



# The impact of smoking and nicotine exposure during pregnancy on fetal nephrogenesis: a systematic review

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## Review

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## Abstract

The effect of smoking and nicotine exposure during pregnancy on fetal nephrogenesis is a growing area of research. The objective of this systematic review is to summarise the current evidence in this research field. Our literature search identified a total of 415 articles from PubMed, Embase, Scopus, and Cochrane. After electronic sorting and manual screening, 18 eligible articles were found, 6 being human studies and 12 being animal studies. Articles that did not study nicotine or smoking, did not focus on fetal kidney development, or did not include nicotine or smoking exposure during pregnancy were excluded from the systematic review. The main outcomes of the studies were kidney weight, volume and size, kidney histopathology and morphology, and kidney function. Evidence from human studies identified a reduction in fetal kidney size, volume, and weight in offspring exposed to smoking during pregnancy; and the greatest impact was seen in offspring exposed to >5–10 cigarettes per day. Animal studies investigated kidney histopathology and highlighted kidney injury and microscopic changes in response to nicotine exposure during pregnancy. Further research is required to determine the impact on kidney function. Recreational nicotine use is evolving, and with the increasing use of urine cotinine in the evaluation of nicotine exposure, further research is needed.

## Introduction

Toxin and drug exposure in utero creates a suboptimal environment for fetal growth and development. It has been hypothesised that the fetus is able to adapt to these conditions by altering their physiological development, which is initially a protective mechanism, however in doing so, these adaptations are somewhat irreversible creating physiological challenges, both prenatally and postnatally, as the fetus continues to develop.<sup>1–3</sup> Studies conducted over many decades outline that maternal smoking during pregnancy is one of the leading preventable causes of birth defects and impaired fetal development.<sup>4</sup> Despite this information, in Australia in 2020 8.8% of women reported smoking during the first 20 weeks of pregnancy. This number has declined from 12.9% in 2011, however, of these women, 70–74% continue to smoke during the last 20 weeks of pregnancy. These rates have remained steady from 2011 to 2020 with an increase to 75% in 2019.

Nicotine is the main addictive teratogen within cigarettes which has been linked to adverse pregnancy outcomes and fetal development.<sup>5</sup> Prenatally, nicotine increases the risk of adverse pregnancy outcomes, including miscarriage, placental abruption, placental previa, premature labour and preterm birth. It is thought that the placental damage caused by nicotine is either the direct cause of or greatly contributes to these outcomes.<sup>5–8</sup> Nicotine acts directly on the placenta altering placental development by disrupting trophoblastic invasion and differentiation, increasing collagen content in villous stroma, decreasing angiogenesis, inducing placental hypoxia and oxidative stress, and downregulating labyrinth vascularisation.<sup>1–3,5,9,10</sup> Holloway et al proposed that changes to trophoblastic invasion and differentiation are likely mediated by placental nAChR (nicotinic acetylcholine receptors).<sup>9</sup> This disruption contributes to an increase in vascular resistance which alters the maternal-fetal circulation. Alongside this, the fetus is at higher risk of stillbirth, intrauterine growth restriction, low birth weight, birth defects, and disrupted organ development.<sup>6,8,11</sup> Hackshaw A et al. summarised a positive correlation with maternal smoking and the following birth defects: cardiovascular/heart defects; limb reduction defects; missing/extra digits; clubfoot; craniosynostosis; facial defects; eye defects; orofacial clefts; gastrointestinal defects; gastroschisis; anal atresia; hernias; and undescended testes.<sup>12</sup>

Studies have demonstrated a significant relationship between nicotine exposure and disrupted organ development. The organs studied, and which seem to be most affected are the lungs, kidneys, and brain.<sup>4–6,8</sup> In the lungs, nicotine induces formation of oxygen radicals and

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reduces the antioxidant capacity of the lungs. These alterations form mutations within the lung DNA resulting in disruption of lung growth and maintenance, which is thought to age the lungs of the offspring much faster than normal.<sup>13</sup> Studies conducted, mostly on animal species, also suggest that nicotine increases the risk of kidney injuries, such as tubular atrophy, dilatation of the tubular lumen, inflammatory infiltration and increased collagen deposition<sup>14</sup> and results in an overall reduction in kidney weight.<sup>15-17</sup> Juanxiu Lv et al demonstrated that in mice nicotine exposure in utero alters the expression of nAChRs in the central nervous system leading to fetal brain growth restriction, fetal hypoxia, and altered brain development. The study also proposed that the altered expression of nAChRs is linked to behavioural neurochemical and cognitive abnormalities in the offspring.<sup>11</sup>

Into adult life, the fetus is at risk of developing chronic conditions. Evidence suggests that this predisposition is linked to the hypothesis that the fetus develops permanent physiological adaptations in response to the suboptimal environment created by nicotine exposure. These changes place the infant at higher risk of metabolic syndromes such as hypertension, dyslipidemia, insulin resistance, and obesity, which are major risk factors for heart disease, type 2 diabetes, and stroke.<sup>2,3,5,18</sup>

This systematic review summarises the current evidence regarding the impact of smoking and nicotine exposure during pregnancy on fetal kidney development.

## Methods

The review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.<sup>19</sup>

### Search strategy

To find appropriate articles for this systematic review we conducted a systematic search of the following electronic databases: PubMed, Embase, Scopus, and Cochrane. The database searches focussed on articles that included the key search terms in the title, abstract or keywords. The key search terms utilised were: (nicotine OR smoking) AND pregnancy AND (kidney development OR fetal kidney development OR nephrogenesis) AND (smokeless tobacco OR nicotine replacement therapy OR e-cigarettes).

### Inclusion and exclusion criteria

The aim of this systematic review is to analyse the current evidence about the impact of smoking and nicotine exposure on fetal kidney development during pregnancy. We included all species, research methods, and timeframes. No timeframe was added to the database searches as limited evidence was published. The articles included in this paper were published between 1997 and 2021. Our systematic review includes any assessments of kidney development at any age, including gestational ages, and includes any amount and timeframe of smoking/nicotine exposure.

