The Effects of Postural Loading, Sacral Orientation, and Age on Sex Differences in Lumbar Functional Morphology and Health

Jeannie F. Bailey

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Reading Committee:

Patricia A. Kramer, Chair

Donna L. Leonetti

Ella Been

Program Authorized to Offer Degree:

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Abstract

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Jeannie F. Bailey

Chairperson of the Supervisory Committee:

Dr. Patricia A. Kramer, PhD

Department of Anthropology

This dissertation explores sexual dimorphism in the human lumbar spine by applying evolutionary theory to understanding variability in lumbar functional morphology and health risks between sexes. Three separate studies were designed to examine how lumbar lordosis (LL) differs between sexes, how sacral orientation differs between sexes, how LL develops in juveniles in relation to sacral orientation, and how age-related changes in lumbar motion and stabilization differ between sexes. Results from this body of work showed that females had greater LL than males, but only in standing posture and not in supine posture. Additionally, vertebral bodies were more lordotically wedged in females than males. For sacral orientation, sacral slope was greater in females than males and pelvic incidence (PI) did not differ by sex. In juveniles, while LL increased with age, PI did not change with age. We found PI is predictive of adult LL. These results may allude to there being higher joint laxity in females that could cause higher standing LL in females than males amid no differences in PI between sexes. Age-related lumbar conditions, like

degenerative spondylolisthesis are greater in females and positively relates to LL and spinal instability. Lumbar intervertebral motion in the sagittal plane differed by sex with males having a greater range of flexion and females having a greater range of extension, which may indirectly relate to sex differences in LL. Furthermore, age-related decreases in lumbar intervertebral motion were greater in females than males, and sex differences in intervertebral translation revealed motion indicative of spondylolisthesis at L4-L5 in females but not in males. These results support that there are sex differences in the lumbar spine with females having greater LL and a greater risk of related orthopaedic conditions. Whether there is a functional purpose for greater LL in females remains unclear, but joint laxity appears to be a factor.

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Chapter 1: Introduction

This dissertation explores sexual dimorphism in the human lumbar spine by applying evolutionary theory to understanding variability in lumbar functional morphology and health risks between sexes. Biological anthropologists have hypothesized that the human lumbar spine is sexually dimorphic, with adult females having greater lumbar curvature (lordosis) than adult males, as an adaptation for bearing a pregnancy load (Whitcome et al. 2007). However, in modern medicine, clinical research provides inconsistent evidence of sex differences in the lumbar spine. Furthermore, when sex differences are reported the potential cause is not considered and remains unexplored. In order to understand how sexual dimorphism in the human lumbar spine may relate to variability in lumbar functional morphology and health risks between sexes, we need to understand how *costs and benefits* of adaptations enabling bipedalism differ between sexes.

Costs and benefits of adaptations for bipedal locomotion

To understand how musculoskeletal adaptations differ by sex, one must first understand the costs and benefits that drive adaptations for bipedal locomotion in hominins. One *benefit* is the role that an adaptation enables. For instance, the lumbar spine biomechanically supports and stabilizes the position of the upper body in upright posture. A *cost* could be the energetic or mechanical expense that accompanies the adaptation. An example might be the energetic cost from muscular stabilization required to keep the spine stable under the load of the upper body or the mechanical cost of failure that may occur from relatively higher compressive forces. 'Trade-offs' between costs and benefits constrain selection for an adaptation to ensure benefits in fitness outweigh necessary costs (Stearns 1989). Within this dissertation, lumbar lordosis (LL) is the focus as an adaptation for

effective bipedal posture and locomotion. For the evolution of LL, enabling effective bipedalism is the benefit for fitness and the prevalence of orthopaedic conditions is arguably the cost (Krogman 1951). More details on the costs and benefits of LL can be found in chapter 2.

Sexually dimorphic adaptations to the musculoskeletal system

Given that males and females have different roles in ensuring fitness for a species, an adaptation can be sexually dimorphic if it is involved with reproduction. For sexually dimorphic adaptations of the musculoskeletal system, reproduction provides an added selective force in addition to selection for effective bipedal locomotion. The human pelvis is a prime example, as it plays a critical role in human bipedalism both by transferring the force of the upper body to the lower limbs and stabilizing upright posture with attachments for muscles that run between the hips and torso. However, in females the need to accommodate a relatively large infant cranium during childbirth also shapes the morphology of the pelvis. The 'obstetrical dilemma' refers to the constraints on the human pelvis of females – selection to facilitate both efficient/effective bipedal locomotion and childbirth, which are both critical for fitness of our species (Rosenberg and Trevathan 2002; Stone 2016; Wittman and Wall 2007). The functional morphology of the pelvis of females differs, therefore, from that of males.

The lumbar spine has been proposed to be sexually dimorphic with more lordosis in females to aid with bearing a pregnancy load (Masharawi et al. 2010; Whitcome et al. 2007). Prior work demonstrates mixed results regarding sex differences in LL (reviewed in Table 3.1). Sex differences in LL exist, but the details of how they develop in the lumbar spine and if the female lumbar spine is better suited than the male to bear a pregnancy load is not clear. While this idea is compelling, an alternative hypothesis regarding sex

differences in growth and development and sex differences in joint laxity may explain sex differences in LL. More work needs to be done, therefore, to clarify *if, how*, and *why* the lumbar spine differs between sexes.

Evolutionary medicine

Evolutionary medicine seeks to understand modern health conditions through an evolutionary lens. The etiology of health conditions may be influenced by human evolution within the 'environment of evolutionary adaptedness' (Trevathan et al. 1999). With the increasingly longer lifespan of modern humans, comes age-related pain and mechanical failure of our musculoskeletal system. For the lumbar spine, prevalent orthopaedic conditions are arguably a cost of being adapted for bipedal locomotion (Anderson 1999; Castillo and Lieberman 2015; Krogman 1951). In addition, some cultural behaviors, such as sitting in chairs, are arguably *mis-matched* with the adapted function of our anatomy and have been shown to exacerbate low back pain and related orthopaedic conditions (Anderson 1999; Fahrni 1965; Mandal 1981). However, due to the sex differences in the lumbar spine that may be related to adaptions for reproductive fitness, I predict sex differences in orthopaedic conditions are related to LL.

Currently, a demand is rising to establish sex-specific standards for diagnosis and treatment of orthopaedic conditions (Hettrich et al. 2015; Leopold et al. 2014). Females are at a higher risk of age-related spinal conditions, including but not limited to: vertebral fractures due to osteoporosis (Cauley et al. 2014), adolescent idiopathic scoliosis (Ueno et al. 2011), spinal osteoarthritis (Wei et al. 2014), hyperkyphosis (Katzman et al. 2012), and degenerative spondylolisthesis (Jacobsen et al. 2007). A better understanding of how and why these spinal conditions differ by sex is needed and because the lumbar spine may be sexually dimorphic to enhance reproductive fitness in females, evolutionary medicine

provides a useful framework for understanding how sexual dimorphic adaptations of the musculoskeletal system can promote sex differences in orthopaedic conditions.

Caution should be applied when using an adaptationist perspective to potentially explain these sex differences in orthopaedic conditions. Even if the lumbar spine differs by sex with females having greater lordosis than males, it does not automatically mean that this difference is driven by an adaptation directly selected to aid reproductive fitness (Gould and Lewontin 1979). Sex differences in the lumbar spine may be an unintended result (pleiotropy) in an adaptation for joint laxity of the pelvis in females. For evolutionary medicine, the goal is to use evolution to better understand health conditions to possibly create more effective prevention and treatments; therefore, it is important not to "tell stories" of adaptive functions (Gould and Lewontin 1979). Alternative hypotheses for sex differences in LL should be considered.

Hypotheses and overview

This dissertation seeks to understand if the lumbar spine is sexually dimorphic and how sex may explain variability in lumbar functional morphology and health risks. My general hypotheses are:

1) ***In-vivo*** **LL is greater in females than males and influenced by postural loading**
2) **Sacral orientation will differ by sex**
3) **Juvenile development of LL will differ by sex**
4) **Lumbar motion will differ by sex**
5) **Age-related lumbar conditions will differ by sex**

What follows is an overview of background literature (chapter 2); then three independent studies (chapters 3 through 5) aimed at exploring these hypotheses and the potential orthopaedic trade-offs that may result; and lastly, my interpretation and the conclusion for the entire body of work (chapter 6).

Chapters 3 through 5 are presented as standalone manuscripts. In chapter 3, LL and pelvic incidence (PI) are compared between adult females and males in either standing or supine posture to characterize sex differences in LL in separate loading conditions and to understand if sex differences are load dependent. In chapter 4, PI and LL in juveniles is assessed to understand if PI predicts the development of adult LL and what this may imply for the development of sex differences in adult LL. In chapter 5, intervertebral rotation and translation is compared between sexes from a sample population with non-traumatic age-related symptoms (i.e. low back pain and degeneration) to understand how lumbar motion and stability differs by sex with progressing age. These three chapters do not link together in a linear fashion, but rather, different aspects of chapter 3 lead to the chapters 4 and 5 separately (Figure 1-1).

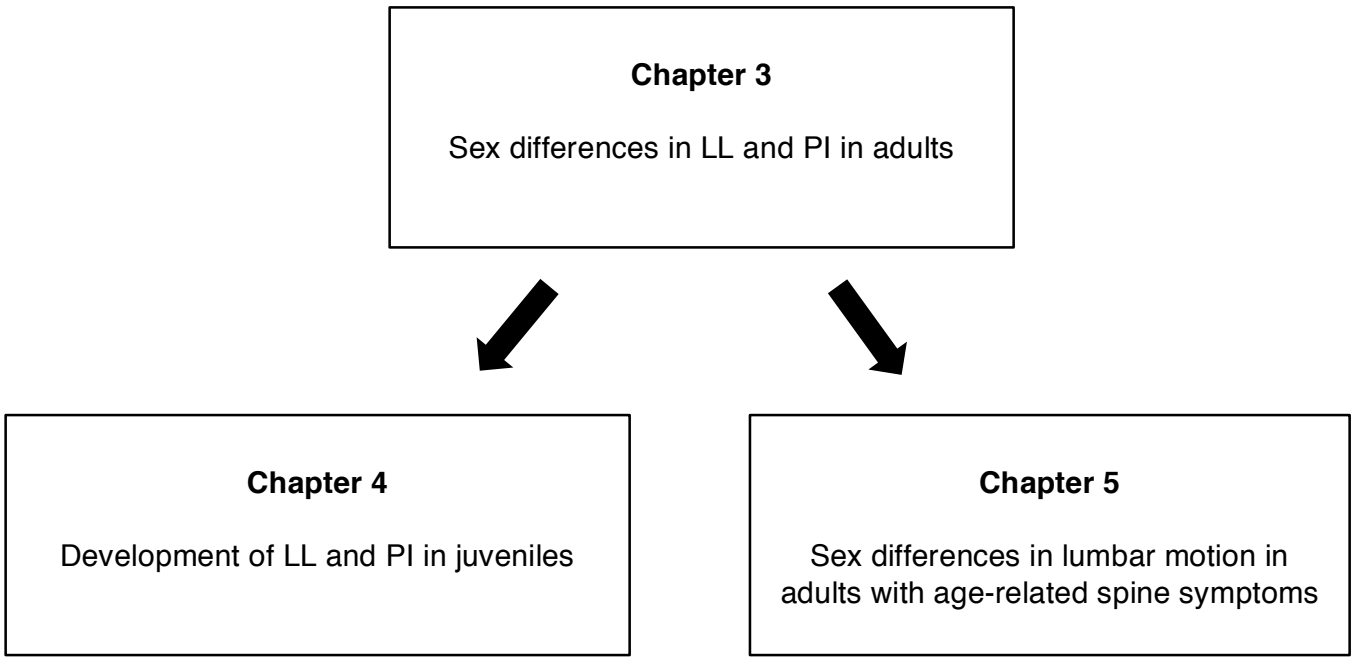


Figure 1-1: Flowchart of relationship between Chapters 3 through 5

Chapter 2: Background

Introduction to sex differences in load bearing joints

Reproduction is a strong selective force in the evolution of the female body, including the skeleton. The pelvis is one of the most discussed and researched examples of sexual dimorphism in the human skeleton. The shape of the female pelvis reflects conflicting demands of some of the hallmarks of human evolution: efficient bipedal locomotion and the birth of infants with relatively large crania (Rosenberg and Trevathan 2002; Stone 2016; Wittman and Wall 2007). As a result of the demands of childbirth, the biacetabular distance in females is relatively greater than in males, creating a greater quadriceps angle in females (Conley and Rosenberg 2007; Table 2-1). Pelvic morphology makes the biomechanical force on the knee under axial load different between sexes with females having more valgus stress on the knee. Consequently, in both adolescents and adults, anterior cruciate ligament (ACL) tears are two to eight times more likely in females than males (LaBella 2014; Ryan et al. 2014; Sutton and Bullock 2013). Additionally, the morphology and geometrical orientation of the joint surfaces comprising the knee is associated with sex differences in ACL injuries (Wahl et al. 2012). This evidence suggests that characteristics of female musculoskeletal anatomy thought to aid in reproduction are also associated with mechanical costs and risk of injury. This cost is considered a trade-off between reproduction and bipedality and is an important selective force driving musculoskeletal sexual dimorphisms.

The lumbar spine is potentially another example of sexual dimorphism in the human body. The functional anatomy of the human lumbar spine is adapted to aid in load-bearing and stabilization of the upper body in upright posture and bipedal locomotion. Low back pain is the leading cause of disability in the world (Buchbinder et al. 2013). The lumbar

spine is a prime example of an evolutionary adaptation for load-bearing that has a trade-off, i.e the anatomy is failure prone – but does the anatomy differ between sexes? The ability to bear pregnancy load should have a strong selective force on the human body to ensure effective bipedal locomotion while carrying a pregnancy or offspring. To begin to hypothesize how sex differences may affect the lumbar spine, we need to understand the functional anatomy and biomechanical factors that shape lumbar lordosis (LL), which is the topic of this chapter.

The human lumbar spine biomechanically supports upright posture

The human lumbar spine has three functions: to protect the spinal cord, to facilitate motion between the upper body and pelvis, and to transfer load from the upper body to the pelvis (White and Panjabi 1978). Humans are obligate bipeds and as such, the human lumbar spine is vertically oriented and adapted to bear the load the upper body throughout the day. The human lumbar spine is built to bear load at both the 'micro' level within each individual motion segment (Figure 2-1) and at the 'macro' level with the lordotic curvature along the whole lumbar spine (Figure 3-1; Figure 4-1).

Functional anatomy of a motion segment

Individual motion segments include an intervertebral disc ('disc') and adjacent vertebrae (Figure 2-1). The human lumbar spine includes five vertebrae (L1-L5) separated by five intervertebral discs, stabilizing ligaments, and trunk musculature. The work included in this dissertation focuses on the anterior column of the lumbar spine, which includes structures that are anterior to the spinal cord: the vertebral bodies and discs. The vertebral bodies are cylindrical and are built to absorb load without catastrophic fracture (McBroom et al. 1985). They are comprised mainly of trabecular bone and have a nutrient rich interior

with many blood vessels. The intervertebral disc is essentially a large ligament, serving as a viscoelastic joint between vertebral bodies, permitting intersegmental motion and absorbing axial load. The intervertebral disc is an avascular structure and is dependent on diurnal loading cycles to receive nutrients from adjacent vertebral bodies (McMillan et al. 1996). Nutrient transfer between the vertebral body and discs is dependent on load bearing, and this, in turn, maintains healthy discs. Lumbar health can, therefore, be considered load dependent.

The biomechanical benefits of LL

The lumbar spine, functioning as a singular unit, is also uniquely adapted to bear load. First, caudally located vertebral bodies and discs are greater in size in response to greater load demands on the lower lumbar segments. Second, and most important for this dissertation, the lordotic curvature of the human lumbar spine aids in bearing the load of the upper body in both upright postures and bipedal locomotion. This is exemplified by four particular functions. *First*, lordotic curvature of the lumbar spine places the upper body atop the pelvis in upright stance, enabling stable sagittal balance (Figure 4-1). *Second*, the lordosis of the lumbar spine deforms in response to perturbations in load bearing. These changes in lordosis can occur from changes in posture (e.g., flexing or extending the lumbar spine) to counter additional off-centered load (Dumas et al. 1995; Shymon et al. 2014; Whitcome et al. 2007). The lumbar spine extends in response to anterior loads, such during pregnancy (Dumas et al. 1995; Whitcome et al. 2007); and it flexes in response to posterior loads, as when a backpack is carried (Rodriguez-Soto et al. 2013; Shymon et al. 2014).

Third, lordotic curvature stabilizes the lumbar spine under compressive load in a neutral upright posture. LL decreases maximum forces on spinal tissues by distributing or sharing load between the disc and facet joints (Adams and Hutton 1985). Lumbar intradiscal

pressure is lowest in neutral lordotic posture and highest in flexed posture (Nachemson 1981; Wilke et al. 1999). Additionally, lordosis theoretically acts to stabilize the lumbar spine under compressive load by acting as a buckled euler column (Crisco and Panjabi 1992; Crisco et al. 1992; Meakin et al. 1996). The lumbar spine as a buckled euler column allows the lumbar spine to bear additional axial load without change in posture (Meakin et al. 1996). However, muscular support is a critical component for supporting the stability and bending stiffness of the lumbar spine under compressive load.

Additionally, trunk stabilizing musculature (i.e. *erector spinae* and *multifidus*) guides vertical axial force through the lordotic curvature of the lumbar spine via a 'follower load' path (Patwardhan et al. 1999). Early work loaded the *ex vivo* lumbar spine by applying a single vertebral load to the superior end of the lumbar spine and the spine buckled under forces far below the weight of the upper body (Crisco et al. 1992). Later work then loaded the *ex vivo* lumbar spine using loads that followed the curvature of the lumbar spine ('follower load'). With force guided through the spine via follower load, the spine could resist a higher compressive load comparable to the weight of the upper body (Patwardhan et al. 1999). Follower load through the lumbar spine combines the efforts of passive stabilization (i.e., LL) and active stabilization (i.e., trunk muscles) and explains how the lumbar spine can resist the high compressive loads of bearing the weight of the upper body. Interestingly, the combined stabilizing effects of muscles and LL is also exemplified in astronauts following prolonged exposure to unloading from microgravity, where a decrease in lumbar extensor muscles corresponds with a decrease in LL (Bailey et al. 2016).

The *fourth* example of LL enabling upright posture and bipedality is that, during bipedal locomotion, the lumbar spine further deforms/buckles like a spring in response to the heightened ground reaction forces of the axial skeleton associated with each heel strike (Syczewska et al. 1999). Energetic benefits are proposed to result from the oscillating

biomechanical response of the lumbar spine to repetitive forces during upright locomotion (Gracovetsky and Iacono 1987). These four examples support the concept that LL stabilizes the spine in both static and dynamic loading conditions by correcting for disruptions to center of mass and bearing additional loads through the vertical axis of the body.

LL as an indicator of bipedality in the fossil record

In the fossil record, evidence of LL is an indicator of bipedalism in hominins. Because the degree of LL is shaped in part by the intervertebral discs, it can be challenging to determine LL for a fossil hominin based on sparse vertebral fragments. From estimates of LL for a small number of fossil hominins, there appears to be a trend of increasing LL over time from genus *Australopithecus* (STS-14, STW-431) to early genus *Homo* (KNM-WT-15000) to modern humans (Been et al. 2012). The increase in LL can be attributed to increased loading demands from greater body size and different forms of locomotion (i.e., running). Evidence from the fossil records supports the critical biomechanical role of LL in as an adaptation for upright posture and bipedal locomotion. *Homo neanderthalensis* is an puzzling exception to the trend, as they overlap in time with anatomically modern humans, yet have particularly flat lumbar spines (Been et al. 2012).

Juvenile development of LL

The degree of LL varies over a lifetime. How LL develops during skeletal maturation is evidence of both its dependence on loading and its role in supporting the position of the upper body in upright posture. LL develops following the onset of unassisted bipedal locomotion in children. Beginning *in utero*, a fetus has only a single kyphotic spinal curve extending from head to sacrum, which is retained in the adult thoracic spine (O'Rahilly et al. 1980). Lordotic curvature of the cervical and lumbar regions develops secondarily, opposing

the primary kyphotic alignment in order to achieve sagittal balance. Lordosis of the cervical spine develops first, while *in utero*, in response to mechanical stimulus from the development of neck musculature with head movement (Bagnall et al. 1977). Lordosis of the lumbar spine develops after birth, following the start of unassisted bipedal locomotion (Abitbol 1987; Dimeglio and Bonnel 1990). The timing of the development of LL with upright loading supports the idea that LL is a morphological response to mechanical stimulus from gravitational loading and developing trunk musculature. This relationship between exposure to upright gravitational loading and the development of LL is further exemplified in paraplegic children, who cannot walk unassisted. In a study of 104 paraplegic children, 97 had severe spinal deformity (Kilfoyle et al. 1965). Furthermore, LL develops in bipedally trained Japanese macaques, which naturally have flat lumbar spines, characteristic of quadrupeds (Preuschoft et al. 1988).

The rate at which LL develops with age in juveniles reflects both the onset of walking and growth. A cross sectional study of how LL in upright posture varies with age from 3-15 years showed that lordotic vertebral wedging begins to take form beginning at 10-12 years (Cil et al. 2005). These findings suggest that adolescent growth spurt advances the development of LL due to increased loads on the spine at that time. Timing of the adolescent growth spurt differs by sex with females beginning at an earlier age. The earlier growth spurt among females may begin to increase lordosis at an earlier age in females and, therefore, may be a potential explanation for adult females having potentially greater lordosis than adult males. Interestingly, adolescent idiopathic scoliosis is 11 times more likely to occur in juvenile females compared to juvenile males (Ueno et al. 2011). The cause of this condition resulting in deformity of spinal curvature is unclear, but the onset in juvenile females coincides with puberty (Schlosser et al. 2015). The potential effect of sex hormones

on joint laxity in females (Quatman et al. 2008) may also play a role in sex differences in spinal curvature and stability, as will be discussed further in this dissertation.

Variation in adult LL between sexes

LL in asymptomatic adults (i.e. those with no low back pain or pathology) in standing posture ranges from 30 to 80° (measured using lumbar angle, defined in Table 2-1; Been and Kalichman 2013). The cause of this range in normal lordosis is unclear. Potential factors that have shown inconsistent effects on LL in the literature include age, sex, height, weight, pregnancy, ethnicity, sports, and occupation. However, many of these things may influence LL via biomechanical loading conditions throughout an individual's life ("load-history"), such as height, weight, pregnancy, sports, and occupation. Additionally, many of these studies do not control for degeneration, which may cause inconsistencies in the results. Biological sex is a variable of interest from an evolutionary medicine perspective, because the cause for sex differences in LL may be adaptive for reproduction or a non-adaptive result of biomechanical loading differences from growth, development, pregnancy, etc.

This dissertation aims to understand how biological sex may influence the degree of lordosis. Prior efforts to compare LL between sexes have produced inconsistent results: some studies have found sex differences in LL, while others report no sex differences in LL. Results from these prior studies are summarized in Table 3-1 (featured in the introduction of Chapter 3 and Bailey et al. 2016). Table 3-1 includes reviews LL from *in vivo* lumbar spine images, including radiography, MRI, or CT-scans. It is worthwhile to note that none of these studies were designed for the purpose of exploring sex differences; the reported results on sex differences were secondary. Therefore, variability in study design is present among prior work with regard to distribution of age and sex within the sample, the inclusion of

spinal degeneration and other pathology, imaging and measurement methodology, and population demographics from which samples were collected.

Only two studies have been conducted that focus specifically on characterizing sex differences in LL of asymptomatic adults. Both of these studies, however, do not measure *in vivo* LL. They, instead, measure vertebral morphology from the same large museum sample (Hamann-Todd Human Osteological Collection, Cleveland Museum of Natural History, Cleveland, OH, USA) and report different results. One study finds that vertebral wedging is more lordotic in females in L1 through L4 vertebrae but not L5 (Whitcome et al. 2007). The other study finds that only L1 and L2 are more lordotic in females and not L3 through L5 (Masharawi et al. 2010). Both studies relate their vertebral morphology results to females having greater LL than males, which may be invalid given the critical role of non-osseous soft tissues (i.e. the intervertebral disc) in shaping *in-vivo* LL. In addition to the vertebral morphology results, Whitcome et al. (2007) tracked external postural changes in females with developing pregnancy and she found an increase in lumbar extension in response to greater fetal load. This study does not explain whether or not there are sex differences in *in vivo* LL and *if* or *how* the functional morphology of LL differs by sex in response to load.

Relationship between pelvic incidence and LL

The degree of LL in an asymptomatic individual is affected by load and dependent on stance. Much research as been done, however, on patients with spinal conditions. With age-related degeneration and other pathological conditions affecting sagittal alignment of the spine, LL may be surgically 'reconstructed' to correct a patient's sagittal balance. However, it is difficult to determine what a patient's optimal LL should be because 1) their lumbar spine is severely symptomatic with immobilizing degeneration/deformity/injury and 2) a wide range of normal LL exists (30-80º, Been and Kalichman 2013). Pelvic incidence

(PI) is a morphological measurement of the orientation of the sacral endplate in relation to the acetabulum (Table 2-1; Figure 3-1; Figure 4-1). PI captures the position of the sacrum between the ilia of the pelvis and is independent of stance due to the limited mobility at the sacral iliac joint. PI has been shown to correlate with asymptomatic LL (Boulay et al. 2006; Legaye et al. 1998; Vialle et al. 2005) and, for that reason, is used to predict optimal LL for surgical correction of sagittal balance (Schwab et al. 2009; Schwab et al. 2012) – on the *assumption* PI does not change with age.

However, if PI and LL are correlated and LL varies by sex – does PI vary by sex? Does PI influence the development of LL? If PI does not develop in response to load, is it then predictive of the degree of LL that is developed in response to load during skeletal maturation? Understanding the relationship between PI and LL in juveniles and adults will aid in our understanding of 1) the wide range of normal LL and 2) if sex differences in LL are selected or a secondary product from an individual's load-history (i.e. sports, occupation, growth spurt, pregnancy, obesity). Understanding the development of sexual dimorphism in LL will aid our understanding of how lumbar functional morphology and health may vary by sex.

Aging and lumbar spine health

Age, as previously mentioned, influences LL, and has a powerful, yet unexplained, effect on lumbar spine health. Lumbar health is dependent on diurnal loading and unloading over a human lifetime. However, within this lifetime of bearing the weight of the upper body, humans often experience low back pain and spinal degeneration (Adams et al. 2013; Buchbinder et al. 2013). Age gradually makes musculoskeletal tissue cells less efficient – weakening tissue properties – and coupled with the non-stop compressive loading on the

lumbar spine, there is a heightened susceptibility to pain, injury, and degeneration with age. Human lumbar spine health generally degrades with age.

