

## REVIEW



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# Deleterious effects of whole-body vibration on the spine: A review of in vivo, ex vivo, and in vitro models

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## Abstract

Occupational exposure to whole-body vibration is associated with the development of musculoskeletal, neurological, and other ailments. Low back pain and other spine disorders are prevalent among those exposed to whole-body vibration in occupational and military settings. Although standards for limiting exposure to whole-body vibration have been in place for decades, there is a lack of understanding of whole-body vibration-associated risks among safety and healthcare professionals. Consequently, disorders associated with whole-body vibration exposure remain prevalent in the workforce and military. The relationship between whole-body vibration and low back pain in humans has been established largely through cohort studies, for which vibration inputs that lead to symptoms are rarely, if ever, quantified. This gap in knowledge highlights the need for the development of relevant in vivo, ex vivo, and in vitro models to study such pathologies. The parameters of vibrational stimuli (eg, frequency and direction) play critical roles in such pathologies, but the specific cause-and-effect relationships between whole-body vibration and spinal pathologies remain mostly unknown. This paper provides a summary of whole-body vibration parameters; reviews in vivo, ex vivo, and in vitro models for spinal pathologies resulting from whole-body vibration; and offers suggestions to address the gaps in translating injury biomechanics data to inform clinical practice.

## KEYWORDS

adverse effects, animal models, intervertebral disc, spine, translational research, vibration

## 1 | INTRODUCTION

Exposure to vibration, whether whole-body (transmitted to the whole body) or hand-arm (transmitted to the hand and arm), has been established as a factor in the development of fatigue and numerous symptoms and disorders such as low back pain (LBP), hand-arm vibration syndrome (HAVS), reproductive disorders, and gastrointestinal distress.<sup>1</sup> Occupational exposure to whole-body

vibration (WBV) is experienced by drivers,<sup>1,2</sup> vehicle operators,<sup>1,3</sup> and off-road machine operators.<sup>4–6</sup> Among military personnel, sources of WBV include ground vehicles and aircraft.<sup>7–10</sup> Although standards for limiting exposure to WBV have been in place for decades; there is a lack of understanding of WBV-associated risks among safety and healthcare professionals.<sup>11</sup> Consequently, disorders associated with WBV exposure remain prevalent in the workforce<sup>12</sup> and military.<sup>10</sup>

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WBV has a variety of adverse physiological and cognitive effects on humans. Vibration transmitted to the eyes reduces manual tracking performance, and vibration can exacerbate hearing loss due to noise.<sup>10</sup> WBV exposure leads to mental fatigue as measured by reduced performance on cognitive tasks<sup>10</sup> and attention while driving,<sup>13</sup> as well as drowsiness.<sup>14</sup> Physical disorders associated with WBV are largely musculoskeletal; however, neurological, gastrointestinal, cardiovascular, and reproductive symptoms have also been noted in occupational medicine.<sup>12</sup>

Perhaps most significantly, WBV has detrimental effects on the spinal column and associated musculature, which can result in LBP. WBV can cause the spine to undergo compression, tension, rotation, and flexion, all of which can engage the back muscles and lead to fatigue. Electromyographic (EMG) studies of the erector spinae muscle have found an increased EMG signal during WBV, and a decreased frequency of the signal leading to muscle fatigue, primarily at the resonant frequency of 5 Hz.<sup>15-17</sup> Measurement of muscle oxygenation using near-infrared spectroscopy found reduced muscle oxygenation oscillations at 4.5 Hz of applied WBV, implying that muscles underwent decreased metabolic activity, neurogenic activity, and blood flow, which corresponds with the muscle fatigue as measured from EMG.<sup>18</sup>

Epidemiological evidence for the association between WBV and LBP, among other spinal pathologies, goes back decades. Such studies have found that greater duration of exposure (over 5 years) to WBV is associated with increased risk for spinal pathologies and that the lumbar region of the spine is more often affected than the thoracic region.<sup>19,20</sup> In part, pathologies of the lumbar spine are due to the reduced myoelectric activity and stabilization of the lumbar spine compared to the thoracic spine.<sup>19,20</sup> Among studies on military personnel, a cohort study on helicopter pilots found an association between cervical and lumbar degenerative changes and accumulated flight hours.<sup>21</sup> Also, a meta-analysis concluded that cervical pathology was associated with exposure in ground vehicles and fixed-wing aircraft.<sup>9</sup> Age-related degenerative changes in the spine can also exacerbate the negative impact of WBV in older subjects more prone to WBV-associated LBP.<sup>20</sup> Occupational exposure to WBV is linked to an increased risk of degenerative changes of the spine including disc herniation and nerve damage, though diagnostic imaging does not correlate well with symptoms.<sup>1</sup> Further, retrospective studies lack measurements of the specific vibration parameters associated with symptoms, and estimating the risk for an individual is not possible. Though a causal link between WBV and spinal pathology is widely agreed upon, there is insufficient quantitative evidence from cohort studies to sufficiently elucidate the biological relationships between WBV exposure and spine health.<sup>22</sup>

