I NETWORK NELLA RICERCA IN MEDICINA DEL LAVORO: UNA PRATICA OBBLIGATA PER LA CRESCITA COMPLESSIVA DELLA NOSTRA DISCIPLINA

Venerdì 1 dicembre 2023

Un Network per studio del rischio muscoloscheletrico: le ernie discali

Roberta Bonfiglioli, Francesco Violante, Università di Bologna

Degenerative Disc Disease (DDD) is a radiographic-anatomical finding (**anulus fissures, loss of nuclear material, inflammation**)

Asymptomatic

	Number of studies	OR (95% CI)	Prevalence asymptomatic (95% CI)	Prevalence symptomatic (95% CI)	p value	Hetero-geneity
Intervertebral disc degeneration-related outcomes						
Disc degeneration	12	2·2 (1·2–4·2)	34% (32–38)	57% (55–60)	0·01	High
Modic change	5	1·6 (0·5–5·4)	12% (10–15)	23% (22–27)	0·43	High
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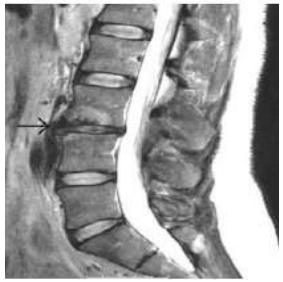
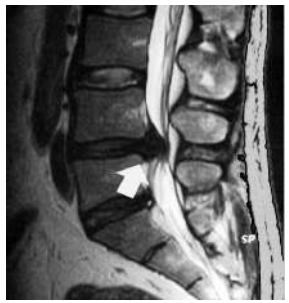
Data are modified from Brinjikji et al (2015).[29] Heterogeneity (I^2) was graded "low" only for "0" values since no CI for I^2 was presented. Prevalence data presented for reference only. OR=odds ratio.

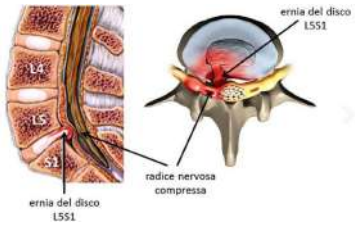
Table 1: **Strength of association between MRI findings and low back pain in younger adults**



Discogenic pain



Lumbar disc Herniation
LDH



Mechanical nerve compression

Low back pain (LBP) is a clinical entity

Hartvigsen J et al. Lancet Low Back Pain Series Working Group. ***What low back pain is and why we need to pay attention.*** *Lancet. 2018 Mar 20*

Kirnaz e coll, ***Pathomechanism and Biomechanics of Degenerative Disc Disease: Features of Healthy and Degenerated Discs****. Int J Spine Surg.* ***2021*** *Apr;15(s1):10-25*

IVD composizione e proprietà

- **NP Nucleo polposo**: gelatinoso, ricco di acqua e povero di cellule (scarsa capacità di riparazione per l'ambiente ipossico e acido) ; la matrice extracellulare, ricca di collagene tipo II, proteoglicani (*aggrecano - CSPCP (Cartilage-Specific Proteoglycan Core Protein*)) e acido ialuronico, è in grado di trattenere acqua, conferendo le caratteristiche alla base della capacità di assorbire le forze compressive, + assenza di innervazione
- **AF Anello fibroso**: parte INTERNA cellule simili a condrociti + matrice; parte ESTERNA collagene tipo I + proteoglicani + cellule simili a fibroblasti, l'orientamento delle fibre diagonale ad anelli concentrici conferisce resistenza (tensile strength)
- **CEP Cartilage endplates**: cartilagine ialina ricca di condrociti e collagene tipo II, vascolarizzata, nutre il disco e lo connette al corpo vertebrale

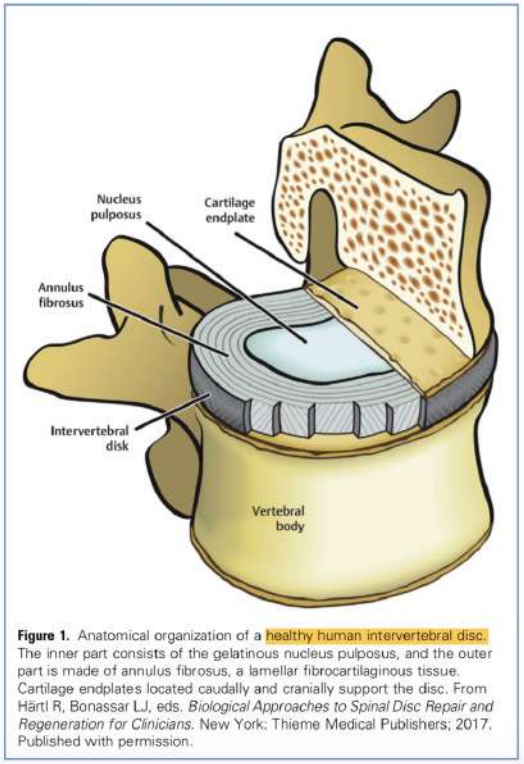


Figure 1. Anatomical organization of a healthy human intervertebral disc. The inner part consists of the gelatinous nucleus pulposus, and the outer part is made of annulus fibrosus, a lamellar fibrocartilaginous tissue. Cartilage endplates located caudally and cranially support the disc. From Härtl R, Bonassar LJ, eds. *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*. New York: Thieme Medical Publishers; 2017. Published with permission.

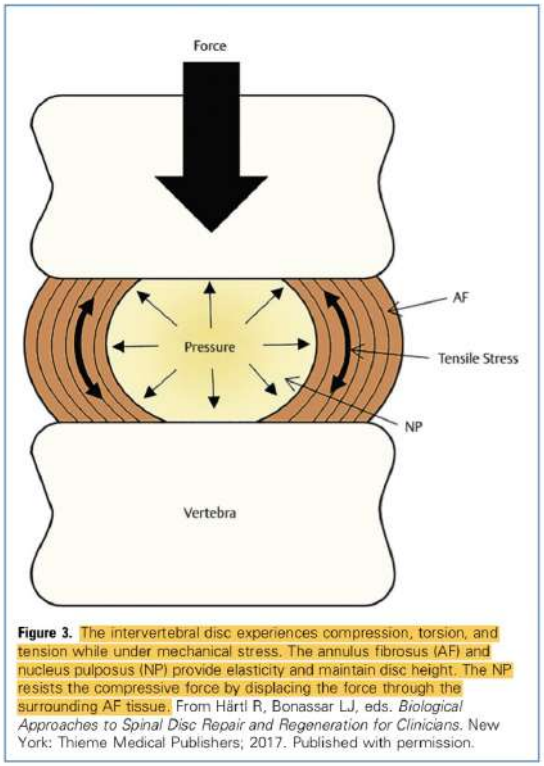


Figure 3. The intervertebral disc experiences compression, torsion, and tension while under mechanical stress. The annulus fibrosus (AF) and nucleus pulposus (NP) provide elasticity and maintain disc height. The NP resists the compressive force by displacing the force through the surrounding AF tissue. From Härtl R, Bonassar LJ, eds. *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*. New York: Thieme Medical Publishers; 2017. Published with permission.