Osteoarthritis (OA) and disc degeneration commonly afflict the human lumbar spine. Estimates for the prevalence of age-related spinal OA ranges from 40-85% (Goode et al. 2013) and some degree of disc degeneration appears to be present in all adults (Battié and Videman 2006). The fossil record contains evidence of spinal OA and degeneration coinciding with LL: vertebral OA in *H. neanderthalensis* (Dawson and Trinkaus 1997), lower lumbar spondylolisthesis in extinct hominins from Sima de los Huesos (Bonmatí et al. 2010), and even a L4-L5 disc herniation in a juvenile from early genus *Homo* (Haeusler et al. 2013).

Furthermore, age-related spinal OA rarely occurs in most quadrupedal animal models of medical research, but macaques demonstrate naturally occurring patterns comparable to humans (Bailey et al. 2014). Although their lumbar spines lack human-like lordosis, macaques vertically load their spines by sitting upright (Gal 2002) and age-related spinal OA severity similarly corresponds to curvature in the thoracolumbar spine (Bailey et al. 2014). There is a link between loading, spinal curvature and age-related degeneration in the spine. If LL is sexually dimorphic, then age-related degeneration and related conditions of the lumbar spine may also differ by sex.

Lumbar range of motion and stability

Lumbar range of motion (ROM) is known to decrease with advancing age (Intolo et al. 2009). This age-related decrease in lumbar ROM is concurrent with the age-related increase in low back pain and spinal degeneration. Clinicians use lumbar ROM diagnostically as an indicator of intervertebral instability. However, like LL, intervertebral ROM of the lumbar spine is variable. This variability could be caused by two factors:

variability among individuals (e.g. sex, age, body mass index, symptoms) and/or variability and poor reliability among techniques for measuring spine motion. Understanding how lumbar ROM differs between females and males will 1) create better sex-specific standards for diagnosing lumbar instability via intervertebral ROM and 2) aid our understanding how the lumbar spine differs between sexes by comparing symptomatic and asymptomatic ROM between females and males.

Potential costs of a sexually dimorphic lumbar spine

Orthopaedic trade-offs between between sexes

Understanding sex differences in orthopaedic conditions has become of greater concern, and societies, journals, and national funding agencies have begun to demand research that will enhance sex-specific treatments (Hettrich et al. 2015; Leopold et al. 2014). With regard to the spine, numerous age-related conditions disproportionately affect females, including: osteoporosis and related vertebral fractures (e.g. Cauley et al. 2014), spinal osteoarthritis (e.g. Wei et al. 2014) and many types of spinal deformity conditions. As already mentioned, adolescent idiopathic scoliosis is 11 times more likely to occur in females than males (Ueno et al. 2011). Additionally, hyperkyphosis of the thoracic spine is more prevalent in older female than similarly aged males (Katzman et al. 2012). Lastly, degenerative spondylolisthesis is age-related and five to six times more likely to occur in females than males (Jacobsen et al. 2007).

Degenerative spondylolisthesis is diagnosed based on the anterior slippage or translation of a vertebra without trauma to the neural arch (MacNab 1950). degenerative spondylolisthesis results from instability that occurs with age and degeneration in the spine and is most common at the L4-L5 level (Fitzgerald and Newman 1976; Frymoyer 1994). The risk for developing degenerative spondylolisthesis positively relates to LL (Been et al.

2011; Chen and Wei 2009; Schuller et al. 2011). Given the potential for females having greater LL than males and a greater risk of degenerative spondylolisthesis, this may be a possible example of a sexually dimorphic adaptation and resulting orthopaedic trade-off. A current link between greater LL as an adaptation for bearing a pregnancy load in females and degenerative spondylolisthesis as a resulting tradeoff is that females with prior pregnancies are at greater risk for developing degenerative spondylolisthesis with age than nulliparous females (Sanderson and Fraser 1996).

The causal link between degenerative spondylolisthesis and sex remains unknown. Understanding *if, how, and why* the lumbar spine is sexually dimorphic would clarify the cause of the higher prevalence of degenerative spondylolisthesis and other spine conditions in females compared to males. A better understanding of sex differences and the functional morphology of the lumbar spine from an evolutionary perspective may enable us to better predict risk of orthopaedic conditions based on sex and create more effective treatments, more preventative and surgical.

Joint laxity is an alternative explanation that may cause both greater LL in females and degenerative spondylolisthesis. With the onset of puberty, females begin to demonstrate greater joint laxity than males (Quatman et al. 2008). Joint laxity in the lumbar spine is linked to greater LL (Kim et al. 2013) and as a result, decreased disc degeneration is due to less compressive loading on the disc from greater LL (Ergun et al. 2010; Barrey et al. 2007). Disc degeneration has been shown to be greater in males (Soini et al. 1991), but this could be due to the link between disc degeneration and physical activity, i.e., with repetitive mechanical loading (Videman et al. 1995). An understanding of how lumbar range of motion (ROM) and stability differs between sexes may aid in teasing apart potential sex differences in LL as either a sexually dimorphic adaptation for load bearing or an unintended result of joint laxity.

Measurement	Angle formed by
Quadriceps angle	Line connecting the anterior superior iliac spine and center of patella with line connecting the center of patella to tibial tuberosity
Vertebral wedge	Line parallel to the superior endplate of a vertebrae intersecting with line parallel to the inferior endplate of the same vertebrae
Intervertebral disc wedge	Line parallel to the inferior endplate of a vertebrae intersecting with line parallel to superior endplate of adjacent vertebral body *(while standing)*
Lumbar angle	Line parallel to L1 superior endplate intersecting with line parallel with S1 superior endplate *(while standing)*
Pelvic incidence	Line perpendicular to the S1 superior endplate intersecting with line connecting the center of the S1 superior endplate to the center of the acetabulum
Sacral slope	Line parallel to the S1 superior endplate intersecting with a transverse plane *(while standing)*
Pelvic tilt	Line connecting the center of the S1 superior endplate to the center of the acetabulum intersecting with a vertical plane *(while standing)*

Table 2-1: Measurement definitions

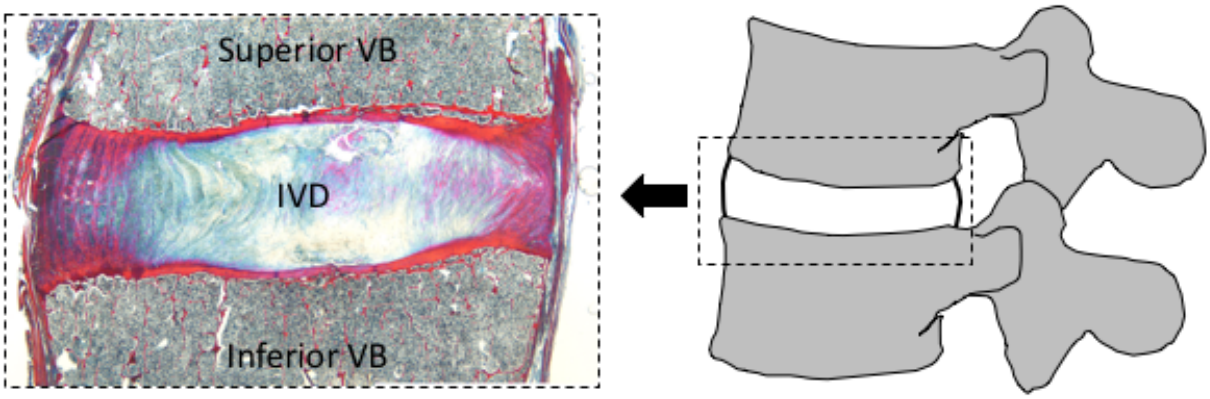


Figure 2-1. A lumbar motion segment. On the left is histology of a lumbar motion segment showing the intervertebral disc with adjacent vertebrae and on the right is a graphic of a complete motion segment with posterior elements.

Chapter 3: Sex differences in lumbar lordosis and pelvic incidence in adults

Preface

The following chapter is a published manuscript in Journal of Anatomy under the title "Morphological and postural sexual dimorphism of the lumbar spine facilitates greater lordosis in females" and authored by Jeannie F. Bailey, Carolyn J. Sparrey, Ella Been, and Patricia A. Kramer.

Abstract

Previous work suggests females are evolutionarily adapted to have greater lumbar lordosis than males to aid in pregnancy load bearing, but no consensus exists. To explore further sex differences in the lumbar spine, and to understand contradictions in the literature, we conducted a cross-sectional retrospective study of sex differences in lumbar spine morphology and sacral orientation. In addition, our sample includes data for separate standing and supine samples of males and females to examine potential sex differences in postural loading on lumbosacral morphology. We measured sagittal lumbosacral morphology on 200 radiographs. Measurements include: lumbar angle (L1-S1), lumbar vertebral body and disc wedging angles, sacral slope and pelvic incidence. Lumbar angle, representative of lordotic curvature between L1-S1, was 7.3° greater in females than males, when standing. There were no significant sex differences in lumbar angle when supine. This difference in standing lumbar angle can be explained by greater lordotic wedging of the lumbar vertebrae (L1-L5) in females. Additionally, sacral slope was greater in females than males, when standing. There were no significant sex differences in pelvic incidence. Our results support that females have greater lumbar lordosis than males when standing, but not when supine – suggesting a potentially greater range of motion in the female spine.

Furthermore, sex differences in the lumbar spine appear to be supported by postural differences in sacral-orientation and morphological differences in the vertebral body wedging. A better understanding of sex differences in lumbosacral morphology may explain sex differences in spinal conditions, as well as promote necessary sex-specific treatments.

Introduction

Lumbar lordosis (LL) refers to the curvature of the lumbar spine, expressed in humans as a response to bipedalism. Lordotic curvature is critical for biomechanical stability in the lumbar spine (Patwardhan et al. 1999), as it contributes to both the load bearing capacity and flexibility of the lumbar spine, which are important for activities of daily living (Sparrey et al. 2014). The lordotic curvature of the lumbar spine resembles a buckled (Euler) column in response to load bearing (Meakin et al. 1996) and promotes load sharing between the disc and facet joints (Sparrey et al. 2014).

Evolutionarily, LL is an adaptation aiding upright posture and bipedal locomotion (Lovejoy 2005) by enabling sagittal balance of the upper body atop the hips (Been and Kalichman 2013; Sparrey et al. 2014). Lordosis in humans develops following the onset of unassisted bipedal locomotion in juveniles (Abitbol 1987; Cil et al. 2005; Shefi et al. 2013) and is argued to be a biomechanical response to gravitational load on the maturing vertebral column. Children who are paraplegic have spinal misalignment (Kilfoyle et al. 1965). In non-human primates, the lumbar spine is not lordotically curved, as it is in humans. Lordosis occurs, however, in Japanese macaque monkeys trained for exclusive bipedal locomotion (Preuschoft et al. 1988). Chimpanzees are most closely related to humans and can only exhibit limited unassisted bipedal locomotion due in part to their flat and less mobile lumbar spines that does not allow the chimpanzee upper body to be positioned above their hips (Lovejoy 2005; Lovejoy and McCollum 2010). Humans with

‘flatback’, a pathologic flattening of the lumbar spine, exhibit impaired gait function (Sarwahi et al. 2002). LL is, then, load dependent and a critical adaption enabling upright posture and bipedal locomotion in humans.

Additionally, LL allows an individual to maintain their posture and adjust the position of their center of mass (CoM) while carrying load (Meakin et al. 1996). Considering sex-specific loading demands (e.g. pregnancy loads), females may be able to exhibit greater lordosis than males in order for females to accommodate increased upper body load and an anteriorly displaced CoM during pregnancy (Hay et al. 2015; Masharawi et al. 2010; Whitcome et al. 2007). Females increasingly extend their lumbar spines with developing pregnancy (Whitcome et al. 2007); however, if and to what extent the lumbar spine is sexually dimorphic in asymptomatic (and non-pregnant) individuals is unclear. Characterizing the sex differences in LL may help explain 1) how sex impacts the wide range of normal LL (30° to 80° in standing asymptomatic adults; Been and Kalichman 2013), and 2) sex differences in conditions pertaining to LL.

Despite extensive research, no consensus on whether or not sex differences in the lumbar spine exist has emerged (Been and Kalichman 2013). As shown in Table 3-1, some studies report sex differences in LL, while others report no differences. The discrepancy in these results may be due to the variability in methodology and exclusion criteria used in the studies. Many of the clinically-oriented studies were designed to examine sagittal balance and reported the effect of sex on LL as a secondary result, without controlling for study characteristics that may affect sex differences (e.g. including juveniles, age-related degeneration, supine stance, skewed sex-ratio in the sample). Only two previous studies have been explicitly designed to examine sex differences in lumbar morphology (Masharawi et al. 2010; Whitcome et al. 2007), but these studies reported significant sex differences in morphology of dry lumbar vertebrae from an osteological collection and, therefore, could not

quantify the effect of the soft tissues (particularly the discs) on LL. *In vivo* sex differences in LL has recently been characterized using the shape of the vertebral canal (Hay et al. 2015), but the role of the discs remains unexplored. Furthermore, given the well-established correlation between sacral orientation and LL (Boulay et al. 2006; Legaye et al. 1998; Vialle et al. 2005), sacral orientation parameters (e.g. pelvic incidence and sacral slope) should also differ by sex if sex differences in LL exist.

We designed a study that includes both males and females and aims to characterize potential anatomical and postural sex differences in the lumbar spine. We aim to clarify the conflicting results of prior work by eliminating age-related degeneration and including both standing and supine individuals. We hypothesize 1) that females have greater LL than males, 2) that sex differences in LL are accentuated when standing, and 3) that pelvic parameters also exhibit sex differences. This study is the first to differentiate and quantify sexual dimorphism in the *in vivo* lumbar spine and pelvis in a controlled population.

Materials and Methods

Study design

To determine the effect of sex on the degree of LL, we designed a cross-sectional retrospective radiographic study that controlled several critical factors known to affect postural measurements. We excluded moderate to severe spinal degeneration (e.g. osteophytosis and disc degeneration) from our study sample. Although many studies of sagittal balance include degeneration as a normal feature of the aging spine (Been and Kalichman 2013), we excluded any factor that could confound the measurement of lordosis. Both standing and supine radiographs were collected to compare sex differences in lordotic morphology under different postural loading conditions. In our study, ‘posture’ refers to standing or supine whole-body orientations. Sex differences in LL were compared using

relevant sagittal spine measures, including: vertebral wedging, disc wedging and sacral orientation.

Sample

Our sample included 200 adults ranging in age from 18 to 56 years with a mean and standard deviation of 32.9 ± 8.9 years. We collected lateral radiographs, either standing or supine, retrospectively from Harborview Medical Center in Seattle, Washington. Standing and supine radiographs are from separate subjects. Radiographs were taken as part of a routine medical examination designed to determine whether or not osseous injury had occurred after a traumatic event and we only collected those where the spinal exam concluded that no injury was present. Data were obtained for this study with human subjects approval (University of Washington #44154). Our exclusion criteria aimed to eliminate factors that may influence lumbar spine morphology and overall curvature, such as: moderate to severe degenerative disease (e.g. osteophytosis and disc space narrowing); congenital abnormalities (e.g. scoliosis, sacralized lumbar segments, and 6 lumbar vertebrae); fractures or other previous spine injuries; and previous spinal surgeries or devices. We also excluded radiographs when the vertebral endplates were unclear. We collected patient information for sex, ethnicity, radiographic orientation (standing or supine), and age at the time of radiography.

Angular measurements

On lateral radiographs, we measured lumbar angle, vertebral body wedging, intervertebral disc wedging, sacral slope and pelvic incidence (Figure 3-1; variables defined in previous studies (Been et al. 2010b; Been et al. 2011; De Carvalho et al. 2010; O'Brien et al. 2004; Vialle et al. 2005). *Lumbar angle* (LA) is a way to assess LL and was defined as

the Cobb angle between the L1 cranial endplate and S1 cranial endplate. Vertebral body and disc wedging angles were defined as the angle between the cranial and caudal endplates of the vertebrae and discs comprising the lumbar spine. *Sacral slope (SS)* was defined as the angle between two lines: 1) a line parallel with the S1 cranial endplate; and 2) a line parallel with the horizontal plane. Note, SS changes as the posture of the body changes (between supine and standing). *Pelvic incidence (PI)* was defined as the angle between two lines: 1) a line perpendicular to the plane formed by the S1 cranial endplate and located at the endplate's mid-point; and 2) a line between the mid-point of the S1 cranial endplate and mid-point of a line connecting the central points of both acetabula. PI does not depend on postural orientation. Measurements were made using the OsiriX DICOM viewer.

Statistics

The first author collected all radiographic measurements while blinded to patient information. Rater reliability was assessed via individual (single) intra- and inter-class correlation coefficients (ICC) for lumbar angle and separate vertebral body and disc measurements. We selected a random subset of 30 radiographs that were measured by first author (JFB) to assess intra-rater reliability and an external rater to assess inter-rater reliability. Student's *t*-tests, power (1-β), and effect size were calculated to assess the independent effect of sex on each morphological variable (lumbar angle, vertebral body and disc wedging angles, PI and SS). Multivariate linear regression analyses were used to assess the relationship between each morphological variable and sex while adjusting for covariates. Covariates included age and ethnicity and have been shown to have a relationship with lumbar curvature in prior reports (Been and Kalichman 2013). Given the correlation between sagittal balance variables (LL, SS, PI), we did secondary multivariate

regression analysis including SS and PI as additional covariates to understand how these sagittal balance variables may influence the relationship between sex and LA. For continuous covariates in the multivariate regression analyses, we used partial correlations for determining the correlation coefficient (r). In any test with a postural dependent variable (i.e. LA, disc wedging, SS), separate analyses were done for standing and supine. A Bonferroni correction was applied to correct for multiple measures for the disc (5 discs between L1-S1, p=0.05/5=0.01) and vertebral (L1-L5, p=0.05/5=0.01) wedging angles. All statistical analyses were conducted using Stata (Stata Corp., College Station, TX).

Results

Of the 200 adults in our sample, 121 adults (f, n=48, 34 ± 1.4 years (*mean* ± *se*); m, n=73, 34 ± 1.0 years) had standing radiographs, 75 adults (f, n=39, 28 ± 1.2 years; m, n=36, 32 ± 1.4 years) were supine, and 4 adults had unknown orientation. Of the 200 individuals in our sample: 36.5% self-identified as Black, 32.5% Caucasian, 9% Hispanic, 6.5% Asian, 2% Native American, while the remaining 13.5% did not disclose their ethnicity.

Lumbar lordosis

For LA measurements, ICC for intra-rater reliability was 1.0 and inter-rater reliability was 0.98. We found LA was 7.3° greater in females than males in the standing group (f, 60.3°±1.6° (*mean* ± *se*); m, 53.0°±1.4°; p=0.001; Table 3-2). Conversely, LA was not significantly different between females and males while supine (f, 49.4°±1.5°; m, 46.5°±1.7°; p=0.208). Overall, LA was 7.9º greater in standing than supine individuals (p<0.001). Similarly, the covariate age was positively associated, albeit with a weak correlation, to LA when standing (*r*=0.19, p=0.024), but not when supine. Ethnicity was not associated with LA

in either posture. See Table 3-3 for results from independent tests between LA and the covariates.

Individual vertebrae and discs

For lumbar vertebral body and disc wedging measurements, the ICCs ranged from 0.88 to 0.94 for intra-rater reliability and 0.76 to 0.93 for inter-rater reliability. We found that the vertebral bodies of all lumbar vertebra were significantly more wedged in females than males (Figure 3-2; Table 3-2; $p \leq 0.001$). Vertebral body wedging angles included data from both standing and supine individuals, since individual vertebral body morphology is not dependent on postural-orientation.

Sex differences in disc wedging were tested separately for standing and supine subsamples, because the disc is flexible and deforms in response to changes in load-bearing and posture (Adams and Hutton 1985; Lord et al. 1997; Meakin et al. 2009; demonstrated in Figure 3-3). Disc wedging for each disc between L1 and S1 was not significantly different between standing females and males. Among supine individuals, males had significantly greater dorsal disc wedging than females for the two cranial-most lumbar discs and the Bonferroni correction makes differences L3-L4 non-significant (Table 3-2).

Sacral orientation

Pelvic measurements (SS, PI) were related to LA in both the standing and supine samples (Table 3-3). SS was measured in all of the standing (n=121) and supine (n=75) adults in our sample; however, PI was measured in 114 adults (standing, n=81; supine, n=33), because the acetabula were not visible in all radiographs. Given the significant sex differences in LA when standing, we tested whether or not sex differences in SS and PI exist. We found that

(standing) SS had a significant relationship with sex (p=0.027), but that PI did not (Table 3-2).

We explored further the relationships among LA, sex, SS and PI. SS and PI are themselves correlated (r^2=0.53), so we included both in a multivariate regression analysis to determine whether or not their effects on LA are independent. From the multivariate regression analysis, SS remains strongly correlated with LA, but there is no longer a significant relationship between PI and LA (Table 3-4). For standing individuals, sex and SS are significantly associated with LA. For supine individuals, only SS is significantly related to LA. This suggests that there are sex differences in postural orientation of the sacrum that relate to sex differences in standing LA.

Discussion

We hypothesized that females have greater lordosis than males, that these differences would be accentuated when standing (i.e., weight bearing), and that sacral orientation parameters predictive of LL would also exhibit sex differences. Our results indicate that sex differences in LL are present when standing, but not when supine. In the standing position, the lumbar spine assumes the shape of a buckled column (Meakin et al. 1996), demonstrating the functional role of curvature when loaded axially. In supine position, the lumbar spine appears to flatten when subjected to transverse loads. We found that in the standing sample, females, on average, have 7.3° greater lordosis than males, but that difference reduces to 2.9° (and is not significant) in the supine sample (Figure 3-3). This result is further supported by sex differences in skeletal morphology (vertebral body wedging angles) and posture (SS while standing).

Compared to previous studies, the unique value of this study is that we quantified sexual dimorphism in lumbar spines free of pathology and degeneration and explored the

source of this variation quantitatively using characteristics which impact LL, including: the contributions of vertebral and disc wedging morphology to LL, the effect of body position on these measures, and the potential contribution of sacral orientation to sex differences in LL. Additionally, while many studies accept degeneration as a normal age-related feature of the spine, we eliminated degenerated spines in order to investigate lumbar spine morphology of females and males without the lordosis-damping effects of spine degeneration.

The primary limitation of this study was its retrospective design. Patient data, including body mass and pregnancy/parity history, were not uniformly available in the patient's medical record. Additionally, it would be valuable to have standing and supine radiographs from the same individuals. Future research should include a controlled prospective study where these data can be collected.

The ranges of LA, SS and PI observed in this study are in accordance with previously published results. Average standing L1-S1 Cobb angles have been reported as 51.3°±10.7° (Been et al. 2010b) and 58.5° (Vialle et al. 2005; no reported standard deviation); we observed 55.9°±12.4°. Of the studies that did differentiate LA by sex, only one had directly comparable methods to our study (Damasceno et al. 2006). That study found that females had, on average, 2.7° greater LA than males when standing and that only L2 and L4 vertebral bodies were significantly more wedged. The differences between our results and theirs are unclear, but may be due to differences between sample populations. Regardless, the sexual dimorphism in LA observed in this study was similarly present in standing radiographs, highlighting the effect of upright posture and load bearing on spinal curvature.

The correlations between pelvic parameters and LA are also well established (Roussouly and Nnadi 2010; Schwab et al. 2009). The PI and SS values observed in this study are in agreement with those previously reported. Sexual dimorphism in the

relationship between SS and LA has, however, not previously been reported. We found that PI does not differ between sexes. Relating LL to a fixed measure like pelvic incidence has value, but should be regarded with caution, as pelvic incidence does not include the significant effect of posture on normal lordosis in standing.

We found that standing females have, on average, 7.3° greater LL than males. In addition, each lumbar vertebral body was significantly more dorsally wedged in females and the sum of mean differences in vertebral wedging between females and males was 9.4° (Table 3-2). Two previous studies characterizing sex differences in dry lumbar vertebrae from an osteological collection (Masharawi et al. 2010; Whitcome et al. 2007) also find evidence of more vertebral wedging in particular lumbar vertebra of females: significant sex differences in vertebral wedging were found for L1-L4 in Whitcome et al. 2007 and in L1-L2 in Masharawi et al. 2010. Our data suggest that the amount of differences in vertebral wedging can account for the differences in LA. In supine patients, the average LA was significantly lower than in standing individuals and no sex differences were apparent. This suggests that changes in LL between standing and supine are sex dependent. We found the difference in LA between standing and supine was on average 10.9° in females ($p<0.001$) and 6.5° in males ($p=0.007$), which may imply differential lumbar range of motion between sexes. Future studies will be directed to understanding sex differences in sagittal range of motion of the lumbar spine. Prior work has shown that there are sex differences in sagittal range of motion of the lumbar spine (Burton and Tillotson 1988; Dreischarf et al. 2014; Sullivan et al. 1994), but determining how sex affects flexion and extension separately at the intervertebral level may provide insight into how vertebral wedging impacts intervertebral motion and whether or not females have a greater range of lumbar spine extension.

Our results for sacral orientation suggest that there are sex differences in the postural orientation of the sacrum that correspond to sex differences in LL, but not to the orientation of the sacrum within the pelvis. LA and SS differ between the supine and standing groups and between sexes, but PI does not. PI has been used to define surgical correction guidelines (Bae et al. 2012; Berjano et al. 2014; Le Huec et al. 2011; Lee et al. 2011; Legaye et al. 1998; Roussouly and Pinheiro-Franco 2011) and PI does correlate with LA and SS. That we found no sex differences in PI corresponding to sex differences in LL was, therefore, surprising. Sex differences in SS do, however, exist. Taken together, this implies that females and males have a different pelvic-orientation when standing that results in differences in SS that override the similarities in PI. In the few prior studies that reported non-significant differences in PI between sexes (Janssen et al. 2009; Peleg et al. 2007), the discordance between no sex differences in PI and sex differences in LL was not investigated. (Note, Vialle et al. 2005 found significant sex differences in PI.) Further research is necessary to investigate how sacral orientation and stance differences contribute to LL, as well as, how sacral orientation and stance may differ by sex.

Understanding the functional reason for greater lordosis in females compared to males is important for understanding developmental and biomechanical differences between the lumbar spines of females and males, as well as exploring potential trade-offs that may accompany greater LL in females. Previous studies have suggested that sexual dimorphism in the lumbar spine is driven by the fetal load in pregnancy (Franklin and Conner-Kerr 1998; Whitcome et al. 2007). This suggestion was not possible to confirm in our study as parity history for our subjects was not available to us. Sex differences in vertebral wedging may imply, however, sex differences in loading, possibly beginning with sex differences in growth and development during skeletal maturation (Cil et al. 2005). Furthermore, the differences in mass distribution in the upper bodies of females and males

or variations in spinal curvature in the cervical and thoracic spine may affect the degree of LL required to maintain stable posture (Hay et al. 2015).

