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. Occupational exposure to whole-body vibration (WBV) is experienced by drivers,1,2 vehicle operators,1,3 and off-road machine operators.4-6 Among military personnel, sources of WBV include ground vehicles and aircraft.7-10 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. 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
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. WBV exposure leads to mental fatigue as measured by reduced performance on cognitive tasks and attention while driving, as well as drowsiness. Physical disorders associated with WBV are largely musculoskeletal; however, neurological, gastrointestinal, cardiovascular, and reproductive symptoms have also been noted in occupational medicine.

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. 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.

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. 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. Among studies on military personnel, a cohort study on helicopter pilots found an association between cervical and lumbar degenerative changes and accumulated flight hours. Also, a meta-analysis concluded that cervical pathology was associated with exposure in ground vehicles and fixed-wing aircraft. Age-related degenerative changes in the spine can also exacerbate the negative impact of WBV in older subjects more prone to WBV-associated LBP. 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. 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.

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, osteoporosis, spinal cord injury, and limb unloading 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, while the resonant frequency of the human spine is 4–5 Hz. 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, and in rats it is 8–9 Hz. 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, i.e., 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 allows for a greater magnitude of vibration without reaching the same level of transmissibility.
time is required for low acceleration magnitudes that occur in the
4-8 Hz frequency range compared to frequencies outside this
range. In rats, altering the displacement magnitude resulted in a
different power relationship between root-mean-square accelera-
tion and frequency, such that a lower displacement exponentially
decreased the acceleration at resonant frequency.

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, accelera-
tion, 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.

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 dis-
tinction 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 or limb unloading. 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. Such alterations were hypothesized
to be linked to increased concentration of vascular intestinal pep-
tide and decreased concentration of substance P (neuropeptides
released in response to tissue damage and inflammation at the pe-
riphery) after 2 weeks of WBV at 4.5 Hz; however, the connection
between organelle and neuropeptide changes was not definitively
established.

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.)
nociceptors, thermoreceptors, and mechanoreceptors. Numerous anti-inflammatory cytokines, pro-inflammatory cytokines, and chemokines were upregulated in the spinal cord after WBV at resonance (8-9 Hz). 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.

### 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. 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.

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. 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). Histological examination of the IVD revealed increased lumbar IVD degeneration as assessed by the Thompson grading scheme and greater MMP-mediated aggrecan and collagen cleavage in the OAF. Microcomputed tomography (micro-CT) imaging additionally showed a reduction in disc height in lumbar IVDs. 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. 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\(^3\) and ~25 g\(^3\) 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.\(^{40}\) In contrast, the 52 and 90 Hz groups showed improve bone histomorphometric parameters compared to non-vibrated controls.\(^{40}\) 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.\(^{36}\)

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.\(^{41}\) Reduced numbers of osteoblasts and increased numbers of osteoclasts in the L5 vertebra coincided with the serum biomarker changes.\(^{41}\) 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.\(^{41}\)

### 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,\(^{42}\) and others used functional spinal units.\(^{33,44}\) 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\(^{45}\) and the isolated IVD\(^{46}\) 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.\(^{53}\) 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.\(^{43}\) 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.\(^{44}\) 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.\(^{42}\) 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.\(^{42}\) These changes were most pronounced at the 15 Hz frequency.\(^{42}\)