The exclusion criteria were articles that did not study nicotine or smoking, articles that did not focus on fetal kidney development or articles that did not include nicotine or smoking exposure during pregnancy.

### Data extraction and article selection

The final database search was conducted in August 2023. All results were imported to EndNote. Using this application articles

were grouped into the relevant databases and then combined to identify duplicates. The remaining articles were manually sorted and either included or excluded based on the title and abstract information. After this, the full text of the remaining articles was screened for eligibility for inclusion. During this time, citation searches of the full-text articles were conducted to identify any eligible articles. Citation searching was successful as two articles were identified and included.

## Results

From our literature search we identified a total of 415 articles (199 from Scopus, 163 from PubMed, 48 from Embase and 4 from Cochrane). Through an electronic sorting application on EndNote, 286 articles were identified as duplicates, leaving 129 articles for screening. These articles were manually screened based on their title and abstract. This process excluded 101 articles. The full texts of the remaining 28 articles were examined for eligibility. This process identified 8 articles that did not focus on fetal kidney development, and 4 articles that did not focus on nicotine exposure during pregnancy, these 12 articles were excluded. We identified 2 eligible articles from citation searching. The exclusion of the 12 articles and the inclusion of 2 articles, identified a total of 18 articles for this systematic review. Of these 18 articles, 6 were human studies, and 12 were animal studies. The process for identifying eligible articles is illustrated by the flow diagram in Fig. 1, and further details about each article can be found in Tables 1 and 2.

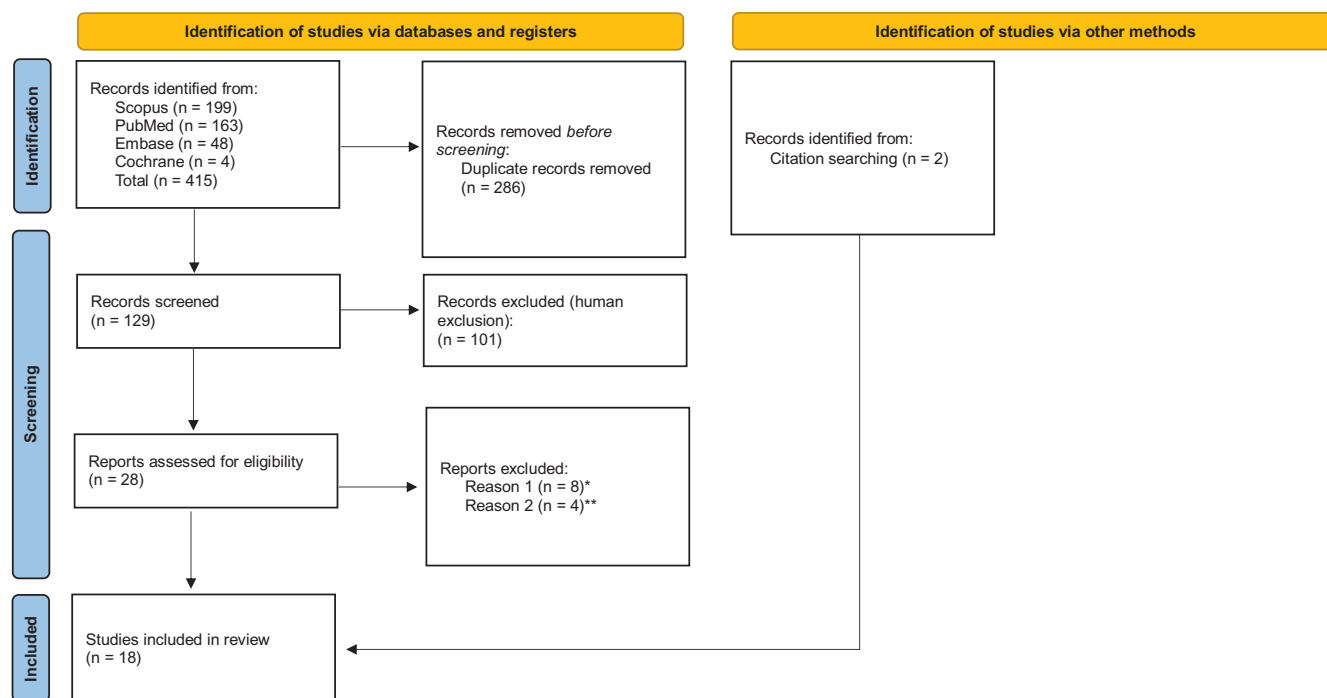
### Animal studies

A total of 12 animal articles were appropriate for the systematic review. Three articles studied Wistar rats,<sup>20-22</sup> five articles studied Sprague-Dawley rats,<sup>14,17,23-25</sup> two articles compared spontaneously hypertensive rats (SHR) to Brown Norway rats (BN),<sup>26,27</sup> one article studied Kunming mice,<sup>28</sup> and one article studied Balb/c mice.<sup>29</sup> Seven studies utilised male rats,<sup>20-23,26,27,29</sup> three studies did not specify sex,<sup>14,25,28</sup> and two studies utilised both female and male rats,<sup>17,24</sup> but only one study compared results to gender.<sup>24</sup>

Across the 12 studies, multiple techniques were utilised to mimic nicotine exposure. The most common technique of nicotine exposure was via subcutaneous osmotic mini pumps. Five studies utilised a concentration of 6 mg/kg/day of nicotine,<sup>14,23,26,27,30</sup> two studies utilised a concentration of 1 mg/kg with one study exposing twice daily<sup>21</sup> and the other study exposing once daily<sup>22</sup>; one study compared concentrations of 1 mg/kg/day, 2 mg/kg/day and 4 mg/kg/day<sup>28</sup>; and one study exposed 25 mg over 7 days.<sup>25</sup> Two studies utilised inhalation as the mode of nicotine exposure. One study used perplex chambers connected to a cigarette apparatus which exposed an equivalent of five cigarettes for 30 minutes twice daily.<sup>31</sup> The other study compared cigarette smoke to e-cigarette vapour exposure. The study groups were exposed twice daily to either two cigarettes, ~18 mL/mL of e-vapour, or ~60 mL of e-vapour.<sup>29</sup> The final study utilised cigarette condensate (1 mg/10 mL) applied to the oral mucosa, exposing 2 mg/kg/day.<sup>24</sup>