Alternatively, sex differences in lordosis could merely be a by-product of sexual dimorphism of the human pelvis (Rosenberg and Trevathan 2002; Tague 1992). Musculoskeletal differences of the hip may affect sacral orientation. Differences in lordosis may be primarily attributable to differences in sacral orientation due to pelvic dimorphism between females and males.

In conclusion, we found that LL is sexually dimorphic with females having greater lordosis than males. This result, along with our findings that morphological and postural differences contribute to sex differences in LL, has functional and clinical implications for lumbosacral alignment. Understanding the variation in LL between sexes is a primary step toward explaining the wide variation in normal LL in adults. Additionally, sex differences in LL could indicate that females and males might be differently predisposed to certain lumbar conditions (e.g. risk of degenerative spondylolisthesis, which is 5 times higher for females than males (Jacobsen et al. 2007; Sanderson and Fraser 1996)). Finally, defining the quantitative sex differences in LL may promote the development of sex-specific treatments for spinal maladies.

Reported sex differences?	Research	n	Age	Method	Differences noted
No	Stagnara et al. 1982	n=100 (m, n=57; f, n=43)	20-29	Standing radiographs	
	Voustinas & MacEwen 1986	n=670 (m, n=251; f, n=419)	4-20	Standing radiographs	
	Lin et al. 1992	n=149 (m, n=76; f, n=73)	18-76	Recumbant radiographs	
	Jackson & McManus 1994	n=100 (m, n=50; f, n=50)	20-65*	Standing radiographs	
	Korovessis et al. 1998	n=99 (m, n=39; f, n=79)	20-79	Standing radiographs	
	Jackson et al. 1998	n=50 (m, n=25; f, n=25)	20-65*	Standing radiographs	
	Korovessis et al. 1999	n=120 (m/f not reported)	20-79	Standing radiographs	
	Jackson et al. 2000	n=20 (m, n=11; f, n=9)	20-65*	Standing radiographs	
	Cil et al. 2005	*n=151 (m, n=79; f, n=72)*	*3-15*	*Standing radiographs*	
	Boulay et al. 2006	*n=149 (m, n=78; f, n=71)*	*19-50*	*Standing radiographs*	
	Been et al. 2007	n=106 (m, n=56; f, n=50)	20-50	Standing radiographs	
	Kalichmann et al. 2011	n=191 (m, n=104; f, n=87)	40-80	Supine MRI	
	Shefi et al. 2013	*n=210 (m, n=173; n=37)*	*2-20*	*Supine CT*	
Yes and no	Gelb et al. 1995	n=100 (m, n=46; f, n=54)	40-82	Standing radiographs	No differences in total LL or sacral inclination, but did find that females had significantly more segmental lordosis at L2-L3, L3-L4, and L4-L5.
	Cheng et al. 1998	n=340 (m, n=142; f, n=198)	54-71	Radiographs, stance unspecified	LA (between L1-L5) was not different between sexes, but vertebral height ratios were significantly lower in males.
	Endo et al. 2012	n=50 (m, n=25; f, n=25)	23-47	Standing & sitting radiographs	LA (between L1-L5) was significantly greater in females in sitting radiographs, but not when standing.
	Masharawi et al. 2012	*n=100 (m, n=51; f, n=49)*	*12-16*	*Supine MRI*	*3-year follow up study in juveniles. Found LL to be significantly greater in females at the 12-13 age time point, but not different at the 15-16 age time point.*
Yes	Fernand & Fox 1985	n=938 (m, n=418; f, n=520)	17-84	Recumbant radiographs	LA (between L2-S1): f=47°, m=43°, p<0.01
	Amonoo-Kuofi 1992	n=485 (m, n=250; f, n=235)	9-61	Recumbant radiographs	LA (between L1-S1) was reported greater in females at every age group tested, no p-values reported. (Age group averages for male LA were very low, ranging from 33-39°)
	Murrie et al. 2003	n=29 (m, n=12; f, n=17)	18-73	Supine MRI	LA (from L1/L2 disc space to L5/S1 disc space): f=52, m=48. (No p-value provided for comparing LA between sexes in control population)

Vialle et al. 2005	n=300 (m, n=190; f, n=110)	20-70	Standing radiographs	LA (between L1-L5): f=46°, m=41°, p<0.001
Damasceno et al. 2006	n=350 (m, n=143; f, n=207)	18-50	Standing radiographs	LA (between L1-S1): f=62, m=59, p<0.01. This study also measured vertebral and disc wedging and found significantly more lordotic wedging in L2 and L4 for females.
Oyakhire et al. 2013	n=300 (m, n=144; f, n=156)	18-77	Standing radiographs	LA (between L1-S1): f=50°, m=47°, p<0.05
Hegazy & Hegazy 2014	n=93 (m, 46; f, m=47)	25-57	Supine MRI	LA (between L1-S1): f=52°, m=41°, p<0.001.
Zhu et al. 2014	n=260 (m, n=104; f, n=156)		Standing radiographs	LA (between L1-S1): f=49°, m=43°, p=0.03. No other measures (SS, PT, PI, thoracic kyphosis) were different between sex. VB and disc wedging not measured.

TABLE 3-1: Review of imaging studies reporting on sex differences in *in-vivo* LL. The literature is divided on whether or not significant sex differences in LL exist. In the table, differences are noted for those studies that found sex differences in LL. Italicized rows are studies comprised primarily of juveniles. (*) refers to some overlap in study populations.

Lumbosacral measurement (°)							
level	*stance*	*females (mean ± se)*	*males* (mean ± se)	*mean diff.*	*p*	*1-β*	*d*
L1 vb	Standing + Supine	-2.44 ± 0.22	-4.06 ± 0.27	1.62	<0.001*	1	0.6
L2 vb	Standing + Supine	0.77 ± 0.24	-1.28 ± 0.26	2.05	<0.001*	1	0.8
L3 vb	Standing + Supine	2.09 ± 0.28	0.6 ± 0.23	1.48	<0.001*	1	0.6
L4 vb	Standing + Supine	4.26 ± 0.34	2.45 ± 0.24	1.80	<0.001*	1	0.6
L5 vb	Standing + Supine	10.48 ± 0.39	8.01 ± 0.32	2.47	<0.001*	1	0.7
L1-L2 disc	Standing	5.28 ± 0.40	5.51 ± 0.31	-0.22	0.654	0.1	-0.1
	Supine	2.3 ± 0.37	4.53 ± 0.33	-2.23	<0.001*	1	-1
L2-L3 disc	Standing	6.78 ± 0.35	6.76 ± 0.30	0.02	0.967	---	0.001
	Supine	2.81 ± 0.35	4.74 ± 0.35	-1.92	<0.001*	1	-0.9
L3-L4 disc	Standing	8.1 ± 0.34	8.11 ± 0.27	0.00	0.998	---	-0.001
	Supine	5.08 ± 0.48	6.68 ± 0.44	-1.59	0.017	0.8	-0.6
L4-L5 disc	Standing	10.89 ± 0.46	11.35 ± 0.41	-0.46	0.470	---	-0.14
	Supine	8.7 ± 0.46	9.72 ± 0.47	-1.02	0.126	0.3	-0.4
L5-S1 disc	Standing	15.08 ± 0.77	15.06 ± 0.58	0.02	0.981	---	0.004
	Supine	14.74 ± 0.88	16.32 ± 0.73	-1.58	0.175	0.2	-0.3
LA	Standing	60.34 ± 1.64	53.01 ± 1.44	7.32	0.001*	0.9	0.6
	Supine	49.39 ± 1.52	46.46 ± 1.74	2.93	0.208	0.3	0.3
SS	Standing	42.58 ± 1.37	38.87 ± 0.99	3.71	0.027*	0.6	0.4
	Supine	42.57 ± 1.50	42.19 ± 1.28	0.37	0.851	0.1	0.04
PI	Standing	54.84 ± 2.41	53.41 ± 1.46	1.43	0.595	0.1	0.1
	Supine	53.07 ± 2.94	57.66 ± 1.90	-4.59	0.181	0.3	-0.5

TABLE 3-2: T-test results comparing angular measurements in the lumbar spine between sexes. Negative angles denote anterior wedging or kyphosis, positive angles denote dorsal wedging or lordosis. In addition to mean and standard error values, difference values are reported (i.e., females - males). P-values indicate whether there are significant sex differences for each lumbosacral measure listed and significant values are defined by $p<0.05$ and denoted by (*). Note, significance for the discs and vertebrae are adjusted by a Bonferroni correction ($p=0.05/(5$ lumbar segments)) to be $p<0.01$, therefore L3-L4 supine discs (0.017) are not significant based on the correction. Power (1-β) and effect size (cohen's *d*) are also reported.

	Standing		Supine	
	Correlation (r)	*p-val*	*Correlation (r)*	*p-val*
E=β0 + β1*Sex	N/A	<0.001*	N/A	0.21
E=β0 + β1*PI	0.66	<0.001*	0.54	0.002*
E=β0 + β1*SS	0.85	<0.001*	0.85	<0.001*
E=β0 + β1*Age	0.15	0.11	0.01	0.94
E=β0 + β1*Ethnicity	N/A	0.76	N/A	0.97

TABLE 3-3: Univariate regression analyses comparing LA with separate variables: Sex, SS, PI, age, and ethnicity. Correlation coefficients are provided for comparisons between LA and continuous variables. P-values indicate whether there are significant sex differences for each relationship between LA and each variable listed and significant values are defined by $p<0.05$ and denoted by (*).

E_{LA}=β0 + β1*Sex + β2*PI + β3*SS + β4*Age + β3*Ethnicity

	Standing		Supine	
Covariates	*Partial corr. (r)*	*p-val*	*Partial corr. (r)*	*p-val*
Sex	N/A	0.02*	N/A	0.53
PI	0.11	0.37	-0.21	0.3
SS	0.79	<0.001*	0.75	<0.001*
Age	-0.03	0.79	-0.19	0.36
Ethnicity	N/A	0.97	N/A	0.58

TABLE 3-4: Multivariate regression analyses for LA with covariates sex, SS, PI, age, and ethnicity. Partial correlation coefficients are provided for comparisons between LA and continuous variables. P-values indicate whether there are significant sex differences for each relationship between LA and each variable listed and significant values are defined by $p<0.05$ and denoted by (*).

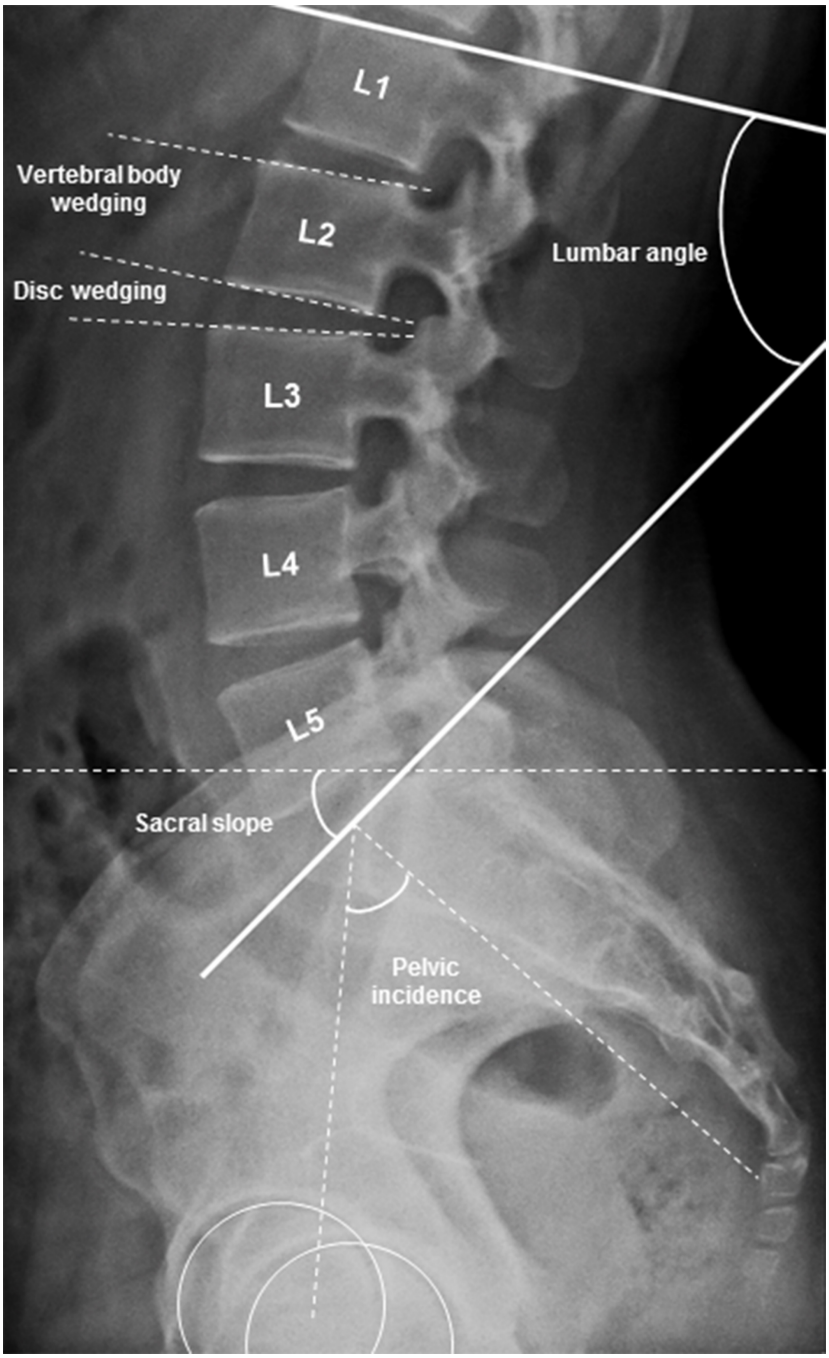


FIGURE 3-1: **Radiographic measurements**

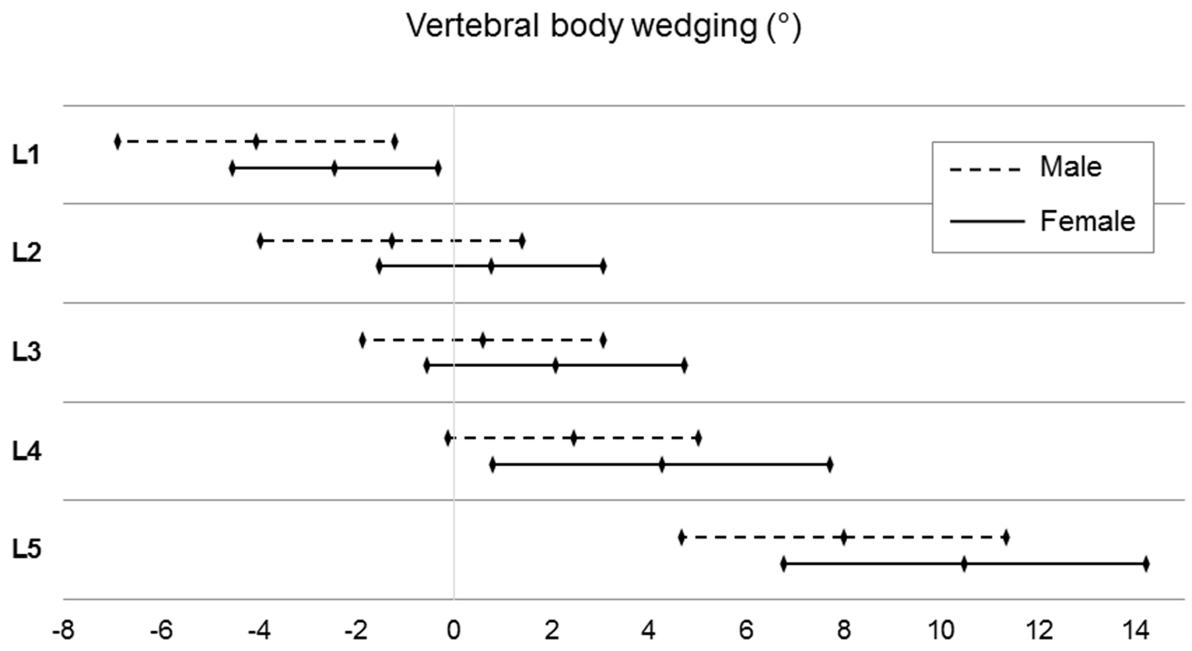


FIGURE 3-2: Sex differences in vertebral body wedging for lumbar vertebral bodies. Means for vertebral body wedging angle (°) are plotted separately for females (solid black line) and males (dashed black line) with standard deviation bars. Trend in wedging patterns among lumbar vertebrae is similar between females and males, but the mean dorsoventral wedging for females is higher for each lumbar vertebrae. Vertebral body wedging is independent of posture and therefore, includes values from both standing and supine individuals.

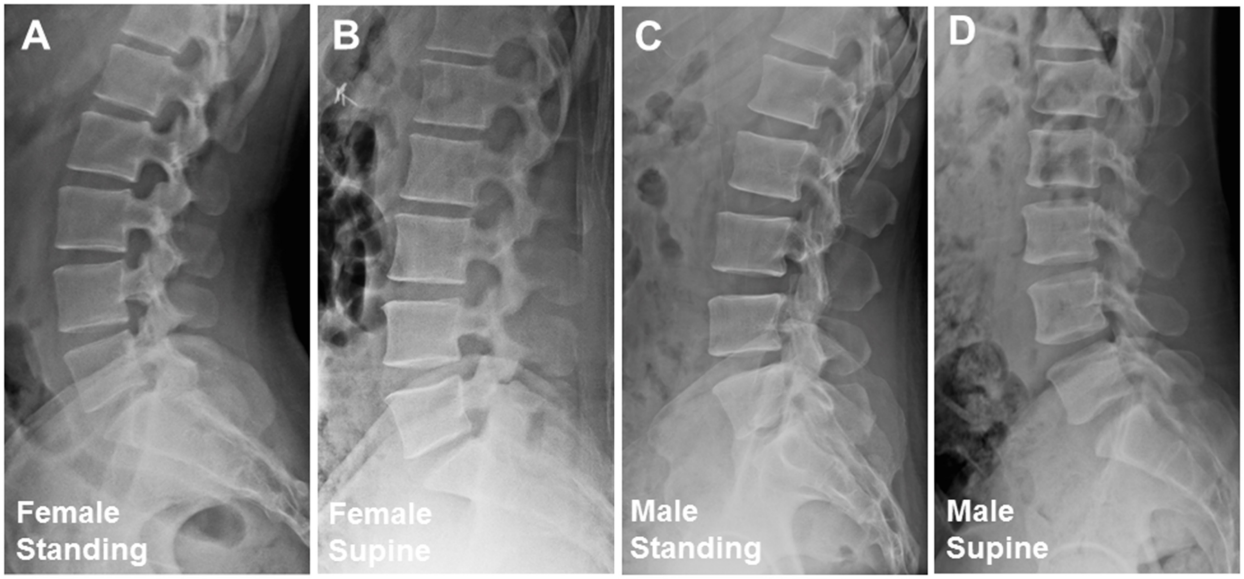


FIGURE 3-3: Examples of sex differences in lumbar curvature in standing and supine orientations. A)Standing female, LA=59.7°; B)Supine female, LA=49.4°; C)Standing male, LA=53.0°; D)Supine male, LA=45.5°**.** Note, each of these were selected from our sample as examples depicting the mean values for standing and supine lordosis in females and males.

Chapter 4: Development of lumbar lordosis and pelvic incidence in juveniles

Preface

These data were provided by committee member and collaborator Ella Been. The results on lumbar lordosis and age have been previously published in (Shefi et al. 2013) and after we completed the first chapter, Ella Been and I had the idea to go back and measure pelvic incidence in order to understand how pelvic incidence may influence the juvenile development of lumbar lordosis and vertebral wedging.

The following manuscript has been submitted to the journal *Spine*, under the title **"**Development of lumbar lordosis and pelvic incidence in juveniles**"** and authored by Jeannie F. Bailey, Sara Shefi, Michalle Soudack, Patricia A. Kramer, and Ella Been. Additional figures can be found in Appendix 1 (A1).

ABSTRACT

Study Design. Cross-sectional retrospective study of 146 juveniles 2 to 20 years old.

Objective. The purpose of this study is to understand how pelvic incidence (PI), lumbar lordosis (LL) and age are related in juveniles.

Summary of Background Data. In asymptomatic adults, the correlation between PI and LL is well established. PI is believed to be 'fixed' and can, therefore, be use to establish LL in surgical correction. The age at which PI can be regarded as 'fixed' and whether juvenile LL can be predicted by PI are, however, unclear.

Methods. PI, LL, and individual wedging angles of the lumbar discs and vertebral bodies were measured on mid-sagittal reformatted images from 146 abdominal computed tomographic scans of individuals aged 2 to 20 years old. Multivariate linear regression analyses were ran using the whole sample, as well as three separate age categories

representing pre-growth spurt (ages 2-9), growth spurt (10-15) and post-growth spurt (16-20).

Results. PI did not relate to age (p=0.09) and there was no significant difference between the youngest and oldest age categories (p=0.07). LL did increase with age (*r*=0.53, p<0.001), as anticipated. PI and LL significantly correlate in the middle (r=0.42, p=0.02) and oldest age categories (r=0.46, p<0.001), but not in the younger age category. Vertebral body wedging did variably associate with PI and age, while disc wedging related mainly with age and not PI.

Conclusion. Our results show that PI does not significantly change with age in juveniles aged 2 to 20 years. While LL does increase with age, we find that the correlative relationship between PI and LL strengthens with increasing age categories and we conclude PI predicts the development of LL in juveniles.

INTRODUCTION

Of all the measures for assessing spinal sagittal balance, pelvic incidence (PI) is possibly the most useful, because it is considered to be a fixed or 'true' measure that does not change with age or posture (Legaye et al. 1998). PI is defined as the sagittal orientation of the sacral endplate relative to the position of the acetabula (Figure 4-1). The angular orientation of the sacral endplate, coupled with the postural orientation of the pelvis, affects the curvature of the lumbar spine (Le Huec et al. 2011; Roussouly and Pinheiro-Franco 2011). The human spine has a sigmoidal curvature in the sagittal plane to balance the center of mass in upright posture; therefore, the curves of the spine (cervical lordosis, thoracic kyphosis, lumbar lordosis) are biomechanically related to ensure balance. PI has been shown to positively correlate with lumbar lordosis (LL) in asymptomatic adults (Boulay et al. 2006; Legaye et al. 1998; Vialle et al. 2005); accordingly, PI can be considered a

guide or predictor of a patient's optimal LL and is used for reconstructing or correcting sagittal alignment (Schwab et al. 2009). Algorithms for correcting sagittal balance depend on the fixed nature of PI in adults, a relationship that has only been shown with cross-sectional studies of asymptomatic adults (Boulay et al. 2006; Legaye et al. 1998; Vialle et al. 2005). Recent studies have shown, however, that PI can change during adulthood in response to chronic low back pain (Legaye 2014) and lumbar segment fixation (Lee et al. 2015). As to whether or not PI is a fixed or changing measure in juveniles is unclear.

Work on pre-natal development of sagittal spine alignment shows lordosis at the L5-S1 segment, which may indicate development of PI prior to birth (Choufani et al. 2009). On the other hand, some argue that PI increases as the juvenile spine develops during skeletal maturation. LL develops after the onset of unassisted bipedal locomotion in juveniles (Cil et al. 2005; Shefi et al. 2013). Given the close relationship between PI and LL in adults, it is plausible that PI changes in tandem with LL in juveniles. Prior studies have shown a positive relationship between PI and age in children and adolescents (Descamps et al. 1999; Lee et al. 2012; Mac-Thiong et al. 2007; Mangione et al. 1997; Marty et al. 2002; Schlosser et al. 2015). Some that suggest PI changes with age in children and adolescents argue that value of PI becomes fixed at the end of skeletal maturation and that LL in juveniles does not develop in response to a 'fixed' PI, supporting the notion that PI and LL develop in tandem (Le Huec et al. 2011). No longitudinal study of PI and LL in juveniles has been done, however, and the strength of the effect of age on increasing PI in children and adolescents in prior work may not be statistically meaningful. A closer look at the association of PI with age in children and adolescents is, therefore, warranted to understand how much of PI may be determined before the onset of walking and whether or not PI informs the development of LL during skeletal maturation.

How vertebral and disc morphology of the lumbar spine relate to PI is unknown and may provide a better understanding of the relationship between PI and LL. Lordotic wedging (i.e., posterior border relatively shorter in height than the anterior border) of the vertebral bodies and discs contributes to overall LL. Compared to the discs, the degree of sagittal wedging of the vertebral bodies is more predictive of the degree of (standing) LL in adults (Been et al. 2010a). It appears, however, that discs contribute more to the developing LL of children and adolescents than do vertebral bodies (Shefi et al. 2013). Understanding how the sagittal morphology of lumbar vertebral bodies and discs relate to PI during skeletal maturation may aid our understanding of how LL and PI relate in adults.

Using sagittally reformatted CT scans from 146 children and adolescents, ranging from 2 to 20 years of age, we explored the relationship between PI and LL during skeletal maturation. We will also measure sagittal wedging of the lumbar vertebral bodies and discs to examine whether or not PI predicts patterns in vertebral morphology with age. We will determine when skeletally mature PI, which is known to correlate with mature LL, develops (i.e. prior to the onset of walking or at what age during childhood or adolescence).

METHODS

Study design

Retrospective cross-sectional study.

Sample

Our sample included 146 juveniles (120 males and 26 females) with ages ranging from 2 to 20 years, rounded down to the nearest year. Abdominal CT scans were collected from the Edmond and Lily Safra Children's Hospital in Tel Hashomer, Israel. CT scans were taken with patients in supine position with knees extended to rule-out unrelated spine disorders that would cause abdominal or pelvic pain. Data were obtained for this study with

approval by the Helsinki committee of the Chaim Sheba Medical Center. Patients were excluded based on positive findings for conditions that may affect patient positioning in the scanner, including: abdominal hematoma, appendicitis, intestinal inflammation, infections, and fractures. Patients were also excluded based on evidence of conditions affecting spinal alignment, including scoliosis, spondylolysis, and spondylolisthesis, or on evidence of metabolic and chronic illness. All these exclusion criteria formed a previously published database (Shefi et al. 2013), from which this sample originates. For this particular study, additional patients were excluded from the original database due to characteristics pertaining to measuring PI from the reformatted CT image, including: inadequate visualization of the sacrum or acetabula. Example CT images are demonstrated in Figure 4-2.

Angular measurements

All geometrical measurements were collected by co-author (SS) on a PACS workstation (Easyvision; Sectra Imtec AB, Linköping, Sweden).

On sagittal reformatted CT images, measurement lines were placed along each vertebral endplate from cranial L1 to cranial S1 vertebral endplates. From these lines, wedging angles for each vertebral body and disc were collected. Lumbar disc and vertebral body segments angled toward posteriorly are referred to as 'lordotic' and those angled anteriorly are referred to as 'kyphotic'. LL was measured as the angle between cranial L1 and cranial S1 vertebral endplates (Been and Kalichman 2013; Figure 4-1). PI was measured as the angle between A) a line perpendicular to the sagittal S1 cranial endplate and B) a line from the center of the S1 cranial endplate and bisecting the central of both acetabula (Figure 4-1).