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.\(^{47}\) 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.\(^{48}\) 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 \(3\)H-proline-labeled protein expression was greatest at 5 Hz for NP cells, and at 5, 8, and 10 Hz for NP/IAF cells.\(^{49}\) A corresponding decrease in incorporated proline in NP cells at 5 Hz and in NP/IAF cells at 3 Hz was observed.\(^{49}\) 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 dis-cogenic LBP, but LBP can result from numerous other pain sources, including nerve roots, joints, vertebrae, and muscles.\(^{50,51}\) LBP may be due to nociceptive pain from musculoskeletal tissue injury or neuropathic pain from damage to neural tissues.\(^{51}\) 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\(^{52}\) and adaptations in motor unit excitability.\(^{53,54}\) 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. |
|------------------------------------|-----------------------------|----------------|------------------------------------------------------------------------|------|
| **Ex vivo**                         |                             |                |                                                                        |      |
| Pig Tail IVD-cortical cartilaginous plate complex | Rheological testing: Frozen and thawed | Cyclic compression | Decreased PG synthesis rate in NP and IAF with increasing frequency; increased solute transport rate with increasing frequency | 45   |
|                                    | PG synthesis rate: 1 h pre-incubation with 35S-sulfate | Rheological testing: 3.5, 11, 35, and 110 Hz | | |
|                                    | Solute transport: Fresh tissue used | PG synthesis rate: 3.5, 10, or 35 Hz | | |
|                                    |                              | Solute transport: 3.5, 10, or 35 Hz | | |
|                                    |                              | 0.25-10 h | | |
| Sheep Caudal tail IVD              | Frozen, thawed, and injected with contrast solution and blue dye | Cyclic compression | Decreased cell viability after 10 Hz cyclic compression and no change in metabolism | 46   |
| Pig Cervical motion segment        | Cyclic flexion/extension 300 N axial compressive preload, 15 min, 1.5 kN axial compressive load, 0.5 Hz, 7000 cycles | Cyclic compression | 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   |
|                                    |                              | WBV*: 4.19 Hz, 414 ± 100 N | | |
|                                    |                              | Shock: 414 N | | |
|                                    |                              | Ramp-up to 1.2 kN | | |
|                                    |                              | Ramp-down to 414 N | | |
|                                    |                              | 2,000 exposures | | |
|                                    |                              | WBV + shock: 15 min WBV, 333 shocks | | |
|                                    |                              | Repeated 6X | | |
|                                    |                              | Flexion or neutral posture | | |
| Mouse Spinal segment               | Incubation in trypsin-EDTA, incubation in type II collagenase | Vibration | Greatest changes in catabolic and anabolic gene expression at 15 Hz after 6 h | 42   |
|                                    |                              | 15, 45, 60, or 90 Hz | | |
|                                    |                              | 0.3 g | | |
|                                    |                              | 30 min | | |
|                                    |                              | 0, 2, 6, 24 h rest after vibration | | |
| Sheep Lumbar motion segment        | 300 N axial compressive preload, 15 min | Cyclic compression | Induced EP tears and physical damage to AF | 44   |
|                                    |                              | 7° flexion | | |
|                                    |                              | 5 Hz, 1300 ± 500 N | | |
|                                    |                              | 20-48 k cycles or 70-120 k cycles | | |
| In vitro                           | Isolation and culture        | Vibration | Downregulated ECM-related genes | 48   |
| Rabbit AF cells                    |                              | 6 Hz, 0.1 g | | |
|                                    |                              | 2, 4, 6, or 8 h | | |
|                                    |                              | 14, 12, 10, or 6 h rest after vibration | | |
| Rabbit AF cells                    | Isolation and culture        | Vibration | Increased ATP concentration | 47   |
|                                    |                              | 6 Hz, 0.1 g | | |
|                                    |                              | 1, 5, 15, or 30 min | | |
|                                    |                              | Supernatant collected 0, 1, 5, and 10 min after vibration | | |
| Pig NP cells                       | Isolation and 3D alginate culture | Cyclic compression | Decreased protein synthesis at 5 Hz | 49   |
|                                    |                              | 1, 3, 5, 8, or 10 Hz | | |
|                                    |                              | 1 MPa | | |
|                                    |                              | 30 min/d, 3 d | | |

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.