Obtaining complete data for occupational exposure to WBV in a cohort and establishing the risk of spinal disorders would take decades and is hardly feasible. These and other limitations on experiments to study the exposure-response relationship of WBV in humans, due primarily to ethical considerations, highlight the need for relevant models to evaluate spinal pathologies resulting from

vibrations. Of models that exist, the majority have been used to study WBV as a therapy for conditions such as bone fracture healing,<sup>23</sup> osteoporosis,<sup>24</sup> spinal cord injury,<sup>25</sup> and limb unloading<sup>26</sup> but do not examine the harmful effects of WBV. The exposure criteria for humans is not necessarily the same for other species, making it difficult to compare human and animal research. Thus, there is a need for models that translate WBV exposure criteria in other species to humans and a holistic assessment of the evidence current models provide.

This paper reviews *in vivo*, *ex vivo*, and *in vitro* models for spinal pathologies resulting from WBV. Existing models for spinal pathologies due to WBV vary in the mechanical stimuli and vibration mode(s) applied, as well as the time points evaluated. Understanding how vibration inputs from situations including occupational and military exposures result in deleterious changes to tissues of the spine including the musculature and intervertebral discs will enhance our understanding of these pathologies, and inform diagnostics and treatments for these injuries. This paper provides a summary of WBV parameters, and a comparison of *in vivo*, *ex vivo*, and *in vitro* models of WBV. In addition, suggestions to address the gaps in translation of animal models to the clinic are provided.

## 2 | WHOLE-BODY VIBRATION PARAMETERS

WBV is the transmission of vibrational waves to the body, and exposure is characterized by frequency, magnitude, direction, and duration. Frequency is the number of cycles per second delivered to the body, expressed in Hertz (Hz). A single sinusoidal frequency can be applied, but more commonly, a range of frequencies is applied, whereby frequency may be random. The relevant frequency range in the context of human WBV is 0.5-80 Hz,<sup>27</sup> while the resonant frequency of the human spine is 4-5 Hz.<sup>15</sup> The resonant frequency of a structure is the frequency at which oscillatory motion is amplified instead of attenuated. In Yucatan mini pigs, this frequency is 5-6 Hz,<sup>25</sup> and in rats it is 8-9 Hz.<sup>28</sup> There exists an inverse relationship between resonant frequency and mass, where resonant frequency is given by the equation  $f = 1/(2\pi) \sqrt{k/m}$ , where  $k$  is the stiffness constant, and  $m$  is the mass. The resonant frequency can be determined experimentally and is characterized using the transmissibility ratio, or the ratio of an object's displacement to the displacement of the source of vibration. At the resonant frequency, the transmissibility is maximal and greater than one, since the object's displacement is greater than the displacement of the source of vibration. For other frequencies, the transmissibility will be less than one, ie, the object's displacement is less than that of the source of vibration. Damping vibration is an important aspect of vehicular design, to reduce the motion and energy transferred to the human occupant.

The magnitude of vibration is defined by either acceleration ( $m/s^2$  or  $g$ 's) or displacement (m). The relationship between exposure limits, acceleration, and frequency are nonlinear; a shorter exposure

time is required for low acceleration magnitudes that occur in the 4-8 Hz frequency range compared to frequencies outside this range.<sup>27</sup> In rats, altering the displacement magnitude resulted in a different power relationship between root-mean-square acceleration and frequency, such that a lower displacement exponentially decreased the acceleration at resonant frequency.<sup>29</sup>

Likewise, the direction of motion results in different effects of WBV. Correspondingly, WBV exposure limit curves, above which WBV has been shown to cause harm, represent the relationship(s) between injury risk and each of the following: frequency, acceleration, and direction of motion. Motion could be in the fore-aft (x-axis, cranial-caudal for quadrupeds), lateral (y-axis, left-right), or vertical (z-axis, ventral-dorsal for quadrupeds) directions, or a combination of the three (Figure 1). For humans, the frequency range of 4-8 Hz in the vertical direction requires shorter exposure times, while that range is 1-2 Hz in either horizontal direction.<sup>27</sup>

Ex vivo and in vitro specimens may be tested under vibration on a platform or cyclic compression between two platens. While both methods are vibration in the sense that they are mechanical oscillations about an equilibrium point, for the sake of clarity a distinction between the two is made here. Under cyclic compression, the tissue specimen is placed between one stationary platen and one moving platen which applies compressive pressure. The moving platen deforms the specimen to a set level before returning to the non-deformed position. In contrast, specimens that are vibrated are placed upon a vibrating platform.

