of nAChRs.

that increased transcriptional activity is not matched by functional maturation of the protein and proBDNF progressively accumulates [14,16]. Experimental evidence further indicates that developmental nicotine exposure can induce multigenerational imbalances in proBDNF proteolysis, suggesting that its effects on neurotrophic signaling may persist across generations [14]. It should be noted that this multigenerational evidence, like most of the mechanistic data in this section, derives from direct nicotine administration rather than SHS exposure, consistent with the active-to-passive extrapolation caveat raised in the Introduction.

## Oxidative stress–mediated mechanisms

Cigarette smoke delivers a substantial oxidant load to fetal tissue, including reactive oxygen species (ROS) generated directly by combustion products and secondary radicals produced through nicotine metabolism [22,24]. This oxidative burden initially triggers a compensatory cellular response, activating CREB-dependent transcriptional upregulation of BDNF as part of an adaptive attempt to preserve neurotrophic support [36,40]. However, persistent oxidative stress progressively overwhelms endogenous antioxidant defenses, particularly the Nrf2 pathway, resulting in sustained redox imbalance and disruption of multiple molecular processes regulating BDNF biology [22,24]. Beyond transcriptional regulation, oxidative stress is also predicted to impair the proteolytic machinery responsible for converting proBDNF into mature BDNF through redox-sensitive effects on intracellular and extracellular proteases [25,28]. Because disruption of this proteolytic network represents the central mechanistic hypothesis proposed in this review, the intracellular and extracellular pathways involved are discussed in greater detail below (Figure 3).