*Whole-body vibration refers to the experimental group naming in the original reference and not the load conditions of the specimens.
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, which may contribute to the back muscle fatigue associated with WBV. Some muscle activity is likely only physiological due to stretching and shortening effects on muscles, which activates stretch reflexes and augments motor output. Therapeutically, this may help strengthen otherwise weakened muscles and generate a better motor control and stability of the spine to limit pain. 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. 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. While IVD degeneration from WBV has been examined in vivo, endplate disruptions were not specifically mentioned as a source of this degeneration. Likewise, endplate tears were noted in one ex vivo study, 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. 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 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. In humans, the chronic pain is typically the most debilitating effect, 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. Finite element models have shown that the spine undergoes cyclic flexion-extension in addition to vertical vibration under cyclic load conditions.

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. 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. Notochordal cells affect IVD degeneration, 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.

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, sheep, and pig 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. 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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REFERENCES

1. Johanning E. Diagnosis of whole-body vibration related health problems in occupational medicine. J Low Freq Noise Vib Active Control. 2011;30(3):207-220.
2. Thamsuwan O, Blood RP, Ching RP, Boyle L, Johnson PW. Whole body vibration exposures in bus drivers: a comparison between a high-floor coach and a low-floor city bus. Int J Ind Ergon. 2013;43(1):9-17.
3. McBride D, Paulin S, Herbison GP, Waite D, Bagheri N. Low back and neck pain in locomotive engineers exposed to whole-body vibration. Arch Environ Occup Health. 2014;69(4):207-213.
4. Milosavljevic S, Bagheri N, Vasilijev RM, McBride DI, Rehn B. Does daily exposure to whole-body vibration and mechanical shock relate to the prevalence of low back and neck pain in a rural workforce? Ann Occup Hyg. 2012;56(10):10-17.
5. Kromulski J, Pawlowski T, Szczepaniak J, et al. Absorbed power distribution in the whole-body system of a tractor operator. Ann Agric Environ Med. 2016;23(2):373-376.
6. Jack RJ, Oliver M. A review of factors influencing whole-body vibration injuries in forestry mobile machine operators. Int J For Eng. 2008;19(1):51-65.
7. Käsin JI, Mansfield N, Wagstaff A. Whole body vibration in helicopters: Risk assessment in relation to low back pain. Aviat Space Environ Med. 2011;82(8):790-796.
8. Kollok RO, Games KE, Wilson AE, Sefton JM. Vehicle exposure and spinal musculature fatigue in military warfighters: a meta-analysis. J Athletic Training. 2016;51(11):981-990.
9. Kollok R, Games K, Wilson AE, Sefton JM. Effects of vehicle-ride exposure on cervical pathology: a meta-analysis. Ind Health. 2015;53:197-205.
10. Nakashima AM. Whole-body vibration in military vehicles: a literature review. Can Acoust. 2005;33(2):35-40.
11. Paeschold BHW, Mayton AG. Whole-body vibration: building awareness in SH&E. Prof Saf. 2011;56(4):30-35.
12. Johanning E. Whole-body vibration-related health disorders in occupational medicine – an international comparison. Ergonomics. 2015;58(7):1239-1252.
13. Park DJ, Choi MG, Song JT, Ahn SJ, Jeong WB. Attention decrease of drivers exposed to vibration from military vehicles when driving in terrain conditions. Int J Ind Ergon. 2019;72(June):363-371.
14. Azizan MA, Fard M. The influence of vibrations on vehicle occupant fatigue. In INTER-NOISE. 2014:1767-1777.
15. Pope MH, Wilder DG, Magnusson M. Possible mechanisms of low back pain due to whole-body vibration. J Sound Vib. 1998;215(4):687-697.
16. Blüthner R, Hinz B, Menzel G, Seidel H. Back muscle response to transient whole-body vibration. Int J Ind Ergon. 1993;12(1-2):49-59.
17. Hansson T, Magnusson M, Broman H. Back muscle fatigue and seated whole-body vibrations: An experimental study in man. Clin Biomech Elsevier Ltd. 1991:6:173-178.
18. Li Z, Zhang M, Chen G, Luo S, Liu F, Li J. Wavelet analysis of lumbar muscle oxygenation signals during whole-body vibration: implications for the development of localized muscle fatigue. Eur J Appl Physiol. 2012;112:3109-3117.
19. Wilder DG, Pope MH. Epidemiological and aetiological aspects of low back pain in vibration environments an update. Clin Biomech Elsevier Ltd. 1996;11(2):61-73.
20. Seidel H. On the relationship between whole-body vibration exposure and spinal health risk. Ind Health. 2005;43(3):361-377.
21. Byeon JH, Kim JW, Jeong HJ, et al. Degenerative changes of spine in helicopter pilots. Ann Rehabil Med. 2013;37(5):706-712.