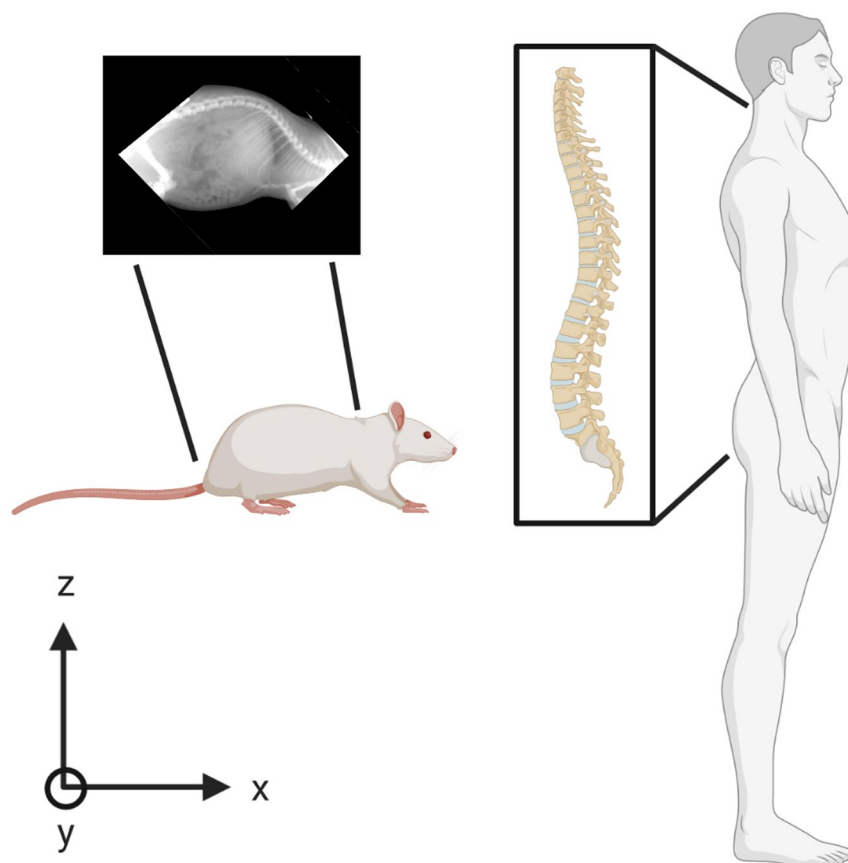
### 3 | IN VIVO MODELS

There are relatively few animal studies on the impact of WBV on the spine, with some evaluating the benefits of WBV for treatment of spinal cord injury<sup>30</sup> or limb unloading.<sup>26</sup> However, the harmful effects of WBV on neural, disc, and vertebral tissues of the spine cannot be discounted. Information on in vivo studies examining the effect of WBV on the spine are summarized in Table 1.

#### 3.1 | Neural tissue

With respect to the spinal cord, the dorsal root ganglion (DRG) and dorsal horn have been most extensively studied, particularly because of their role in nociception. In rabbits, a single 2-hour WBV session at 4.5 Hz resulted in increases in metabolic organelles in DRG neurons, specifically the numbers of mitochondria and lysosomes, as well as nuclear membrane clefting.<sup>31</sup> Such alterations were hypothesized to be linked to increased concentration of vascular intestinal peptide and decreased concentration of substance P (neuropeptides released in response to tissue damage and inflammation at the periphery) after 2 weeks of WBV at 4.5 Hz; however, the connection between organelle and neuropeptide changes was not definitively established.<sup>32</sup>

In rats, protein kinase C epsilon expression was increased in small-diameter neurons of the cervical DRG, which innervate



**FIGURE 1** Orientation of quadrupeds relative to humans and reference axes for WBV. (Created with BioRender.com.)

**TABLE 1** Summary of IN VIVO models of spinal pathologies from whole-body vibrations (WBV)

| Species             | WBV exposure   | Effects  | Ref. |
|---------------------|--|--|------|
| Rabbit              | 4.5 Hz, 0.35 g, x-axis<br>2 h  | Changed neuropeptide levels in lumbar DRG  | 32   |
| Rabbit <sup>a</sup> | 4.5 Hz, 0.2 g, x-axis<br>3 h/d, 2 wks  | Altered organelle numbers and nuclear membrane structure in lumbar DRG neurons   | 31   |
| Rabbit <sup>b</sup> | 4 Hz, 5 Hz, or 6 Hz<br>0.7 mm<br>2 h/day, 5 days/wk, 6 wks   | Altered serum markers and lumbar vertebrae parameters associated with vertebral degeneration   | 41   |
| Rat                 | 8 Hz, 2.74 mm; 52 Hz, 0.0459 mm; or 90 Hz, 0.0153 mm<br>0.7 g, z-axis<br>10 min/day, 5 days/wk, 4 wks                  | Reduced bone formation in lumbar vertebrae at 8 Hz   | 40   |
| Rat <sup>c</sup>    | 15 Hz, 1.5 mm, 0.55 g, x-axis<br>30 min/day, 7 days<br>7 days rest after WBV   | Increased neurotrophin gene and protein expression in cervical IVD   | 34   |
| Rat <sup>c</sup>    | 8 Hz, 5 mm or 15 Hz, 1.5 mm<br>0.5 g, x-axis<br>30 min/day, days 0 and 7<br>7 days rest after WBV                      | Increased neuropeptide expression in cervical DRG and dorsal horn  | 28   |
| Rat <sup>c</sup>    | 8 Hz, 5 mm or 15 Hz, 1.5 mm<br>0.5 g, x-axis<br>30 min/day, days 0 and 7<br>7 days rest after WBV                      | Neuroimmune cell activation in lumbar dorsal horn  | 33   |
| Mouse               | 45 Hz, 74 $\mu$ m, 0.3 g, z-axis<br>30 min/day, 5 days/wk, 2 or 4 wks  | Increased degeneration and anabolic gene expression in thoracic IVD  | 35   |
| Mouse               | 45 Hz, 74 $\mu$ m, 0.3 g, z-axis<br>30 min/day, 5 days/wk, 4 or 8 wks  | No change in gene expression in thoracic IVD or degeneration in lumbar IVD   | 37   |
| Mouse               | 45 Hz, 74 $\mu$ m, 0.3 g, z-axis<br>30 min/day, 5 days/wk<br>2, 4, or 8 wks WBV, or 4 wks WBV and 4 wks rest after WBV | Induced degeneration of lumbar IVD and increased gene expression of matrix degradation enzymes in thoracic IVD; no changes in lumbar vertebrae microarchitecture | 36   |