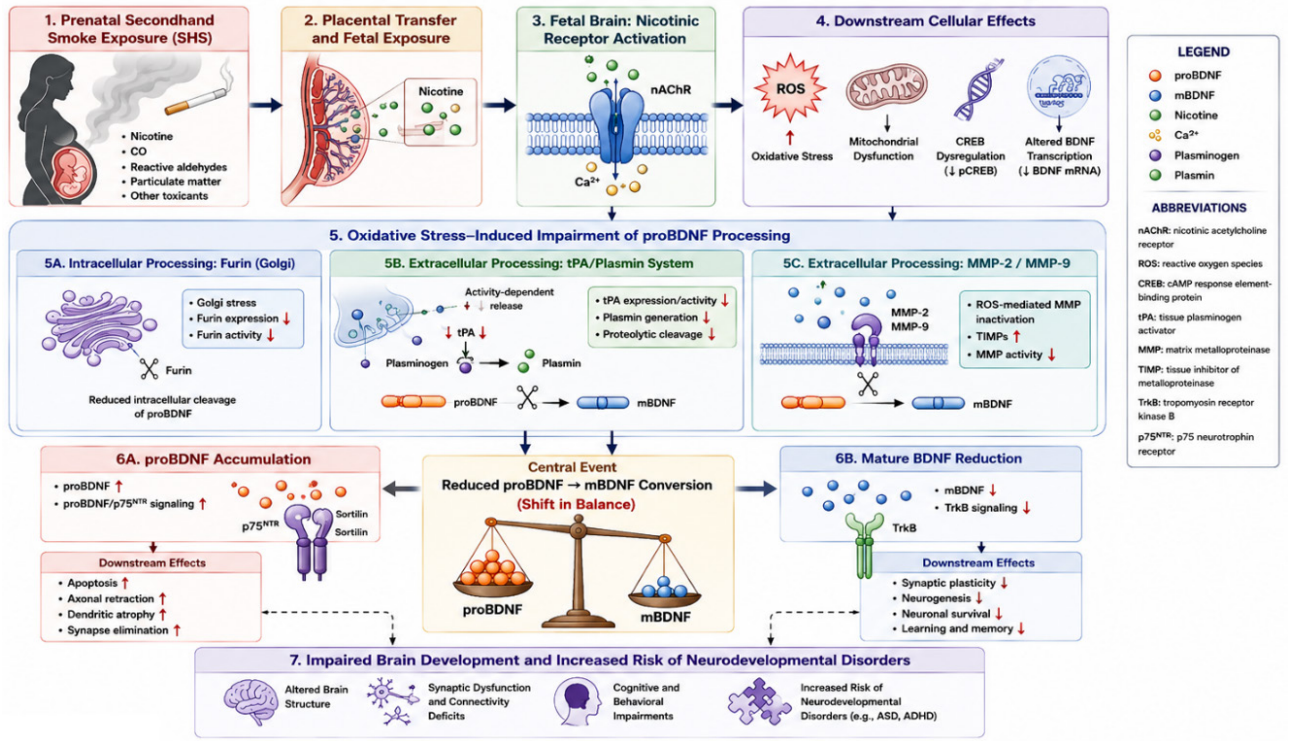


**Figure 3.** Proposed conceptual model of proBDNF/mBDNF imbalance underlying prenatal secondhand smoke-induced neurodevelopmental dysfunction.

While intracellular processing by furin generates mature BDNF before secretion, a substantial proportion of proBDNF is released into the extracellular space, where it undergoes activity-dependent proteolytic cleavage primarily through the tissue plasminogen activator (tPA)/plasmin system and, to a lesser extent, matrix metalloproteinases (MMP-2 and MMP-9) [11,28]. Among these extracellular pathways, the tPA/plasmin cascade is regarded as the principal mechanism mediating conversion of proBDNF to mature BDNF in the hippocampus, a process essential for long-term potentiation, synaptic plasticity, and memory formation [28]. Upon neuronal activation, tPA is released into the extracellular milieu and converts plasminogen into plasmin, which subsequently cleaves proBDNF into mature BDNF, thereby promoting TrkB-mediated neuronal survival while simultaneously limiting activation of the pro-apoptotic p75NTR-sortilin receptor complex [26,28]. MMP-2 and MMP-9 provide complementary extracellular proteolytic activity and may partially compensate depending on brain region, developmental stage, and physiological context [11].

Oxidative stress generated by nicotine and cigarette smoke has the potential to disrupt this coordinated proteolytic network at multiple levels [22,24]. Intracellularly, excessive reactive oxygen species impair Golgi homeostasis and reduce furin expression and enzymatic activity, thereby limiting intracellular maturation of proBDNF [11,25]. Extracellularly, oxidative stress may suppress tPA expression and plasmin generation while simultaneously promoting plasminogen activator inhibitor-1 (PAI-1), reducing the efficiency of activity-dependent proBDNF cleavage. Likewise, oxidative modification of MMPs together with increased tissue inhibitors of metalloproteinases (TIMPs) may further diminish extracellular processing efficiency. Although direct evidence demonstrating these events specifically following prenatal secondhand smoke exposure remains limited, the convergence of these redox-sensitive pathways provides a biologically plausible explanation for impaired proBDNF-to-mBDNF conversion under chronic prenatal SHS

exposure [4,22,24]. Collectively, disruption of both intracellular and extracellular proteolytic processing is expected to shift the neurotrophin balance toward proBDNF accumulation, favoring p75NTR-mediated apoptotic signaling at the expense of TrkB-dependent neuronal survival, synaptic maturation, and neurodevelopment [25–27].