22. Hill TE, Desmulin GT, Hunter CJ. Is vibration truly an injurious stimulus in the human spine? J Biomech. 2009;42(16):2631-2635.
23. Butezloff MM, Zamarioli A, Leoni GB, Volpon JB. Whole-body vibration improves fracture healing and bone quality in rats with ovariec-tomy-induced osteoporosis. Acta Cirúrgica Brasileira. 2015;30(11):727-735.
24. Xie P, Tang Z, Qin F, et al. Bone mineral density, microarchitectural and mechanical alterations of osteoporotic rat bone under long-term whole-body vibration therapy. J Mech Behav Biomed Mater. 2016;53:341-349.
25. Streijger F, Lee JHT, Chak J, et al. The effect of whole-body resonance vibration in a porcine model of spinal cord injury. J Neurotrauma. 2015;32:908-921.
26. Pengfei Y, Bin J, Chong D, Zhe W, Airong Q, Peng X. Whole-body vibration effects on bone before and after hind-limb unloading in rats. Aviat Space Environ Med. 2009;80(2):88-93.
27. ISO. ISO 2631-1:1997 Mechanical vibration and shock — Evaluation of human exposure to whole-body vibration — Part 1: General requirements. Published online; 1997.
28. Zeeman ME, Kartha S, Jaumard N, et al. Whole-body vibration at thoracic resonance induces sustained pain and widespread cervical neuroinflammation in the rat. Clin Orthop Relat Res. 2015;473:2936-2947.
29. Holsgrove TP, Zeeman ME, Welch WC, Winkelstein BA. Pain after whole-body vibration exposure is frequency dependent and independent of the resonant frequency: lessons from an in vivo rat model. J Biomech Eng. 2020;142(6):061005.
30. Wirth F, Schempf G, Stein G, et al. Whole-body vibration improves functional recovery in spinal cord injured rats. J Neurotrauma. 2013;30(6):453-468.
31. McLain RF, Weinstein JN. Ultrastructural changes in the dorsal root ganglion associated with whole body vibration. J Spinal Disord. 1991;4(2):142-148.
32. Weinstein J, Pope M, Schmidt R, Seroussi R. Neuropathologic effects of vibration on the dorsal root ganglion: an animal model. Spine. 1988;13(5):521-525.
33. Zeeman ME, Kartha S, Winkelstein BA. Whole-body vibration induces pain and lumbar spinal inflammation responses in the rat that vary with the vibration profile. J Orthop Res. 2016;34(8):1439-1446.
34. Kartha S, Zeeman ME, Baig HA, Guarino BB, Winkelstein BA. Upregulation of BDNF and NGF in cervical intervertebral discs exposed to painful whole-body vibration. Spine. 2014;39(19):1542-1548.
35. McCann MR, Patel P, Pest MA, et al. Repeated exposure to high-frequency low-amplitude vibration induces degeneration of murine intervertebral discs and knee joints. Arthritis Rheumatol. 2015;67(8):2164-2175.
36. McCann MR, Veras MA, Yeung C, et al. Whole-body vibration of mice induces progressive degeneration of intervertebral discs associated with increased expression of II-1p and multiple matrix degrading enzymes. Osteoarthritis Cartilage. 2017;25:779-789.
37. Kerr GJ, McCann MR, Branch JK, et al. C57BL/6 mice are resistant to joint degeneration induced by whole-body vibration. Osteoarthritis Cartilage. 2017;25(3):421-425.
38. CD-1® IGS Mouse. Charles River. https://www.criver.com/products-services/find-model/cd-1-igs-mouse?region=3611. Accessed November 30, 2020.
39. C57BL/6 Mouse. Charles River. https://www.criver.com/products-services/find-model/c57b6-mouse?region=3611
40. Pasqualini M, Lavet C, Elbadou M, et al. Skeletal site-specific effects of whole body vibration in mature rats: From deleterious to beneficial frequency-dependent effects. Bone. 2013;55(1):69-77.
41. Chang Q, Wei F, Zhang L, et al. Effects of vibration in forced posture on biochemical bone metabolism indices, and morphometric
and mechanical properties of the lumbar vertebra. PLoS One. 2013;8(11):e78640.