Note: The x-axis refers to the fore-aft direction, and the z-axis refers to the vertical direction. The vibration magnitude is given in acceleration and/or displacement, as reported in the respective reference.

Abbreviations: DRG, dorsal root ganglion; IVD, intervertebral disc.

<sup>a</sup>Immobilized in horizontal position.

<sup>b</sup>One group immobilized in upright position.

<sup>c</sup>Isoflurane anesthesia used during WBV.

nociceptors, thermoreceptors, and mechanoreceptors.<sup>28</sup> Numerous anti-inflammatory cytokines, pro-inflammatory cytokines, and chemokines were upregulated in the spinal cord after WBV at resonance (8–9 Hz).<sup>28</sup> These changes were associated with decreased withdrawal threshold of the forepaws following repeated WBV and astrocytic and microglial activation in the cervical spinal cord. The same effect was shown in the hind paws and lumbar spinal cord in a separate study.<sup>33</sup>

### 3.2 | Intervertebral disc

WBV has been associated with molecular and structural changes in the intervertebral disc (IVD) as well. Repeated WBV for 7 days at 15 Hz in rats resulted in increased nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) mRNA and protein expression in the cervical IVD compared to non-vibrated controls.<sup>34</sup> NGF protein expression increased most in the nucleus pulposus (NP)

rather than the outer annulus fibrosus (OAF), while BDNF expression increased most in the NP and inner annulus fibrosus (IAF) rather than the OAF.<sup>34</sup>

In mice, repeated WBV for 2 or 4 weeks led to increased expression of matrix metalloproteinase-3 (*Mmp3*), aggrecan, and collagen type 1 alpha 1 genes in thoracic IVDs, which suggested early disc degeneration.<sup>35</sup> Similar alterations were found in a subsequent study that included longer exposure to WBV (4 or 8 weeks) and a recovery period (4 weeks WBV, then 4 weeks recovery).<sup>36</sup> Histological examination of the IVD revealed increased lumbar IVD degeneration as assessed by the Thompson grading scheme<sup>35,36</sup> and greater MMP-mediated aggrecan and collagen cleavage in the OAF.<sup>35</sup> Micro-computed tomography (micro-CT) imaging additionally showed a reduction in disc height in lumbar IVDs.<sup>36</sup> While these studies used CD-1 mice, interestingly, C57BL/6 mice under the same WBV exposure did not show IVD degeneration, suggesting animal strain differences in the effects of WBV.<sup>37</sup> Although both strains were the

same age (10 weeks), it is important to note that CD-1 and C57BL/6 mice have different weights (~38 g<sup>38</sup> and ~25 g,<sup>39</sup> respectively), but the same vibration (45 Hz frequency, 74  $\mu$ m displacement, and 0.3 g acceleration) was applied to both strains. Because the effect of frequency on the spine is mass-dependent, an adjustment in the vibration exposure for C57BL/6 mice may have been necessary in order to compare the results to those of CD-1 mice.

### 3.3 | Vertebrae

The response of bone to WBV is highly dependent on the frequency applied and animal model used. In rats, when comparing the effects of 10 minutes of exposure per day at 8, 52, or 90 Hz on bone parameters of the vertebrae, the 8 Hz frequency resulted in greater peak acceleration at the skin and bone of the L2 vertebra. The 8 Hz frequency was also associated with greater bone resorption measured by decreased mineral apposition rate, reduced bone formation rate, and increased osteoid surface.<sup>40</sup> In contrast, the 52 and 90 Hz groups showed improved bone histomorphometric parameters compared to non-vibrated controls.<sup>40</sup> In the CD-1 mice mentioned previously, while WBV at 45 Hz reduced the disc height index of lumbar IVDs, this exposure did not significantly alter L6 vertebral trabecular bone mineral density or bone volume fraction with 30 minutes of daily exposure.<sup>36</sup>