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway occupies a central position within this broader system because it not only orchestrates the cellular antioxidant response but also influences neurotrophic signaling [24]. Experimental studies have demonstrated that activation of Nrf2 attenuates oxidative stress, preserves neuronal survival, and is associated with increased BDNF expression and enhanced TrkB signaling in several models of oxidative brain injury. Conversely, impaired Nrf2 signaling exacerbates oxidative damage, suppresses neurotrophic support, and compromises neuronal plasticity, thereby providing a mechanistic link between persistent redox imbalance and disrupted BDNF biology [24]. Although direct evidence specifically examining Nrf2-mediated regulation of BDNF following prenatal secondhand smoke exposure remains limited, these observations support the biological plausibility that chronic oxidative stress may influence both antioxidant defenses and neurotrophin homeostasis through interconnected Nrf2-dependent pathways [4,22,24]. Under acute or moderate oxidative stress, Nrf2 activation can partially buffer oxidative injury and preserve neurotrophic signaling. However, with the chronic and repeated oxidative insult characteristic of prenatal smoke exposure, this adaptive capacity becomes progressively exhausted, further amplifying oxidative damage and favoring a sustained shift toward proBDNF accumulation [22,24]. Consequently, the signaling environment becomes dominated by unconverted proBDNF, which preferentially engages the p75NTR-sortilin receptor complex rather than TrkB. Activation of this receptor complex initiates pro-apoptotic intracellular cascades, including RhoA-JNK signaling, thereby reversing the neuroprotective role normally mediated by mature BDNF during periods of intense neuronal proliferation, differentiation, and synaptic remodeling [25–27].

Importantly, the evidence supporting an imbalance between proBDNF and mature BDNF is not uniform across the studies summarized in this review. Most experimental and clinical investigations, including the human post-mortem studies in Table 1 [54–56], have quantified BDNF immunoreactivity, protein, or mRNA expression using pan-BDNF detection methods without antibody-based discrimination between proBDNF and mature BDNF isoforms, thereby precluding direct assessment of the proBDNF/mBDNF ratio [4,11,54–56]. Consequently, these studies cannot directly demonstrate an altered proBDNF/mBDNF ratio, even when overall BDNF immunoreactivity or expression is significantly changed in smoke-exposed cases [4,11]. Direct evidence for impaired proBDNF processing itself currently derives from a limited number of mechanistic and biochemical studies describing furin-, matrix metalloproteinase (MMP)-, and tissue plasminogen activator (tPA)/plasmin-mediated proteolytic disruption [25,28], rather than from isoform-specific measurements in human tissue. Therefore, the proBDNF/mBDNF imbalance proposed throughout this review should be interpreted as a mechanistically informed hypothesis that integrates indirect human observations of altered total BDNF expression with mechanistic evidence describing oxidative stress, altered neurotrophin signaling, and impaired proteolytic processing, rather than as definitive proof of causality [22–28]. Further studies employing isoform-specific quantification of both proBDNF and mature BDNF in experimental prenatal secondhand smoke (SHS) models and prospective human cohorts are required to directly validate this proposed mechanism.

## Clinical implications of BDNF dysregulation

The downstream clinical correlates of this molecular disruption warrant careful framing. Prenatal impairment of BDNF signaling has been associated in the literature with deficits in cognitive development, including reductions in intellectual quotient (IQ), attentional dysfunction, and a heightened risk of behavioral disorders such

as ADHD; these associations should be regarded as hypothesis-generating rather than as demonstrated consequences of the isoform imbalance proposed here, since the underlying studies are largely observational and cannot establish that proBDNF/mBDNF imbalance specifically, rather than other correlated aspects of prenatal smoke exposure, is the causal driver [6,7]. Beyond its mechanistic significance, the proBDNF/mBDNF ratio has been proposed as a candidate translational biomarker; however, its clinical applicability remains uncertain because current evidence is derived predominantly from post-mortem brain tissue rather than accessible biological samples from living individuals [57]. Direct support for the isoform imbalance model comes from human post-mortem studies summarized in Table 1, which demonstrate elevated proBDNF concentrations in brainstem tissue obtained from smoke-exposed infants who died suddenly and unexpectedly [54–56]. These findings suggest an imbalance in BDNF isoform distribution rather than a simple reduction in total BDNF. Nevertheless, this evidence remains preliminary, originates exclusively from post-mortem brain tissue, and differs fundamentally from the predominantly mechanistic animal studies discussed elsewhere in this review.