Cobb angle measurements from a larger dataset of 210 juveniles were previously published (Shefi et al. 2013). This current study includes the 146 of those 210 juveniles that

had CT scans with both acetabula in view so that PI could be measured. For Cobb angle measurements, intra-class correlation coefficients (ICC) were calculated to assess intra-rater reliability on a subset of 10 random subjects (LA, >0.96; summed vertebral wedging, 0.67<ICC<0.86; summed disc wedging 0.75<ICC<0.94).

Statistical analyses

Univariate and multivariate regression analyses were used to assess the relationships between measurements. Univariate analyses were used for variables PI and LL in relation to age. For these univariate analyses, we examined the potential for non-linear growth patterns common for juvenile development. Multivariate analyses were used for LL and wedging measurements in relation to PI and age. For multivariate analyses (independent variable: L1 vertebral wedging; dependent variables: PI and age), we also created added value plots and report partial correlation values for separate covariates in order to demonstrate the relationship between the independent variable with separate covariates within a multivariate regression model.

Additionally, we created three age categories (2-9 years, 10-15 years, and 16-20 years) in order to compare relationships between PI, LL and age during pre-growth spurt, growth spurt, and post-growth spurt (age ranges for pubertal development are from Dimeglio 2001). T-tests between youngest (2-9 years) and oldest (16-20 years) age categories were used as an additional analysis of age-related changes in LL or PI.

All statistical analyses were conducted using Stata (Stata Corp., College Station, TX) and significant was based on $p<0.05$.

RESULTS

Within the whole sample of 146 juveniles, 8 individuals on average comprised each age between 2 to 20 years of age (sample size for each age is presented in Table 4-1).

Mean age for the whole sample was 11.7 ± 5.5 years (mean ± sd). Results for age categories are presented in Table 4-2.

Pelvic incidence

Within our sample of children and adolescents, PI ranged from 30º to 64º (46º ± 8º). We assessed the effect of age on PI using three methods and found little evidence of a statistically meaningful effect. Using linear regression with age as a continuous variable, we found no evidence of a relationship between PI and age (r=0.14, p=0.09; Figure 4-3). No relationship existed between PI and age when data from each of the three age categories was analyzed separately using regression (Table 4-2). Furthermore, t-tests indicated no significant difference in PI between the youngest and oldest age categories (p=0.07).

Lumbar lordosis

Supine LL increased with age from 2 to 20 years (r=0.53, p<0.001) and demonstrated a non-linear growth pattern (Figure 4-3). Within age categories, we found a positive relationship between LL and age for the youngest and middle age categories, but not for the older age, as would be expected given the overall non-linear pattern (Table 4-2). The current results are in agreement with those published previously (Shefi et al. 2013).

Lumbar lordosis, pelvic incidence, and age

Despite the fact that PI does not change with age, in multivariate regression LL positively correlated with PI (p<0.001, r=0.38) and age (p<0.001, r=0.49). LL and PI are correlated in the middle and oldest age categories, but not for the youngest category (Table 4-2). We found that the difference between average LL and PI decreased with advancing age (Table 4-1). In the youngest age category, mean PI was 9.8º greater than LL and this mean difference narrowed to 5.7º in the middle age category and 3.5º in the oldest age category (Table 4-2).

Lumbar vertebral body and disc wedging

The sum of the wedging angles for all five lumbar vertebral bodies (sumVB) was associated with both PI and age. Using multivariate regression, we found sumVB is negatively associated with advancing age (r=-0.37, p<0.001) and positively associated with higher PI (r=0.25, p=0.003; Figure 4-4). The sum of the wedging angles for all five lumbar discs (sumD) was associated with age but not PI. Using multivariate regression, we found sumD was positively associated with age, with a mean difference of 17.5° between 2 and 20 years of age (r=0.61, p<0.001), and that PI was not associated with sumD (r=0.09, p=0.3; Figure 4-4).

Individual vertebral and disc wedging angles

We explored the association of wedging of individual lumbar vertebral bodies (L1 through L5, separately) with PI and age, using multivariate regression. PI had a positive association with L3 and L4 body wedging angles and age had a negative association with those of L1 and L2. Greater PI was associated with higher (lordotic) wedging (L3: r=0.18, p=0.03; L4:r=0.29, p<0.001), with no effect from age, while age was associated with higher (kyphotic) wedging in L1 (r=-0.60, p<0.001) and L2 (r=-0.28, p<0.001), with no effect from PI. Added value plots (Figure A1-2) demonstrate these relationships.

Further, we found that wedging of each disc increased with age (L1-L2: r=0.65; L2-L3: r=0.52; L3-L4: r=0.47; L4-L5: r=0.41; L5-S1: r=0.29; p<0.001 for all) but that only the L4-L5 disc was positively associated with PI (p<0.001, r=0.34; Figure A1-3).

DISCUSSION

Our results indicate that PI does not significantly change during juvenile growth, which implies that PI may be close to its adult value from an early stage of human development. While we found that PI did not change with age, LL did increase with age. The correlation between LL and PI is well established in asymptomatic adults (Legaye et al.

1998; Vialle et al. 2005) and we found that the correlation between LL and PI was significant in the middle and oldest age categories of juveniles (10-15 and 16-20), but not for the youngest group (2-9). Given that we found that PI does not change with age while LL does, and that the predictive strength between PI and LL increases with age among our juveniles, it appears from our data that PI in juveniles may be predictive of adult LL.

How PI develops prior to unassisted bipedal walking is unclear. Our youngest subjects were two years old and, by that age, most children have already begun to walk and vertically load their spines. The presence of lordosis at the L5-S1 segment during pre-natal development has been reported in one study (Choufani et al. 2009). Another study of infants aged 4 to 15 months found that PI was 43.5°±8.3° (Marty et al. 2002), which is similar to the PI for our youngest age group (44°±6.4° for ages 2-9 years). From an early, possibly pre-natal developmental phase, PI may be in the range of skeletally mature values and then guide development of the degree of LL in adults.

Prior studies characterizing the development of sagittal balance in juveniles report an increase in PI with age (Descamps et al. 1999; Lee et al. 2012; Mac-Thiong et al. 2007; Mangione et al. 1997; Marty et al. 2002; Schlosser et al. 2015; Tardieu et al. 2013). To what extent this statistical relationship between PI and age meaningfully contributes to understanding PI is unclear. Some of these studies do not report their correlation results for age and PI (Marty et al. 2002; Schlosser et al. 2015; Tardieu et al. 2013) and of the studies that do report their correlation results (Lee et al. 2012; Mac-Thiong et al. 2007; Mangione et al. 1997), the strength of the relationship is weak and/or unaccompanied by a significance (Mangione et al., r=0.36, p is not reported and r may be skewed by outliers; Mac Thiong et al., r=0.21, p<0.001; Lee et al., r=0.18, p=0.015). PI is not significantly different between our youngest and oldest age categories. We are suggesting that the previously reported increases in PI during juvenile development may not, therefore, be meaningful in relation to

the development of other spinopelvic measures. The fact that PI does not change as LL does with age and that the correlation between PI and LL becomes stronger with age suggests that juvenile PI may be predictive of mature LL.

We found that sagittal wedging of the individual lumbar vertebral bodies and discs responded variably to age and PI. The result for disc wedging is limited because disc wedging is affected by the supine posture – it is possible that in standing posture, disc wedging is related to PI. The bony morphology of the vertebral body wedging is, however, not impacted by the position during imaging and compared to disc wedging, vertebral body wedging has shown to relate more to changes in overall LL (Been et al. 2010a). The upper lumbar vertebral bodies (L1 and L2) of older adolescents are more kyphotic than those of younger children, potentially due to the development of the transitional curvature necessary to connect the thoracic and lumbar spines. PI was not related to the age-related morphological differences in L1 and L2, but PI did predict L3 and L4, which did not change with age. Interestingly, L5 did not relate to PI or age, but other work has shown that L1 and L5 segments do not correlate with adult standing LL in comparison to the mid-lumbar segments (L2-L4; Been et al. 2010b). Our results indicate that while factors like age and PI are related to LL, they do not have an equal effect on all developing segments of the lumbar spine.

The juvenile development of LL following unassisted bipedal locomotion is biomechanically driven and although juvenile PI may predict mature LL, additional factors and forces also influence the development in curvature in the lumbar spine. For instance, variation in body mass and stature may affect juvenile development of LL. Unfortunately, none of the previous studies of the development of LL and PI in juveniles includes stature or body mass as covariates. Additionally, whether or not sex affects the development of LL is unclear. Unfortunately, our sample was heavily skewed toward males and we, therefore,

could not reliably test for sex-differences. The lumbar spine is sexually dimorphic and among adults, females are known to have greater LL than males (Bailey et al. 2016). A recent study has shown significant sex-differences in sagittal alignment during and after an adolescent growth spurt and the authors inferred that higher prevalence of scoliosis in young females is a biomechanical consequence of differences in growth and spinal development (Schlosser et al. 2015). Future work needs to address how factors like stature, body mass and sex influence the development of LL and PI.

Our results show that, while LL does increase with age during juvenile development, PI does not. Additionally, the relationship between LL and PI, which is correlated in adults, is significant only in our oldest juvenile age category. The relationship between LL and PI is not significant in our younger age categories. Our result suggest that juvenile PI may be predictive of adult LL. The range of normal adult LL is wide and uncovering the factors that influence the development of LL in individuals will aid our understanding of the etiology of spinopelvic morphological deformity.

Age(y)	*n*	Lumbar angle(°) mean ± *sd*	Pelvic incidence(°) mean ± *sd*
2	*3*	31 ± *0.5*	46 ± *2.7*
3	*4*	27 ± *9.3*	44 ± *5.7*
4	*7*	32 ± *6.2*	46 ± *5.7*
5	*12*	33 ± *6.9*	46 ± *5.5*
6	*8*	32 ± *10.7*	44 ± *7.8*
7	*9*	40 ± *5.1*	42 ± *7.0*
8	*12*	35 ± *3.8*	42 ± *7.1*
9	*8*	36 ± *4.4*	43 ± *7.5*
10	*5*	38 ± *8.1*	48 ± *6.1*
11	*3*	37 ± *3.9*	45 ± *5.6*
12	*6*	35 ± *8.7*	40 ± *9.6*
13	*8*	48 ± *8.2*	51 ± *6.9*
14	*4*	46 ± *1.7*	50 ± *10.9*
15	*7*	45 ± *8.1*	53 ± *6.8*
16	*9*	46 ± *8.3*	48 ± *8.0*
17	*11*	44 ± *7.4*	47 ± *7.7*
18	*9*	40 ± *10.1*	44 ± *8.0*
19	*13*	43 ± *7.7*	48 ± *9.4*
20	*8*	43 ± *7.2*	45 ± *9.3*

Table 4-1. Mean and standard deviation of LL and PI at each age year

		Ages 2-9 (youngest) *n=63*	**Ages 10-15** (middle) *n=33*	**Ages 16-20** (oldest) *n=50*
Age (y)		6.10 ± 2.0	12.7 ± 1.7	18.0 ± 1.4
PI	*mean ± sd*	44.0 ± 6.5	48.1 ± 8.5	46.6 ± 8.4
LL		34.2 ± 6.9	42.4 ± 8.7	43.1 ± 8.0
PI + Age	*r*	*-0.20*	*0.29*	*-0.10*
	p	0.12	0.1	0.51
LL + Age	*r*	*0.34*	*0.41*	*-0.12*
	p	**0.01***	**0.02***	0.40
PI + LL	*r*	*0.16*	*0.42*	*0.46*
	p	0.21	**0.02***	**0.001***

Table 4-2. Correlation and linear regression results for Age, PI, and LL within separate age categories

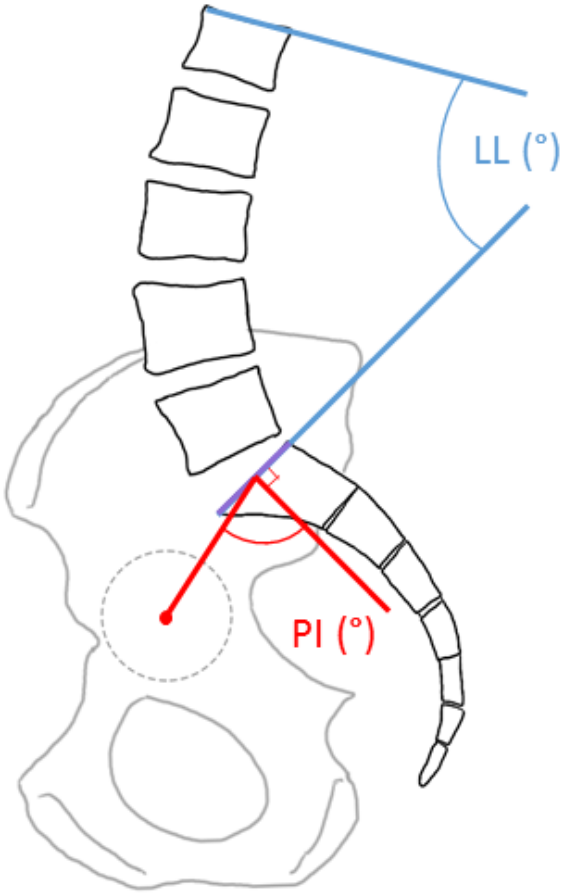


Figure 4-1. A schematic defining LL and PI.

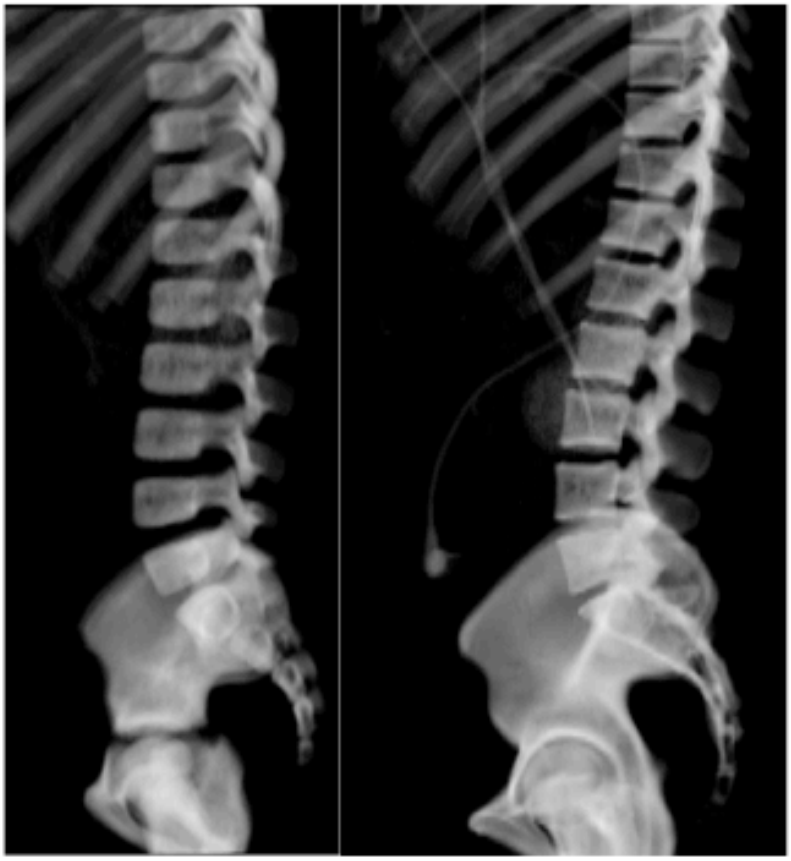


Figure 4-2. Example CT images comparing “young” and “old” juvenile subjects. On the left is a reformatted CT scan of a 5 year old male. On the right is a 19 year old male.

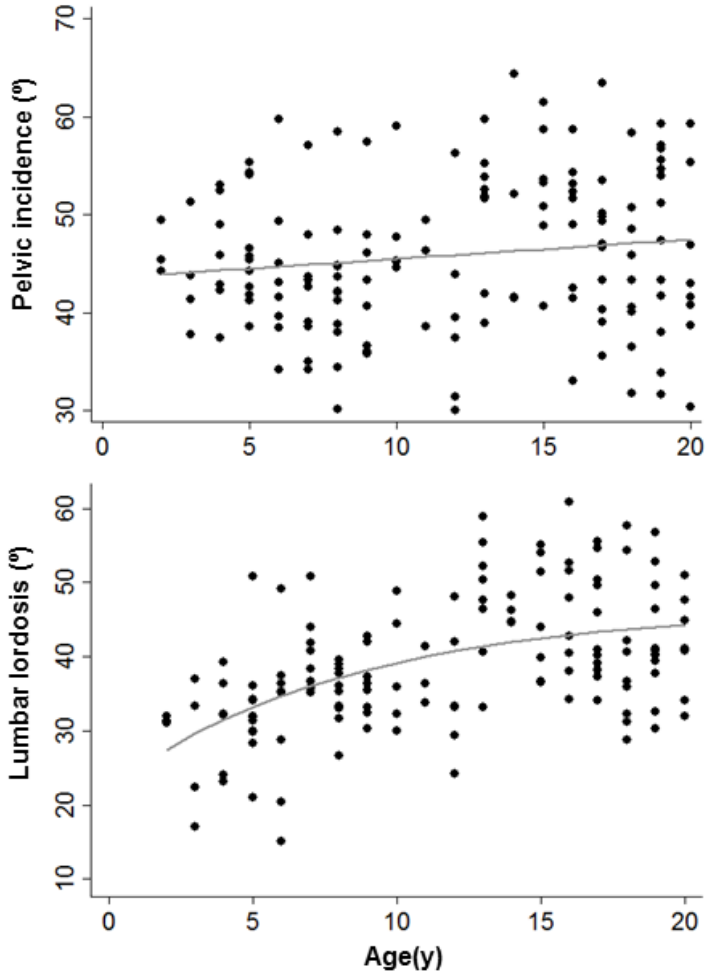


Figure 4-3. PI and LL with age. The plot above demonstrates the non-significant relationship between PI and age (p=0.09). The plot below demonstrates the positive curvilinear relationship between LL and age (r=0.53, p<0.001)

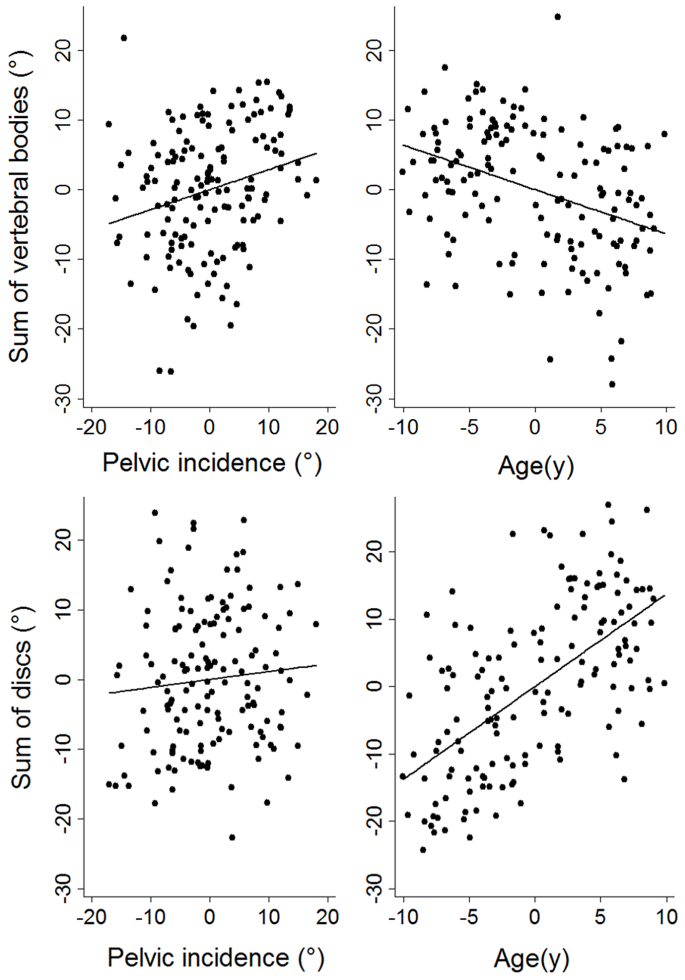


Figure 4-4. Added value plots for sumVB and sumD with PI and age. These plots show the partial correlation results for sumVB and sumD with covariates PI and age.

Chapter 5: Age-related differences in lumbar motion between symptomatic adult males and females

Preface

Data for this study were provided by collaborator Chip Wade. The following manuscript will be submitted to the Journal of Bone and Joint Surgery and authored by Jeannie F. Bailey, Chip Wade, Jeffrey C. Lotz, and Patricia A. Kramer. Additional figures can be found in Appendix 2 (A2).

Abstract

Background. Functional anatomy and prevalence of lumbar spine conditions differs between males and females. For instance, females have greater lumbar lordosis than males do and females are also at a greater risk for age-related spinal conditions, such as degenerative spondylolisthesis. If and to what extent lumbar mobility and intervertebral stability differ by sex, however, remains unclear. Given that intervertebral motion is used to diagnose spinal stability, better understanding how lumbar intervertebral segment mobility and stability differ by sex in patient populations is needed.

Methods. We conducted a retrospective analysis of lumbar intervertebral rotational (IVR) and translation (IVT) motion in the sagittal plane using dynamic fluoroscopy image analysis of age-matched males (n=350) and females (n=350) with non-traumatic symptoms and no prior spinal surgeries. Multivariate linear regression analyses were used to examine how intervertebral motion variables related to sex with age and BMI adjusted.

Results. We found IVR in flexion was lesser in females than males for the two segments between L3 and L5 and IVR in extension was greater in females compared to males for the

three segments between L2 and L5. The significant interaction between age and sex for IVR in flexion at L1-L2 and L2-L3 demonstrated that the range of flexion at these levels decreased significantly with age more severely in females than males. For IVT, the greatest difference between the sexes occurred at L4-L5 with average translation in males indicating retrolisthesis and in females spondylolisthesis. Sex differences in IVT at L4-L5 were significant in flexion, neutral posture and extension for both our younger and older halves of our sample.

Conclusions. Our results indicate that there are sex differences in intervertebral motion and that females have more age-related decreases of lumbar intervertebral mobility. Additionally, sex differences in intervertebral translation reflect a greater prevalence for spondylolisthesis in females. Future work will compare these findings to similar motion data from a sample of asymptomatic adults to create sex-specific standards of spinal instability.

Introduction

If and to what extent lumbar mobility and intervertebral stability differs by sex remains unclear. Considering the rising importance of sex-specific standards in diagnosis and treatment of orthopaedic conditions (Leopold et al. 2014; Hettrich et al. 2015), and the higher risk of conditions relating to spinal instability in females (Manson et al. 2006; Jacobsen et al. 2007), a better understanding of how lumbar intervertebral segment mobility and stability differs by sex in patient populations is needed.

Based on current knowledge of sex differences in functional anatomy and of the prevalence of various spine conditions, lumbar mobility and intervertebral stability should differ between sexes. For instance, the human lumbar spine is sexually dimorphic with females having greater lumbar lordosis on average than males (Bailey et al. 2016) and females have been shown be more at risk for overall joint laxity than males (Kim et al.

2013). Additionally, females are 5 to 6 times more likely to develop lumbar degenerative spondylolisthesis with age than males (Jacobsen et al. 2007). Interestingly, prior pregnancy positively predicts risk of (Sanderson and Fraser 1996), potentially due to the increases in ligamentous laxity associated with childbirth (Calguneri et al. 1982; Charlton et al. 2001; Casagrande et al. 2015). Greater lordosis may, then, be an unintended consequence of increased joint laxity in females. Alternatively, some (Whitcome et al. 2007) have argued that greater lumbar lordosis provides females with an adaptive advantage for increased lumbar extension while bearing a pregnancy load. Regardless of why lumbar lordosis is greater in females, sex differences in lordosis could correspond to sex differences in lumbar motion and possibly intervertebral stability.

The literature provides mixed results concerning whether or not lumbar mobility differs between females and males. Many studies do not include females (Pearcy & Tibrewel 1984; Pearcy et al. 1984; Pearcy et al. 1985; Hayes et al. 1989; Harada et al. 2000; Ng et al. 2001) and among studies that include both sexes, some report sex differences (Burton & Tillotson 1988; Sullivan et al. 1994; McGregor et al. 1995; Dreischarf et al. 2014) and some report no differences (Dvorak et al. 1991; Dvorak et al. 1995; Wong et al. 2004) in lumbar mobility. Of the studies that have reported sex differences, common results are that males have greater lumbar flexion than females (Burton and Tillotson 1988; Sullivan et al. 1994; McGregor et al. 1995) and that females have greater lumbar extension than males (Burton and Tillotson 1988; Sullivan et al. 1994; Dreischarf et al. 2014). Most of this work examines whole lumbar spine motion, i.e., the combined motion of all lumbar intervertebral segments, and not motion between the individual intervertebral segments. Clinically, intervertebral rotational and translational motion in flexion and extension is used to assess lumbar stability (Liu et al. 2015). Examining the motion that occurs at individual lumbar intervertebral segments will enable a detailed comparison of lumbar stability

between sexes and will enable us to understand how the segments of the lumbar spine are contributing to sex differences in gross lumbar mobility reported in previous studies listed above.

In order to clarify the validity of a relationship between motion standards and spinal conditions, three factors that may produce variability in motion results need to addressed: variability among individuals (e.g. age, body mass index (BMI), symptoms), variability in techniques, and repeatability of each technique for measuring spine motion (Andersson et al. 1981; Saraste et al. 1985). For instance, of the few imaging studies that assessed the effect of sex on lumbar intervertebral motion and did not report differences (Dvorak et al. 1991; Wong et al. 2004), age was not adjusted. Because lumbar motion has been widely shown to decline with age (e.g. Intolo et al. 2009), not adjusting for age may confound differences between sexes.

Substantial variation in normative values of both the complete lumbar spine and segmental motion creates a roadblock for being able to establish useful standards indicative of instability. Because results from prior studies are mixed in supporting (Fujiwara et al. 2000) and refuting (Dvorak et al. 1991; Pitkanen et al. 2002) a correlation between imaging measurements of instability and symptoms, we compared rotation and translation between sexes from a patient population of age-matched males (n=350) and females (n=350), who had non-traumatic age-related conditions and no prior surgeries. Intervertebral motion data was collected via a guided dynamic fluoroscopy system, previously validated for accuracy and repeatability (Yeager et al. 2013; Davis et al. 2015). Additionally, our analyses adjusted for age and BMI in effort to reduce variability that may otherwise confound our results. We want to understand if there are sex differences in intervertebral motion that may link the anatomical differences in lordosis (Bailey et al. 2016) to differences in age-related spinal instability conditions like degenerative spondylolisthesis (Jacobsen et al. 2007). We

hypothesized that, for intervertebral motion of the lumbar spine, females would have a lesser range of intervertebral flexion and greater range of intervertebral extension and more intervertebral translation indicative of instability than males.