In rabbits, up to 6 weeks of WBV at 4 Hz combined with forced upright posture resulted in increased serum concentration of bone-specific alkaline phosphatase and tartrate-resistant acid phosphatase, indicative of bone remodeling.<sup>41</sup> Reduced numbers of osteoblasts and increased numbers of osteoclasts in the L5 vertebra coincided with the serum biomarker changes.<sup>41</sup> Comparing 4, 5, and 6 Hz, the load at failure of post-mortem ex vivo lumbar bone under dynamic compression decreased the most in the 4 Hz frequency group compared to all other groups.<sup>41</sup>

## 4 | EX VIVO AND IN VITRO MODELS

There are significantly fewer studies utilizing ex vivo and in vitro models for evaluation of the impact of WBV on spinal health. Such studies have focused on the IVD only, and no studies were identified that examined the isolated vertebrae or neural tissues of the spinal column under vibration. A summary of ex vivo and in vitro studies are shown in Table 2.

For the IVD, there is variation in the specimens used for testing ex vivo. One group used the whole mouse spine divided into three segments composed of multiple IVD and vertebrae,<sup>42</sup> and others used functional spinal units.<sup>43,44</sup> The functional spinal unit, or spinal motion segment, is composed of one IVD and two adjacent vertebrae. A partial motion segment made up of the IVD-cartilaginous endplate complex<sup>45</sup> and the isolated IVD<sup>46</sup> have been used as well.

Cyclic compression of the spinal motion segment results in physical damage to the IVD consistent with that seen in vivo. Cyclic flexion and extension of porcine cervical motion segments for 1.5 hours

resulted in disc herniation in 62/64 samples, and a significant decrease in specimen height was observed.<sup>43</sup> Cyclic compression combined with shock (rapid acceleration to a peak force) produced a greater extent of partial disc herniation than cyclic compression or shock alone, as measured by change in location of the NP.<sup>43</sup> Cyclic compression of the ovine lumbar motion segment for 20 000–48 000 cycles or 70 000–120 000 cycles resulted in greater damage compared to the unloaded control, quantified by the presence of AF lamellar delamination, endplate and NP tears, and disc-endplate damage.<sup>44</sup> No difference was found between the two experimental groups, likely due to the wide range of cycle numbers used. Only one ex vivo model examined biochemical changes of the IVD, at 0, 2, 6, and 24 hours after vibration.<sup>42</sup> The most drastic changes in murine IVD mRNA were found 6 hours post-vibration when increases in the anabolic genes aggrecan, Sox9, biglycan, decorin, connective tissue growth factor, and hypoxia-inducible factor 1 $\alpha$  were observed.<sup>42</sup> These changes were most pronounced at the 15 Hz frequency.<sup>42</sup>

A commonality of the reviewed in vitro models is a decrease in protein synthesis due to vibration or cyclic compression. Vibration of rabbit annulus cells at 6 Hz for 30 minutes increased ATP concentration.<sup>47</sup> The same stimulus for 6 or 8 hours was associated with a decrease in the mRNA expression of aggrecan, collagen type 1, collagen type 3, *Mmp1*, and *Mmp3*.<sup>48</sup> Similarly, cyclic compression at 1, 3, 5, 8, and 10 Hz of porcine NP cells or NP/IAF co-cultured cells resulted in decreased total DNA at all frequencies, while total <sup>3</sup>H-proline-labeled protein expression was greatest at 5 Hz for NP cells, and at 5, 8, and 10 Hz for NP/IAF cells.<sup>49</sup> A corresponding decrease in incorporated proline in NP cells at 5 Hz and in NP/IAF cells at 3 Hz was observed.<sup>49</sup> Results from these in vitro models collectively suggest reduced ECM assembly by IVD cells after vibration or cyclic compression.

## 5 | UTILITY OF CURRENT MODELS

Figure 2 provides a summary of the current evidence, including interrelationships among tissues, for back pain due to WBV reported in animal models, and highlights areas where further research is needed. In particular, the relationship between the IVD and spinal cord has been established, but connections between other tissues of the spine are largely unknown.

The preclinical research presented here focuses mostly on discogenic LBP, but LBP can result from numerous other pain sources, including nerve roots, joints, vertebrae, and muscles.<sup>50,51</sup> LBP may be due to nociceptive pain from musculoskeletal tissue injury or neuropathic pain from damage to neural tissues.<sup>51</sup> In particular, current evidence suggests a neuromuscular component to LBP following WBV. However, no in vivo studies were found that examined the back muscular response to WBV. The gastrocnemius and soleus responses have been studied, showing increased vascularization<sup>52</sup> and adaptations in motor unit excitability,<sup>53,54</sup> but it is unclear if these data are associated with similar changes in back muscles. Furthermore, while the changes were deemed beneficial, increased