Kirnaz S, et al. Fundamentals of Intervertebral Disc Degeneration. World Neurosurg. ***2022*** *Jan;157:264-273.*

IVD Adulto

(*Kirnaz S, et al **2022**)*

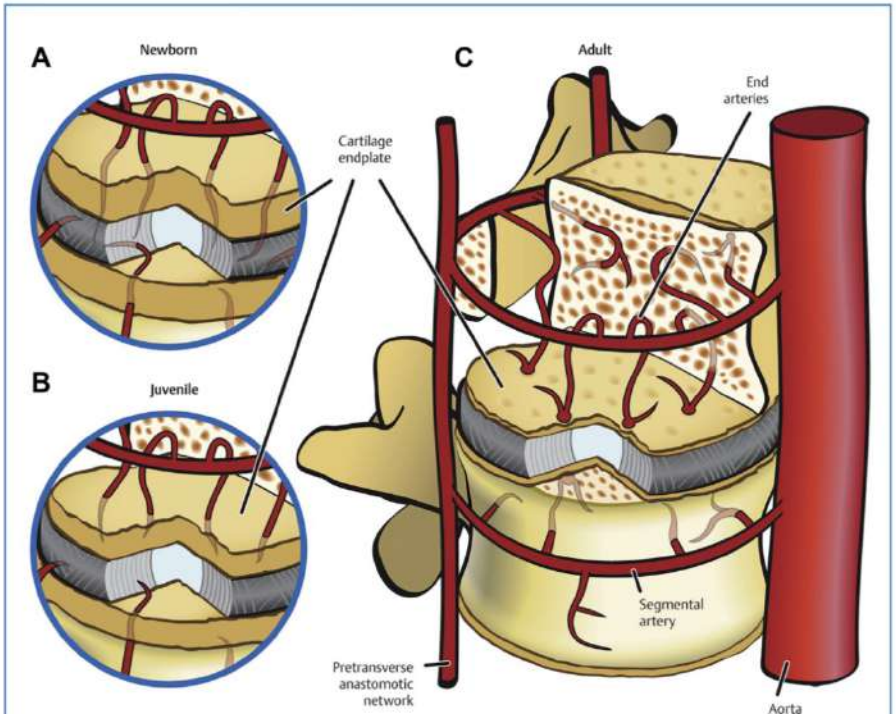


Figure 4. (**A**) Neonate's vertebral body and disc vascular network; blood supply can extend into the innermost regions of the annulus fibrosis (AF). (**B**) Vessels retract further from the disc to the outer region of the AF during adolescence. (**C**) Vessels are regressed further away from the AF and fix themselves within and surrounding the endplate and connective tissues in adult spines. Arterial organization around the vertebral body and intervertebral disc. Blood vessels extend into the innermost AF in newborns (**A**), regress to outer AF in adolescents (**B**), and are limited to the cartilage endplate in adults (**C**). From Härtl R, Bonassar LJ, eds. *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*. New York: Thieme Medical Publishers; 2017. Published with permission.

Vascolarizzazione - solo la cartilagine

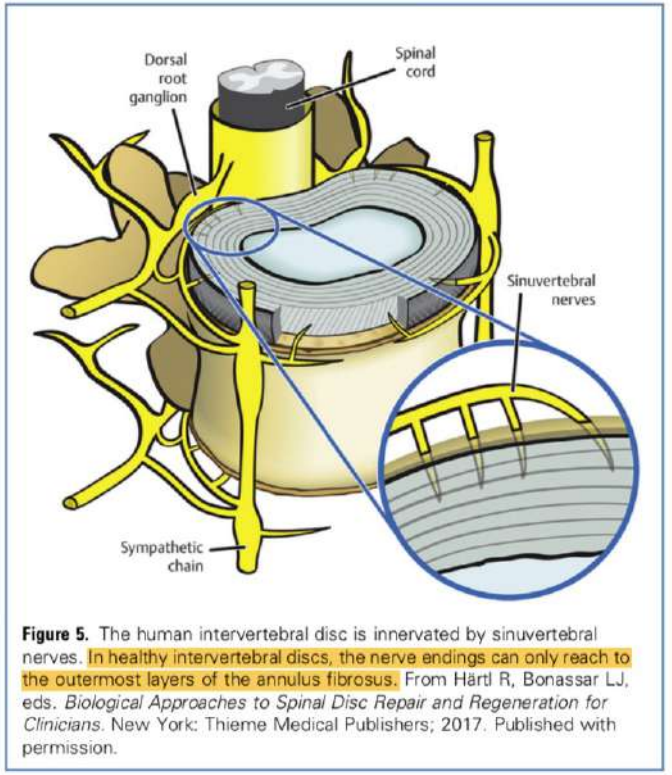
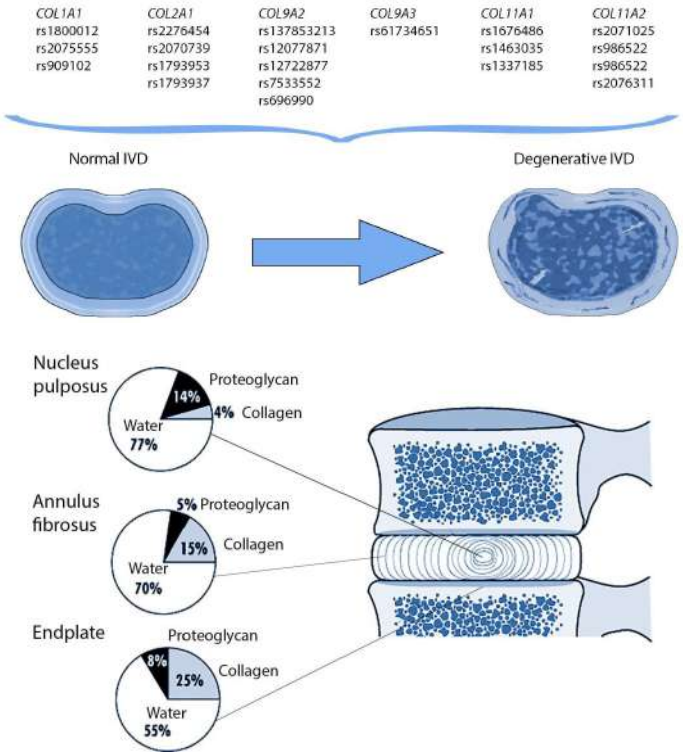


Figure 5. The human intervertebral disc is innervated by sinuvertebral nerves. In healthy intervertebral discs, the nerve endings can only reach to the outermost layers of the annulus fibrosus. From Härtl R, Bonassar LJ, eds. *Biological Approaches to Spinal Disc Repair and Regeneration for Clinicians*. New York: Thieme Medical Publishers; 2017. Published with permission.