### Kidney weight and volume

Kidney weight and/or volume were the main outcomes measured across the majority of articles, with eight studies including this parameter. Block et al. studied Wistar rats and demonstrated a reduction in kidney volume in the exposed offspring ( $p = 0.0278$ ),<sup>20</sup> whereas Mao et al. studied Sprague-Dawley rats and found a



**Figure 1.** PRISMA flow diagram. \*Reason 1: Article did not focus on fetal kidney development. \*\*Reason 2: Article did not focus on nicotine exposure during pregnancy.

reduction in kidney volume in the exposed offspring ( $p < 0.05$ ).<sup>17</sup> Toledo-Rodriguez et al and Pausová Z et al compared SHR and BN. Both articles demonstrated a reduction in kidney weight in SHR exposed to nicotine, compared to non-exposed SHR ( $p = 0.006$ ,  $p < 0.0001$ , respectively), with no differences observed between BN groups.<sup>26,27</sup> The study by Li G et al studied the exposure to cigarette smoke compared to nicotine-containing e-cigarette vapour, and the exposure to nicotine-containing e-cigarettes (E-cig18) compared to nicotine-free e-cigarettes (E-cig0) in Balb/c mice. This study found an increase in kidney weight in the E-cig0 group and a reduction in kidney weight in the cigarette smoke-exposed group compared to the control ( $p < 0.05$ ,  $p < 0.05$ , respectively).<sup>29</sup> No significant differences in kidney weight or volume were observed in the remaining four studies.<sup>14,22,24</sup>

### Kidney histology and morphology

Seven studies investigated changes to kidney histology or morphology. The largest study, which was published in 1988 by Nash et al, investigated the impact of prenatal nicotine exposure via kidney microscopy. The results showed no change in kidney development between the exposed, untreated, and control groups at gestational day 20.<sup>25</sup>

Chen et al. demonstrated histological changes to the kidney in exposed groups (prenatal nicotine, and prenatal and postnatal nicotine). These changes included tubular atrophy, dilatation of the tubular lumen, increased space between the renal tubules, inflammatory infiltration, and smaller mean glomerular size.<sup>14</sup> Sun et al. identified many histological changes to the kidneys in the exposed group compared to the control group, indicating likelihood of fetal renal dysplasia. These changes included thinner cortical and nephrogenic zones ( $p < 0.01$ ), reduction in the renal cortical zone, increased nephrogenic zone/cortical zone ratio ( $p < 0.01$ ), reduced total number of mature glomeruli, dilated Bowman's capsules, shrunken glomerular tufts, thickened

basement membranes, fusion and effacement of podocyte foot processes, reduced number of foot processes and filtration slits, and mitochondrial dysfunction.<sup>21</sup> Zarzecki et al showed a reduction in the podocyte number ( $p < 0.01$ ), mesangial cell number (males  $p < 0.01$ , females  $p < 0.001$ ) and endothelial cell number per glomerulus ( $p < 0.01$ ) in the exposed group compared to the control group.<sup>24</sup>

Another aspect of kidney histology examined was renal collagen content. Chen et al. demonstrated higher renal collagen content in the exposed groups compared to the control group ( $p < 0.05$ ),<sup>14</sup> whereas Block et al. did not find any significant increase in renal collagen.<sup>20</sup> Li G et al demonstrated increased collagen expression in the cigarette and e-cigarette-exposed groups compared to the control ( $p < 0.01$ ,  $p = 0.05$ , respectively), with the cigarette-exposed group also demonstrating increased fibronectin ( $p < 0.05$ ).<sup>29</sup>

Total nephron number, total glomeruli number, and glomerular size were measured in six studies<sup>14,20-22,24,29</sup> and renal nephron endowment was measured in one study.<sup>23</sup> Zarzecki et al. compared males and females and found that exposed males had significantly more glomeruli when compared to non-exposed males ( $p = 0.01$ ). However, no changes were present between the exposed and control female groups. This same study exhibited smaller glomerular diameters and volumes in the exposed group, for both males and females ( $p < 0.001$ ).<sup>24</sup> Chen et al. demonstrated reduced mean glomerular size in the prenatal and postnatal exposure group at day 7 ( $p < 0.05$ ), compared to the other two groups (prenatal exposure and control). However, when measured again on day 21, there was no difference in glomerular size between the groups. Sun et al. found that the exposed group had a reduced total number of mature glomeruli when compared to the non-exposed group.<sup>21</sup> Li G et al studied glomerular number, perimeter and density at 1-day old, 20 days old and 13 weeks old. The cigarette-exposed group demonstrated reduced glomerular number at all three ages ( $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.01$ , respectively)

