Prenatal Gender-Related Nicotine Exposure Increases Blood Pressure Response to Angiotensin II in Adult Offspring

DaLiao Xiao, Zhice Xu, Xiaohui Huang, Lawrence D. Longo, Shumei Yang, Lubo Zhang

Abstract—Epidemiological studies suggest that maternal cigarette smoking is associated with an increased risk of elevated blood pressure (BP) in postnatal life. The present study tested the hypothesis that prenatal nicotine exposure causes an increase in BP response to angiotensin II (Ang II) in adult offspring. Nicotine was administered to pregnant rats via subcutaneous osmotic minipumps throughout the gestation. BP and vascular responses to Ang II were measured in 5-month-old adult offspring. Prenatal nicotine had no effect on baseline BP but significantly increased Ang II–stimulated BP in male but not female offspring. The baroreflex sensitivity was significantly decreased in both male and female offspring. Prenatal nicotine significantly increased arterial media thickness in male but not female offspring. In male offspring, nicotine exposure significantly increased Ang II–induced contractions of aortas and mesenteric arteries. These responses were not affected by inhibition of endothelial NO synthase activity. Losartan blocked Ang II–induced contractions in both control and nicotine-treated animals. In contrast, PD123319 had no effect on Ang II–induced contractions in control but inhibited them in nicotine-treated animals. Nicotine significantly increased Ang II type 1 receptor but decreased Ang II type 2 receptor protein levels, resulting in a significant increase in the ratio of Ang II type 1 receptor/Ang II type 2 receptor in the aorta. Furthermore, the increased contractions of mesenteric arteries were mediated by increases in intracellular Ca\(^{2+}\) concentrations and Ca\(^{2+}\) sensitivity. These results suggest that prenatal nicotine exposure alters vascular function via changes in Ang II receptor–mediated signaling pathways in adult offspring in a gender-specific manner, which may lead to an increased risk of hypertension in male offspring. (Hypertension. 2008;51:1-9.)

Key Words: nicotine ■ fetal programming ■ gender ■ angiotensin II ■ vascular contractility

Maternal cigarette smoking probably is the single most widespread prenatal insult in the world. Recent epidemiological studies have demonstrated that in utero exposure to maternal smoking is associated with elevated blood pressure (BP) and/or cardiovascular disease in offspring later in life.\(^1,2\) As one of the major components in cigarette smoking, nicotine is likely to contribute to the developmental programming of cardiovascular disorders. Nicotine readily crosses the placenta, and maternal cigarette smoking produces higher nicotine concentrations in fetal circulation than that experienced by the mother.\(^3,4\) In the developing fetus, chronic nicotine exposure resulted in permanent changes in nicotinic receptors and alterations in the activity of the central and peripheral nervous systems.\(^5\) Our recent studies in the rat have demonstrated that fetal nicotine exposure causes reprogramming of vascular reactivity and produces gender-dependent alterations in both \(\alpha_1\)-adrenoceptor–mediated contractions and endothelial NO synthase (eNOS) activity of arteries in adult offspring.\(^6\) In addition, fetal nicotine exposure resulted in an in utero reprogramming of protein kinase C isozyme gene expression pattern in the developing heart and increased heart susceptibility to ischemia and reperfusion injury in adult offspring.\(^7\)

Angiotensin II (Ang II) plays a fundamental role in the regulation of cardiovascular homeostasis and has been implicated in the pathophysiology of hypertension induced by adverse in utero environment during the fetal development.\(^8-10\) In an animal model of a low-protein diet during pregnancy, elevated BP in adult offspring was associated with increased pulmonary and plasma angiotensin-converting enzyme activity,\(^11\) and angiotensin-converting enzyme inhibitors prevented the increased BP.\(^12\) In addition, it has been demonstrated that an increased sensitivity to Ang II contributes to hypertension caused by prenatal undernutrition.\(^10\) Inhibition of Ang II type 1 receptor (AT\(_R1\)) in early postnatal life after maternal dietary restriction prevented development of hypertension in adult offspring.\(^10,12\) In spontaneously hypertensive rats, there was an accelerated increase in the AT\(_R1\), whereas the Ang II type 2 receptor (AT\(_R2\)) tended to decrease at an early age.\(^13\) Collectively, these findings...