Terminazioni nervose fino alla parte esterna dell'AF

Degenerative Disc Disease DDD often accompanies normal aging, it can be accelerated by several risk factors, such as genetics, smoking, and obesity

Individual and external risk factors (Multifactorial nature)



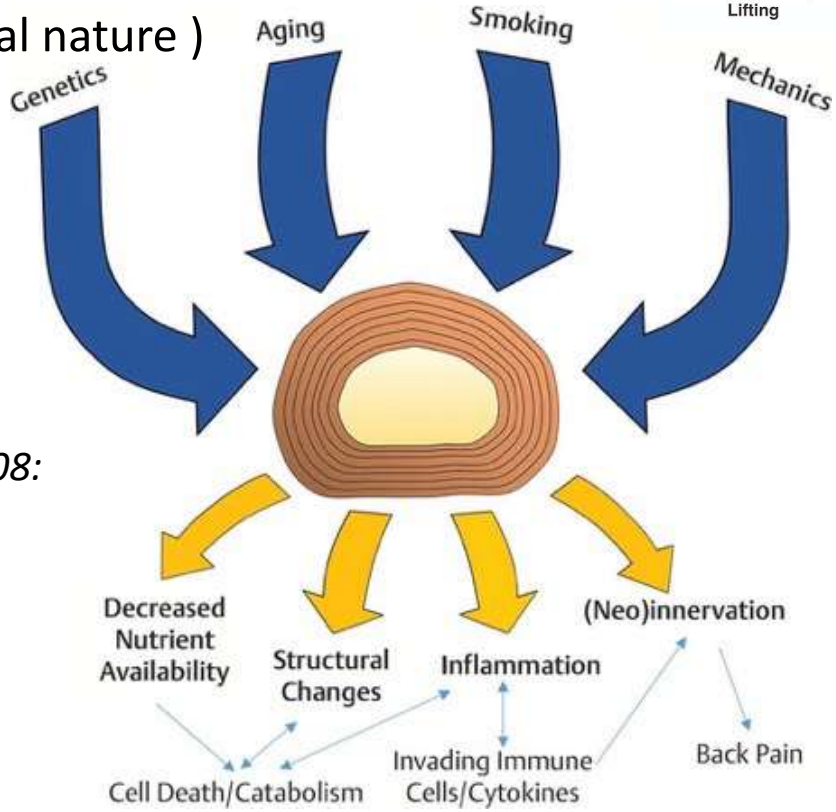
Role of genetics

Sambrook et al. 1999: 73-74%;

Kalichman and Hunter 2008: 34-61%

Collagene

Proteine aggrecani



Trefilova VV, et al The Role of Polymorphisms in Collagen-Encoding Genes in Intervertebral Disc Degeneration. Biomolecules. ***2021****; 11(9):1279*

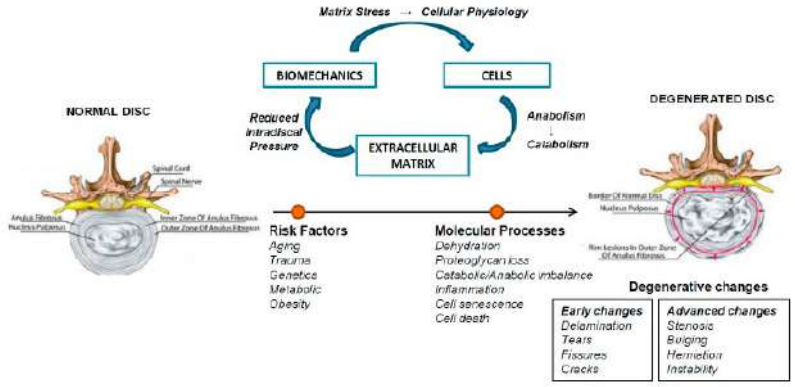
Kirnaz S, et al Pathomechanism and Biomechanics of Degenerative Disc Disease: Features of Healthy and Degenerated Discs. Int J Spine Surg. ***2021*** *Apr;15(s1):10-25*