**Table 1.** Summary of animal studies

Source	Species	Sample Size	Intervention (Nicotine Exposure)	Outcome	Conclusion
1 Block DB et al (2015) <sup>20</sup>	Wistar HanUnib rats Sex: male	Control (no intervention): Group 1 (n = 5) Group 2 (n = 5) Group 3 (n = 5) Group 4 (n = 15) Group 5 (n = 5) Group 6 (n = 5) Exposed: Group 1 (n = 5) Group 2 (n = 5) Group 3 (n = 5) Group 4 (n = 11) Group 5 (n = 6) Group 6 (n = 5)	Cigarette smoke exposure via Perspex chambers connected to multi-cigarette smoking apparatus (equivalent to five cigarettes) Timeframe: exposed for one week prenatally and throughout gestation for 2 × 30-minute sessions per day	Postnatal day 12: Kidney weight and volume (Group 1) Total nephron number (Group 2) Total glomeruli number (Group 3) 5-week-old and 13-week-old: Renal function (Group 4) 13-week-old: Proteinuria (Group 5) 16-week-old: TGF-β1 and fibronectin (Group 6)	The exposed group demonstrated reduced kidney volume at postnatal day 12, and significantly increased proteinuria at 13 weeks. At 5 weeks old the fractional urinary sodium excretion, fractional post proximal sodium excretion, and the fractional potassium excretion was higher in the exposed group. At 16 weeks, the exposed group demonstrated an increase in TGF-β1 immunoreactivity in glomeruli and parietal epithelium and an increased in fibronectin immunoreactivity in the glomeruli and peritubular spaces.
2 Chen CM et al (2015) <sup>14</sup>	Sprague-Dawley rats Sex: did not specify	Control (saline) (n = 23) Exposed: PNE (n = 25) PPNE (n = 24)	Nicotine administration (6 mg/kg/day) via subcutaneous osmotic mini pumps Timeframe: PNE: day 7–21 gestation PPNE: gestation day 7 to postnatal day 14	Kidney weight Body weight and kidney weight ratio Kidney histology Total collagen content CTGF expression Data collection: postnatal day 7 and postnatal day 21	PNE and PPNE groups exhibited higher tubular injury scores on postnatal day 7 and day 21. Injuries observed: tubular atrophy; dilatation of the tubular lumen; increased space between the renal tubules; and inflammatory infiltration. The PPNE group exhibited smaller mean glomerular size on postnatal day 7. The PNE and PPNE groups exhibited higher total collagen content, higher CTGF expression in kidney tissues and higher optical density of CTGF on both postnatal day 7 and day 21.
3 Sun Z et al (2015) <sup>21</sup>	Wistar rats Sex: male	Control (distilled water) (n = 9) Exposed (n = 11)	Nicotine exposure (1 mg/kg) via subcutaneous injection twice per day (mimics <5 cigarettes per day) Timeframe: GD 9–20	Kidney histology (n = 3) CDNF/c-Ret pathway (n = 3–6) ATR1 and ATR2 expression (n = 3) Data collection: GD 20	The exposed group demonstrated likelihood of fetal renal dysplasia compared to the control group. The exposed group demonstrated decreased mRNA expressions of Pax2, GDNF, c-Ret and phosphatidylinositol 3-kinase (PI3K), indicating reduced CDNF/c-Ret signalling. The exposed group exhibited marked reduction in AT1bR mRNA, AT2R mRNA, AT1R and AT2R expression. There was no difference in AT1aR mRNA. The exposed group demonstrated a reduction in kidney weight compared to the control group. However, the kidney-to-body weight ratio did not differ between the two groups.
4 Rogers JM et al (2014) <sup>23</sup>	Sprague-Dawley rats Sex: male	Control (no intervention) (n = 25) Exposed (n = 25)	Nicotine exposure (6 mg/kg/day) via subcutaneous osmotic minipumps Timeframe: GD 2–20	Renal nephron endowment Renal glucocorticoid receptor gene expression (mRNA) Data collection: 22 days old	No differences observed.

Table 1. (Continued)

5	Zarzecki M et al (2012) <sup>24</sup>	Sprague-Dawley rats Sex: male and female	Control (saline): Males (n = 26) Females (n = 25) Exposed: Males (n = 22) Females (n = 32)	Nicotine exposure (2mg/kg/day) via cigarette condensate (1 mg nicotine/10 mg) which was applied to the oral mucosa twice daily Timeframe: GD 10 to delivery	Kidney weight Urine albumin excretion, serum creatinine, and creatinine clearance Number of glomeruli Glomerular cells Data collection: 12 weeks old	Exposed males had significantly more glomeruli compared to the control group. No differences observed in the females. Exposed males and females exhibited smaller glomerular diameters and volumes compared to their respective control groups.
6	Toledo-Rodríguez, M et al (2012) <sup>26</sup>	SHR BN Sex: males	Control (saline): SHR (n = 12) BN (n = 12) Exposed: SHR (n = 13) BN (n = 12)	Nicotine exposure (6 mg/kg/day) via subcutaneous osmotic minipumps Timeframe: gestation	Kidney weight Kidney morphology Expression of Agtr1b Data collection: 9 weeks old	In nicotine exposed SHR, the kidney weight was reduced when corrected to body weight, and Agtr1b expression was increased compared to the control SHR. There were no differences in the BN rats.
7	Mao C et al (2009) <sup>17</sup>	Sprague-Dawley rats Sex: male and female	Control (saline) (n = not provided) Exposed (n = not provided)	Nicotine exposure (6 mg/kg/day) via subcutaneous osmotic minipumps Timeframe: gestation to postnatal day 10	Kidney weight and kidney/body weight ratio Expression of AT1R and AT2R proteins Renal AT1R and AT2R mRNA abundance Data collection: 14 days old, 30 days old, and 5 months old	The exposed group exhibited reduced kidney weight and reduced kidney/body weight ratio at 14 days, 30 days, and 5 months compared to the control group. No differences observed between male and female. The exposed group demonstrated a reduced amount of AT2R proteins and AT2R mRNA at 14 days, 30 days, and 5 months, compared to the control group. No differences observed in AT1R proteins or AT1R mRNA expression.
8	Gao, Y. J et al (2008) <sup>22</sup>	Wistar rats Sex: males	Control (saline) (n = 6) Exposed (n = 6)	Nicotine bitartrate (1 mg/kg/day) via subcutaneous injections Timeframe: 14 days before mating to postnatal day 21	Kidney weight Nephron number Glomerulus size Data collection: 26 weeks old	No differences observed.
9	Pausová Z et al (2003) <sup>27</sup>	SHR BN Sex: males	SHR (n = 25) Control (saline) (n = 12) Exposed (n = 13) BN (n = 24) Control (saline) (n = 12) Exposed (n = 12)	Nicotine exposure (6mg/kg/day) via subcutaneous osmotic minipumps Timeframe: GD 4–21	Kidney weight IGFR in kidneys Data collection: 9 weeks old	In exposed SHR, kidney weight was significantly decreased compared to the SHR control group. No differences observed in BN rats. In exposed SHR, IGFR expression was significantly downregulated in the kidneys compared to the SHR control group. In exposed BN rats, IGFR expression was significantly upregulated in the kidneys compared to the BN control group.
10	Nash, J. E et al (1988) <sup>25</sup>	Sprague-Dawley rats Sex: did not specify	Control (no intervention) (n = 136) Control (saline) (n = 129) Exposed (n = 128)	Nicotine exposure (25 mg over 7 days) via subcutaneous mini-osmotic pumps Timeframe: GD 6–12	Kidney histology Data collection: mothers were sacrificed at GD 20 and the fetus was fixed in Bouin's solution for a minimum of 2 weeks before analysis.	No differences observed.