Despite these promising observations, several biological and methodological barriers currently limit the translation of the proposed proBDNF/mBDNF ratio into a clinically useful biomarker. Isoform-specific assays capable of reliably distinguishing proBDNF from mature BDNF are not yet standardized or widely available for clinically accessible biospecimens such as cord blood, dried blood spots, serum, or plasma. Moreover, whether peripheral proBDNF/mBDNF concentrations accurately reflect neurotrophin dynamics within the developing central nervous system remains an unresolved and actively debated question. Furthermore, blood-derived BDNF originates from multiple peripheral sources, including platelets, endothelial cells, and immune cells, and is influenced by sample type (serum versus plasma), platelet degranulation, pre-analytical handling, storage conditions, assay methodology, systemic inflammation, and other environmental factors independent of neurodevelopment. Consequently, peripheral BDNF measurements cannot presently be assumed to represent central nervous system isoform balance. Recent studies have further emphasized that standardized isoform-specific analytical methods and harmonized sampling protocols are prerequisites before the proBDNF/mBDNF ratio can be evaluated as a robust biomarker of neurodevelopmental injury. Likewise, although cord blood represents an attractive and minimally invasive biospecimen for neonatal risk stratification, current evidence supports its use primarily as a research tool, and prospective longitudinal studies correlating cord blood proBDNF/mBDNF concentrations with neuroimaging findings and long-term neurodevelopmental outcomes remain lacking.

Taken together, the available evidence supports the proBDNF/mBDNF ratio as a promising mechanistic and translational research biomarker rather than a validated tool for routine clinical screening. Future prospective studies integrating isoform-specific peripheral assays, neuroimaging, and longitudinal neurodevelopmental assessment will be essential to determine whether peripheral proBDNF/mBDNF measurements accurately reflect central nervous system biology and possess sufficient diagnostic accuracy for clinical application.

The mechanisms described so far center on post-translational processing, but they do not represent the only pathway by which prenatal tobacco exposure disrupts BDNF biology. Epigenetic alterations, particularly DNA methylation within regulatory regions of the BDNF gene promoter, provide an additional and partially independent layer of dysregulation that can influence baseline BDNF transcription well before any proteolytic conversion occurs [14,58]. Taken together, these converging mechanisms, spanning transcriptional regulation, oxidative enzyme inhibition, extracellular proteolysis, and epigenetic modification, offer several plausible points of therapeutic intervention, including strategies to preserve or restore furin, MMP, and tPA/plasmin activity, approaches to reduce the oxidative burden responsible for enzymatic

inhibition, and pharmacological modulation of p75NTR signaling to limit downstream apoptotic activation. These candidate interventions remain speculative and have not, to our knowledge, been tested in the specific context of prenatal SHS exposure.

## Public health and preventive implications

Framed against this mechanistic backdrop, secondhand smoke exposure emerges as a significant yet fundamentally preventable contributor to adverse neurodevelopmental outcomes. The scale of this exposure in Indonesia is considerable: the Global Adult Tobacco Survey reported that approximately 78% of non-smokers experienced SHS exposure within their own homes, and an estimated 97 million Indonesians, a figure that includes a substantial number of pregnant women, are exposed to SHS on a regular basis [19]. This pattern is not unique to Indonesia; across LMICs more broadly, household SHS exposure affects hundreds of millions of children during the prenatal and early postnatal periods, a burden made more concerning by the fact that policy protections in these settings continue to lag well behind those established in high-income countries [20,21]. The contrast with high-income countries is instructive: nations that have implemented comprehensive smoke-free household legislation alongside targeted cessation programs for pregnant women have achieved measurable reductions in both preterm birth rates and SHS-attributable neurodevelopmental morbidity, demonstrating that the neurodevelopmental harm associated with SHS is not an inevitable consequence of exposure but a modifiable one, contingent on the implementation of adequately resourced, enforceable, and culturally appropriate prevention frameworks [5,42].