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strongly suggest that the regulation of Ang II receptor-mediated signaling pathways provides a mechanistic link between programmed hypertension and various risk factors during early development.

The present study was designed to test the hypothesis that maternal nicotine administration during pregnancy causes reprogramming of vascular reactivity to Ang II, leading to an increased risk of hypertension in adult offspring. The specific aims of the present study were to determine in adult offspring to what extent prenatal nicotine exposure affects the following: (1) baseline and Ang II–stimulated BP in vivo; (2) the baroreflex sensitivity; (3) vascular contractile function and Ang II–mediated signaling pathways in isolated large and resistance arteries in vitro; (4) arterial AT,R and AT,R protein levels; and (5) vascular remodeling. To investigate the potential gender effects of prenatal nicotine exposure, the studies were performed in both male and female offspring.

**Materials and Methods**

**Materials**

Ang II and PD123319 were obtained from Sigma. Losartan was obtained from Merck. Osmotic minipumps (Type 2ML4) were from Alza Corp. AT,R rabbit polyclonal IgG (SC-1173) and AT,R rabbit polyclonal IgG (SC-9040) were from Santa Cruz Biotechnology Inc. Anti-Ig HRP Detection Kits were from BD Biosciences. Mouse eNOS monoclonal antibody was from Transduction Laboratory. All of the other chemicals were obtained from Sigma Chemical.

**Table 1. Effect of Prenatal Nicotine Exposure on Basal Arterial BP and Body Weight of Adult Rat Offspring at 5 Months of Age**

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>MAP, mm Hg</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>HR, bpm</th>
<th>BW, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control M</td>
<td>123.4±4.4</td>
<td>128.7±5.6</td>
<td>115.7±2.8</td>
<td>342.8±14.6</td>
<td>609.6±20.4</td>
</tr>
<tr>
<td>Nicotine M</td>
<td>123.8±1.9</td>
<td>137.4±4.0</td>
<td>112.8±4.0</td>
<td>360.0±7.3</td>
<td>573.0±15.5</td>
</tr>
<tr>
<td>Control F</td>
<td>127.6±3.5</td>
<td>144.4±3.4</td>
<td>121.6±4.5</td>
<td>397.7±6.9</td>
<td>342.1±6.1</td>
</tr>
<tr>
<td>Nicotine F</td>
<td>127.5±2.3</td>
<td>144.3±4.0</td>
<td>120.5±2.7</td>
<td>399.8±10.3</td>
<td>350.2±8.4</td>
</tr>
</tbody>
</table>

M indicates male; F, female. n=5 to 13.
Experimental Animals
All of the procedures and protocols were approved by the Loma Linda University Institutional Animal Care and Use Committee and followed the guidelines by the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Time-dated pregnant Sprague-Dawley rats were purchased from Charles River Laboratories (Portage, Mich). Nicotine was administered to pregnant rats through implanted osmotic minipumps at a dose rate of 6 mg/kg per day from day 4 of gestation until 10 days after delivery, as described previously.6,7 The dose of nicotine closely resembled that occurring in moderate-to-heavy human smokers.5,14 Control rats received saline as the vehicle control. Newborn pups were kept with their mothers until weaning. At weaning, male and female pups were separated and housed in groups of 2. The offspring were studied at 5 months of age.

Measurement of Arterial BP
Animals were implanted with catheters in femoral arteries for recording of arterial BP and heart rate (HR), as described previously.15 A catheter was subcutaneously implanted in the back of animals for drug administration. Two days after recovery from surgery, BP and HR were measured continuously in conscious animals. After the baseline recording for ~60 minutes, animals were administered Ang II (10 μg/kg of body weight) with subcutaneous injection via the implanted catheter, and BP and HR were recorded for 60 minutes. Arterial BP responses at this dose of Ang II reached a submaximal level, as determined in preliminary studies. Arterial systolic BP (SBP) and diastolic BP (DBP), mean BP (MAP), and HR data were recorded continuously throughout each study with data acquisition software (Powerlab 16/SP and Chart version 4, ADInstruments).