(Continued)

Table 1. (Continued)

Source	Species	Sample Size	Intervention (Nicotine Exposure)	Outcome	Conclusion
11 Li G et al (2019) <sup>29</sup>	Balb/c mice Sex: males	Control (air) (n = 44) Intermittent exposure Cigarette smoke (n = 50) E-cigarettes (nicotine) (n = 49) Continuous e-vapour exposure Nicotine-free (E-cig0) (n = 51) Nicotine-containing (E-cig18) (n = 45)	Intermittent exposure Nicotine exposure (2 cigarettes ( $\leq$ 1.2 mg nicotine) or 18 mg/mL e- vapour from e-liquid) via inhalation twice per day. Continuous exposure Exposed to ~60 mL of e-vapour twice daily. Timeframe: 6 weeks before mating, throughout gestation and lactation	Kidney weight and kidney/ body weight ratio Glomerular histology Inflammatory response and fibrotic changes (MCP-1, TNF- $\alpha$ , IL-6, Nox4, ROS, 8-OHdG and nitrotyrosine) Urine ACR Data collection: Day 1, 20 and 13 weeks of age	At 1-day old, the cigarette smoke exposed, e-cigarette- exposed and E-cig0 groups demonstrated reduced glomerular number compared to the control. At 20 days old, the cigarette smoke-exposed and E-cig0 groups demonstrated reduced glomerular perimeter compared to the control group. The cigarette smoke-exposed group had reduced glomerular number and the E-cig0 group had heavier kidneys compared to the control group. Both the E-cig18 and E-cig0 groups has reduced glomerular density compared to the control group. At 13 weeks old, the cigarette smoke-exposed group demonstrated reduced kidney weight, glomerular number and perimeter, increased urine ACR, and increased levels of MCP-1, Nox4, 8-OHdG and nitrotyrosine. The e-cigarette-exposed group demonstrated increased mitochondrial densities and free radial total ROS compared to the control and cigarette-exposed groups. Both the E-cig18 and E-cig0 groups demonstrated reduced glomerular density, and increased ROS and nitrotyrosine. The E-cig0 group demonstrated reduced glomerular perimeter and 8-OHdG levels compared to the control. MCP-1 expression was doubled in the E-cig18 groups compared to the E-cig0 and control groups
12 Li Y et al (2015) <sup>28</sup>	Kunming mice Sex: did not specify	Control (n = 3) Exposure (n = 9) 1 mg/kg/day (n = 3) 2 mg/kg/day (n = 3) 4 mg/kg/day (n = 3)	Nicotine exposure (1, 2, 4 mg/kg/day) via subcutaneous injection. Timeframe: GD 7 to birth	Kidney histology Data collection: 35 days old	No differences observed.

Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1); prenatal nicotine (PNE); prenatal and postnatal nicotine (PPNE); connective tissue growth factor (CTGF); gestational day (GD); glial cell line derived neurotrophic factor/ c-Ret tyrosine kinase receptor (GDNF/c-Ret); renal angiotensin 1 receptor (AT1R); renal angiotensin 2 receptor (AT2R); renal paired box 2 (Pax2); phosphatidylinositol 3-kinase (PI3K); spontaneously Hypertensive Rats (SHR); normotensive Brown Norway rats (BN); angiotensin II type 1b receptor gene (Agt1b); insulin-like growth factor receptor (IGFR); Macrophage chemoattractant protein (MCP)-1; tumour necrosis factor-alpha (TNF- $\alpha$ ); interleukin (IL)-6; NADPH oxidase 4 (Nox4); reactive oxygen species (ROS); 8-hydroxy-2'-deoxyguanosine (8-OHdG).