Materials and Methods

We conducted a retrospective analysis of lumbar intervertebral motion using patient-based dynamic fluoroscopy image analysis. Imaging data was collected at four neurosurgery facilities that utilize the Vertebral Motion Analysis (VMA) system (Orthokinematics, Austin, TX, USA). From a collection of 2,631 patients who underwent VMA testing at participating facilities between January 2011 and April 2014, we enrolled 700 age-matched individuals. Specifically, we have an equal number of males (n=350) and females (n=350) with similar mean and standard deviation of age (57.3yr±14.0). Subjects were excluded based on the occurrence of prior trauma to the spine or spine surgery, but may have experienced low back pain and age-related degeneration. Then, from the dataset of 700 subjects, individuals were excluded if deemed outliers based on regression analyses between height and weight or under age 18. Height and weight ranges were not part of the initial exclusion criteria.

Dynamic fluoroscopy and image acquisition

The VMA system measures intervertebral motion using four elements.

1. Patients perform controlled bending on a platform that bolsters their pelvis to ensure bending motion is a product of the lumbar spine, in the sagittal plane (Figure 5-1). We only assessed upright motion for active lumbar bending under normal physiologic weight-bearing conditions, as this method is most comparable to standard radiographic flexion and extension (FE) tests. Total FE motion was

controlled to span a 70° arc, allowing 50° of flexion and 20° of extension beginning from a baseline neutral position.

2. Video fluoroscopy captured lumbar motion using a standard 12-inch surgical C-arm (OEC 9800 Radiographs, General Electric, Fairfield, CT, US; 2006 Phillips BV Pulsera, Andover, MA, USA) at 8 pulses per second on high level fluoroscopy during the motion.
3. An adjacent computer with data acquisition hardware (Accustream Express As205A, Foresight Imaging, Chelmsford, MA, USA) digitized the video signals from the fluoroscopy, creating four sagittal images of the lumbar spine per second.
4. Clinicians placed markers at vertebral body corners (Figure 5-2) of an initial image frame. Proprietary image processing software tracked the motion of the vertebral bodies and calculated intervertebral rotation (IVR) and translation (IVT; Ortho Kinematics, Austin, TX, USA). Previous work has validated the accuracy and repeatability of the VMA system (Yeager et al. 2013; Davis et al. 2015).

Intervertebral rotation (IVR)

IVR is defined as the change in angle between inferior and superior endplates adjacent to an intervertebral disc (Figure 5-3). IVR data were analyzed in three fashions: each separate lumbar disc segment (L1-L2, L2-L3, L3-L4, L4-L5, and L5-S1), combined over the entire lumbar spine (L1-S1), and combined over the mid-lumbar spine (L2-L5). The reason for examining the mid-lumbar L2-L5 discs in addition to L1-S1 is that L1-L2 and L5-S1 discs were not reliably visible for all patients. IVR was measured in lumbar flexion and extension.

Intervertebral translation (IVT)

IVT (%) is defined as the translation of the inferior vertebral body relative to the superior vertebral body as a percentage of the total superior vertebral body length (Stokes and Frymoyer 1987; Deitz et al. 2010). Anterior displacement or slippage of the superior vertebra relative to the inferior vertebra of a motion segment is indicative of anterolisthesis (or spondylolisthesis) and posterior displacement or slippage of the superior vertebra is indicative of retrolisthesis (Figure 5-3). IVT data was analyzed for each separate lumbar disc segment (L1-L2, L2-L3, L3-L4, L4-L5, & L5-S1). IVT was collected in flexion, extension, and neutral position.

Statistical analyses

Multivariate linear regression (MLR) analyses were conducted to understand if sex differences for IVR and IVT response variables exist. (The list of response variables is presented in Tables 5-1 and 5-2.) All MLR analyses estimated robust standard error (RSE) using the Huber-White sandwich estimators and adjusted for continuous covariates: age and BMI. Two MLR models were created. Model 1 included sex, age and BMI as dependent variables for each individual IVR and IVT response variable (E): ($E=\beta_0+\beta_1*Sex+\beta_2*Age+\beta_3*BMI$). Model 2 was similar to model 1, but with an interaction between sex and age added: ($E=\beta_0+\beta_1*Sex+\beta_2*Age+ \beta_3*BMI+ \beta_4*Sex*Age$). Additional exploratory analyses, using the MLR model 1, examined the effect of sex in two separate age categories: below ('younger') and above ('older') the mean age for the sample. All analysis was conducted using STATA (Stata Corp, College Station, TX, USA) and significance was based on $p<0.05$.

Results

Of the 700 age-matched females and males, 39 individuals (f, n=23; m, n=16) were excluded as outliers based on height and weight and four were excluded as under age 18. In the final sample, ages ranged from 20 to 91 years. Age did not differ by sex, but BMI was higher in males than females (Table 5-3).

Intervertebral rotation (IVR)

IVR was examined separately for flexion and extension. For flexion, using MRL Model 1, we found that females had significantly less flexion over the complete lumbar spine (L1-S1), mid-lumbar spine (L2-L5) and two individual segments (L3-L4 and L4-L5) than males (Table 5-1). Females had significantly greater extension over the mid-lumbar spine (L2-L5) and three individual segments (L2-L3, L3-L4, and L4-L5) than males (Table 5-1). Flexion decreased significantly with age for every IVR flexion response variable, except L5-S1. Extension decreased significantly with age for every IVR flexion response variable, except L3-L4 and L4-L5.

Using MRL Model 2, we found a significant interaction between sex and age for flexion of the complete spine (L5-S1) and two individual segments (L1-L2 and L2-L3; Figures A2-1 and A2-2). We found no interactions between age and sex for any IVR extension variables (Figure A2-3).

Comparing IVR variables between sexes for the younger and older age categories, we found that sex-differences are greater in the older category (Table 5-4). Extension of L3-L4 and L4-L5 showed sex-differences in both younger and older categories. No variable showed sex-differences only in the younger age category. Mean and standard deviation values for IVR in males and females for the younger and older age categories are provided in Table A2-1.

Intervertebral translation (IVT)

Using MRL Model 1, IVT was examined at three separate standing positions: flexion, neutral, and extension (Table 4-2; Figure 5-2).

For the upper three lumbar segments (L1-L2, L2-L3, and L3-L4) in extension and neutral position, average translation in both sexes was negative, indicating retrolisthesis (negative IVT). For the lower two segments (L4-L5 and L5-S1) in extension and neutral position, average translation in males was negative, indicating retrolisthesis, and average translation in females was positive, indicating spondylolisthesis (Figure 5-4; Table A2-2).

In flexion, the lumbar spine flattened (Figure 5-2). In the upper three lumbar segments (L1-L2, L2-L3, and L3-L4), translation was reduced for both sexes and significantly differed by sex at only L3-L4. For the lower two segments (L4-L5 and L5-S1), average translation in females was positive, indicating spondylolisthesis, with a significant difference between the sexes only at L4-L5.

In all three positions, the largest difference in IVT between males and females occurred in the L4-L5 segment where the sexes had opposing translational directions, i.e., males with retrolisthesis and females with spondylolisthesis (Figure 5-4; Table A2-2). For neutral posture and extension, both IVT of L4-L5 and L5-S1 were significantly different between sexes. In flexion, only L4-L5 was different between sexes.

Using MRL model 2, we found a significant interaction between sex and age for IVT in all three positions at L4-L5 (Figure A2-4). For no other segments in any of the three positions was an interaction between age and sex indicated.

We found sex differences in both younger and older age categories (Table 5-4) for L3-L4 and L4-L5 in all three positions for both younger and older age categories. Sex differences were present for L2-L3 in both younger and older categories in extension and

only in the older category for neutral position. Mean and standard deviation values for IVT in males and females for the younger and older age categories are provided in Table A2-2.

Discussion

Our results for IVR support our hypothesis that females have a greater range of lumbar intervertebral extension, while also indicating that males have a greater range of flexion than females, which has been shown in prior work using different motion measurement methods (Burton & Tillotson 1988; Sullivan et al. 1994; McGregor et al. 1995; Dreischarf et al. 2014). Furthermore, we found a significant interaction between age and sex for IVR of the complete lumbar spine (L1-S1) and at specific levels (L1-L2 and L2-L3). This interaction means that the effect of age was stronger in females than males. We found that these rotational variables decreased significantly with age in females, but not males (Figures A2-1 and A2-2). Thus, when we compared the younger half of our sample to the older half, we found a significant sex difference in IVR variables for the older individuals, but not in the younger individuals. This decrease in motion in females with age led to the significant sex difference in IVR in older individuals.

Our results for IVT at L4-L5 support our hypothesis that females have more intervertebral translation than males. Although we found sex differences in IVT for each lumbar segment, the greatest difference occurred at L4-L5 where the average translation was in opposite directions in females and males. At L4-L5, average IVT in males indicates retrolisthesis and in females indicates anterolisthesis/spondylolisthesis. Females are known to be more at risk for degenerative spondylolisthesis (Jacobsen et al. 2007) and degenerative spondylolisthesis occurs most frequently at L4-L5 (Sanderson et al. 2007; Schuller et al. 2011). Furthermore, we found a significant interaction between age and sex for IVT at L4-L5 in neutral position, flexion and extension.

Age-related sex differences in lumbar intervertebral motion could be explained by several factors. The differences in IVR that indicate that females have less flexion and more intervertebral extension than males may correspond to differences in lumbar lordosis. Females have greater lumbar lordosis, which has been hypothesized to be adaptive as an aid for extension of the lumbar spine while bearing a pregnancy load (Whitcome et al. 2007). Females may, however, have greater lumbar lordosis as a result of higher overall joint laxity. One study showed that greater joint laxity results in greater lumbar lordosis and that females have more joint laxity than males (Kim et al. 2013). The differences we found in IVT at the L4-L5 level could indicate greater joint laxity in females, especially because these differences at L4-L5 were present in both our younger and older age groups. Interestingly, in upper three intervertebral segments of the lumbar spine, IVT in neutral and extended positions indicated retrolisthesis in both sexes and was significantly greater in males (Figure 5-4). Another potential explanation may be that sex differences in paraspinal muscle activity decline with age differently in males and females (Kienbacher et al. 2015). While we are able to show sex differences in intervertebral motion, it remains unclear what the cause of these sex differences is.

A limitation of this study is that we did not have access to radiographic images and, therefore, could not measure lumbar lordosis or disc height. In future work, we want to understand how morphological differences in lumbar lordosis and disc health may influence motion data. Statistically adjusting for lumbar lordosis or disc health may further clarify sex differences in lumbar motion. Another limitation is that we analyzed total IVR and IVT separately even though the data were collected simultaneously from the VMA system. We used measures of total IVR and IVT in order to compare our results to the previous studies of lumbar motion which almost exclusively measured complete lumbar spine and/or intersegmental motion at maximum flexion and extension. Our data was collected from

individuals in a controlled rate of guided flexion and extension, which has shown to be more reliable than standard FE radiographs (Davis et al. 2015). In future work, we plan to compare the rate of change in intervertebral motion between males and females. It would be advantageous to know how the rate of IVR and IVT change relate and contribute to instability. Reliable motion standards of intervertebral instability have been sought in orthopaedics for a long time (Deitz et al. 2011), but such standards remain to be determined. Moving away from using static measures of lumbar mobility and toward using dynamic motion data will potentially aid our ability to diagnose intervertebral instability.

In conclusion, our study demonstrates that females have a greater range of lumbar intervertebral extension in the mid-lumbar disc segments, which may relate to greater lumbar lordosis in females (Bailey et al. 2016). Also, females appear to be more affected by age-related decreases of lumbar intervertebral mobility. This decrease in rotational motion may coincide with the sex differences in translation, supporting previous work that females have a greater prevalence for degenerative spondylolisthesis (Jacobsen et al. 2007). Our work highlights the importance of accounting for age and BMI in studies of lumbar motion, as well as using valid and repeatable methods. To create clearer lumbar motion standards indicative of instability, future work will compare our results to similar intervertebral motion data from an asymptomatic population.

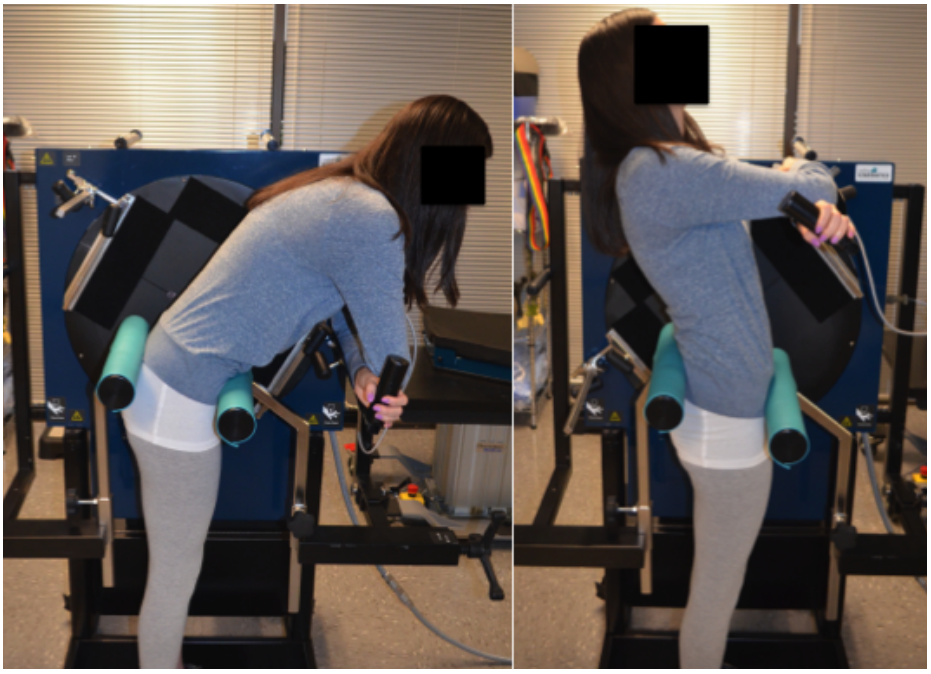


Figure 5-1: Controlled flexion and extension. Subject demonstrates controlled flexion (left) and extension (right) by the VMA system. Photos are originally featured in Davis et al. 2015 in the International Journal of Spine Surgery.

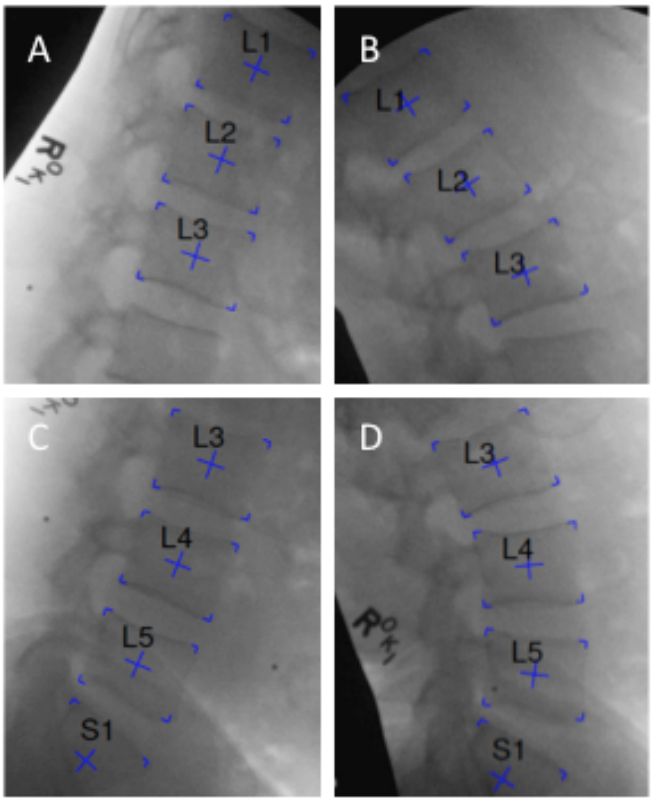


Figure 5-2: Dynamic fluoroscopy views. A and C are used to capture the total lumbar spine in flexion. B and D are for extension.

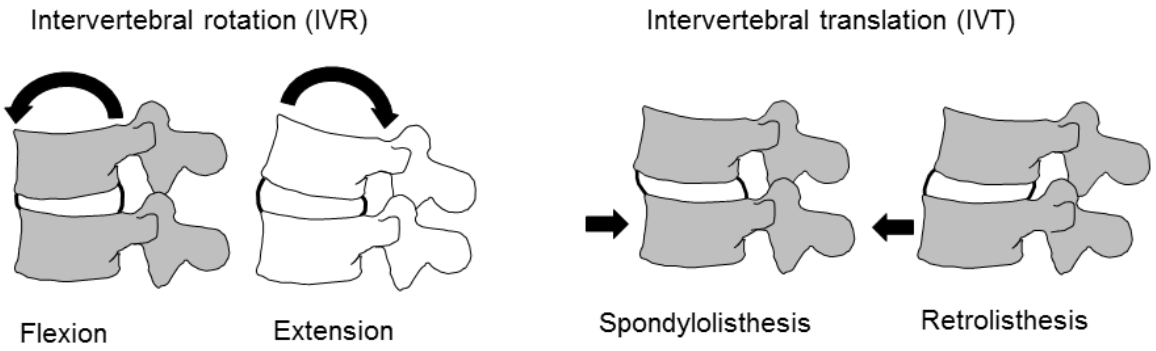


Figure 5-3: Motion of IVR and IVT. IVR include flexion and extension motion (°) in the sagittal plane. IVT is a measure of the displacement offset of a lumbar vertebral body relative to the adjacent superior vertebral body. Data for IVT is presented as a percentage (%) defined by the offset between vertebral bodies (mm) divided by the length (mm) of endplate. A negative percent IVT represents a retrolisthesis and a positive percent IVT represents an anterolisthesis (spondylolisthesis).

		Sex			Age			BMI		
		β_1	*RSE*	p-val	β_2	*RSE*	p-val	β_3	*RSE*	p-val
Flexion	L1-S1*	-2.00	*0.82*	**0.02**	-0.14	*0.03*	**<0.00**	-0.22	*0.09*	**0.02**
	L2-L5*	-1.45	*0.52*	**0.01**	-0.14	*0.02*	**<0.00**	-0.14	*0.05*	**0.01**
	L1-L2	-0.05	*0.27*	0.84	-0.04	*0.01*	**<0.00**	-0.06	*0.03*	0.07
	L2-L3	-0.14	*0.26*	0.58	-0.07	*0.01*	**<0.00**	-0.04	*0.03*	0.10
	L3-L4	-0.58	*0.22*	**0.01**	-0.04	*0.01*	**<0.00**	-0.06	*0.02*	**0.01**
	L4-L5	-0.47	*0.23*	**0.04**	-0.02	*0.01*	**0.00**	-0.02	*0.02*	0.34
	L5-S1	-0.19	*0.17*	0.28	0.01	*0.01*	0.42	0.03	*0.02*	0.08
Extension	L1-S1*	0.61	*0.33*	0.07	-0.04	*0.01*	**0.01**	0.05	*0.04*	0.21
	L2-L5*	0.67	*0.17*	**<0.00**	-0.01	*0.01*	0.25	0.06	*0.02*	**0.01**
	L1-L2	0.06	*0.12*	0.62	-0.02	*0.01*	**0.00**	0.00	*0.01*	0.94
	L2-L3	0.18	*0.09*	**0.04**	-0.01	*0.00*	**0.00**	0.02	*0.01*	**0.03**
	L3-L4	0.23	*0.07*	**0.00**	0.00	*0.00*	0.09	0.02	*0.01*	**0.01**
	L4-L5	0.29	*0.09*	**0.00**	0.00	*0.00*	0.50	0.03	*0.01*	**0.01**
	L5-S1	0.04	*0.12*	0.74	-0.01	*0.00*	**0.01**	0.04	*0.01*	**0.00**

Table 5-1: IVR data for sex, age and BMI using Model 1 ($E=\beta_0+\beta_1*Sex+\beta_2*Age+\beta_3*BMI$).

β_1 is the coefficient for change in ROM in females relative to males. B_2 is the predicted change in degree of motion per increase in each year of age in our sample. B_2 is the predicted change in degree of motion per increase in a single unit of BMI.

		Sex			Age			BMI		
		β_1	*RSE*	p-val	β_2	*RSE*	p-val	β_3	*RSE*	p-val
Neutal posture	L1-L2	0.59	*0.26*	**0.03**	-0.15	*0.01*	0.08	-0.02	*0.03*	0.47
	L2-L3	0.88	*0.29*	**0.00**	0.01	*0.01*	0.58	0.00	*0.03*	0.89
	L3-L4	2.07	*0.39*	**0.00**	0.06	*0.01*	**0.00**	0.10	*0.04*	**0.02**
	L4-L5	4.37	*0.66*	**0.00**	0.21	*0.02*	**0.00**	0.14	*0.07*	0.06
	L5-S1	1.60	*0.81*	**0.05**	0.05	*0.04*	0.17	0.05	*0.10*	0.65
Flexion	L1-L2	0.19	*0.26*	0.47	-0.01	*0.01*	0.45	-0.07	*0.03*	**0.01**
	L2-L3	0.40	*0.30*	0.18	-0.01	*0.01*	0.24	-0.03	*0.03*	0.33
	L3-L4	1.39	*0.04*	**0.00**	0.04	*0.01*	**0.00**	0.06	*0.04*	0.18
	L4-L5	3.52	*0.64*	**0.00**	0.19	*0.02*	**0.00**	0.07	*0.07*	0.33
	L5-S1	1.06	*0.75*	0.16	0.05	*0.03*	0.10	-0.08	*0.09*	0.36
Extension	L1-L2	0.82	*0.26*	**0.00**	-0.01	*0.01*	0.35	-0.04	*0.03*	0.18
	L2-L3	1.00	*0.29*	**0.00**	0.01	*0.01*	0.21	0.01	*0.03*	0.75
	L3-L4	1.94	*0.37*	**0.00**	0.06	*0.01*	**0.00**	0.08	*0.04*	0.05
	L4-L5	4.05	*0.57*	**0.00**	0.19	*0.02*	**0.00**	0.08	*0.06*	0.23
	L5-S1	1.56	*0.75*	**0.04**	0.05	*0.03*	0.13	0.01	*0.09*	0.91

Table 5-2: IVT data for sex, age and BMI using Model 1 ($E=\beta_0+\beta_1*Sex+\beta_2*Age+\beta_3*BMI$).

β_1 is the coefficient for change in range of motion in females relative to males. B_2 is the predicted change in degree of motion per increase in each year of age in our sample. B_2 is the predicted change in degree of motion per increase in a single unit of BMI.

		Females			Males			p-value
		n	Mean	SD	*n*	Mean	SD	
Entire sample	Age	*327*	58.1	14.2	*334*	56.6	13.2	0.154
	BMI		24.4	5.4		26.41	4.1	<0.000
Younger age category	Age	*137*	44.5	8.6	*147*	44.6	8.4	0.910
	BMI		25.1	5.8		26.3	4.2	0.014
Older age category	Age	*190*	68.0	7.8	*187*	66.1	7.2	0.054
	BMI		23.9	5.0		26.4	4.0	<0.000

Table 5-3: Age and BMI. Covariate data for entire sample and for younger and older age categories.

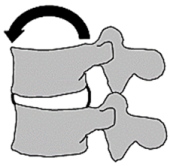
		Younger category			Older category		
		β_1	*RSE*	p	β_1	*RSE*	p
Flexion IVR 	*L1-S1	0.08	*1.27*	0.95	-3.52	*1.07*	**0.002**
	*L2-L5	-0.50	*0.86*	0.56	-2.22	*0.64*	**0.001**
	L1-L2	0.45	*0.39*	0.25	-0.42	*0.37*	0.26
	L2-L3	0.72	*0.40*	0.07	-0.83	*0.32*	**0.01**
	L3-L4	-0.45	*0.37*	0.23	-0.66	*0.28*	**0.02**
	L4-L5	-0.65	*0.37*	0.08	-0.34	*0.29*	0.24
	L5-S1	-0.30	*0.24*	0.22	-0.16	*0.24*	0.51
Extension IVR 	*L1-S1	0.14	*0.54*	0.79	1.00	*0.42*	**0.02**
	*L2-L5	0.53	*0.27*	**0.05**	0.80	*0.23*	**0.001**
	L1-L2	0.15	*0.22*	0.50	0.02	*0.15*	0.90
	L2-L3	0.11	*0.15*	0.45	0.24	*0.11*	**0.03**
	L3-L4	0.18	*0.09*	0.05	0.25	*0.10*	**0.01**
	L4-L5	0.27	*0.13*	**0.03**	0.29	*0.12*	**0.01**
	L5-S1	-0.23	*0.18*	0.21	0.25	*0.16*	0.11
IVT in neutral posture	L1-L2	0.25	*0.33*	0.45	0.82	*0.39*	**0.04**
	L2-L3	0.54	*0.31*	0.09	1.18	*0.46*	**0.01**
	L3-L4	1.66	*0.45*	**<0.000**	2.54	*0.60*	**<0.000**
	L4-L5	3.28	*0.87*	**<0.000**	5.21	*0.96*	**<0.000**
	L5-S1	2.12	*1.23*	0.09	1.06	*1.07*	0.32
IVT in flexion	L1-L2	-0.25	*0.35*	0.48	0.55	*0.37*	0.15
	L2-L3	0.11	*0.35*	0.76	0.72	*0.47*	0.12
	L3-L4	1.33	*0.47*	**0.01**	1.58	*0.57*	**0.01**
	L4-L5	2.35	*0.88*	**0.01**	4.36	*0.90*	**<0.000**
	L5-S1	1.49	*1.17*	0.21	0.63	*0.99*	0.53
IVT in extension	L1-L2	0.45	*0.35*	0.20	1.08	*0.38*	**0.00**
	L2-L3	0.86	*0.32*	**0.01**	1.11	*0.46*	**0.02**
	L3-L4	1.46	*0.44*	**<0.000**	2.44	*0.56*	**<0.000**
	L4-L5	3.18	*0.74*	**<0.000**	4.72	*0.84*	**<0.000**
	L5-S1	2.33	*1.16*	**0.04**	0.82	*1.00*	0.41

Table 5-4 – IVR and IVT data from younger and older age categories. Results are only reported for sex (β_1) using Model 1 ($E=\beta_0+\beta_1*Sex+\beta_2*Age+\beta_3*BMI$). β_1 is the coefficient for change in range of motion in females relative to males.