In LMIC settings where regulatory enforcement capacity is limited, alternative and more feasible strategies become particularly important, including community-based interventions and the integration of SHS counseling into routine antenatal care, both of which represent cost-effective approaches that do not depend on broad legislative enforcement. Early identification of at-risk children, potentially guided by candidate biomarkers such as the proBDNF/mBDNF ratio once validated, could further sharpen these efforts by directing clinical resources toward those most likely to benefit from timely intervention [53,57]. Collectively, these considerations reinforce the importance of translating molecular insight into population-level prevention strategies and highlight the continued need for policy frameworks that protect pregnant women and young children from secondhand smoke exposure in both domestic and occupational environments.

## Synthesis of molecular mechanisms

Drawing these threads together, this review advances a coherent mechanistic framework in which prenatal SHS exposure disrupts pediatric brain development not through a straightforward increase or decrease in total BDNF, but through a specific and biologically meaningful imbalance in its active isoforms. Three converging processes, nicotine-mediated nAChR activation, oxidative stress-induced suppression of proteolytic enzyme activity via furin, MMP, and tPA/plasmin, and dysregulated CREB-dependent transcription, are proposed to act in concert to impair the conversion of proBDNF into mBDNF, redirecting neurotrophic signaling away from the pro-survival TrkB pathway and toward the pro-apoptotic p75NTR pathway [24,26]. This synthesis is illustrated schematically in Figure 4.

Earlier work by Machaalani and Chen reviewed the relationship between BDNF, TrkB, and nicotine in detail [4]; the present review differs in its explicit focus, proposing the proBDNF/mBDNF ratio, together with the convergence of transcriptional, proteolytic, and epigenetic mechanisms that govern it, as a single unifying construct intended to reconcile the directionally inconsistent total-BDNF findings reported across the wider literature. This framing, and the synthesis diagram Figure 4, represent the primary original contribution of the present review rather than a restatement of prior work. The significance of this framework extends beyond mechanistic explanation: because