**TABLE 2** Summary of ex vivo and in vitro models of cyclic compression and vibration

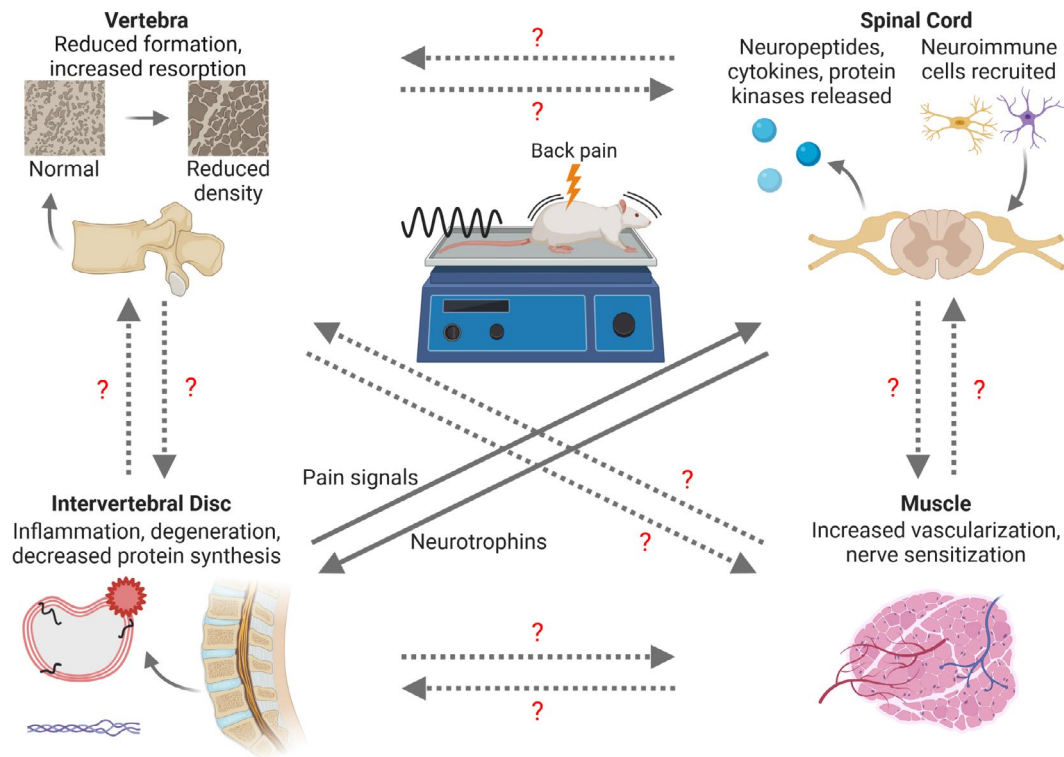
| Specimens                               | Pre-experimental conditions   | Load conditions   | Results   | Ref. |
|---|---|---|---|------|
| <b>Ex vivo</b>                          |   |   |   |      |
| PigTail IVD-cartilaginous plate complex | Rheological testing:<br>Frozen and thawed<br>PG synthesis rate:<br>1 h pre-incubation with $^{35}\text{S}$ -sulfate<br>Solute transport:<br>Fresh tissue used | Cyclic compression<br>Rheological testing:<br>3.5, 11, 35, and 110 Hz<br>$5 \pm 0.3$ N or $5 \pm 3$ N<br>4 h<br>PG synthesis rate:<br>3.5, 10, or 35 Hz<br>$5 \pm 0.3$ N<br>4 h<br>Solute transport:<br>3.5, 10, or 35 Hz<br>$5 \pm 0.3$ N<br>0.25-10 h | Decreased PG synthesis rate in NP and IAF with increasing frequency; increased solute transport rate with increasing frequency  | 45   |
| Sheep Caudal tail IVD                   | Frozen, thawed, and injected with contrast solution and blue dye  | Cyclic compression<br>0.2 or 10 Hz<br>$0.6 \pm 0.2$ MPa<br>4 h $\times$ 2<br>0.6 MPa, 2-3 h $\times$ 3<br>0.2 MPa, 8 h<br>Repeated 7 d  | Decreased cell viability after 10 Hz cyclic compression and no change in metabolism   | 46   |
| Pig Cervical motion segment             | Cyclic flexion/extension<br>300 N axial compressive preload, 15 min<br>1.5 kN axial compressive load, 0.5 Hz, 7000 cycles                                     | Cyclic compression<br>WBV <sup>a</sup> : 4.19 Hz, $414 \pm 100$ N<br>1.5 h<br>Shock: 414 N<br>Ramp-up to 1.2 kN<br>Ramp-down to 414 N<br>2,000 exposures<br>WBV + shock: 15 min WBV, 333 shocks<br>Repeated 6X<br>Flexion or neutral posture            | Cyclic flexion/extension produced partial IVD herniation in most samples; cyclic flexion/extension was most severe, followed by vibration + shock; no effect of posture | 43   |
| Mouse Spinal segment                    | Incubation in trypsin-EDTA, incubation in type II collagenase   | Vibration<br>15, 45, 60, or 90 Hz<br>0.3 g<br>30 min<br>0, 2, 6, 24 h rest after vibration  | Greatest changes in catabolic and anabolic gene expression at 15 Hz after 6 h   | 42   |
| Sheep Lumbar motion segment             | 300 N axial compressive preload, 15 min   | Cyclic compression<br>7° flexion<br>5 Hz, $1300 \pm 500$ N<br>20-48 k cycles or 70-120 k cycles   | Induced EP tears and physical damage to AF  | 44   |
| <b>In vitro</b>                         |   |   |   |      |
| Rabbit AF cells                         | Isolation and culture   | Vibration<br>6 Hz, 0.1 g<br>2, 4, 6, or 8 h<br>14, 12, 10, or 6 h rest after vibration  | Downregulated ECM-related genes   | 48   |
| Rabbit AF cells                         | Isolation and culture   | Vibration<br>6 Hz, 0.1 g<br>1, 5, 15, or 30 min<br>Supernatant collected 0, 1, 5, and 10 min after vibration  | Increased ATP concentration   | 47   |
| Pig NP cells<br>NP/IAF cells            | Isolation and 3D alginate culture   | Cyclic compression<br>1, 3, 5, 8, or 10 Hz<br>1 MPa<br>30 min/d, 3 d  | Decreased protein synthesis at 5 Hz   | 49   |