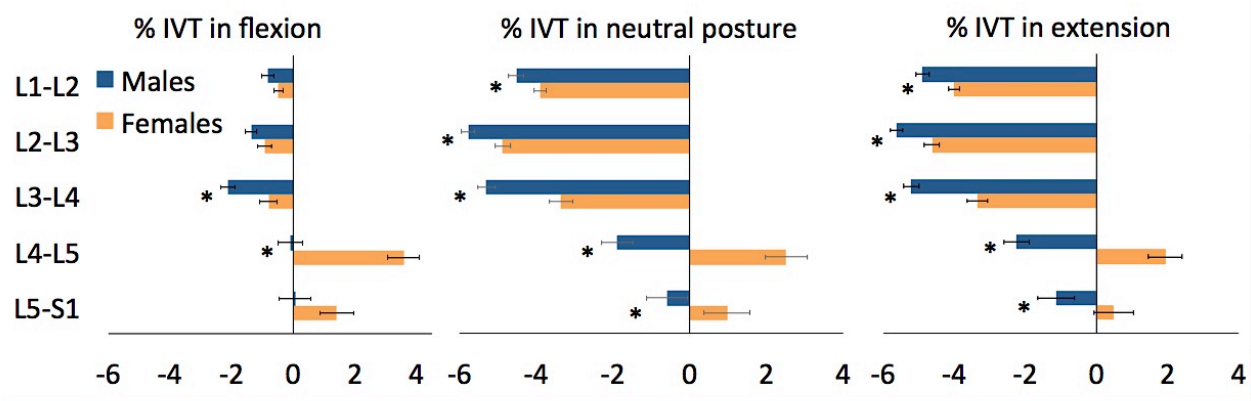


Figure 5-4: Mean and SE for IVT in males and females. The three graphs show the means and standard errors for sex-specific IVT (%) data from separate positions (flexion, neutral posture, and extension). Negative % indicates retrolisthesis and positive % indicates spondylolisthesis. (*) indicate statistical significance based on results from Model 1, where age and BMI are adjusted.

Chapter 6: Interpretation, conclusions, and future work

With this dissertation, I sought to understand if there were indeed sex differences in lumbar lordosis (LL). In the end, I found that while there are sex differences in LL, it is not a simple matter of females having greater LL than males. Differences in LL between males and females are influenced by postural load, sacral orientation and age. In this final chapter, I will show how my results relate to the hypotheses laid out in my introduction, interpret my results in the context of evolutionary medicine, make conclusions, and describe future work.

Hypotheses

In-vivo LL is greater in females than males and influenced by postural loading

My results indicate that sex differences in LL are dependent on upright posture in asymptomatic adults. Specifically, **females had greater LL than males, but only while standing**. In the supine individuals, average LL was greater in females, but not significantly different between sexes. The average measure of standing LL was 7.3° greater in females than males ($p=0.001$) and in supine LL was 2.9° greater in females than males ($p=0.208$). This finding indicates a postural dependence on sex differences in LL. However, I also found sex differences in the bony morphology of the lumbar spine that support greater LL in females than males. Lumbar vertebral bodies (L1 through L5) were more lordotically wedged in females than males. The mean difference in vertebral wedging summed over all five lumbar vertebral bodies was 9.4° greater in females than males, while lumbar disc wedging did not significantly differ between sexes in standing posture. The differences in vertebral body wedging support differences in standing LL, however, did

not have the same influence on supine posture seeing that supine LL did not differ by sex.

The effect of increasing load on the spine by standing has a greater impact on LL in females than males, as the average difference between standing and supine LL in females (10.9°) was significantly greater than the average difference in males (6.5°). The result showing that supine LL does not differ by sex and females had a significantly greater degree of LL when standing may reflect sex differences in lumbar range of motion and/or greater joint laxity.

Sacral orientation will differ by sex

Sacral slope (SS) and pelvic incidence (PI) are two measures I examined in relation to sex differences in LL. While SS is dependent on the postural orientation of the pelvis, PI is not because it is a measure of how the sacrum is positioned within the bony pelvis. Both of these measures correlate with standing LL in asymptomatic individuals (Legaye et al. 1998; Vialle et al. 2005). My results showed that **SS did differ by sex, but that PI did not**. SS was significantly greater in adult females, which relates to standing LL being greater in females. By doing a multivariate linear regression analysis, I found the relationship between PI and standing LL was not significant when including SS as a covariate. These results indicate females orient their pelvis differently when standing compared to males and this may be one of the factors driving sex differences in individuals when standing.

That PI does not differ by sex is interesting and possibly unsettling for orthopaedic patient care. PI is assumed to be a fixed measurement in adults and correlates with asymptomatic LL (Legaye et al. 1998) and for those reasons, PI is used to estimate the degree of LL to surgically reconstruct pathological LL for correcting a patient's sagittal

balance (Schwab et al. 2009). Results from our juvenile population indicate that PI does not change with development, while LL does. Furthermore, while LL is changing with age, the strength of the correlation between PI and LL is stronger in the older age categories, meaning that PI may be predictive of adult LL. This result shows how PI and LL develop in relation to each another during juvenile maturation and supports how they eventually correlate in adults. However, there must be additional factors (beyond PI) influencing LL in adults considering my results from an adult population showing that standing LL does differ by sex and PI does not.

Because the results from the juvenile sample are based on supine posture, it is unclear how posture dependent variables like SS or LL relate to PI in standing posture during juvenile development. Two prior studies examining spinopelvic alignment in juveniles did not report sex differences in standing LL or sacral orientation (Cil et al. 2005; Schlosser et al. 2015). However, this may due to a lack of adjusting for age in the statistical analyses. Considering my results showing sex differences in LL and SS in adults, how sagittal balance develops in juveniles should reveal these differences between sexes.

Juvenile development of LL will differ by sex

I was unable to show whether or not juvenile development differed by sex because my sample of juveniles was heavily skewed toward males (m, n=120; f, n=26). No sex differences were found, but the unequal distribution may have made capturing sex differences in how LL changes with age problematic. An additional and unforeseen limitation is the supine posture, because results from our adult population show that sex differences in LL are present in standing posture, but not in supine posture.

Lumbar motion will differ by sex

In my study comparing lumbar intervertebral motion between adult males and females with non-traumatic age-related symptoms like low back pain and degeneration, I found that **lumbar intervertebral rotation during flexion and extension differed by sex**. A few early studies examining maximum lumbar flexion and extension varyingly show males having a greater range of flexion and females having a greater range of extension, but these studies did not compare intervertebral motion between sexes, so it is unclear to what extent motion differs by sex in individual lumbar motion segments. My results for controlled flexion and extension at each lumbar motion segment show that males have greater flexion in two mid-lumabr segments (L3-L4 and L4-L5) and females have greater extension in three mid-lumbar segments (L2-L3, L3-L4, L4-L5). A greater range of lumbar extension corresponds to hypotheses and prior studies showing females extend their lumbar spines in response to a pregnancy load (Whitcome et al. 2007); however, why males would have a greater range of flexion is unclear. It may be due to greater LL in females with greater lordotic vertebral wedging causing a restriction in flexion. Unfortunately, lumbosacral morphological data was not available for symptomatic subjects from Chapter 5, so I could not directly link the degree of LL to intervertebral motion.

Age-related lumbar conditions will differ by sex

With age, lumbar range of motion is shown to decrease (Intolo et al. 2009) and prevalence of conditions indicative of intervertebral instability increase (Andersson 1997). From the same sample of adult males and females with non-traumatic age-related symptoms like low back pain and degeneration, I found sex differences in age-related decreases in intervertebral rotation and sex differences in intervertebral translation indicating instability conditions, like degenerative spondylolisthesis, in females.

My results for lumbar intervertebral rotation showed that age-related decreases in flexion differed between males and females. Multivariate linear regress analyses showed a significant interaction between age and sex for flexion at the two uppermost lumbar segments (L1-L2, L2-L3). This result indicated that **flexion decreased with age more in females than it did in males** and that sex differences in flexion became greater with age. When examining younger and older age groups of the sample population, females had significantly less flexion than males only in the older group. Sex differences in extension did not relate to age as they did with flexion. Flexion accounts for the majority of lumbar sagittal motion; therefore age-related decreases in flexion might substantially impact total sagittal motion more in females than males.

Lumbar instability is greater in females than in males. In standing posture, the amount of translation or slippage of vertebrae in the sagittal plane increases with age and is related to spinal instability and degenerative spondylolisthesis. L4-L5 is the motion segment most affected by degenerative spondylolisthesis and I found the greatest degree of sex differences in translation at that level in neutral standing posture and extension. Average intervertebral translation in females at L4-L5 indicated degenerative spondylolisthesis (L5 vertebra posteriorly translates relative to L4) and average translation in males indicated retrolisthesis (L5 vertebra anteriorly translates relative to L4). Risk of degenerative spondylolisthesis is five to six times greater in females (Jacobsen et al. 2007) and is positively associated with higher degrees of LL and SS (Schuller et al. 2011), as well as prior pregnancy (Sanderson and Fraser 1996). If greater LL in females is actually an adaptation to aid in bearing a pregnancy load, degenerative spondylolisthesis would be the orthopaedic trade-off.

Interpretation

The results presented in this dissertation indicate there are sex differences in LL, but that is it not simply a matter of females having greater lumbar curvature than males. Three factors influencing lumbar sex differences are **posture, sacral orientation,** and **age**. LL differs by sex in standing posture, but not in supine posture. Both SS and PI have been shown to correlate with LL in prior work (Legaye et al. 1998; Vialle et al. 2005) and my results show SS differs by sex while PI does not. Age-related decrease in lumbar motion is more severe in females with older females having significantly less lumbar flexion than males. My work shows that factors like postural loading, sacral orientation, and age affect LL differently in females and males. These factors have aided my interpretation of if, how, and why the lumbar spine is sexually dimorphic.

Adaptation or joint laxity?

In this dissertation, I show that females have greater LL than males, but that **it is not clear if this musculoskeletal sexual dimorphism is shaped directly by selection or is an unintended result of selection for greater joint laxity in females**.

The introduction of fluctuating sex hormones with the onset of puberty in the female body has been linked to joint laxity in the knee (Shultz et al. 2005), and presumably affects other musculoskeletal joints. Joint laxity in females following puberty is a possible explanation for sex differences in risk of ACL tears. The majority of research on sex differences in joint laxity concerns the ACL. Joint laxity in females has been shown to be greatest during menstruation and pregnancy (Charlton et al. 2001; Shultz et al. 2005) and associated with increased levels of estrodiol (Charlton et al. 2001) and relaxin (Dehghan et al. 2014). More work needs to be done on the effect of hormone-related joint laxity on the stability of other joints, as well as the evolutionary purpose for joint laxity in human females. Assuming increased joint laxity during pregnancy is adaptive for reproduction, is the

potential global effect in the body (e.g., ACL tears) that is shown to occur outside of pregnancy (e.g., following puberty and during menstruation) a trade-off?

Regardless, evidence from my dissertation to supports that sex differences in lumbar spine posture and intervertebral motion is a result of increased joint laxity in females. The differences in LL between standing and supine postures were greater in females than males and I equated this to a potential sex difference in range of motion. This may arguably, however, be a result of greater joint laxity in the stabilizing ligaments of the lumbar spine. Additionally, I found that females had greater LL and SS when standing, but that PI did not differ by sex. This result corresponds to similar results from a study comparing a sample of individuals with joint laxity to a group without joint laxity (Kim et al. 2013). This study found that LL and SS were greater for the group with joint laxity, but that PI was not different between the two groups. LL and SS are dependent on posture and, therefore, may be affected by joint laxity, while PI, which is not dependent on posture, may not be similarly affected by joint laxity, because range of motion of the sacroiliac joint is limited (~2°) and is not shown to differ by sex (Vleeming et al. 2012). Females having higher overall joint laxity than males (Quatman et al. 2008) may explain my results comparing LL, SS, and PI between adult males and females in standing posture.

In addition, my results for sex differences in intervertebral translation in neutral standing posture at L4-L5 are not dependent on age, meaning that females have spondylolisthesis at that level, while males do not, in both my younger and older adult groups. Heightened joint laxity in the stabilizing ligaments of the lumbar spine could be causative of relatively higher risk for sagittal balance deformity in females, including idiopathic scoliosis and degenerative spondylolisthesis. The morphological differences in vertebral wedging between males and females from both my results and other studies

measuring osteological collections (Masharawi et al. 2010; Whitcome et al. 2007) may be a secondary result of the greater LL induced by joint laxity.

I am not declaring that joint laxity is the cause of sex differences in LL, but my research supports that it may be a contributing factor. Whether sex differences in the lumbar spine are adaptive or an unintentional result of joint laxity remains unclear, but it appears that joint laxity affects the female lumbar spine. Given that females appear to develop joint laxity with the onset of puberty (Shultz et al. 2005), joint laxity may also influence sex differences in risk of idiopathic scoliosis, a spinal deformity condition that typically begins during puberty (Schlosser et al. 2015).

Implications for evolutionary medicine

Evolutionary medicine utilizes evolutionary theory to better understand health and disease (Williams and Nesse 1991) and provides the underlying theory for arguing that musculoskeletal sexual dimorphism may lead to orthopaedic tradeoffs. The results from this dissertation, however, bring to light that caution needs to be applied when using evolutionary medicine to try and explain musculoskeletal conditions. Not all things are necessarily *adaptive* (Gould and Lewontin 1979).

The unanticipated result that joint laxity may cause sex differences in both lumbar curvature and orthopaedic conditions may highlight a pitfall with musculoskeletal examples of evolutionary medicine. The response of joint laxity from the introduction of sex hormones with menstruation and pregnancy is the result of an evolutionary adaptation aiding reproduction. However, the potential effect of joint laxity on the lumbar spine may or may not be intentional. Joint laxity in the lumbar spine could be argued to enabled greater extension in females and helps balance a pregnancy load. On the other hand, the increase of joint laxity may be selected for its action on the pelvis and its effect on other joints an

unintended result. Therefore, heightened laxity in the lumbar spine in females could be non-adaptive for aiding in load bearing. This is an example of a pleiotropy.

Within the field of biological anthropology, adaptive functions are often determined from skeletal material alone (i.e., osteological collections). This is because the hominin fossil record is drawn exclusively from skeletal material. A sexual dimorphism where females have greater LL to bear a pregnancy load was suggested based on vertebral morphology and postural adjustments with advancing pregnancy. As my dissertation shows, sex differences in vertebral morphology could result from greater LL due to joint laxity. My work shows that it is critical to validate theories from the fossil record with *in vivo* function.

Conclusion

In this dissertation, I showed that females had greater LL than males. These sex differences in LL were dependent on posture. Additionally, vertebral bodies were more lordotically wedged in females than males. For sacral orientation, SS was greater in females than males and there were not sex differences in PI. In juveniles, while LL increased with age, PI did not change with age. In addition, the correlation between PI and LL was strongest in the oldest age category, meaning that PI may be predictive of adult LL. Relatively higher joint laxity in females may be the cause of higher standing LL in females than males while PI does not differ by sex.

Furthermore, I found that lumbar intervertebral motion in the sagittal plane differed by sex with males having a greater range of flexion and females having a greater range of extension, which may indirectly relate to sex differences in LL. In addition, an age-related decrease in lumbar intervertebral motion was greater in females than males and sex differences in intervertebral translation revealed spondylolisethsis at L4-L5 in females, but

not in males. Females are at a greater risk of developing degenerative spondylolisthesis (Jacobsen et al. 2007), which is linked to relatively higher LL (Schuller et al. 2011).

My work supports that there are sex differences in the lumbar spine with females having greater LL and a greater risk of related orthopaedic conditions. Whether functional purpose exists for greater LL in females remains unclear, but joint laxity appears to be a factor. Understanding the cause of sex differences in lumbar morphology and function may lead to more effective sex-specific treatments and prevention.

Future work

I plan to continue exploring sex differences in lumbar function and health. First, I will be investigating how pregnancy history impacts standing LL and how other spinopelvic measures differ between adult female twins. Second, I will be comparing intervertebral ROM between asymptomatic males and females with similar methods to those used in Chapter 5. I will interpret results with joint laxity in mind and hopefully advance the work to begin considering preventative measures and other treatments to increase lumbar stability in females.

References

Abitbol MM. 1987. Evolution of the lumbosacral angle. Am J Phys Anthropol 72:361-372.

Adams MA, Burton AK, Dolan P, and Bogduk N. 2013. The biomechanics of back pain, 3rd Edition. Oxford: Churchill Livingstone.

Adams MA, Hutton WC. 1985. The effect of posture on the lumbar spine. J Bone Joint Surg Br 67:625-629.

Amonoo-Kuofi HS. 1992. Changes in the lumbosacral angle, sacral inclination and the curvature of the lumbar spine during aging. Acta Anat 145:373-377.

Anderson R. 1999. Human evolution, low back pain, and dual-level control. In: Trevathan WR, Smith EO, McKenna JJ, editors. Evolutionary Medicine. Cary, US: Oxford University Press (US). p 333-349.

Andersson GBJ, Schultz A, Nathan A, Irstam L. 1981. Roentgenographic Measurement of Lumbar Intervertebral Disc Height. Spine 6:154-158.

Andersson GB. 1997. The epidemiology of spinal disorders. In: Frymoyer JW, editor. The Adult Spine: Principles and Practice, 2nd Edition. Philidelphia: Lippincott-Raven. p 93-141.

Bae JS, Jang JS, Lee SH, Kim JU. 2012. Radiological analysis of lumbar degenerative kyphosis in relation to pelvic incidence. Spine J 12:1045-1051.

Bagnall KM, Harris PF, Jones PR. 1977. A radiographic study of the human fetal spine. 1. The development of the secondary cervical curvature. J Anat 123:777-782.

Bailey JF, Fields AJ, Liebenberg E, Mattison JA, Lotz JC, Kramer PA. 2014. Comparison of vertebral and intervertebral disc lesions in aging humans and rhesus monkeys. Osteoarthr Cartil 22:980-985.

Bailey JF, Sparrey CJ, Been E, Kramer PA. 2016. Morphological and postural sexual dimorphism of the lumbar spine facilitates greater lordosis in females. J Anat [Epub ahead of print]

Bailey JF, Miller SL, Healey RM, Coughlin D, Hargens AR, Lotz JC. Long-duration spaceflight affects passive and active lumbar stabilization and health: an imaging study on NASA crew. Annual Meeting, Orthopaedic Research Society; Mar 5-8, 2016; Orlando, FL.

Barrey C, Jund J, Noseda O, Roussouly P. 2007. Sagittal balance of the pelvis-spine complex and lumbar degenerative diseases. A comparative study about 85 cases. Eur Spine J 16:1459-1467.

Battié MC, Videman T. 2006. Lumbar disc degeneration: epidemiology and genetics. J Bone Joint Surg Am 88:3-9.

Been E, Barash A, Marom A, Kramer PA. 2010a. Vertebral bodies or discs: which contributes more to human-like lumbar lordosis? Clin Orthop Relat Res 468:1822-1829.

Been E, Barash A, Pessah H, Peleg S. 2010b. A new look at the geometry of the lumbar spine. Spine 35:E1014-1017.

Been E, Gomez-Olivencia A, Kramer PA. 2012. Lumbar lordosis of extinct hominins. Am J Phys Anthropol 147:64-77.

Been E, Kalichman L. 2013. Lumbar lordosis. Spine J 14:87-97.

Been E, Li L, Hunter DJ, Kalichman L. 2011. Geometry of the vertebral bodies and the intervertebral discs in lumbar segments adjacent to spondylolysis and spondylolisthesis: pilot study. Eur Spine J 20:1159-1165.

Been E, Pessah H, Been L, Tawil A, Peleg S. 2007. New method for predicting the lumbar lordosis angle in skeletal material. Anat Rec (Hoboken) 290:1568-1573.

Berjano P, Langella F, Ismael M-F, Damilano M, Scopetta S, Lamartina C. 2014. Successful correction of sagittal imbalance can be calculated on the basis of pelvic incidence and age. Eur Spine J 23:587-596.
Bonmatí A, Gómez-Olivencia A, Arsuaga JL, Carretero JM, Gracia A, Martínez I, Lorenzo C, de Castro JMB, Carbonell E. 2010. Middle Pleistocene lower back and pelvis from an aged human individual from the Sima de los Huesos site, Spain. Proc Natl Acad Sci U S A 107:18386-18391.
Boulay C, Tardieu C, Hecquet J, Benaim C. 2006. Sagittal alignment of spine and pelvis regulated by pelvic incidence: standard values and prediction of lordosis. Eur Spine J 15:415-422.
Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. 2013. Placing the global burden of low back pain in context. Best Pract Res Clin Rheumatol 27:575-589.
Burton AK, Tillotson KM. 1988. Reference values for 'normal' regional lumbar sagittal mobility. Clin Biomechanics (Bristol, Avon) 3:106-113.
Calguneri M, Bird HA, Wright V. 1982. Changes in joint laxity occurring during pregnancy. Ann Rheum Dis 41:126-128.
Casagrande D, Gugala Z, Clark SM, Lindsey RW. 2015. Low Back Pain and Pelvic Girdle Pain in Pregnancy. J Am Acad Orthop Surg 23:539-549.
Castillo ER, Lieberman DE. 2015. Lower back pain. Evol Med Public Health 1:2-3.
Cauley JA, Chalhoub D, Kassem AM, Fuleihan GEH. 2014. Geographic and ethnic disparities in osteoporotic fractures. Nat Rev Endocrinol 10:338-351.
Charlton WPH, Coslett-Charlton LM, Ciccotti MG. 2001. Correlation of Estradiol in Pregnancy and Anterior Cruciate Ligament Laxity. Clin Orthop Relat Res 387:165-170.
Chen IR, Wei TS. 2009. Disc height and lumbar index as independent predictors of degenerative spondylolisthesis in middle-aged women with low back pain. Spine 34:1402-1409.
Cheng XG, Sun Y, Boonen S, Nicholson PH, Brys P, Dequeker J, Felsenberg D. 1998. Measurements of vertebral shape by radiographic morphometry: sex differences and relationships with vertebral level and lumbar lordosis. Skeletal radiol 27:380-384.
Choufani E, Jouve JL, Pomero V, Adalian P, Chaumoitre K, Panuel M. 2009. Lumbosacral lordosis in fetal spine: genetic or mechanic parameter. Eur Spine J 18:1342-1348.
Cil A, Yazici M, Uzumcugil A, Kandemir U, Alanay A, Alanay Y, Acaroglu RE, Surat A. 2005. The evolution of sagittal segmental alignment of the spine during childhood. Spine 30:93-100.
Conley S, Rosenberg A. 2007. The female knee: anatomic variations. J Am Acad Orthop Surg 15:S31-S36.
Crisco JJ, Panjabi MM. 1992. Euler stability of the human ligamentous lumbar spine. Part I: Theory. Clin Biomech (Bristol, Avon) 7:19-26.
Crisco JJ, Panjabi MM, Yamamoto I, Oxland TR. 1992. Euler stability of the human ligamentous lumbar spine. Part II: Experiment. Clin Biomech (Bristol, Avon) 7:27-32.
Damasceno LHF, Catarin SRG, Campos AD, Defino HLA. 2006. Lumbar lordosis: a study of angle values and of vertebral bodies and intervertebral discs role. Acta Ortop Bras 14:193-198.
Davis RJ, Lee DC, Wade C, Cheng B. 2015. Measurement Performance of a Computer Assisted Vertebral Motion Analysis System. Int J Spine Surg 9:36.
Dawson J, Trinkaus E. 1997. Vertebral Osteoarthritis of the La Chapelle-aux-Saints 1 Neanderthal. J Archaeol Sci 24:1015-1021.

De Carvalho DE, Soave D, Ross K, Callaghan JP. 2010. Lumbar spine and pelvic posture between standing and sitting: a radiologic investigation including reliability and repeatability of the lumbar lordosis measure. J Manipulative Physiol Ther 33:48-55.
Descamps H, Commare-Nordmann MC, Marty C. 1999. Modification of pelvic angle during the human growth. Biom Hum Anthropol 17:59-63.
Dietz AK, Breen AC, Mellor FE, Teyhen DS, Wong KWN, Panjabi MM. 2011. Kinematics of the aging spine: a review of past knowledge and survey of recent developments, with a focus on patient-management implications for the clinical practitioner. In The Comprehensive Treatment of the Aging Spine: Minimally Invasive and Advanced Techniques. Edited by Yue G, Johnson JP, Khoo LT, Hochschuler SH. Philadelphia: Saunders. p51–62.
Dimeglio A. 2001. Growth in pediatric orthopaedics. J Pediatr Orthop 21:549-555.
Dimeglio A, Bonnel F. 1990. Le rachis en croissance. France: Springer-Verlag.
Dreischarf M, Albiol L, Rohlmann A, Pries E, Bashkuev M, Zander T, Duda G, Druschel C, Strube P, Putzier M, Schmidt H. 2014. Age-related loss of lumbar spinal lordosis and mobility - a study of 323 asymptomatic volunteers. PLoS ONE 9:e116186.
Dumas GA, Reid JG, Wolfe LA, Griffin MP, McGrath MJ. 1995. Exercise, posture, and back pain during pregnancy. Clin Biomech (Bristol, Avon) 10:98-103.
Dvorák J, Panjabi MM, Chang DG, Theiler R, Grob D. 1991. Functional radiographic diagnosis of the lumbar spine. Flexion-extension and lateral bending. Spine 16:562-571.
Dvorák J, Vajda EG, Grob D, Panjabi MM. 1995. Normal motion of the lumbar spine as related to age and gender. Eur Spine J 4:18-23.
Endo K, Suzuki H, Nishimura H, Tanaka H, Shishido T, Yamamoto K. 2012. Sagittal lumbar and pelvic alignment in the standing and sitting positions. J Orthop Sci 17:682-686.
Ergun, T, Lakahamyali, H, Sahin MS. 2010. The relation between sagittal morphology of the lumbosacral spine and the degree of lumbar intervertberal disc degeneration. Acta Orthop Traumatol Turc 44:293-9.
Fahrni WH, Trueman GE. 1965. Comparative radiological study of the spines of a primitive population with north americans and northern europeans. J Bone Joint Surg Bri. 47:552-555.
Fernand R, Fox DE. 1985. Evaluation of lumbar lordosis. A prospective and retrospective study. Spine 10:799-803.
Fitzgerald JA, Newman PH. 1976. Degenerative spondylolisthesis. J Bone Joint Surg Br. 58:184-192.
Franklin ME, Conner-Kerr T. 1998. An analysis of posture and back pain in the first and third trimesters of pregnancy. J Orthop Sports Phys Ther 28:133-138.
Frymoyer JW. 1994. Degenerative spondylolisthesis: diagnosis and treatment. J Am Acad Orthop Surg 2:9-15.
Fujiwara A, Lim TH, An HS, Tanaka N, Jeon CH, Andersson GB, Haughton VM. 2000. The effect of disc degeneration and facet joint osteoarthritis on the segmental flexibility of the lumbar spine. Spine 25:3036-3044.
Gal J. 2002. Mammalian spinal biomechanics: postural support in seated macaques. J Exp Biol 205:1703-1707.
Gelb DE, Lenke LG, Bridwell KH, Blanke K, McEnery KW. 1995. An analysis of sagittal spinal alignment in 100 asymptomatic middle and older aged volunteers. Spine 20:1351-1358.
Goode AP, Carey TS, Jordan JM. 2013. Low back pain and lumbar spine osteoarthritis: how are they related? Curr Rheumatol Rep 15:305.