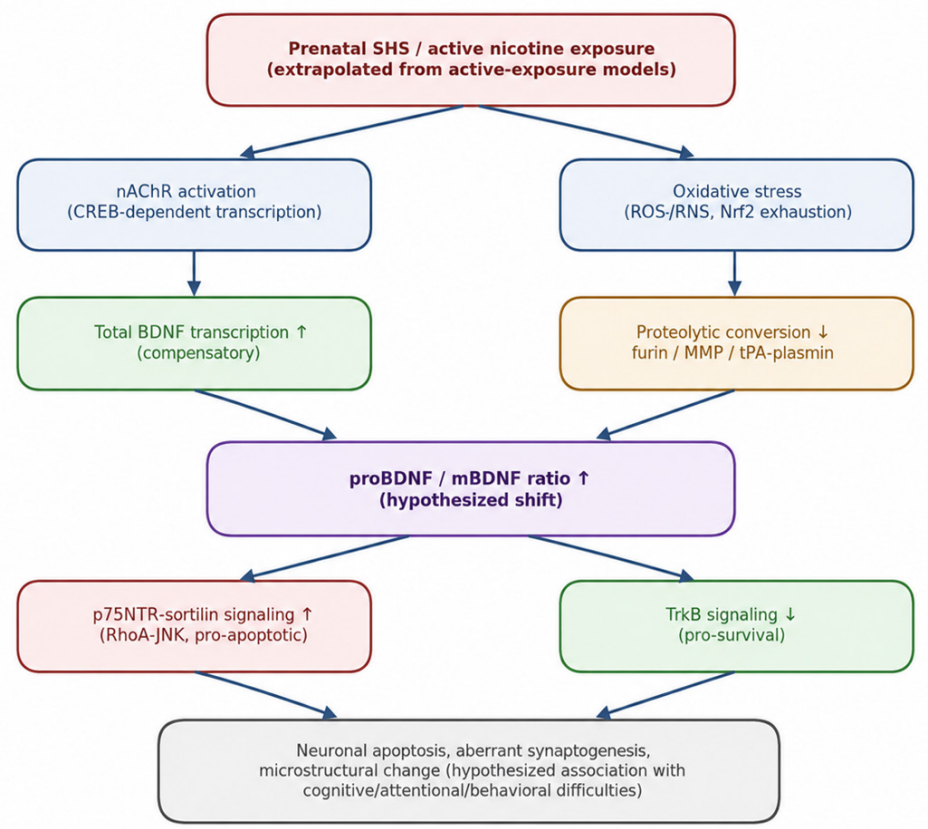


**Figure 4.** Proposed synthesis model of the isoform imbalance hypothesis. Prenatal SHS or active nicotine exposure is proposed to activate two converging pathways, nAChR-mediated CREB signaling and oxidative stress, which together increase total BDNF transcription while impairing furin-, MMP-, and tPA/plasmin-mediated proteolytic conversion of proBDNF to mBDNF. The resulting elevation in the proBDNF/mBDNF ratio is hypothesized to favor p75NTR-sortilin signaling over TrkB signaling, with a plausible downstream association with neurodevelopmental risk. This diagram is an original synthesis constructed for this review and is not adapted from a prior source.

the proBDNF/mBDNF ratio reflects this proposed shift directly, it represents a candidate biomarker construct that, if validated in prospective human cohorts, could in principle allow smoke-exposed neonates at elevated risk of later cognitive or behavioral difficulties to be identified earlier than is currently possible. Realizing this potential would require isoform-specific assays capable of reliably distinguishing protective from pathological states in accessible sample types, a capability that does not yet exist for this population and is addressed further in the Limitations and Future Directions sections below [10,22,25].

## Reconciling sources of heterogeneity

While the isoform imbalance framework offers a parsimonious explanation for the divergent total BDNF findings reported across the literature, it is unlikely to be the sole source of this heterogeneity, and several additional factors merit consideration. A substantial proportion of human data relies on peripheral, that is serum or plasma, BDNF measurements, and the extent to which peripheral concentrations faithfully reflect central proBDNF and mBDNF dynamics in the fetal or neonatal brain remains incompletely established; this measurement gap represents a source of variability that is independent of the biological mechanisms proposed here [13]. Genetic variation constitutes a second contributing factor: common polymorphisms in the BDNF gene, most notably the Val66Met variant, alter activity-dependent secretion and intracellular trafficking of the protein and could plausibly modulate individual susceptibility to smoke-induced proteolytic disruption, yet this genetic dimension has rarely been examined in the context of prenatal tobacco exposure [52].

Finally, the timing of biological sampling relative to the exposure course may itself explain part of the apparent contradiction, since the compensatory transcriptional upregulation of BDNF described earlier is likely to predominate during the early or acute phase of oxidative and cholinergic stimulation, whereas depletion of functional mBDNF and accumulation of proBDNF would be expected to become more evident as adaptive capacity is progressively exhausted with chronic exposure [24]. Future studies that account for peripheral-to-central measurement validity, BDNF genotype, and exposure chronicity will therefore be necessary to determine the relative contribution of isoform imbalance to the broader heterogeneity observed across the literature.

## Limitations

Several limitations in the current evidence base warrant explicit acknowledgment. First, the majority of mechanistic data derive from rodent models, and translation to human fetal brain development must be approached cautiously given known species differences in the timing of brain maturation, receptor expression patterns, and nicotine metabolism. Second, and directly relevant to the central premise of this review, most of the mechanistic evidence synthesized here derives from active nicotine administration or whole-smoke inhalation at doses substantially higher than those experienced through passive prenatal SHS exposure; the proBDNF/mBDNF imbalance described throughout this review is therefore an extrapolated hypothesis for the SHS context rather than a directly demonstrated phenomenon, and dose-response studies that specifically model passive, low-dose exposure are needed to confirm whether, and to what degree, the same mechanisms operate at typical household SHS exposure levels. Third, the human post-mortem studies summarized in Table 1 are constrained by a small sample size (n = 45, drawn from a single underlying cohort of SIUDS/SIDS cases and controls reported across two publications), which limits statistical power, and by their retrospective, cross-sectional design, which precludes any causal inference regarding the relationship between exposure and BDNF alteration; moreover, as noted above, these studies used a pan-BDNF antibody and did not directly measure the proBDNF/mBDNF isoform ratio. Fourth, no prospective longitudinal study has yet measured the proBDNF/mBDNF ratio directly in SHS-exposed pregnancies while simultaneously tracking neurodevelopmental outcomes over time; as a result, the central biomarker proposition of this review, while mechanistically motivated, remains clinically unvalidated. Fifth, considerable heterogeneity exists across the available studies in terms of exposure type (isolated nicotine, whole cigarette smoke, or waterpipe tobacco), route of administration, and the developmental window examined, all of which limit direct comparability across the literature. Finally, this review does not address electronic cigarettes or heated tobacco products, forms of nicotine delivery that are becoming increasingly common in Indonesia and other LMICs and that may exert BDNF-related effects distinct from those of conventional combustible cigarettes.