Note: The load conditions (cyclic compression and vibration) are indicated according to the description of the methodology.

Abbreviations: AF, annulus fibrosus; ECM, extracellular matrix; EP, endplate; IAF, inner annulus fibrosus; IVD, intervertebral disc; NP, nucleus pulposus; PG, proteoglycan; WBV, whole-body vibration.

<sup>a</sup>Whole-body vibration refers to the experimental group naming in the original reference and not the load conditions of the specimens.





**FIGURE 2** Proposed model for relationships between pathological changes that contribute to back pain due to whole-body vibrations (WBV) in animal models. Top left: WBV leads to reduced bone formation and increased bone resorption in vertebrae. Top right: Dorsal root ganglia release neuropeptides and inflammatory cytokines and recruit neuroimmune cells. Center: Neurotrophins from the spinal cord are delivered to the intervertebral disc, which in return signals pain. Bottom left: Intervertebral discs undergo inflammation, degeneration, and reduced protein synthesis. Bottom right: Muscle becomes more vascularized and peripheral nerves are sensitized. Relationships between other spinal tissues remain unknown. (Created with BioRender.com.)

muscle activity during WBV is not necessarily an indicator of physiological improvement. Spinal muscles have repeatedly been shown to contribute significantly to the biodynamic response of the spine under WBV. The increased motion of the spine at resonant frequencies requires a corresponding increase in muscle activity to stabilize the spine,<sup>16,55</sup> which may contribute to the back muscle fatigue associated with WBV.<sup>8,17</sup> Some muscle activity is likely only physiological due to stretching and shortening effects on muscles, which activates stretch reflexes and augments motor output.<sup>56</sup> Therapeutically, this may help strengthen otherwise weakened muscles and generate a better motor control and stability of the spine to limit pain.<sup>57</sup> On the other hand, WBV could cause muscle microtrauma, inflammation, and more nociceptive input to the spinal cord. The increased muscle activity is more a reflection of these pathological processes. The balance of beneficial or harmful effects may very well depend on not only the underlying biological substrates but also the nature of the WBV (amplitude, frequency, duration, etc).

Since vertebrae are innervated and vascularized, they can be another source of LBP. In silico stress analysis of the lumbar spine under vertical vibration showed the greatest risk of tissue damage was to the cancellous bone and cartilaginous endplate.<sup>58</sup> Another study on cadaveric human lumbar motion segments under cyclic axial compression also showed fractures primarily to the vertebral

endplate.<sup>59</sup> Endplate fractures subsequently alter the distribution of compressive forces on the IVD, and because the endplates are the source of nutrition for the avascular IVD, such endplate fractures have the capacity to initiate IVD degeneration by altering disc metabolism.<sup>60,61</sup> While IVD degeneration from WBV has been examined in vivo, endplate disruptions were not specifically mentioned as a source of this degeneration.<sup>35-37</sup> Likewise, endplate tears were noted in one ex vivo study,<sup>43</sup> but any effects of chronic WBV exposure on endplate disruptions and subsequent loss of IVD nutrition cannot be captured ex vivo.

There is a need for novel diagnostic biomarkers for spinal pathologies that do not rely on imaging. Structural changes observed using diagnostic imaging do not correlate well with LBP symptoms, and imaging has found pathologies in study participants with no reported LBP.<sup>1,51</sup> In addition, LBP, like all pain, demonstrates a broad spectrum of clinically reported symptoms for even a narrow spectrum of injury. As in vivo studies that rely on imaging techniques such as micro-CT<sup>36</sup> do not translate well to the clinic due to lack of correlation between symptoms and tissue structure/properties, future research is needed to assess the utility of other diagnostics like serum biomarkers.