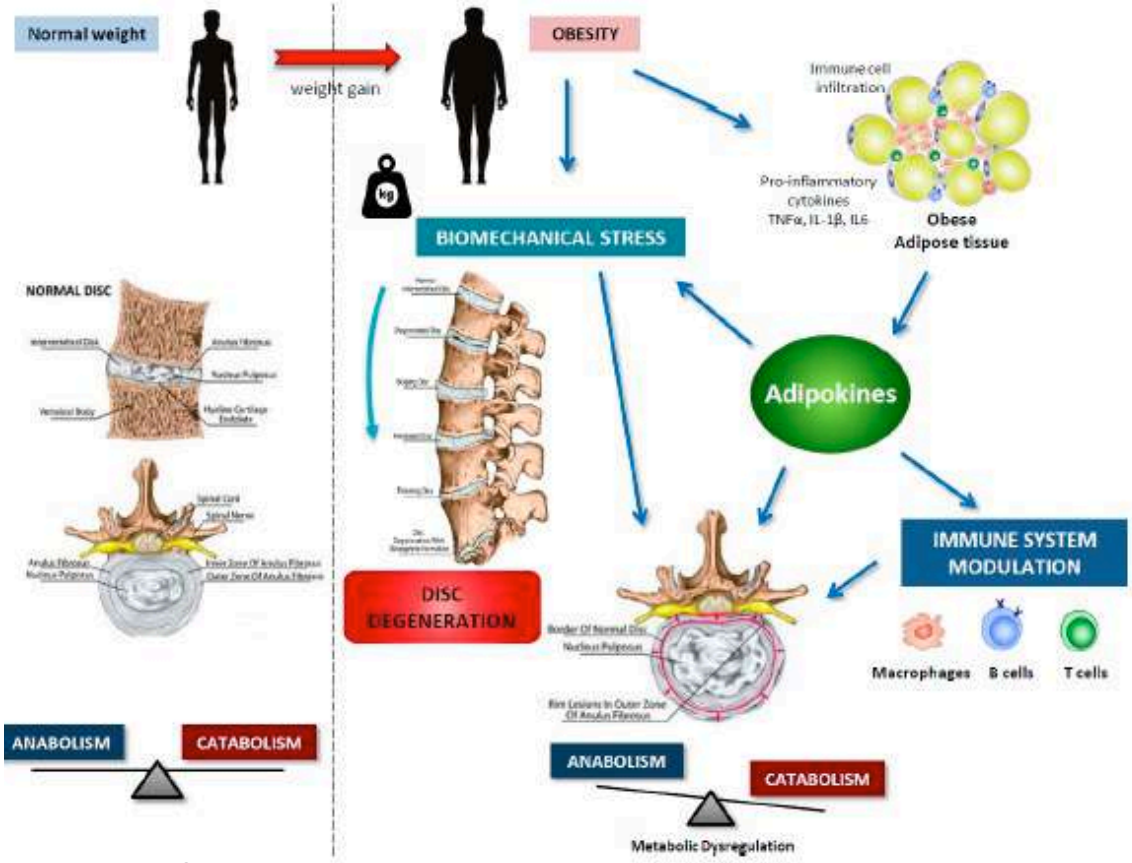
Ruiz-Fernández et al ***2019***

Disc disease – Multifactorial nature

Obesity and degenerative disc disease

The interrelationships among **inflammation, obesity** and the pathogenic mechanisms involved in the disc disease, with particular emphasis on the contribution of adipokines

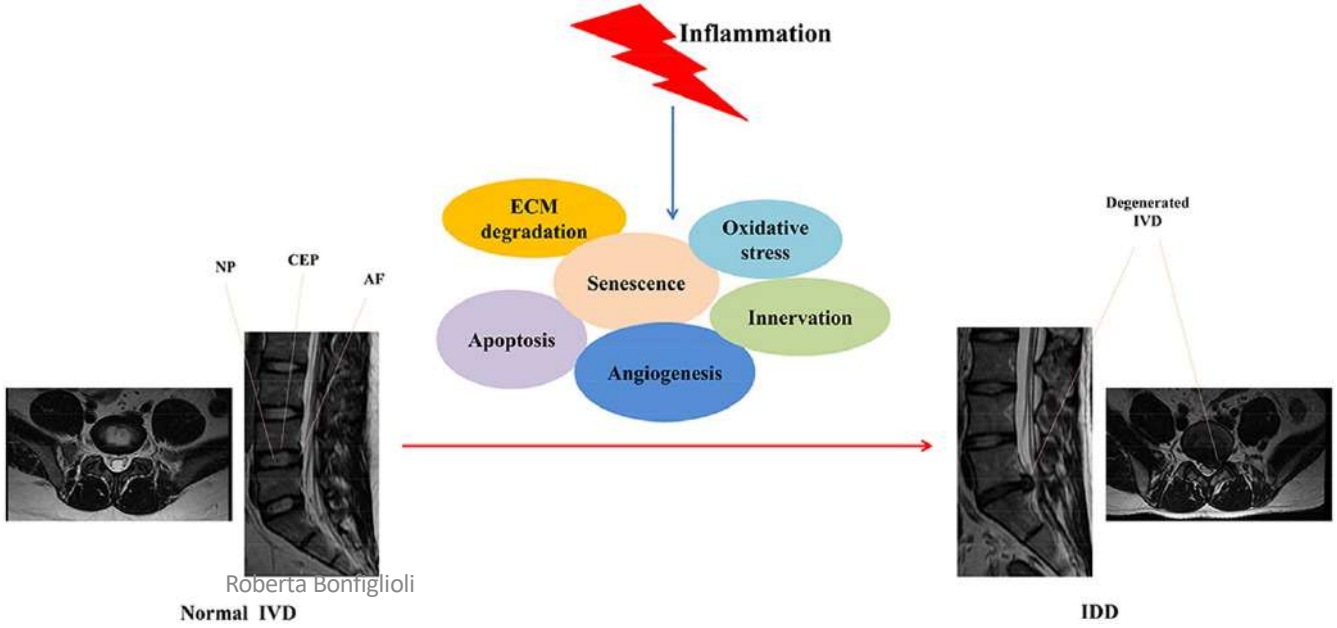




Kang L, Zhang H, Jia C, Zhang R, Shen C. Epigenetic modifications of inflammation in intervertebral disc degeneration. Ageing Res Rev. ***2023*** *Jun;87:101902*

- ***Inflammation is involved in multiple pathological processes of IDD***
- The factors **triggering inflammation** in IDD have not been fully elucidated
- Epigenetic: DNA methylation, Histone modification, non-coding RNAs regulation (which could contribute through dysregulated cytokines)

Inflammation plays an important role in the occurrence and development of IDD by regulating the ***continuous loss of extracellular matrix*** *(anabolism/catabolism imbalance****), apoptosis, senescence, oxidative stress, angiogenesis and nerve ingrowth.***



International Journal of *Molecular Sciences*

MDPI

Review

Macrophages and Intervertebral Disc Degeneration

Jinsha Koroth [1], Erick O. Buko [2,3], Rebecca Abbott [4], Casey P. Johnson [2,3], Brenda M. Ogle [5,6], Laura S. Stone [7], Arin M. Ellingson [1,4] and Elizabeth W. Bradley [1,6,*]

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[3] Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN 55455, USA
[4] Department of Rehabilitation Medicine, School of Medicine, University of Minnesota, Minneapolis, MN 55455, USA
[5] Department of Biomedical Engineering, College of Science and Engineering, University of Minnesota, Minneapolis, MN 55455, USA
[6] Stem Cell Institute, University of Minnesota, Minneapolis, MN 55455, USA
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2023

Abstract: The intervertebral disc (IVD) aids in motion and acts to absorb energy transmitted to the spine. With little inherent regenerative capacity, degeneration of the intervertebral disc results in intervertebral disc disease, which contributes to low back pain and significant disability in many individuals. Increasing evidence suggests that IVD degeneration is a disease of the whole joint that is associated with significant inflammation. Moreover, studies show elevated macrophage accumulation within the IVD with increasing levels of disease severity; however, we still need to understand the roles, be they causative or consequential, of macrophages during the degenerative process. In this narrative review, we discuss hallmarks of IVD degeneration, showcase evidence of macrophage involvement during disc degeneration, and explore burgeoning research aimed at understanding the molecular pathways regulating macrophage functions during intervertebral disc degeneration.