**Table 2.** Summary of human studies

Source	Sample Size	Intervention (Nicotine Exposure)	Outcome	Conclusion
1 De Smidt JJA et al (2021) <sup>4</sup>	Control (non-smoker) (n = 146) Exposed (n = 165)	Smoking during pregnancy Timeframe: gestation	Kidney size Data collection: 5 years of age	The exposed group demonstrated a shorter kidney length.
2 Diehm CJ et al (2018) <sup>16</sup>	Control (non-smoker) (n = 70) Males (n = 39) Females (n = 31) Exposed (n = 48) Males (n = 32) Females (n = 16)	Smoking during pregnancy Timeframe: throughout gestation	Kidney size and volume Data collection: throughout gestation, no set times documented.	The exposed group demonstrated smaller kidney weight, but when sex was considered, there was no difference between groups. The renal AP diameter and kidney length was shorter for the exposed group, but when gender was considered, this trend persisted for males, but not for females.
3 Anblagan D et al (2013) <sup>32</sup>	Control (non-smoker) (n = 8) Exposed (n = 10)	Smoking during pregnancy (5–13 cigarettes/day) Time frame: gestation	Kidney volume Data collection: GA 22–27 weeks (visit 1) and GA 33–38 weeks (visit 2)	The exposed group demonstrated decreased kidney volume and decreased kidney volume percentage at both visit 1 and visit 2.
4 Kooijman MN et al (2015) <sup>33</sup>	Exposed Smoking until pregnancy known (n = 498) Continued smoking (n = 925) Smoking in second or third trimester (n = 80) Control (non-smoker) (n = 4199)	Smoking during pregnancy (maternal and paternal exposure) Categorised into <5 cigarettes per day and >5 cigarettes per day. Timeframe: smoking until pregnancy was known, smoking in second or third trimester, or continued smoking throughout pregnancy	Kidney volume (n = 5164) eGFR (n = 3745) ACR (n = 5406) Data collection: median age of 6 years old	Children who were exposed to maternal smoking had smaller kidney volumes compared to the control group. The strongest statistical difference was in children who were exposed to >5 cigarettes per day. Continued maternal smoking during pregnancy was associated with a lower eGFR. The strongest statistical difference was in children who were exposed to >5 cigarettes per day. Children exposed to first trimester only smoking showed an increased risk of a higher ACR compared to the other groups. Among mothers who did not smoke during pregnancy, but the father did, children demonstrated a smaller combined kidney volume compared to the control group. The strongest statistical difference was in children who were exposed to >5 cigarettes per day.
5 Taal HR et al (2011) <sup>15</sup>	Control (non-smoker) (n = 805) Exposed First trimester (n = 110) Whole pregnancy (n = 166) 30 weeks gestation measurement (n = 1031) Control (n = 769) Exposed (n = 262) 24 months measurement (n = 538) Control (n = 415) Exposed (n = 123)	Smoking during pregnancy Categorised into <5 cigarettes per day and >10 cigarettes per day. Timeframe: exposure during the first trimester and exposure throughout pregnancy	Kidney volume Data collection: GA 30 weeks and postnatal age of 24 months	Smoking throughout pregnancy was associated with changes in kidney volume, compared to only smoking in the first trimester. Smoking <5 cigarettes per day was associated with a larger kidney volume, but this was not continued to post natal life (24 months). Smoking >10 cigarettes per day was associated with a smaller kidney volume in both fetal and postnatal life.
6 Kallen K (1997) <sup>34</sup>	Kidney malformation (n = 483) Control (non-smokers) (n = 332) Exposed (n = 151) Other urinary organ tract malformations with no primary kidney malformation (n = 719) Control (non-smokers) (n = 541) Exposed (n = 178)	Smoking during pregnancy Categorised into any smoking, <10 cigarettes per day, and >10 cigarettes per day. Timeframe: throughout pregnancy	Kidney malformation Data collection: 1 week old to 6 months old	A moderate statistically significant association between maternal smoking (any smoking) and kidney malformations were found. No association between maternal smoking and other urinary tract malformation were found.

Anteroposterior (AP); gestational age (GA); estimated glomerular filtration rate (eGFR); albumin creatinine ratio (ACR).

and reduced glomerular perimeter at 20 days and 13 weeks old ( $p = <0.05$ ,  $p = <0.05$ , respectively). The e-cigarette-exposed group only demonstrated reduced glomerular number at 1-day old ( $p = <0.05$ ). The E-cig0 and E-cig18 groups demonstrated reduced glomerular densities at 20 days old ( $p = <0.01$ ,  $p = <0.05$ , respectively) and at 13 weeks old (both  $p = <0.05$ ). The E-cig0 group also demonstrated reduced glomerular number at 1-day old and reduced glomerular perimeter at 20 days and 13 weeks old ( $p = <0.05$ ,  $p = <0.05$ ,  $p = <0.05$ , respectively).<sup>29</sup> Three other studies showed no significant differences in the total nephron number and glomeruli volume.<sup>20,22,23</sup>

### Kidney function

Two studies looked at the impact of nicotine exposure on renal function. Block et al. looked at proteinuria and found that the exposed group had increased proteinuria compared to the control group ( $p = 0.0087$ ).<sup>20</sup> Zarzecki et al. demonstrated no changes in urine albumin excretion, serum creatinine, or creatinine clearance between the exposed and control groups for both male and female offspring.<sup>24</sup>

### Human studies

A total of six human articles were included in the systematic review.<sup>4,15,16,32,34</sup> One article collected data at gestational age of 30 weeks and at 24 months old,<sup>15</sup> one article collected data at 22–27 weeks and at 33–38 weeks of age<sup>32</sup>; one article collected data at one week old and at six months old<sup>34</sup>; one article collected data at six years of age<sup>33</sup>; one article collected data at five years of age<sup>4</sup>; and one article did not specify the time of data collection.<sup>16</sup>

### Kidney volume and size

Kidney volume and/or size were the two most common parameters studied across all articles. Five studies included one or both parameters in the results,<sup>4,15,16,32,33</sup> with the sixth study focussing on kidney malformations.<sup>34</sup> De Smidt et al. collected data at five years of age and demonstrated a reduction in kidney length in the exposed group compared to the control (right kidney  $p = 0.03$  and left kidney  $p = 0.04$ ). All other kidney measurements exhibited no differences between the exposed and control groups.<sup>4</sup> Diehm et al. also looked at kidney size and demonstrated a shorter anteroposterior (AP) renal pelvis diameter ( $p = 0.03$ ) and a shorter kidney length ( $p = 0.05$ ) in the exposed male group compared to the control male group. This same study found that the exposed group exhibited a smaller kidney volume compared to the control group ( $p = 0.02$ ), but there was no difference when subgroup analyses were carried out according to sex. This study did not specify the time data was collected.<sup>16</sup>

Anblagan et al. and Kooijman et al. demonstrated that kidney volume was reduced in the exposed group compared to the control group ( $p = 0.001$  and  $p = <0.01$ , respectively).<sup>32,33</sup> Anblagan et al. measured kidney volume at 22–27 weeks and at 33–38 weeks, whereas Kooijman et al. measured kidney volume at six years. Kooijman et al. found that children who were exposed to >5 cigarettes per day had a stronger statistical difference in kidney volume, compared to children exposed to <5 cigarettes per day ( $p = <0.05$ ). The same study investigated the impact of paternal smoking. The results of this analysis demonstrated a reduced kidney weight in children who were exposed (exposed to second-hand smoking via the mother's partner) compared to

non-exposed, and children who were exposed to >5 cigarettes per day had a stronger statistical difference ( $p = <0.05$ ).<sup>33</sup>

Taal et al. compared the impact of nicotine exposure on kidney volume in women smoking during the first trimester only, the whole gestation, and no smoking exposure. Data for this study was collected at gestational age of 30 weeks and at 24 months old. The study found that smoking throughout gestation is associated with changes in kidney volume compared to only smoking during the first trimester, and that these changes are dependent on the number of cigarettes smoked per day. Smoking <5 cigarettes per day was associated with a larger kidney volume when measured at 30 weeks gestation ( $p = <0.01$ ), however, this trend was not seen at 24 months old. However, smoking >10 cigarettes per day was associated with a smaller kidney volume at both gestational age 30 weeks ( $p = 0.05$ ) and 24 months of age.<sup>15</sup>