With respect to pain, most in vivo models evaluate changes in stimulus response aspects, looking for hypersensitivity or allodynia



with noxious and non-noxious stimuli in behavioral testing.<sup>28,33,34</sup> In humans, the chronic pain is typically the most debilitating effect,<sup>51,62</sup> and it is difficult to relate chronic pain in humans with stimulus response in animals. In vivo models that examine the impact of WBV on normal behaviors (eg, burrowing in rodents) may translate better to the clinic, since these behaviors most closely relate to the behaviors affected by chronic pain in humans. Careful consideration should inform the selection of a preclinical model, which is most useful for a mechanistic investigation that cannot be studied in humans (eg, histology on the spinal tissues), or for safety/ethical reasons, versus human studies which would be advantageous for studying, eg, conservative treatments for LBP.

The effect of WBV on the IVD is in part due to the stresses the body places on the spine. Ex vivo testing of the spine has been performed primarily under cyclic compression, while the in vivo scenario likely involves more complex loading that includes tension and shear stress.<sup>63</sup> Finite element models have shown that the spine undergoes cyclic flexion-extension in addition to vertical vibration under cyclic load conditions.<sup>64,65</sup>

The evidence for IVD degeneration from WBV is limited due to the variation within animal models and ex vivo and in vitro specimens, as well as inconsistent experimental environment/conditions and mechanical stimuli applied. IVD degeneration, which can be graded histologically in spinal motion segments using, for example, the Thompson grading score, includes cartilaginous endplate tears and thinning that cannot be captured with testing of the isolated IVD, which does not include the endplates.<sup>66,67</sup> With respect to in vitro models, an examination of a specific cell type of the IVD does not account for the role of the IVD microenvironment in the development of IVD degeneration. For example, notochordal cells are present in rabbits, mice, and pigs through adulthood, but reportedly disappear in humans by 10 years of age, though they have been detected in cadaveric tissue from individuals up to 32 years old in at least one study.<sup>68</sup> Notochordal cells affect IVD degeneration,<sup>69</sup> but to date have not been included in in vitro cell culture models. Several key cellular responses are missing from the literature. For example, no ex vivo or in vitro models of neural tissues/cells have been used to study the contributions of WBV to LBP. Further, evaluation of the immune response to vibration in vivo is very limited, and has been performed only in the spinal cord.<sup>28,33</sup>

The use of quadrupeds to study the human spine raises the question of the clinical relevance of such models. Rabbits, mice, rats, pigs, and sheep were used in the studies presented in this paper. Anatomical comparisons of the human spine with the rat,<sup>70</sup> sheep,<sup>71</sup> and pig<sup>72</sup> spine have found that the lumbar region of the spine is similar enough for these species to be suitable models for the human spine. These species, as well as rabbits and mice, have a kyphotic curvature of the lumbar spine relative to humans (Figure 1). Biomechanically, the spine of quadrupeds and bipeds is loaded under axial compression during walking and standing, and muscle activity resists torsion of the spine.<sup>73</sup> Biomechanically speaking, quadrupeds can be an adequate model for the human spine.

The current literature lacks several key components; namely, neural tissues have not been examined ex vivo or in vitro, and ex vivo and in vitro mechanical testing of the IVD vary in the specimens used and in the applied stimuli. With the emphasis on the IVD as a source of back pain, no research to date has looked at the response of the back muscle in vivo, ex vivo, or in vitro. Although diagnostic imaging is commonly used in in vivo studies, these results do not necessarily translate to the clinic, where imaging findings do not correlate to symptoms. It may take a wider sampling of all relevant tissues (muscle, bone, IVD, and spinal cord) at multiple levels of study (imaging, physiology, histology, biochemical, gene expression changes) under different WBV conditions before salient contributing features can be identified and targeted for therapeutic intervention. Studying isolated components of the underlying pathology may not provide the necessary insights to address the main questions, namely: (a) what are the effects of WBV on the spine? (b) how do these changes relate to clinically relevant issues like pain and subsequent degenerative changes? and (c) what therapeutic targets may be used to mitigate the impact of WBV?

Thus far, there is a disconnect between the molecular changes immediately following WBV and the system-level degenerative processes in the spine that occur over years of WBV exposure. A multiscale paradigm for vibrational injury that connects pathological processes across spatial and temporal length scales would improve injury prediction, diagnosis, and development of novel therapeutics. Development of an exposure scaling function across species that is relevant to human WBV exposures would aid in translating findings from the current animal models to inform clinical practice.

## 6 | CONCLUSIONS

The body of evidence suggests that WBV results in peptide changes in neural tissues, reduced vertebrae density, and inflammation and degeneration of the IVD. The IVD, in particular, undergoes mechanical damage and reduced protein synthesis. Based on research on gastrocnemius and soleus muscles, back muscles likely undergo peripheral nerve sensitization and increased vascularization due to WBV. Continuing and improving on the use of in vivo, ex vivo, and in vitro models for WBV is needed to further our understanding of its effects on the spine and LBP.

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