Keywords: Tgfβ; inflammation; spine; macrophage polarization; hypoxia; low back pain

Citation: Koroth, J.; Buko, E.O.; Abbott, R.; Johnson, C.P.; Ogle, B.M.; Stone, L.S.; Ellingson, A.M.; Bradley, E.W. Macrophages and Intervertebral Disc Degeneration. *Int. J. Mol. Sci.* **2023**, *24*, 1367. https://doi.org/10.3390/ijms24021367

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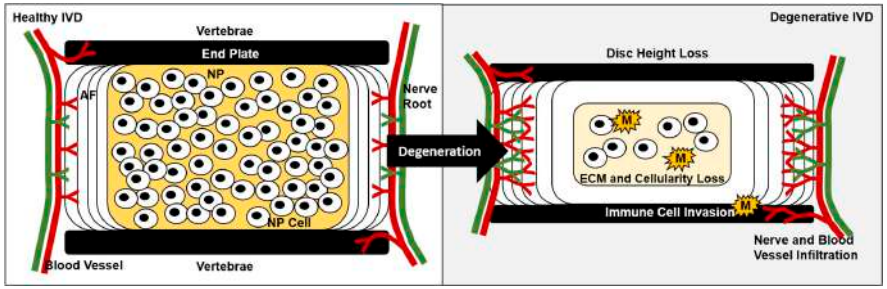
1. Introduction

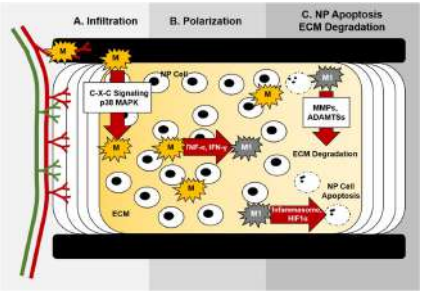
Low back pain (LBP), one of the most prevalent musculoskeletal conditions, has an estimated lifetime occurrence of 70–85% and often results in significant disability and financial burden [1,2]. Although causes of LBP are often unclear, the intervertebral disc (IVD) is a primary source of LBP, with an estimated 34–68% of patients classified with discogenic pain, or pain due to intervertebral disc degeneration [3]. Signs of degeneration are very common in the general population (upwards of 70% of adults) [4], and do not always relate directly to symptomology [5]. However, IVD degeneration is more prevalent in those with LBP [6].

01/12/23 Roberta Bonfiglioli

Figure 1. Changes associated with intervertebral disc degeneration. Disc height loss, ECM degradation, nerve and blood vessel infiltration, inflammatory cell invasion, and loss of cellularity accompany degenerative disc disease.



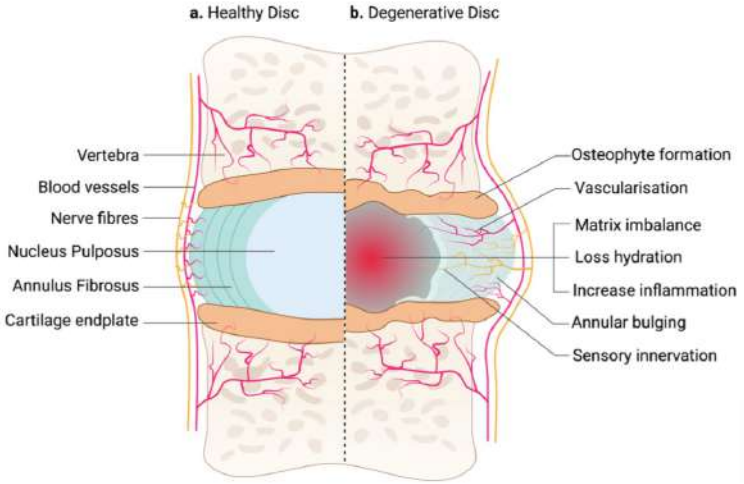
Molecular control of macrophages during IDD



IDD – changes in subcondral bone and cartilaginous endplates (Modic changes RM) – osteophyte formation – **significant nerve ingrowth (disc pain)** (sciatic nerve and dorsal root ganglia) – **degradation and remodelling extracellular matrix**

Mohd Isa IL, Teoh SL, Mohd Nor NH, Mokhtar SA. Discogenic Low Back Pain: Anatomy, Pathophysiology and Treatments of Intervertebral Disc Degeneration. Int J Mol Sci. ***2022*** *Dec 22;24(1):208.*

extracellular matrix (ECM)



- Lower cell numbers can alter cell functions in the NP during disc degeneration, resulting in an imbalance between ECM synthesis and degradation (loss of proteoglycan and tissue hydration that also causes glycosaminoglycans to be lost)
- Reducing type II collagen synthesis and increasing type I collagen synthesis occurs with a transition to fibrillated tissue quality, and an increase in matrix-degrading enzyme activity, resulting in reduced elasticity and mechanical integrity of the disc. **The load-bearing function of the disc is also changed due to reducing hydration**
- In the AF, degenerative changes are indicated by the delamination of the lamellae and an increased incidence of **radial fissures.**
- **Degenerative discs have reduced disc height and abnormal mechanical response to loads**

As a result of all these changes, **mobility is reduced, and symptoms have often appeared.**
At an advanced stage of disc degeneration, a decrease in joint space causes **severe loss of mobility.**
As a consequence of structural changes, **the disc loses its biomechanical function.**

The **nociceptive nerve fibers** project into the inner third of the AF and into the NP in degenerative discs of chronic LBP patients, indicating an important role for nerve ingrowth into the IVD in the pathogenesis **of chronic LBP**

Degenerative Disc Disease (DDD) is a radiographic-anatomical finding (**anulus fissures, loss of nuclear material, inflammation**)

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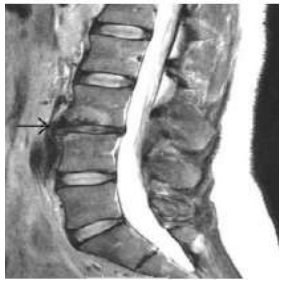
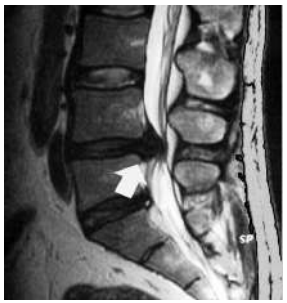
DDD alters disco-vertebral biomechanics