Gould SJ, Lewontin RC. 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. Proc R Soc Lond B Biol Sci 205:581-598.
Gracovetsky SA, Iacono S. 1987. Energy transfers in the spinal engine. J Biomed Eng 9:99-114.
Haeusler M, Schiess R, Boeni T. 2013. Evidence for juvenile disc herniation in a homo erectus boy skeleton. Spine 38:E123-128.
Harada M, Abumi K, Ito M, Kaneda K. 2000. Cineradiographic motion analysis of normal lumbar spine during forward and backward flexion. Spine 25:1932-1937.
Hay O, Dar G, Abbas J, Stein D, May H, Masharawi Y, Peled N, Hershkovitz I. 2015. The Lumbar Lordosis in Males and Females, Revisited. PLoS ONE 10:e0133685.
Hayes MA, Howard TC, Gruel CR, Kopta JA. 1989. Roentgenographic evaluation of lumbar spine flexion-extension in asymptomatic individuals. Spine 14:327-331.
Hegazy AA, Hegazy RA. 2014. Midsagittal Anatomy of Lumbar Lordosis in Adult Egyptians: MRI Study. Anat Res Int 2014:370852.
Hettrich CM, Hammoud S, LaMont LE, Arendt EA, Hannafin JA. 2015. Sex-specific Analysis of Data in High-impact Orthopaedic Journals: How Are We Doing? Clin Orthop Relat Res 473:3700-3704.
Intolo P, Milosavljevic S, Baxter DG, Carman AB, Pal P, Munn J. 2009. The effect of age on lumbar range of motion: A systematic review. Man Ther 14:596-604.
Jackson RP, Hales C. 2000. Congruent spinopelvic alignment on standing lateral radiographs of adult volunteers. Spine 25:2808-2815.
Jackson RP, McManus AC. 1994. Radiographic analysis of sagittal plane alignment and balance in standing volunteers and patients with low back pain matched for age, sex, and size. A prospective controlled clinical study. Spine 19:1611-1618.
Jackson RP, Peterson MD, McManus AC, Hales C. 1998. Compensatory spinopelvic balance over the hip axis and better reliability in measuring lordosis to the pelvic radius on standing lateral radiographs of adult volunteers and patients. Spine 23:1750-1767.
Jacobsen S, Sonne-Holm S, Rovsing H, Monrad H, Gebuhr P. 2007. Degenerative lumbar spondylolisthesis: an epidemiological perspective: the Copenhagen Osteoarthritis Study. Spine 32:120-125.
Janssen MMA, Drevelle X, Humbert L, Skalli W, Castelein RM. 2009. Differences in Male and Female Spino-Pelvic Alignment in Asymptomatic Young Adults: A Three-Dimensional Analysis Using Upright Low-Dose Digital Biplanar X-rays. Spine 34:E826-E832.
Kalichman L, Li L, Hunter DJ, Been E. 2011. Association between computed tomography-evaluated lumbar lordosis and features of spinal degeneration, evaluated in supine position. Spine J 11:308-315.
Katzman W, Cawthon P, Hicks GE, Vittinghoff E, Shepherd J, Cauley JA, Harris T, Simonsick EM, Strotmeyer E, Womack C, Kado DM. 2012. Association of spinal muscle composition and prevalence of hyperkyphosis in healthy community-dwelling older men and women. J Gerontol A Biol Sci Med Sci 67:191-195.
Kienbacher T, Fehrmann E, Habenicht R, Koller D, Oeffel C, Kollmitzer J, Mair P, Ebenbichler G. 2016. Age and gender related neuromuscular pattern during trunk flexion-extension in chronic low back pain patients. J Neuroeng Rehabil 13:16.
Kilfoyle RM, Foley JJ, Norton PL. 1965. Spine and pelvic deformity in childhood and adolescent paralegia: a study of 104 cases. J Bone Joint Surg Am 47:659-682.

Kim TH, Lee HM, Moon SH, Kwak DK, Oh JK, Kim YC, Park MS, Alday FBI, Kim SW. 2013. Joint Laxity Negatively Correlates With Lumbar Disc Degeneration in Young Adults. Spine 38:E1541-E1547.
Korovessis P, Stamatakis M, Baikousis A. 1999. Segmental roentgenographic analysis of vertebral inclination on sagittal plane in asymptomatic versus chronic low back pain patients. J Spinal Disord 12:131-137.
Korovessis PG, Stamatakis MV, Baikousis AG. 1998. Reciprocal angulation of vertebral bodies in the sagittal plane in an asymptomatic Greek population. Spine 23:700-705.
Krogman WM. 1951. The scars of human evolution. Sci Am 185:54-57.
LaBella CR, Hennrikus W, Hewett TE. 2014. Anterior Cruciate Ligament Injuries: Diagnosis, Treatment, and Prevention. Pediatrics 133:e1437-e1450.
Le Huec JC, Aunoble S, Philippe L, Nicolas P. 2011. Pelvic parameters: origin and significance. Eur Spine J 20:564-571.
Lee CS, Chung SS, Kang KC, Park SJ, Shin SK. 2011. Normal patterns of sagittal alignment of the spine in young adults radiological analysis in a Korean population. Spine 36:E1648-1654.
Lee CS, Noh H, Lee DH, Hwang CJ, Kim H, Cho SK. 2012. Analysis of sagittal spinal alignment in 181 asymptomatic children. J Spinal Disord Tech 25:E259-263.
Lee JH, Na KH, Kim JH, Jeong HY, Chang DG. 2015. Is pelvic incidence a constant, as everyone knows? Changes of pelvic incidence in surgically corrected adult sagittal deformity. Eur Spine J [Epub ahead of print].
Legaye J. 2014. Influence of age and sagittal balance of the spine on the value of the pelvic incidence. Eur Spine J 23:1394-1399.
Legaye J, Duval-Beaup re G, Marty C, Hecquet J. 1998. Pelvic incidence: a fundamental pelvic parameter for three-dimensional regulation of spinal sagittal curves. Eur Spine J 7:99-103.
Leopold SS, Beadling L, Dobbs MB, Gebhardt MC, Lotke PA, Manner PA, Rimnac CM, Wongworawat MD. 2014. Fairness to all: gender and sex in scientific reporting. Clin Orthop Relat Res 472:391-392.
Lin RM, Jou IM, Yu CY. 1992. Lumbar lordosis: normal adults. J Formos Med Assoc 91:329-333.
Liu N, Wood KB, Schwab JH, Cha TD, Pedlow Jr FX. 2015. Utility of flexion-extension radiographs in lumbar spondylolisthesis: a prospective study. Spine 40:E929-935.
Lord MJ, Small JM, Dinsay JM, Watkins RG. 1997. Lumbar lordosis. Effects of sitting and standing. Spine 22:2571-2574.
Lovejoy CO. 2005. The natural history of human gait and posture: Part 1. Spine and Pelvis. Gait Posture 21:95-112.
Lovejoy CO, McCollum MA. 2010. Spinopelvic pathways to bipedality: why no hominids ever relied on a bent-hip-bent-knee gait. Philos Trans R Soc Lond B Biol Sci 365:3289-3299.
Mac-Thiong JM, Labelle H, Berthonnaud E, Betz RR, Roussouly P. 2007. Sagittal spinopelvic balance in normal children and adolescents. Eur Spine J 16:227-234.
MacNab I. 1950. Spondylolisthesis with an intact neural arch; the so-called pseudo-spondylolisthesis. J Bone Joint Surg Br 32:325-333.
Mandal AC. 1981. The seated man (Homo Sedens) the seated work position. Theory and practice. Appl Ergon 12:19-26.
Mangione P, Gomez D, Senegas J. 1997. Study of the course of the incidence angle during growth. Eur Spine J 6:163-167.

Manson NA, Goldberg EJ, Andersson GBJ. 2006. Sexual dimorphism in degenerative disorders of the spine: Orthop Clin North Am 37:549-553.
Marty C, Boisaubert B, Descamps H, Montigny J, Hecquet J, Legaye J, Duval-Beaupere G. 2002. The sagittal anatomy of the sacrum among young adults, infants, and spondylolisthesis patients. Eur Spine J 11:119-125.
Masharawi Y, Dar G, Peleg S, Steinberg N, Medlej B, May H, Abbas J, Hershkovitz I. 2010. A morphological adaptation of the thoracic and lumbar vertebrae to lumbar hyperlordosis in young and adult females. Eur Spine J 19:768-773.
Masharawi Y, Kjaer P, Manniche C, Bendix T. 2012. Lumbar sagittal shape variation vis-à-vis sex during growth: a 3-year follow-up magnetic resonance imaging study in children from the general population. Spine 37:501-507.
McBroom RJ, Hayes WC, Edwards WT, Goldberg RP, White AA. 1985. Prediction of vertebral body compressive fracture using quantitative computed tomography. J Bone Joint Surg Am 67:1206-1214.
McGregor AH, McCarthy ID, Hughes SP. 1995. Motion Characteristics of the Lumbar Spine in the Normal Population. Spine 20:2421.
McMillan DW, Garbutt G, Adams MA. 1996. Effect of sustained loading on the water content of intervertebral discs: implications for disc metabolism. Ann Rheum Dis 55:880-887.
Meakin JR, Gregory JS, Aspden RM, Smith FW, Gilbert FJ. 2009. The intrinsic shape of the human lumbar spine in the supine, standing and sitting postures: characterization using an active shape model. J Anat 215:206-211.
Meakin JR, Hukins DWL, Aspden RM. 1996. Euler Buckling as a Model for the Curvature and Flexion of the Human Lumbar Spine. Proc Biol Sci 263:1383-1387.
Murrie VL, Dixon AK, Hollingworth W, Wilson H, Doyle TAC. 2003. Lumbar lordosis: study of patients with and without low back pain. Clin Anat 16:144-147.
Nachemson AL. 1981. Disc Pressure Measurements. Spine 6:93-97.
Ng JKF, Kippers V, Richardson CA, Parnianpour M. 2001. Range of Motion and Lordosis of the Lumbar Spine: Reliability of Measurement and Normative Values. Spine 26:53-60.
O'Brien M, Blanke K, Lenke LG, Kuklo TR. 2004. Spinal Deformity Study Group Radiographic Measurement Manual. Memphis, TN: Medtronic Sofamor Danek. p 110.
O'Rahilly R, Muller F, and Meyer DB. 1980. The human vertebral column at the end of the embryonic period proper. 1. The column as a whole. J Anat 131:565-575.
Oyakhire MO. 2013. Radiographic evaluation of lumbar lordotic angle of the spine in a population of Nigerians. Asian J Med Sci 4:69-75.
Patwardhan AG, Havey RM, Meade KP, Lee B. 1999. A Follower Load Increases the Load-Carrying Capacity of the Lumbar Spine in Compression. Spine 24:1003-1009.
Pearcy M, Portek I, Shepherd J. 1984. Three-dimensional x-ray analysis of normal movement in the lumbar spine. Spine 9:294-297.
Pearcy MJ. 1985. Stereo radiography of lumbar spine motion. Acta Orthop Scand Suppl 212:1-45.
Pearcy MJ, Tibrewal SB. 1984. Axial rotation and lateral bending in the normal lumbar spine measured by three-dimensional radiography. Spine 9:582-587.
Peleg S, Dar G, Medlej B, Steinberg N, Masharawi Y, Latimer B, Jellema L, Peled N, Arensburg B, Hershkovitz I. 2007. Orientation of the human sacrum: anthropological perspectives and methodological approaches. Am J Phys Anthropol 133:967-977.

Pitkänen MT, Manninen HI, Lindgren KAJ, Sihvonen TA, Airaksinen O, Soimakallio S. 2002. Segmental Lumbar Spine Instability at Flexion–Extension Radiography can be Predicted by Conventional Radiography. Clin Radiol 57:632-639.
Preuschoft H, Hayama S, Gunther MM. 1988. Curvature of the Lumbar Spine as a Consequence of Mechanical Necessities in Japanese Macaques Trained for Bipedalism. Folia Primatol (Basel) 50:42-58.
Quatman CE, Ford KR, Myer GD, Paterno MV, Hewett TE. 2008. The effects of gender and pubertal status on generalized joint laxity in young athletes. J Sci Med Sport 11:257-263.
Rodriguez-Soto AE, Jaworski R, Jensen A, Niederberger B, Hargens AR, Frank LR, Kelly KR, Ward SR. 2013. Effect of Load Carriage on Lumbar Spine Kinematics. Spine 38:E783-E791.
Rosenberg K, Trevathan W. 2002. Birth, obstetrics and human evolution. BJOG 109:1199-1206.
Roussouly P, Nnadi C. 2010. Sagittal plane deformity: an overview of interpretation and management. Eur Spine J 19:1824-1836.
Roussouly P, Pinheiro-Franco JL. 2011. Biomechanical analysis of the spino-pelvic organization and adaptation in pathology. Eur Spine J 20:609-618.
Ryan J, Magnussen RA, Cox CL, Hurbanek JG. 2014. ACL Reconstruction: Do Outcomes Differ by Sex? J Bone Joint Surg Am 96:507-512.
Sanderson PL, Fraser RD. 1996. The influence of pregnancy on the development of degenerative spondylolisthesis. J Bone Joint Surg Br 78:951-954.
Saraste H, BrostrÖM, Aparisi T, Axdorph G. 1985. Radiographic Measurement of the Lumbar Spine: A Clinical and Experimental Study in Man. Spine 10:236.
Sarwahi V, Boachie-Adjei O, Backus SI, Taira G. 2002. Characterization of gait function in patients with postsurgical sagittal (flatback) deformity: a prospective study of 21 patients. Spine 27:2328-2337.
Schlosser TPC, Vincken KL, Rogers K, Castelein RM, Shah SA. 2015. Natural sagittal spino-pelvic alignment in boys and girls before, at and after the adolescent growth spurt. Eur Spine J 24:1158-1167.
Schuller S, Charles YP, Steib J-P. 2011. Sagittal spinopelvic alignment and body mass index in patients with degenerative spondylolisthesis. Eur Spine J 20:713-719.
Schwab F, Lafage V, Patel A, Farcy JP. 2009. Sagittal plane considerations and the pelvis in the adult patient. Spine 34:1828-1833.
Schwab F, Ungar B, Blondel B, Buchowski J, Coe J, Deinlein D, DeWald C, Mehdian H, Shaffrey C, Tribus C, Lafage V. 2012. Scoliosis Research Society-Schwab Adult Spinal Deformity Classification A Validation Study. Spine 37:1077-1082.
Shefi S, Soudack M, Konen E, Been E. 2013. Development of the lumbar lordotic curvature in children from age 2 to 20 years. Spine 38:E602-608.
Shymon S, Hargens AR, Minkoff LA, and Chang DG. 2014. Body posture and backpack loading: an upright magnetic resonance imaging study of the adult lumbar spine. Eur Spine J 23:1407-1413.
Soini J, Antti-Poika I, Tallroth K, Konttinen YT, Honkanen V, Santavirta S. 1991. Disc Degeneration and Angular Movement of the Lumbar Spine: Comparative Study Using Plain and Flexion-Extension Radiography and Discography. J Spinal Disord 4:183-187.
Sparrey CJ, Bailey JF, Safaee M, Clark AJ, Lafage V, Schwab F, Smith JS, Ames CP. 2014. Etiology of lumbar lordosis and its pathophysiology: a review of the evolution

of lumbar lordosis, and the mechanics and biology of lumbar degeneration. Neurosurg Focus 36(5):E1.
Stagnara P, De Mauroy JC, Dran G, Gonon GP, Costanzo G, Dimnet J, Pasquet A. 1982. Reciprocal angulation of vertebral bodies in a sagittal plane: approach to references for the evaluation of kyphosis and lordosis. Spine 7:335-342.
Stearns SC. 1989. Trade-offs in life-history evolution. Funct Ecol 3:259-268.
Stokes IAF, Frymoyer JW. 1987. Segmental Motion and Instability. Spine 12:688-691.
Stone PK. 2016. Biocultural perspectives on maternal mortality and obstetrical death from the past to the present. Am J Phys Anthropol 159:S150-171.
Sullivan MS, Dickinson CE, Troup JD. 1994. The influence of age and gender on lumbar spine sagittal plane range of motion. A study of 1126 healthy subjects. Spine 19:682-686.
Sutton KM, Bullock JM. 2013. Anterior cruciate ligament rupture: differences between males and females. J Am Acad Orthop Surg 21:41-50.
Syczewska M, Oberg T, Karlsson D. 1999. Segmental movements of the spine during treadmill walking with normal speed. Clin Biomech (Bristol, Avon) 14:384-388.
Tague RG. 1992. Sexual dimorphism in the human bony pelvis, with a consideration of the Neandertal pelvis from Kebara Cave, Israel. Am J Phys Anthropol 88:1-21.
Tardieu C, Bonneau N, Hecquet J, Boulay C, Marty C, Legaye J, Duval-Beaupère G. 2013. How is sagittal balance acquired during bipedal gait acquisition? Comparison of neonatal and adult pelves in three dimensions. Evolutionary implications. J Hum Evol 65:209-222.
Trevathan WR, Smith EO, McKenna JJ. 1999. Evolutionary Medicine. Cary, US: Oxford University Press (US).
Ueno M, Takaso M, Nakazawa T, Imura T, Saito W, Shintani R, Uchida K, Fukuda M, Takahashi K, Ohtori S et al. 2011. A 5-year epidemiological study on the prevalence rate of idiopathic scoliosis in Tokyo: school screening of more than 250,000 children. J Orthop Sci 16:1-6.
Vialle R, Levassor N, Rillardon L, Templier A, Skalli W, Guigui P. 2005. Radiographic analysis of the sagittal alignment and balance of the spine in asymptomatic subjects. J Bone Joint Surg Am 87:260-267.
Videman T, Sarna S, Battié MC, Koskinen S, Gill K, Paananen H, Gibbons L. 1995. The Long-Term Effects of Physical Loading and Exercise Lifestyles on Back-Related Symptoms, Disability, and Spinal Pathology Among Men. Spine 20:699-709.
Voutsinas SA, MacEwen GD. 1986. Sagittal profiles of the spine. Clin Orthop Relat Res 210:235-242.
Wahl CJ, Westermann RW, Blaisdell GY, Cizik AM. 2012. An Association of Lateral Knee Sagittal Anatomic Factors with Non-Contact ACL Injury: Sex or Geometry? J Bone Joint Surg Am 94:217-226.
Wei T, Yanwei L, Yajun L, Bin X, Xiao H. 2014. The High Prevalence of Symptomatic Degenerative Lumbar Osteoarthritis in Chinese Adults: A Population-Based Study. Spine 39:1301-1310.
Whitcome KK, Shapiro LJ, Lieberman DE. 2007. Fetal load and the evolution of lumbar lordosis in bipedal hominins. Nature 450:1075-1078.
White AA, Panjabi MM. 1978. Clinical biomechanics of the spine. Philadelphia: Lippincott.
Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE. 1999. New in vivo measurements of pressures in the intervertebral disc in daily life. Spine 24:755-762.

Wittman AB, Wall LL. 2007. The evolutionary origins of obstructed labor: Bipedalism, encephalization, and the human obstetric dilemma. Obstet Gynecol Surv 62:739-748.
Wong KWN, Leong JCY, Chan MK, Luk KDK, Lu WW. 2004. The flexion-extension profile of lumbar spine in 100 healthy volunteers. Spine 29:1636-1641.
Yeager MS, Cook DJ, Cheng BC. 2014. Reliability of computer-assisted lumbar intervertebral measurements using a novel vertebral motion analysis system. Spine J 14:274-281.
Zhu Z, Xu L, Zhu F, Jiang L, Wang Z, Liu Z, Qian B. 2014. Sagittal alignment of spine and pelvis in asymptomatic adults: norms in Chinese populations. Spine 39:E1-6.

A1: Excess figures and tables from Chapter 3

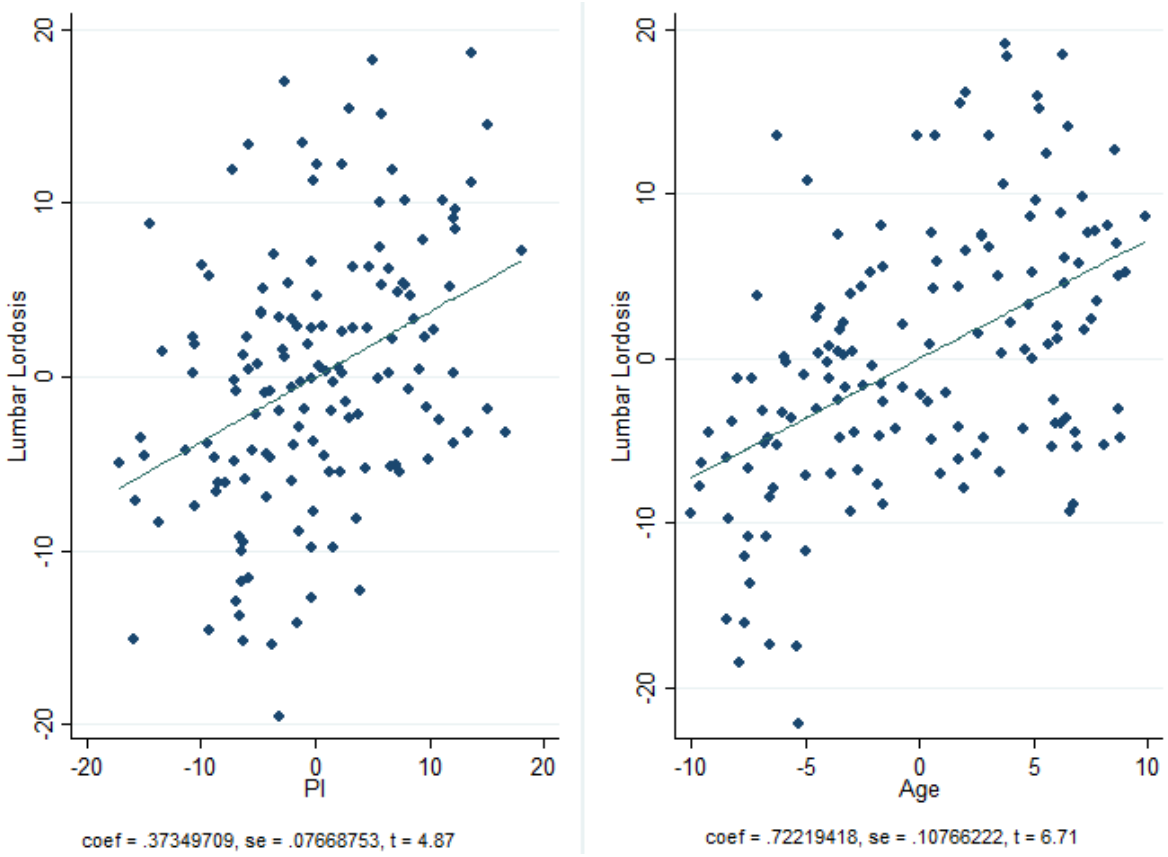
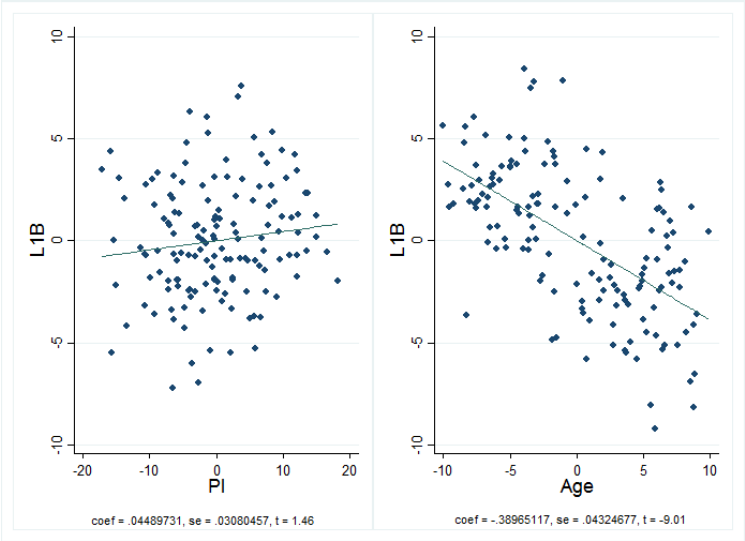
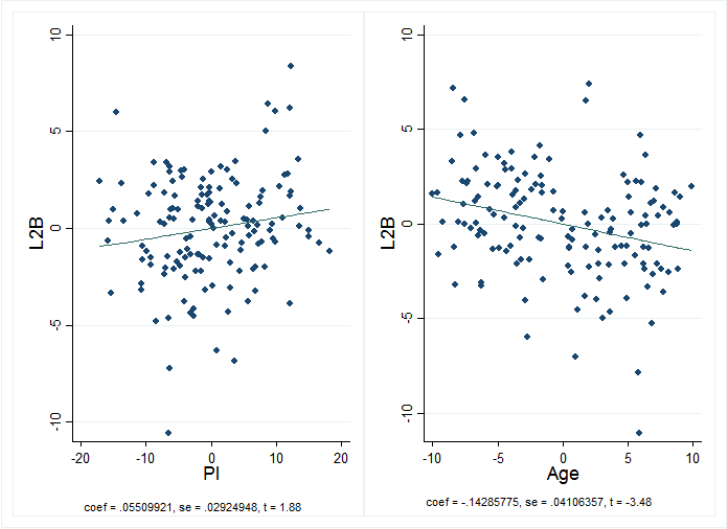
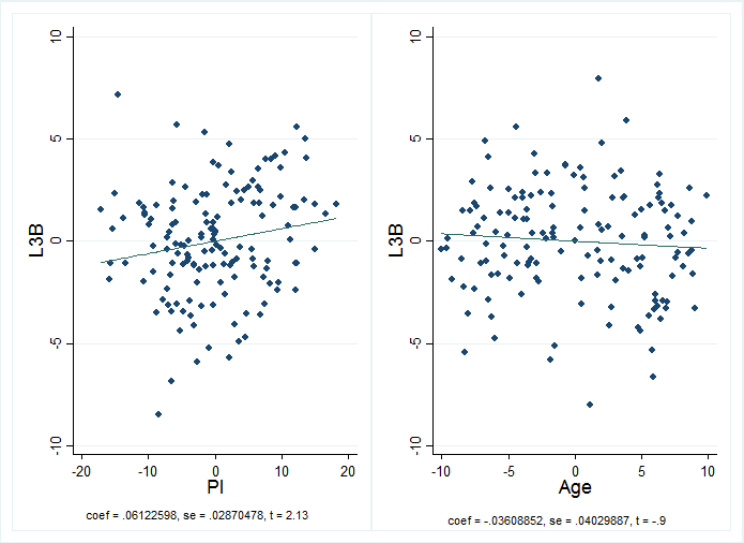
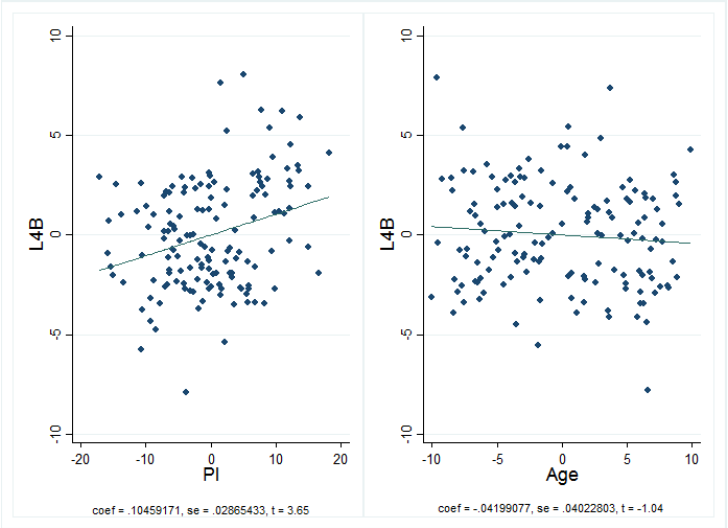


Figure A1-1. Added value plots showing the relationship for LL with PI and Age, separately.