Contractions of Aortic Rings
Aortas were isolated and cut into 4-mm rings and mounted in 10-mL tissue baths containing modified Krebs solution equilibrated with a mixture of 95% O2 and 5% CO2. Isometric tensions were measured at 37°C, as described previously.6 Ang II–induced concentration-dependent contractions were obtained by cumulative additions of the agonist in approximate one-half log increments. In certain experiments, tissues were pretreated for 20 minutes with the AT1R inhibitor losartan (10 μmol/L), the AT1R inhibitor PD123319 (10 μmol/L), or the NO synthase inhibitor Nω-nitro-L-arginine (L-NNA; 100 μmol/L) and then stimulated with increased concentrations of Ang II. Because repeated exposure of arterial segments to Ang II results in tachyphylaxis, additional experiments were performed in which vessel segments were exposed to single Ang II concentrations. Vessels were used for 1 experiment only and were not reused.

Contractions of Pressurized Small Mesenteric Arteries
Mesenteric arcade was excised, and small mesenteric arteries (~200 μm in diameter) were dissected out under a dissecting microscope. The arterial segments were mounted and pressurized in an organ chamber (Living Systems), as described previously.16 Vascular intracellular Ca2+ concentrations ([Ca2+]i) were measured in the same tissues loaded with the Ca2+ indicator Fura 2-AM, as described previously.16 The vessels were pressurized to 45 mm Hg, which was considered the optimum pressure as shown in our preliminary and other studies.17 The pressurized arteries were stimulated with single Ang II concentrations until the maximal decrease in arterial diameter was obtained. Because of tachyphylaxis, each arterial segment was used for only 1 single Ang II concentration. Arterial diameter and Ca2+ signal were recorded using the SoftEdge Data Acquisition Subsystem (IonOptix), as described previously.16

Western Immunoblotting
Arteries were homogenized in a lysis buffer. Homogenates were ultrasonicated for 15 seconds and then centrifuged at 4°C for 10 minutes. The supernatant was mixed with loading dye and electrophoresed in 12% SDS-PAGE gels. Proteins were transferred to PVDF membranes and immunoblotted using rabbit polyclonal antiserum against AT1R antibodies and mouse monoclonal antiserum against GAPDH antibodies. Immunoreactive bands were detected using enhanced chemiluminescence (ECL) reagents and exposed to X-ray film. The density of each band was quantified by densitometry and normalized against GAPDH.
Ang II–Induced BP Response
Ang II produced time-dependent increases in arterial BP in both control and nicotine-treated adult offspring. In male offspring, BP responses to Ang II reached the maximum at 5 minutes (Figure 1). Prenatal nicotine exposure caused significant increases in Ang II–stimulated SBP, DBP, and ΔMAP in male offspring, as compared with the control group (P<0.05; Figure 1). As shown in Figure 2, increases in BP in response to Ang II resulted in decreases in HR via baroreflex. The baroreflex sensitivity was calculated as slope of Δpulse interval/ΔSBP (in milliseconds per millimeter of mercury). Prenatal nicotine treatment resulted in a significant decrease in the baroreflex sensitivity from 0.083±0.011 ms/mm Hg in the control group to 0.039±0.005 ms/mm Hg in the treatment group (P<0.05; Figure 2).

In contrast to the finding in males, in females Ang II–induced changes of SBP, DBP, and ΔMAP were not significantly different between the control and prenatal nicotine-exposed-offspring (Figure 1). The baroreflex sensitivity in the control female offspring in response to Ang II stimulation was 0.101±0.017 mm Hg, which was not significantly different from that of control male offspring (P>0.05). Similar to the finding in male offspring, prenatal nicotine treatment significantly decreased the baroreflex sensitivity in females (0.035±0.001 versus 0.101±0.017 ms/mm Hg; P<0.05; Figure 2).

Ang II–Induced Contractions of Aortas in Male Offspring
In male offspring, Figure 3 shows the effect of prenatal nicotine exposure on Ang II–induced concentration-dependent contractions of aortas in the absence or presence of the eNOS inhibitor L-NNA. As shown in Table 2, in the absence of L-NNA, the maximal response and the pD2 values of Ang II–induced contractions were significantly increased in aortas of nicotine-treated animals, as compared with those of the control. In control animals, inhibition of eNOS with L-NNA significantly potentiated Ang II–induced maximal response. Similarly, in nicotine-exposed males, Ang II–induced contractions were also significantly affected by L-NNA. In the presence of L-NNA, there remains a significant increase in Ang II–induced maximal contraction in nicotine-treated animals, as compared with that of the control.