Discogenic pain



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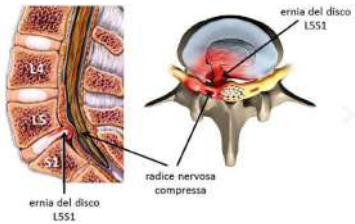
LDH



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Hartvigsen J et al. Lancet Low Back Pain Series Working Group. ***What low back pain is and why we need to pay attention.*** *Lancet. 2018 Mar 20*

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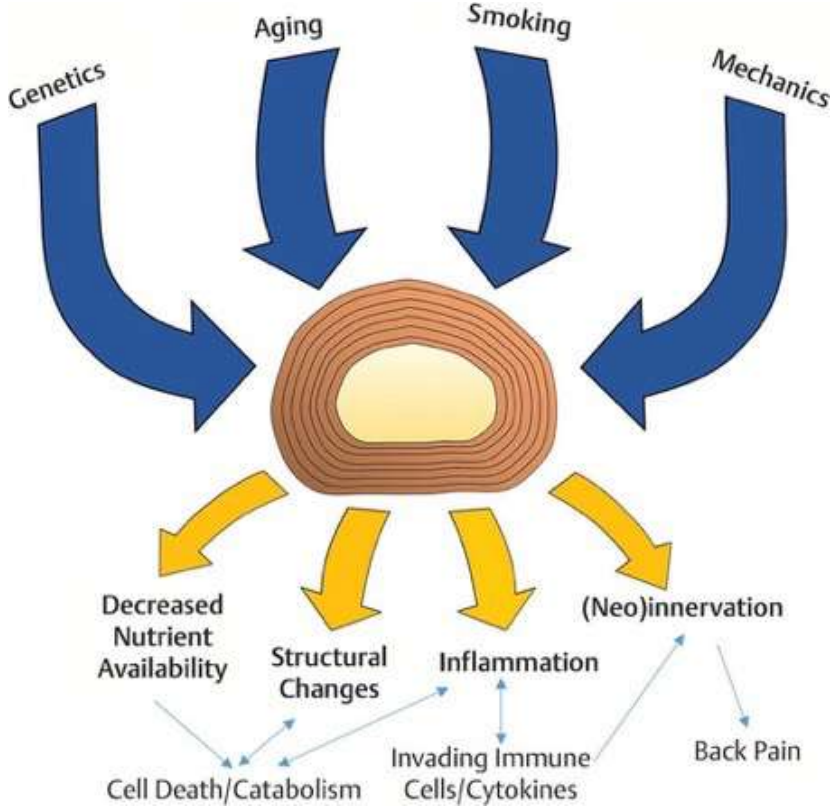
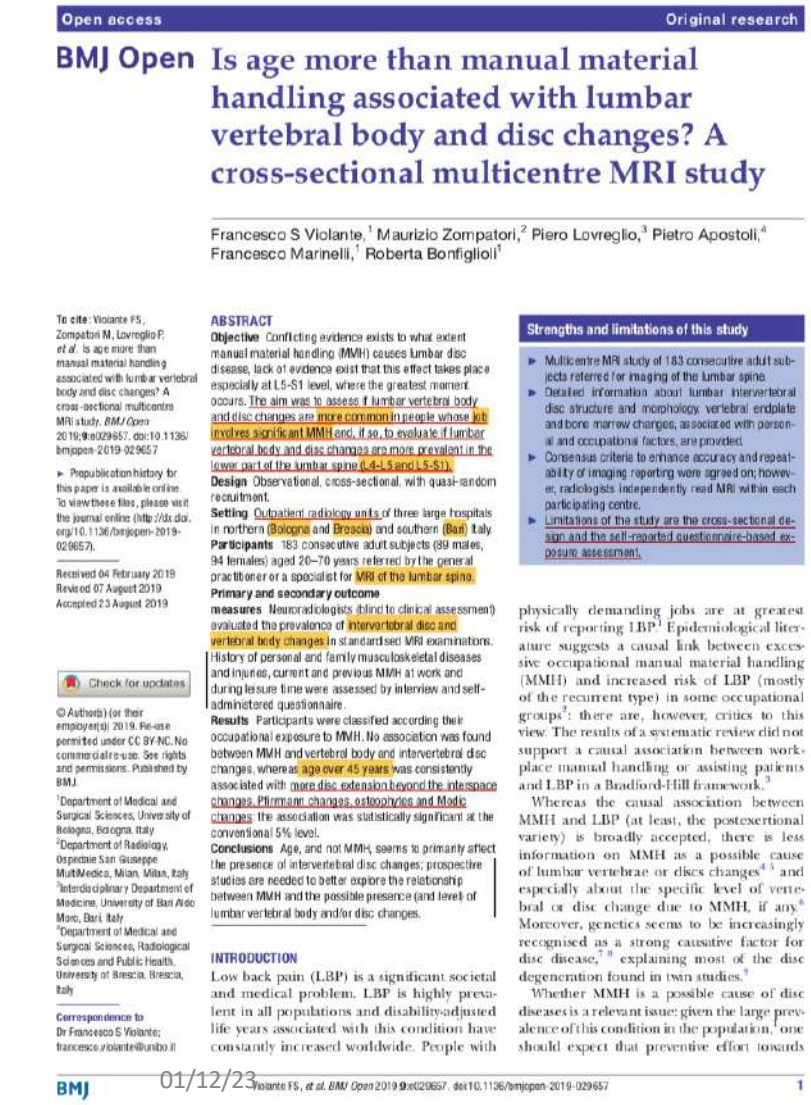
Disc disease – Multifactorial nature



Role of mechanics?

Kirnaz S, et al Pathomechanism and Biomechanics of Degenerative Disc Disease: Features of Healthy and Degenerated Discs. Int J Spine Surg. 2021 Apr;15(s1):10-25



Open access Original research

BMJ Open

Is age more than manual material handling associated with lumbar vertebral body and disc changes? A cross-sectional multicentre MRI study

Francesco S Violante,[1] Maurizio Zompatori,[2] Piero Lovreglio,[3] Pietro Apostoli,[4] Francesco Marinelli,[1] Roberta Bonfiglioli[1]

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ABSTRACT

Objective Conflicting evidence exists to what extent manual material handling (MMH) causes lumbar disc disease, lack of evidence exist that this effect takes place especially at L5-S1 level, where the greatest moment occurs. The aim was to assess if lumbar vertebral body and disc changes are more common in people whose job involves significant MMH and, if so, to evaluate if lumbar vertebral body and disc changes are more prevalent in the lower part of the lumbar spine (L4-L5 and L5-S1).