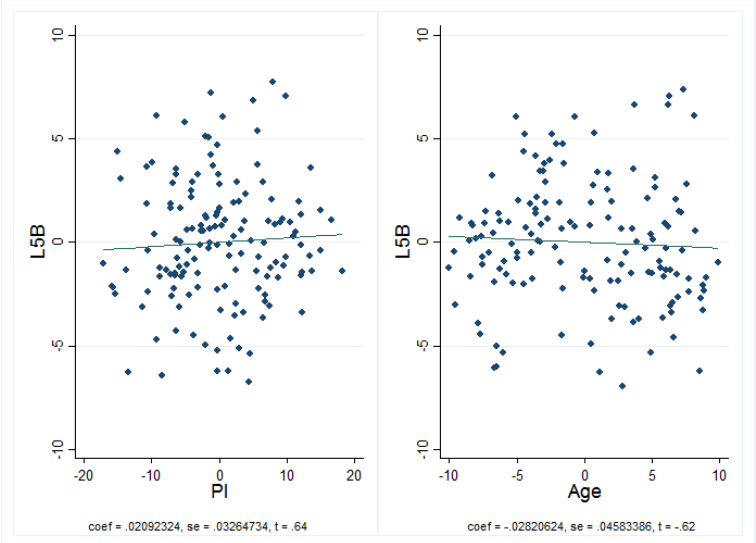


Figure A1-2. Added value plots showing the relationship for each lumbar vertebral body with PI and age, separately.

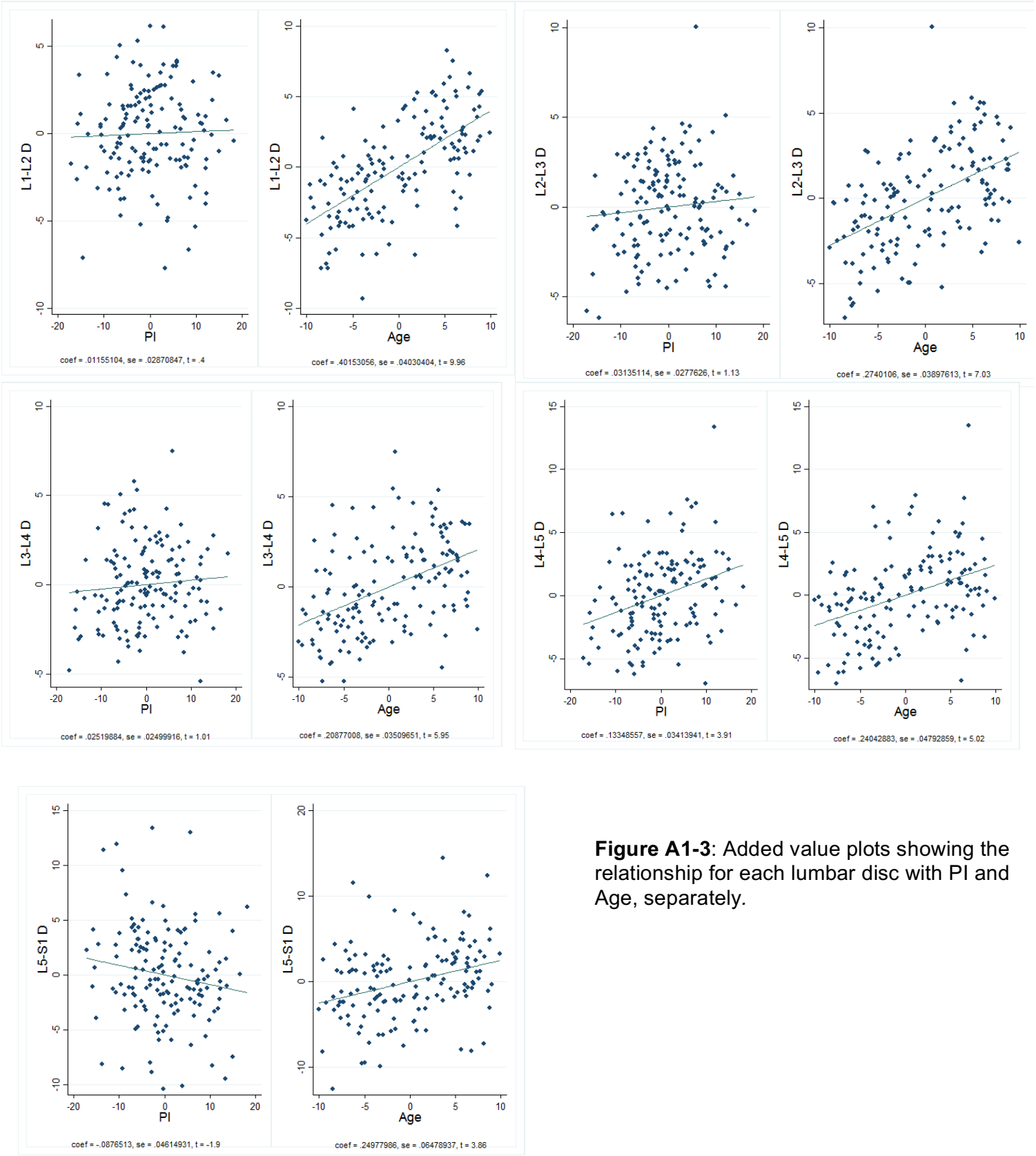


Figure A1-3: Added value plots showing the relationship for each lumbar disc with PI and Age, separately.

A2: Excess figures and tables from Chapter 4

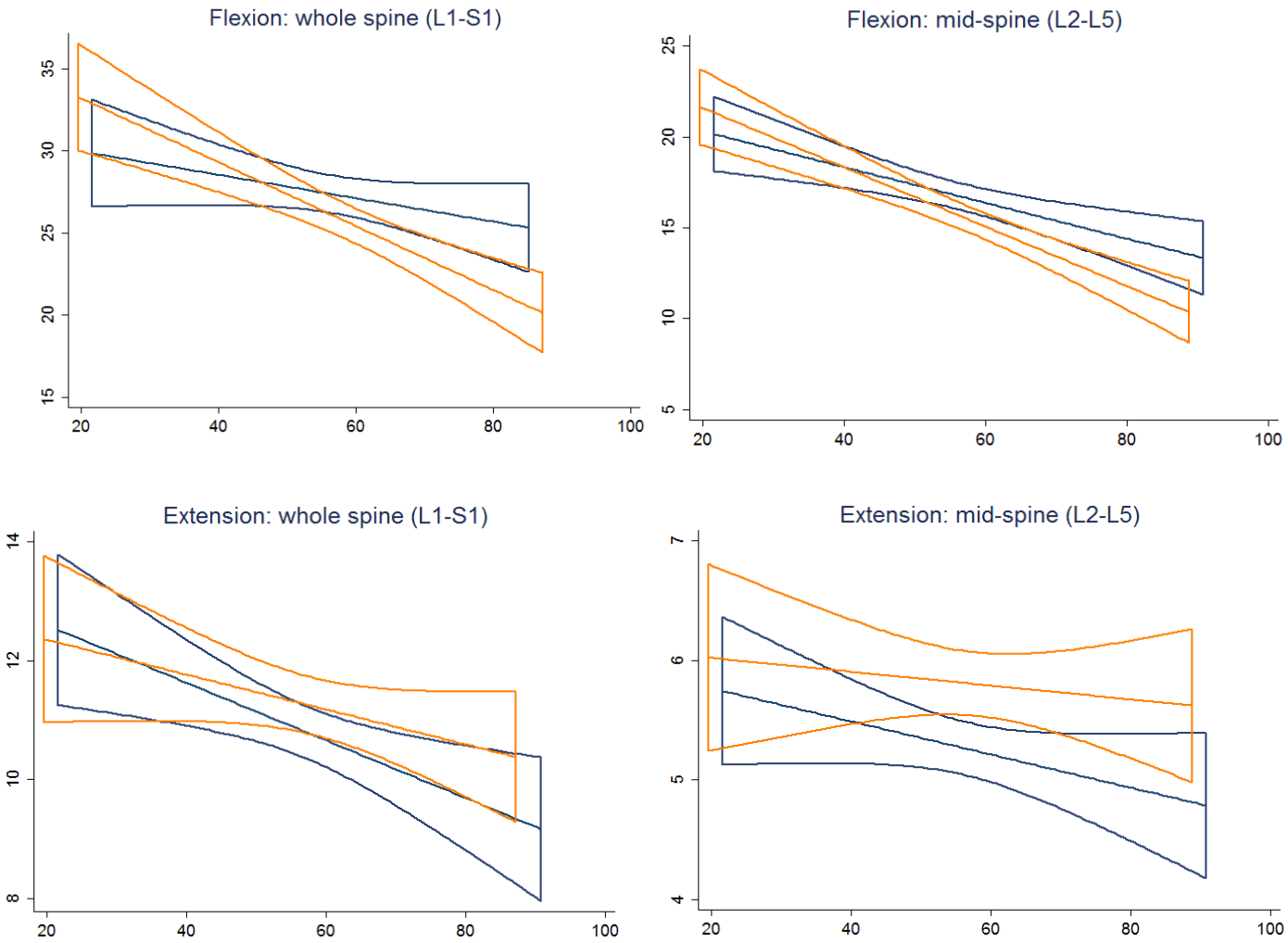


Figure A2-1: IVR in whole lumbar (L1-S1) and mid-lumbar (L2-L5) flexion and extension with age for separate sexes (males and females).

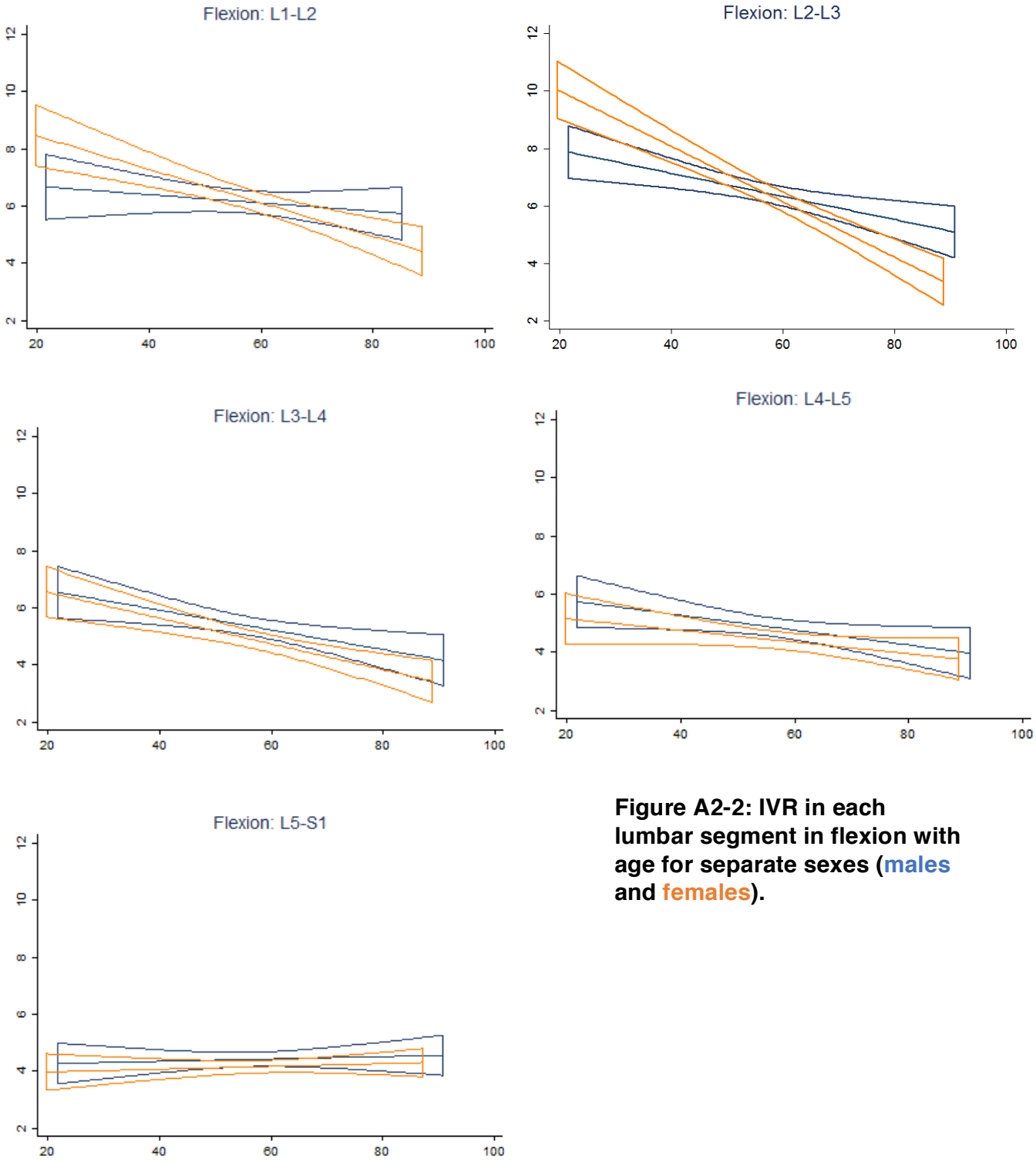


Figure A2-2: IVR in each lumbar segment in flexion with age for separate sexes (males and females).

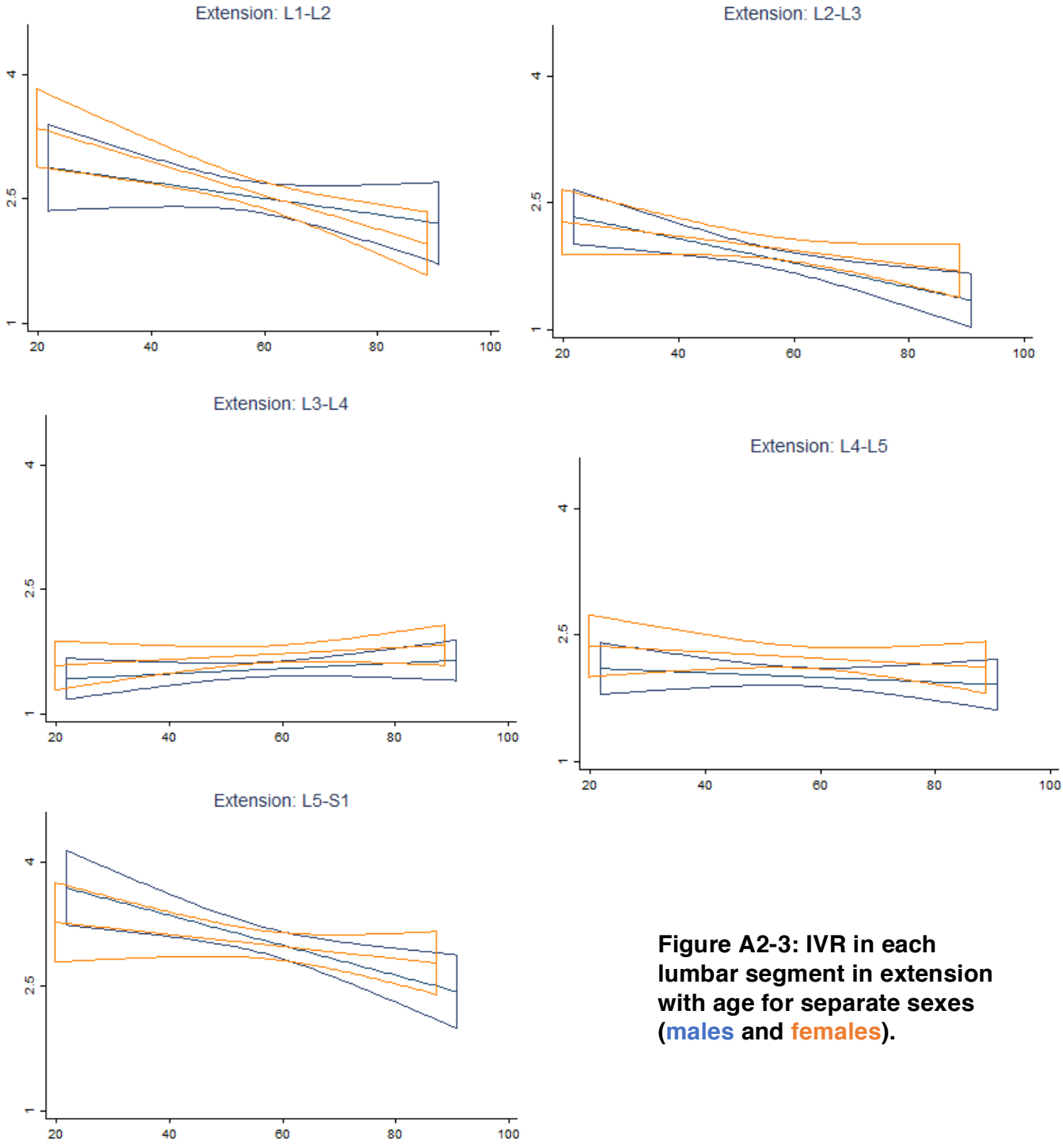


Figure A2-3: IVR in each lumbar segment in extension with age for separate sexes (males and females).

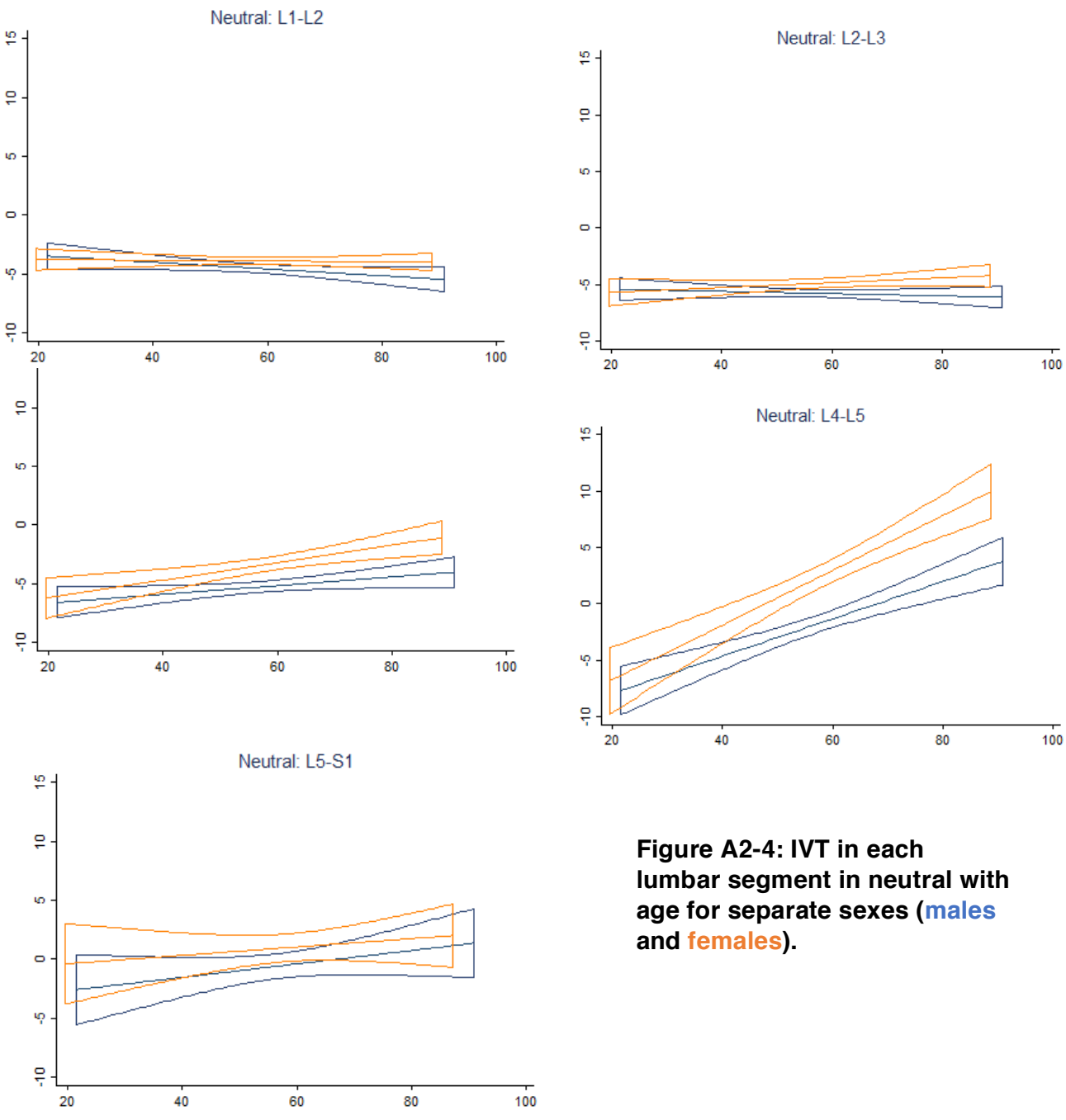


Figure A2-4: IVT in each lumbar segment in neutral with age for separate sexes (males and females).

		Whole sample				Younger half of sample				Older half of sample			
		Females		**Males**		**Females**		**Males**		**Females**		**Males**	
		Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Neutal	L1-L2	-3.90	*2.65*	-4.52	*3.16*	-3.90	*2.39*	-4.18	*2.37*	-3.90	*2.83*	-4.76	*3.61*
	L2-L3	-4.87	*3.74*	-5.78	*3.15*	-5.09	*2.52*	-5.67	*2.70*	-4.72	*4.41*	-5.86	*3.47*
	L3-L4	-3.35	*5.48*	-5.30	*4.30*	-4.24	*4.07*	-5.97	*3.52*	-2.72	*6.23*	-4.77	*4.77*
	L4-L5	2.52	*9.80*	-1.89	*7.39*	-0.54	*7.82*	-3.68	*6.40*	4.72	*10.48*	-0.47	*7.81*
	L5-S1	0.98	*10.36*	-0.59	*9.58*	0.50	*11.09*	-1.43	*9.17*	1.31	*9.82*	0.08	*9.86*
Flexion	L1-L2	-0.48	*2.45*	-0.83	*3.06*	-0.56	*2.46*	-0.58	*2.76*	-0.43	*2.46*	-1.03	*3.27*
	L2-L3	-0.93	*3.86*	-1.37	*3.21*	-0.92	*2.95*	-1.18	*2.85*	-0.93	*4.41*	-1.52	*3.47*
	L3-L4	-0.80	*5.19*	-2.13	*4.28*	-1.36	*4.16*	-2.78	*3.68*	-0.40	*5.81*	-1.61	*4.65*
	L4-L5	3.58	*9.27*	-0.09	*7.01*	0.58	*7.27*	-1.58	*6.63*	5.70	*9.95*	1.11	*7.09*
	L5-S1	1.41	*9.48*	0.07	*9.09*	0.80	*10.27*	-0.87	*8.47*	1.84	*8.90*	0.81	*9.50*
Extension	L1-L2	-4.01	*2.64*	-4.90	*3.22*	-4.04	*2.61*	-4.56	*2.73*	-3.99	*2.67*	-5.17	*3.54*
	L2-L3	-4.63	*3.76*	-5.63	*3.17*	-4.87	*2.64*	-5.73	*2.69*	-4.46	*4.40*	-5.56	*3.51*
	L3-L4	-3.35	*5.18*	-5.21	*3.94*	-4.28	*3.99*	-5.79	*3.32*	-2.68	*5.82*	-4.75	*4.32*
	L4-L5	1.94	*8.61*	-2.25	*6.49*	-0.79	*6.62*	-3.88	*5.49*	3.92	*9.33*	-0.94	*6.96*
	L5-S1	0.49	*9.52*	-1.13	*9.06*	0.21	*10.38*	-2.09	*8.52*	0.69	*8.89*	-0.35	*9.45*

Table A2-1. Mean and standard deviation for intervertebral translation. Data is presented for males and females from the whole sample, the younger half of the sample, and the older half of the sample. Postive values are % spondylolisthesis/anterolisthesis and negative values are % retrolisthesis.

		Whole sample				Younger half of sample				Older half of sample			
		Females		**Males**		**Females**		**Males**		**Females**		**Males**	
		Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Flexion	L1-L2	6.16	*2.71*	6.15	*2.71*	7.04	*2.67*	6.34	*2.48*	5.59	*2.58*	5.99	*2.89*
	L2-L3	6.32	*3.30*	6.46	*2.98*	7.84	*3.20*	7.10	*2.94*	5.21	*2.91*	5.98	*2.92*
	L3-L4	4.18	*2.80*	5.34	*2.96*	5.48	*2.96*	5.79	*3.24*	4.33	*2.57*	4.97	*2.67*
	L4-L5	4.38	*2.66*	4.85	*2.87*	4.63	*2.87*	5.23	*3.13*	4.21	*2.49*	4.53	*2.61*
	L5-S1	4.16	*1.85*	4.41	*2.15*	4.08	*1.72*	4.52	*2.04*	4.21	*1.93*	4.33	*2.23*
Extension	L1-L2	2.58	*1.37*	2.53	*1.47*	2.81	*1.63*	2.63	*1.57*	2.41	*1.13*	2.46	*1.39*
	L2-L3	1.95	*1.18*	1.84	*1.07*	2.06	*1.25*	1.98	*1.24*	1.87	*1.13*	1.72	*0.91*
	L3-L4	1.72	*0.92*	1.53	*0.81*	1.61	*0.83*	1.47	*0.73*	1.80	*0.98*	1.58	*0.87*
	L4-L5	2.23	*1.15*	2.01	*0.99*	2.22	*1.17*	1.99	*0.99*	2.24	*1.14*	2.02	*1.00*
	L5-S1	3.00	*1.13*	3.06	*1.42*	2.98	*1.44*	3.29	*1.46*	3.01	*1.43*	2.87	*1.37*

Table A2-2. Mean and standard deviation for intervertebral rotation. Data is presented for males and females from the whole sample, the younger half of the sample, and the older half of the sample.