The study by Kallen et al. looked at kidney malformation at one week old and at six months old. The results demonstrated an association between maternal smoking and kidney malformations in the exposed groups (<10 cigarettes per day and >10 cigarettes per day) when compared to the control group, indicating that children of women who smoke during pregnancy have an increased risk of developing a kidney malformation, although the results were not statistically significant.<sup>34</sup>

### Kidney function

Only one study investigated the impact of nicotine exposure on fetal renal function using the estimated glomerular filtration rate (eGFR) and albumin creatinine ratio (ACR). The study measured this data at six years old. The results demonstrated a reduced eGFR in the group exposed to smoking throughout gestation when compared to the group exposed to smoking during the first trimester and to the control group ( $p = <0.05$ ). The strongest statistical difference was seen in the children exposed to >5 cigarettes per day ( $p = <0.05$ ). The study also found that children who were exposed during the first trimester only had an increased ACR compared to the other two groups (exposed throughout pregnancy and control) ( $p = <0.05$ ). This study also evaluated the impact of parental smoking, but no differences in renal function parameters were seen for this group.<sup>33</sup>

### Discussion

A reduction in fetal kidney size, volume and weight has been linked to smoking during pregnancy in human studies,<sup>4,15,16,32,33</sup> whereas results from animal studies are mixed.<sup>17,20,21</sup> Almost all human studies evaluated either kidney size, volume, weight, or a combination of the three. Statistically significant results were linked to kidney size. The studies measured kidney length and the AP renal pelvis diameter and demonstrated a reduction in both parameters in the exposed groups compared to the control.<sup>4,16</sup> Kidney volume and weight were assessed in relation to the number of cigarettes smoked per day. Overall, the results demonstrated a reduction in kidney volume and weight in the exposed groups compared to the control,<sup>15,32,33</sup> however more statistically significant results were associated with women who smoked more than 5–10 cigarettes per day during pregnancy.<sup>15,33</sup> This suggests that children born to women who smoke more than 5–10 cigarettes per day during pregnancy have a greater chance of developing smaller kidneys compared to children born to women who smoke less than 5–10 cigarettes per day during pregnancy.<sup>15,33</sup>



In animal studies, it was difficult to assess the impact of prenatal nicotine exposure on kidney size, volume, and weight as the results were mixed. The nicotine administration across all studies varied between 2 and 6 mg/kg subcutaneous injections or oral mucosal condensate per day. It was suggested that 2 mg/kg/day reflects exposure of less than 5 cigarettes per day,<sup>21</sup> and 6 mg/kg/day reflects exposure of greater than 20 cigarettes per day.<sup>27</sup> Two studies evaluated inhaled exposure with one study investigating e-cigarette e-vapour containing nicotine compared to cigarette smoke; however, both studies examined different amounts of nicotine exposure.<sup>20,29</sup> This highlights a disparity between the animal studies and may be a contributing reason for mixed results. Interestingly, two studies compared the same two species of rats and found that pregnant SHR exposed to nicotine had offspring with reduced kidney weight, whereas BN rats showed no differences.<sup>26,27</sup> These results highlight that each species may respond differently to nicotine, resulting in mixed outcomes across all animal studies. Further evaluation of the animal studies detailed two studies on Wistar rats<sup>20,21</sup> and one study on Sprague-Dawley rats<sup>17</sup> which had reduced kidney weight in the exposed groups, compared to the control; and one study on Wistar rats<sup>22</sup> and three studies on Sprague-Dawley rats<sup>14,23,24</sup> which depicted no changes in kidney weight between the exposed and control groups. Therefore, the evidence is too ambiguous to define clear results and further research is required.

Animal studies evaluated kidney function and histological changes in the kidney, such as collagen content, glomeruli number, glomeruli size, and total nephron number, but the results were mixed.<sup>14,20,21,24,29</sup> Only one human study evaluated kidney function based on eGFR and ACR. The results demonstrated a reduction in the eGFR and an increase in the ACR in children exposed to smoking during pregnancy. Interestingly, the study found that the increase in ACR was only significant in women who smoked during the first trimester, not throughout pregnancy. A plausible explanation for a reduced eGFR would be reduced kidney volume.<sup>33</sup>

Second-hand smoke exposure was investigated in only one human study. Kooijman et al. demonstrated that children exposed to second-hand smoke during pregnancy had reduced kidney weight compared to children who were not exposed, and of the exposed groups, children who were exposed to >5 cigarettes per day had a stronger statistical difference compared to the control group. These results align with the results of maternal smoke exposure, as discussed above. However, the study found that parental smoke exposure was not associated with changes in kidney function (eGFR and ACR), unlike maternal smoke exposure. It is thought that maternal smoking poses greater adverse effects on the fetus compared to second-hand smoking due to the direct intrauterine effects, whereas parental smoke exposure may be related to other external factors such as lifestyle and family factors.<sup>33</sup>

The use of e-cigarettes, as an alternative method of nicotine exposure, compared to cigarettes was explored in one animal study by Li G et al. The study found that glomerular number in both cigarette smoke and e-cigarette-exposed groups was reduced at birth, but this reduction only continued into “adult life” (13 weeks) for the cigarette smoke-exposed group. Markers of inflammation, oxidative stress and fibrosis were markedly increased in both the cigarette smoke and e-cigarette-exposed groups, but only the cigarette smoke-exposed group demonstrated an increased urine ACR. These results suggest generally improved renal

outcomes in the adult offspring exposed to e-cigarette e-vapour compared to cigarette smoke.<sup>29</sup>