Design Observational, cross-sectional, with quasi-random recruitment.

Setting Outpatient radiology units of three large hospitals in northern (Bologna and Brescia) and southern (Bari) Italy.

Participants 183 consecutive adult subjects (89 males, 94 females) aged 20–70 years referred by the general practitioner or a specialist for MRI of the lumbar spine.

Primary and secondary outcome measures Neuroradiologists (blind to clinical assessment) evaluated the prevalence of intervertebral disc and vertebral body changes in standardised MRI examinations. History of personal and family musculoskeletal diseases and injuries, current and previous MMH at work and during leisure time were assessed by interview and self-administered questionnaire.

Results Participants were classified according their occupational exposure to MMH. No association was found between MMH and vertebral body and intervertebral disc changes, whereas age over 45 years was consistently associated with more disc extension beyond the interspace changes, Pfirrmann changes, osteophytes and Modic changes; the association was statistically significant at the conventional 5% level.

Conclusions Age, and not MMH, seems to primarily affect the presence of intervertebral disc changes; prospective studies are needed to better explore the relationship between MMH and the possible presence (and level) of lumbar vertebral body and/or disc changes.

Strengths and limitations of this study

- Multicentre MRI study of 183 consecutive adult subjects referred for imaging of the lumbar spine.
- Detailed information about lumbar intervertebral disc structure and morphology, vertebral endplate and bone marrow changes, associated with personal and occupational factors, are provided.
- Consensus criteria to enhance accuracy and repeatability of imaging reporting were agreed on; however, radiologists independently read MRI within each participating centre.
- Limitations of the study are the cross-sectional design and the self-reported questionnaire-based exposure assessment.

INTRODUCTION

Low back pain (LBP) is a significant societal and medical problem. LBP is highly prevalent in all populations and disability-adjusted life years associated with this condition have constantly increased worldwide. People with physically demanding jobs are at greatest risk of reporting LBP.[1] Epidemiological literature suggests a causal link between excessive occupational manual material handling (MMH) and increased risk of LBP (mostly of the recurrent type) in some occupational groups[2]: there are, however, critics to this view. The results of a systematic review did not support a causal association between workplace manual handling or assisting patients and LBP in a Bradford-Hill framework.[3]

Whereas the causal association between MMH and LBP (at least, the postexertional variety) is broadly accepted, there is less information on MMH as a possible cause of lumbar vertebrae or discs changes[4 5] and especially about the specific level of vertebral or disc change due to MMH, if any.[6] Moreover, genetics seems to be increasingly recognised as a strong causative factor for disc disease,[7 8] explaining most of the disc degeneration found in twin studies.[9]

Whether MMH is a possible cause of disc diseases is a relevant issue: given the large prevalence of this condition in the population,[1] one should expect that preventive effort towards

Collaborazione tra le Università di Bologna, Brescia e Bari

- Medici del lavoro
- Neuroradiologi
- Statistici

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Aim of the study and *hypothesis*

To investigate the association between **occupational biomechanical risk factors**, **disco-vertebral degeneration** and its spatial distribution along the lumbar spine

To identify a MR imaging pattern of lumbar disco-vertebral changes related to occupational biomechanical overload

Hypothesis - Disco-vertebral changes associated to mechanical overload should involve al least the L5-S1 level or be more prevalent where the greatest moment and compressive forces arise (L4-S1). - Changes affecting only the upper lumbar segment should characterize mainly an individual susceptibility without a significant contribution of physical overload

Methods

- Study design: Cross-sectional
- Study group: all consecutive patients aged 20-70 referred for magnetic resonance imaging (MRI) of the lumbar spine to the outpatient radiology units of three large hospitals in northern (Bologna and Brescia) and southern (Bari) Italy.
- Participants were consecutively recruited during the period October 2013 - March 2017 using a quasi-random sampling (i.e. patients were invited regardless of whether they were or had been previously exposed to manual material handling (MMH)).
- Exclusion criteria: recent acute trauma, history of cancer, spine deformities (severe scoliosis)

Methods – Health and job data collection

Occupational physicians, blind to MR findings

Structured interview to collect detailed information on

- Anthropometric data
- Lifestyle, hobbies and leisure activities
- Family history of disc degeneration disease
- Clinical history, personal history of musculoskeletal diseases
- Lifelong exposure to biomechanical factors

Work history: current and past exposure levels at work.
Presence, duration and frequency of spine postures (including kneeling/crouching positions), lifting operations, forces applied for pushing or pulling, exposure to vibration

Methods - Imaging

Neuroradiologists, blind to clinical assessment

- Intervertebral disc changes
- Vertebral endplate and marrow changes

- *Osteophytes*
- *Vertebral morphometry*
- *Spondylolystesis and Spondylolysis*

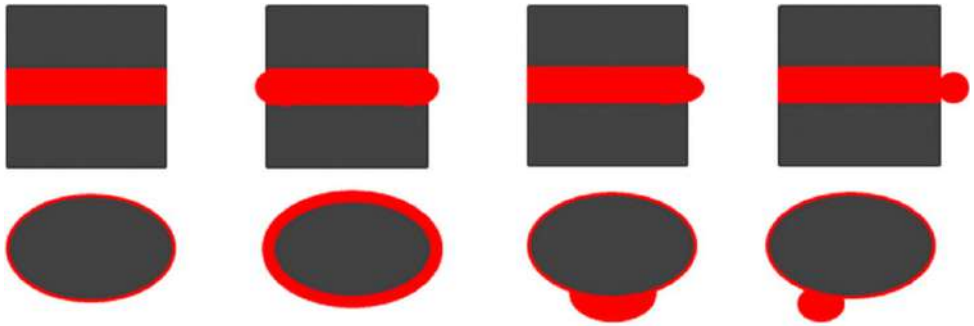
Intervetrebral disc changes
Pfirrmann classification system

- Structure of the disc
- Distinction of nucleus and annulus
- MRI Signal intensity
- Height of intervertebral disc

Grade	Structure	Distinction of nucleus and annulus	Signal intensity	Height of intervertebral disc
I	Homogenous, bright white	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
II	Inhomogenous with or without horizontal bands	Clear	Hyperintense, isointense to cerebrospinal fluid	Normal
III	Inhomogenous, gray	Unclear	Intermediate	Normal to slightly decreased
IV	Inhomogenous, gray to black	Lost	Intermediate to hypointense	Normal to moderately decreased
V	Inhomogenous, black	Lost	Hypointense	Collapsed disc space