Because of the potential tachyphylaxis by accumulative additions of Ang II, we carried out additional experiments in which aortas were stimulated with single doses of Ang II from 1 nmol/L to 1 µmol/L. Single-dose experiments pro-

| Table 2. Effect of Prenatal Nicotine Exposure on Ang II–Mediated Contraction of Aortas in Adult Male Offspring at 5 Months of Age in the Absence or Presence of L-NNA |
|----------------|----------------|----------------|
| Treatment      | pD2            | Emax           |
| L-NNA          | 7.99±0.13      | 6.99±0.37      |
| Nicotine       | 8.45±0.17*     | 16.60±0.92*    |

*pD2 indicates -log EC_{50}; Emax, maximal response (% KCl response). n=5 to 7.*P<0.05, nicotine vs control; †P<0.05, +L-NNA vs −L-NNA.
duced higher contractile tensions of aortas in response to Ang II in both control and nicotine-treated male offspring (Figure 4). In control offspring, PD123319 had no significant effect on Ang II–induced contractions (Figure 4, left). However, PD123319 significantly shifted the curve of Ang II–induced concentration-dependent contractions to the right in nicotine-treated offspring (pD2: 7.9±0.2 versus 8.6±0.2; P<0.05) and significantly decreased Ang II–elicited maximal contractions (19.4±1.5 versus 25.2±1.7% of KCl responses; P<0.05; Figure 4, right).

**Ang II–Induced Contractions and [Ca²⁺]ᵢ in Small Mesenteric Arteries in Adult Male Offspring**

In pressurized small mesenteric arteries, Ang II (10 nmol/L to 3 μmol/L) produced concentration-dependent increases in vasoconstrictions and decreases in the arterial diameter, which were associated with increases in [Ca²⁺]ᵢ (Figure 5). As shown in Figure 5, the magnitude of Ang II–induced contractile responses in all 3 of the concentrations was significantly higher in nicotine-treated animals than those in the control (Figure 5, middle). However, Ang II–induced increases in [Ca²⁺]ᵢ were significantly higher in nicotine-treated animals only at the lowest concentration of Ang II (10 nmol/L) among the 3 doses used (Figure 5, bottom).

**Arterial AT₁R and AT₂R in Adult Male Offspring**

To determine whether Ang II receptor expression was correlated with the alteration of Ang II–induced BP response and vascular contractility in adult male offspring of prenatal nicotine exposure, AT₁R and AT₂R protein levels and distribution in aortas were determined with immunoblotting and immunohistochemistry. As shown in Figure 6, AT₁R immunoreactivity was primarily detected in the smooth muscle media of the arterial wall. In contrast, AT₂R was much less abundant and primarily located in the adventitia. Neither AT₁R nor AT₂R was detected in the endothelium. Western immunoblotting showed that AT₁R protein levels were significantly increased in the aorta from nicotine-treated animals, as compared with that from the control (Figure 7). In contrast to AT₁R, AT₂R levels were significantly decreased, resulting in a significant increase in the ratio of AT₁R/AT₂R in arteries from nicotine-treated animals (Figure 7).

**Arterial Media Thickness in Adult Offspring**

As shown in Figure 8, the aortic medial wall thickness was significantly increased in male offspring after prenatal nicotine exposure. In contrast, prenatal nicotine treatment had no significant effect on the female aorta (Figure 8). In resistance-sized mesenteric arteries, neither lumen diameter nor medial wall thickness was significantly different between control and nicotine-treated animals in female offspring. In contrast, in male offspring, both the medial wall thickness and the ratio of the medial thickness/lumen diameter were significantly increased in nicotine-treated animals, as compared with the control animals (Table 3).
The present study demonstrated in male offspring that prenatal nicotine exposure caused an increased risk of hypertension in the adult. Although the baseline BP was not significantly altered, the nicotine treatment significantly increased arterial BP response to Ang II, suggesting an increased susceptibility of elevated BP in male adult offspring. Consistent with the present finding, previous studies in rats have demonstrated that intrauterine exposure to nicotine does not increase resting BP in normotensive male offspring but significantly increased BP in spontaneously hypertensive male offspring. The finding that prenatal nicotine affected male offspring predominantly in the present study is in agreement with previous studies showing that female offspring were less sensitive in the manifestation of hypertension caused by adverse prenatal stimuli. Our recent study demonstrated that prenatal nicotine treatment significantly increased norepinephrine-induced contractions of aortas in male but not female adult offspring. In contrast, prenatal nicotine resulted in a more pronounced impairment in cardiac function and reduction in postischemic recovery of left ventricle function in the heart of female offspring. These studies suggest an organ and/or tissue specificity of gender-dependent fetal programming induced by prenatal nicotine exposure.