## Future directions

Several research priorities follow directly from the gaps identified above. Foremost among these is the need for prospective human cohort studies that longitudinally measure proBDNF and mBDNF using isoform-specific ELISA or proteomic techniques in neonates born to SHS-exposed mothers, paired with structured follow-up assessment of cognitive and behavioral development through childhood. Complementing this clinical work, animal studies would benefit substantially from standardized exposure protocols, which would allow more direct comparison of BDNF isoform dynamics across different tobacco constituents, exposure doses, and gestational windows, an area where current heterogeneity limits cross-study synthesis. Validating the proBDNF/mBDNF ratio as a practical screening biomarker constitutes another essential step, requiring both the determination of clinically actionable thresholds and an assessment

of feasibility using accessible sample sources such as cord blood or neonatal dried blood spots. At a more mechanistic level, targeted investigation of furin and MMP activity is warranted to determine whether pharmacological agents or nutritional interventions, such as antioxidant supplementation, can restore normal proBDNF processing in the setting of prenatal tobacco exposure. Epigenetic profiling of BDNF promoter methylation in SHS-exposed offspring also merits dedicated attention, particularly within Indonesian and other LMIC cohorts, where such work could clarify whether neurotrophic dysregulation carries transgenerational consequences. Finally, policy-oriented research should evaluate whether concrete public health measures, including smoke-free household mandates and antenatal cessation programs, produce measurable reductions in BDNF isoform dysregulation and its associated neurodevelopmental morbidity within LMIC populations. Taken together, these directions would substantially advance both the mechanistic understanding and the translational application of BDNF isoform biology in the context of prenatal SHS exposure.

## Conclusion

This review proposes a candidate mechanistic explanation for a long-standing paradox in the literature on cigarette smoke-induced BDNF dysregulation, centered on the relative balance between the proBDNF and mBDNF isoforms rather than on total BDNF expression alone. Three converging processes, impaired furin-, MMP-, and tPA/plasmin-mediated proteolysis, oxidative suppression of this proteolytic machinery, and dysregulated CREB-dependent transcription, are proposed to act together to shift signaling from the pro-survival TrkB pathway toward the pro-apoptotic p75NTR pathway. This framework is derived predominantly from active nicotine and whole-smoke exposure models and extrapolated to the SHS context; moreover, no currently available human study combines isoform-specific proBDNF/mBDNF measurement with a direct smoke-exposed versus non-exposed comparison, so its direct evidentiary support in human tissue remains indirect. It should therefore be regarded as a testable hypothesis that reframes previously contradictory findings into a coherent research agenda, rather than as an established mechanism. Realizing the clinical potential of the proBDNF/mBDNF ratio as an early biomarker of neurodevelopmental risk will require prospective validation, standardized isoform-specific assays suitable for accessible sample types, and clarification of the peripheral-central BDNF correlation. Collectively, these considerations reinforce the public health importance of preventing prenatal secondhand smoke exposure and outline a concrete research agenda, spanning mechanistic, translational, and policy domains, for the field to pursue.

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## Author contributions

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## Declaration of interest

The authors declare no conflict of interest.

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