42. McCann MR, Patel P, Beaucage KL, et al. Acute vibration induces transient expression of anabolic genes in the murine intervertebral disc. Arthritis Rheum. 2013;65(7):1853-1864.

43. Yates JP, Mcgill SM. The effect of vibration and posture on the progression of intervertebral disc herniation. Spine. 2011;36(5):386-392.

44. Wadde KR, Schollum ML, Robertson PA, Thambyah A, Broom ND. ISSLS prize winner: Vibration really does disrupt the disc. Spine. 2016;41(15):1185-1198.

45. Ishihara H, Tsuji H, Hirano N, Ohshima H, Terahata N. Effects of intermittent whole-body vibration on motor unit recruitment and threshold. J Appl Physiol. 2002;92(6):1415-420.

46. Kasra M, Merryman WD, Loveless KN, Goel VK, Martin JD, Yamazaki S, Banes AJ, Weinhold PS, Tsuzaki M, Kawakami M. Frequency response of pig intervertebral disc cells subjected to dynamic hydrostatic pressure. J Orthop Res. 2006;24:1967-1973.

47. Yamazaki S, Weinhold PS, Graff RD, et al. Annulus cells release ATP in response to vibratory loading in vitro. J Cell Biochem. 2003;90:812-818.

48. Yamazaki S, Banes AJ, Weinhold PS, Tsuzaki M, Kawakami M, Minchew JT. Vibrationary loading decreases extracellular matrix and matrix metalloproteinase gene expression in rabbit annulus cells. Spine. 2002;27(6):1357-1362.

49. Kasra M, Merryman WD, Loveless KN, Goel VK, Martin JD, Buckwalter JA. Frequency response of pig intervertebral disc cells subjected to dynamic hydrostatic pressure. J Orthop Res. 2006;24:1967-1973.

50. Manchikanti L, Singh V, Pampati V, et al. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Phys. 2001;4(4):308-316.

51. Allegri M, Montella S, Salici F, et al. Mechanisms of low back pain: a guide for diagnosis and therapy. F1000Research. 2016;5(1530):1-11.

52. Kaneguchi A, Tsuji H, Hirano N, Ohshima H, Terahata N. Effects of continuous quantitative vibration on rheologic and biological behaviors of the intervertebral disc. Spine. 1992;17(35):S7-S12.

53. Illien-Junger S, Gantenbein-Ritter B, Grad S, et al. The combined effects of limited nutrition and high-frequency loading on intervertebral discs with endplates. Spine. 2010;35(19):1744-1752.

54. Baczyk M, Haluszka A, Mrówczyński W, Celichowski J, Krutki P. Vibratory effects on the progression of intervertebral disc herniation. Spine J. 2014;15(1):1-9.

55. Allegri M, Montella S, Salici F, et al. Mechanisms of low back pain: a guide for diagnosis and therapy. F1000Research. 2016;5(1530):1-11.

56. Pollock RD, Woledge RC, Martin FC, Newham DJ. Effects of whole body vibration on motor unit recruitment and threshold. J Appl Physiol. 2012;112(3):388-395.

57. Yang J, Seo D. The effects of whole body vibration on static balance, spinal curvature, pain, and disability of patients with low back pain. J Phys Ther Sci. 2015;27:805-808.