The finding that fetal nicotine exposure increased susceptibility of elevated BP in adult offspring is consistent with recent studies in humans and animal models showing a link between adverse intrauterine environments and fetal programming, resulting in an increased risk of hypertension and ischemic heart disease in adulthood. It is likely that multiple mechanisms are involved in fetal programming of cardiovascular response. In the present study, we found that prenatal nicotine treatment caused a significant decrease in the baroreflex sensitivity in both male and female offspring. Given that baroreflex is not best quantified in response to Ang II–induced vasoconstriction, and previous studies in sheep demonstrated that Ang II decreased the baroreflex sensitivity, the effect of nicotine is likely on the modification of baroreflex rather than on the activity of baroreflex itself. Consistent with the present finding, previous studies have demonstrated that cigarette smoking reduces the baroreflex sensitivity, which contributes to the higher risk of cardiovascular disease. In addition, male and female smokers showed similar reductions in the baroreflex sensitivity. Studies in other models of fetal programming also showed a decrease in baroreflex function in offspring, suggesting a common mechanism of impaired baroreflex in fetal programming of cardiovascular response in offspring. The present finding of a similar reduction in the baroreflex sensitivity in male and female offspring, but a significant change in BP response primarily in males, suggests that mechanisms other than baroreflex are involved in increased BP response in males.

In the present study, Ang II–induced contractions of both large arteries and pressurized, resistance-sized arteries were significantly increased in nicotine-treated male offspring, suggesting that an increased arterial sensitivity to Ang II contributes to increased BP in the male. Enhanced vascular contractility associated with programmed elevation of BP has been reported in several different animal models, including in utero exposure to secondhand smoke, prenatal glucocorticoid exposure, and maternal dietary restriction. The finding that the inhibition of eNOS by L-NNA increased Ang II–mediated vasoconstrictions in both control and nicotine-treated animals suggests a common mechanism of impaired eNOS function in fetal programming of cardiovascular response in offspring.
treated animals suggests a significant component of the basal eNOS activity in the regulation of Ang II–mediated contractions. Nicotine treatment produced a similar increase in Ang II–induced contractions in the absence or presence of L-NNa. This suggests that the enhanced arterial sensitivity to Ang II is primarily because of increased Ang II–induced contractions, per se, rather than the loss of the eNOS-mediated relaxation component. The involvement of endothelium/NO in fetal programming of vascular function has been studied, and the results are controversial. It has been shown that adverse intrauterine environments cause an impairment of endothelium/NO-mediated relaxation in some animal models and in humans. Other studies found no changes in endothelium/NO-mediated relaxation in fetal programming of vascular reactivity. Recently, we demonstrated that enhanced α1-adrenoceptor–mediated contractions of the aorta in male adult offspring after prenatal nicotine exposure was primarily because of the loss of the eNOS-mediated relaxation component in α1-adrenoceptor–mediated contractions. Thus, it is likely that fetal programming of the basal eNOS activity and its effect on vasoconstrictors is agonist dependent. In addition, these findings suggest that prenatal nicotine-mediated programming occurs at the agonist-specific level rather than at common intracellular signaling pathways. Although the in vitro vascular reactivity was determined primarily in male offspring in the present study, because the in vivo effects were demonstrated in male offspring and not female, future studies of female vessels are needed to seek out whether the sex difference observed in BP response occurs at the tissue or systemic levels.