The effect of nicotine on nephrogenesis remains to be fully understood but it is likely due to its effect on placental perfusion. Nicotine vasoconstricts the placental vessels causing a reduction in blood supply to the fetus. Fetal organogenesis relies on nutrients and oxygen supplied through these vessels, so limiting the blood supply deprives the developing fetal organs. Moreover, increasing the number of cigarettes smoked by the mother assumes an increase in nicotine concentration in maternal circulation presenting a greater chance of significant placental injury.<sup>4,11,32</sup> Despite this evidence and applied knowledge, more human studies and larger study sizes are required to draw definitive conclusions. Aoyagi Y et al. found that in mice, the groups exposed to nicotine prenatally demonstrated a reduced blood supply to all fetal organs, compared with the control group. This reduction in blood flow has potential to cause fetal tissue hypoxia, intrauterine growth restriction and other adverse postnatal outcomes.<sup>35</sup> Nicotine precipitates placental changes which contribute to placental dysfunction. As the placenta functions as both a metabolic and endocrine organ creating an effective maternal-fetal barrier, any disruption in placental function has the potential to disrupt fetal growth and development.<sup>5,7</sup> Nicotine induces changes such as altering trophoblastic invasion and differentiation, increasing collagen content in villous stroma, decreasing angiogenesis, inducing placental hypoxia and oxidative stress, and down-regulating labyrinth vascularisation.<sup>1-3,5,9,10</sup> Holloway et al proposed that changes to trophoblastic invasion and differentiation are likely mediated by placental nAChR.<sup>9</sup> Alongside this, nicotine crosses the placental barrier and enters fetal circulation. The concentration of nicotine in the fetal circulation is much greater compared to maternal circulation. In adults, 70–80% of circulating nicotine is metabolised through the liver, however, in utero the fetal liver is underdeveloped and does not express the appropriate enzymes to allow nicotine metabolism, resulting in a higher circulating concentration of nicotine which accumulates in fetal tissues.<sup>4,5,11</sup> These adverse effects of nicotine exposure create an abnormal feto-maternal circulation, establishing a suboptimal environment for fetal growth and development.<sup>1-5,11</sup>

One major benefit of animal studies is the ability to accurately titrate the amount of nicotine administered to the study subject, allowing the concentration of nicotine to be standardised. Whereas the human studies relied on self-reporting on the number of cigarettes smoked per day during pregnancy. The way nicotine is used has changed dramatically over the last few decades with an evolution in the way consumers access and abuse nicotine products. The use of these alternative products, such as e-cigarettes/vapes, heated tobacco products, smokeless tobacco (Snus), and tobacco-free nicotine pouches, was a strategy to encourage cigarette smoking cessation, however, this deemed not to be the case, as these products are perceived by consumers to have less severe risks than cigarettes.<sup>36</sup> These new products are marketed as attractive to consumers due to the variety of options, choice of features (design, nicotine levels, adjustable settings), choice of flavours, pricing, avoidance of smoking restrictions, and social acceptance of the perceived safety by bystanders.<sup>37</sup> A study conducted by Tehrani H et al. demonstrated an overall upward trend of e-cigarette smoking from 2011 to 2019. The current prevalence of e-cigarette vaping worldwide is 11% with the lifetime prevalence of e-cigarette vaping being 23%. Of the population currently using e-cigarettes 43% are previous cigarette smokers,

and 39% had previous history of cigarette smoking.<sup>38</sup> Despite the current health promotions educating women about the harms of nicotine during pregnancy, pregnant women continue to use nicotine-containing products. This evolution has potential to create many challenges to the healthcare system. A standard smoking history proves inadequate at gauging the use of nicotine products since many patients still understand “smoking” as cigarette use.<sup>36,37</sup> This challenge is particularly relevant to all human studies included in the systematic review, as all human studies relied on smoking history to quantify nicotine use.<sup>4,15,16,32-34</sup> Urine cotinine, the major metabolite of nicotine, is increasingly being used to assess nicotine exposure during pregnancy or environmental tobacco smoke (passive smoking).<sup>39,40</sup> It has a long biological half-life of between 19 and 40 hours in the body compared with nicotine, which has a short half-life of about 30 minutes to 2 hours.<sup>40</sup> This method of measuring nicotine exposure may be considered in future studies.

Besides the differences discussed previously between human and animal models, the study designs also display many disparities. The method of nicotine exposure varied between human and animal studies. In humans, nicotine exposure is via inhalation, whereas in animal studies the method of nicotine exposure was varied. Methods of exposure included subcutaneous pumps or subcutaneous injections, a chamber where study subjects were exposed to smoke equivalent to five cigarettes, and application of cigarette condensate to the oral mucosa.<sup>14,17,20-28</sup>

### Limitations

Human and animal studies collected data at different times. This adds a level of complexity when comparing data sets since the offspring are at different developmental stages and have been exposed to other external factors which may impact kidney parameters. Alongside this, histological examinations of the kidneys are only available for animal studies, making comparison between species difficult. The few animal studies which evaluated histological changes did demonstrate kidney injury, therefore, to gain greater evidence to support these changes in human models, further animal studies are required. Another limitation of both studies was the sex of the study subjects. Majority of animal studies focussed on male sex, whereas human studies included both male and female sex. Due to this, it is difficult to identify differences between sexes and to draw conclusions about the species as a whole. Human studies relied on self-reporting of smoking hence nicotine exposure could not be quantified. A prospective human study that utilises a quantifiable way to determine nicotine exposure, such as urine cotinine (a product of nicotine metabolism), could be of greater value. Utilising urine cotinine measurements will provide objective results compared to relying on patient history and enables assessment of other nicotine exposures such as e-cigarettes, smokeless tobacco, NRT and second-hand exposure.

Finally, the studies available focus on the short-term impact of nicotine on kidney development, however evaluating the long-term impacts would give further insight into disease predisposition into adult life.

### Conclusion

This systematic review aimed to summarise the impact of smoking and nicotine exposure during pregnancy on fetal nephrogenesis. Current research suggests changes to kidney weight, volume, and

size in response to nicotine in utero, particularly in offspring that are exposed to >5-10 cigarettes per day. Further research is required to analyse nicotine's effect on kidney function and histopathology. Future studies could consider using urine cotinine measurement to accurately quantify nicotine exposure, especially as ways to abuse nicotine continue to evolve.

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