The primary distributions of AT1R in the arterial media and AT2R in the adventitia observed in the present study are consistent with previous findings. The inhibition of Ang II–induced arterial contractions by losartan in both control and nicotine-treated animals indicated a primary role of AT1R in vasoconstrictions. The present study demonstrated a reprogramming of AT1R expression pattern caused by fetal nicotine exposure, resulting in significantly increased AT1R levels in the arteries of nicotine-treated animals. This is likely to contribute to the increased arterial sensitivity and BP response to Ang II in male offspring after prenatal nicotine exposure. Unlike AT1R, the exact role and the extent to which AT2R plays a role in the regulation of arterial contractions are unclear. In the present study, we found that the selective AT1-R blocker PD123319 lacked the effect on Ang II–induced arterial contractions in control animals but significantly attenuated the contractions in prenatally nicotine-treated animals. This is intriguing and suggests a transition/increase in coupling of AT1R to vasoconstrictions in nicotine-treated animals. Previous studies have demonstrated that AT1-R activation induces vasodilation in normotensive rats but induces vasoconstriction in various pathological states of the vasculature, including hypertension.

In contrast to AT1R, arterial AT2R levels were significantly reduced in nicotine-treated animals. Previous studies demonstrated that arterial AT2-R expression was downregulated in spontaneously hypertensive rats. In addition, it has been shown in spontaneously hypertensive rats there is an acceleration in postnatal transition of AT1R/AT2R and overexpression of the AT1R and deficiency of the AT2R at an early age. These findings suggest a crucial role for the increased AT1R/AT2R ratio in the development of hypertensive phenotype. In the present study, we demonstrated a significant increase in the arterial ratio of AT1R/AT2R in male offspring after prenatal nicotine exposure. Not only does this contribute to the increased arterial sensitivity to Ang II, it is also likely to play a key role in arterial remodeling observed in nicotine-treated animals. The present study also demonstrated a gender-specific increase in arterial media thickness in male offspring after prenatal nicotine treatment. Arterial remodeling because of smooth muscle hyperplasia/hypertrophy has been demonstrated as a typical hypertensive phenotype. It has been well demonstrated that both Ang II receptor subtypes contribute to vascular remodeling with AT1-R mediating smooth muscle proliferation and hypertrophy and AT2-R inhibiting them.

In addition to alterations in Ang II receptors, previous studies have demonstrated an upregulation of multiple Ang II–mediated signaling pathways and downstream effectors and suggested a postreceptor phenomenon of augmented Ang II signaling in hypertension. The present study, we found that the increased Ang II–mediated contractions in nicotine-treated animals were associated with increased [Ca2+]i, only at the lowest dose of 10 nmol/L. Ang II among the 3 doses used. Plasma concentrations of Ang II in rats are from 0.1 to 0.2 nmol/L, and the common concentration ranges of Ang II used in the in vitro studies have been from 0.1 nmol/L to 10 μmol/L. This suggests that increases in both Ang II–mediated Ca2+ mobilization and Ca2+ sensitivity contribute to the enhanced arterial contractions in nicotine-treated animals. Indeed, Ca2+ elevation and increased Ca2+ sensitivity
have been demonstrated to be critical in Ang II–induced vascular hyperreactivity and dysfunction in hypertension.38

Perspectives
The present study has demonstrated that prenatal nicotine exposure results in vascular remodeling, increased arterial sensitivity to Ang II, and decreased baroreflex sensitivity, leading to an increased susceptibility of elevated arterial BP in adult offspring. These findings indicate that fetal nicotine exposure not only causes increased perinatal morbidity and mortality, as recognized previously,3 but also has long-lasting effects and increases the risk of cardiovascular disease later in adult life. Together with previous studies, the present finding re-enforces the notion that multiple in utero adverse factors during pregnancy cause fetal programming and increase the risk of hypertension in the adult. Given that maternal cigarette smoking with fetal nicotine exposure is one of the most widespread prenatal insults, the present finding has obvious clinical significance. As is often the case with novel findings, the present study may raise more questions than it answers. For instance, are the effects mediated by a direct effect of nicotine on the fetus or indirectly through its effect on the mother? What are the epigenetic mechanisms involved in reprogramming of the baroreflex sensitivity and the gene expression pattern of Ang II receptors in arteries that persist into adulthood? In addition, to what extent do sex hormones contribute to the gender differences observed in fetal programming of cardiovascular function? Undoubtedly, these questions warrant further investigations.

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Disclosures
None.

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