Pfirrmann CW et al., Spine (Phila Pa 1976). 2001 Sep 1;26(17):1873-8

Intervetrebral disc changes - Disc Extension Beyond the Interspace (DEBIT)



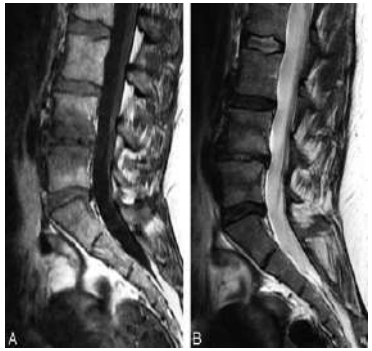
0. *Intact*
1. Bulging
2. Median protrusion
3. Paramedian protrusion
4. Intraforaminan protrusion
5. Median extrusion
6. Paramedian extrusion
7. Intraforaminan extrusion
8. Extraforaminan extrusion

Brant-Zawadzki MN et al. Spine (Phila Pa 1976). 1995 Jun 1; 20(11):1257-63; discussion 1264.

Vertebral endplate and marrow changes – Modic type

Modic type I

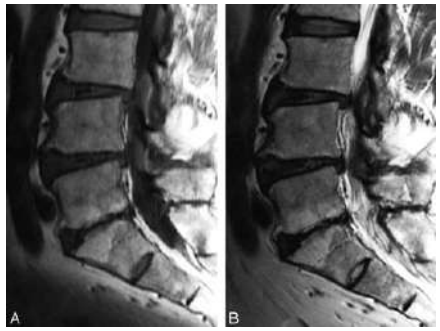
T1: low signal, **T2:** high signal, indicative of **bone marrow edema and inflammation**



edema del midollo osseo

Modic type II

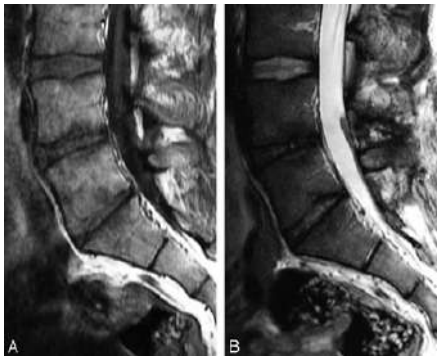
T1: high signal, **T2:** iso to high signal, indicative of normal **red haemopoietic bone marrow conversion into yellow fatty marrow** as a result of marrow ischaemia



degenerazione adiposa

Modic type III

T1: low signal, **T2:** low signal, indicative of **subchondral bony sclerosis**

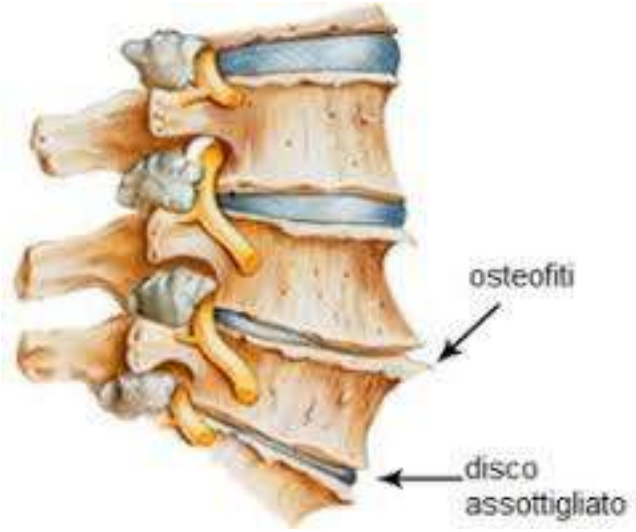


sclerosi ossea subcondrale

Arana E et al. Spine J. 2011 May;11(5):402-11

Osteophytes

- Absent/Marginal
- Discontinuous
- Continuous, table osteophyte



Benneker LM et al. Eur Spine J. 2005 February; 14(1): 27–35

Spondylolisthesis and Spondylolysis

- **Spondylolisthesis**
  - absent
  - <25%
  - 25-50%
  - 50-75%
  - 75-100%
  - >100% (spondyloptosis)
- **Spondylolysis**
  - absent
  - present

Meyerding HW. Surg Gynecol Obstet 1932;54:371–7

Methods – exposure assessment **by job title**

Exposed: categories of physical MMH workload (ref. The **job exposure matrix (JEM) proposed by Seidler et al. (2001)**

- LOW - Technicians, police officers, soldiers, hairdressers, biologists, physicians, nursery home teachers
- INTERMEDIATE - Maintenance workers, waiters, grocery stores workers, electrical and electronics workers, painters, barmen, caregivers/in-home nurses
- HIGH - Agricultural and construction workers, nurses, warehouse and production workers

White collar workers (administrative, teachers, managers, call center operators) formed the **control (unexposed**) group.

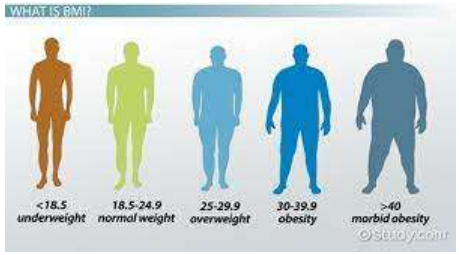
Methods – exposure assessment (**self-assessment**)

- Current and previous jobs lasting for more than five years and occurring in the last ten years were considered for classification.
- The three classes of MMH based on job title were found to be correspondent with the detailed description of MMH given by the patients, according to **weight and frequency of loads lifted.**

<5 kg	☐ Never	☐ Sometimes	☐ Often	☐ Always/Almost always
5 - 15 kg	☐ Never	☐ Sometimes	☐ Often	☐ Always/Almost always
>15 - 25 kg	☐ Never	☐ Sometimes	☐ Often	☐ Always/Almost always
>25 kg	☐ Never	☐ Sometimes	☐ Often	☐ Always/Almost always

- Unexposed
- Exposed *sometimes*
- Exposed *often*
- Exposed *always*

Age: 20-70 aa



All subjects were symptomatic for LBP during the last 12 months, 84,8% reported pain in the last 7 days and 66.8% were disabled by LBP.

Independent t-tests for continuous variable
Pearson's Chi-squared test for categorical variables
No variables reached p-value < 0,05

Study population	**Males (N=89)**				**Females (N=94)**			
	Unexposed (N=27, 30%)		*Exposed (N=62, 70%)*		*Unexposed (N=48, 51%)*		*Exposed (N=46, 49%)*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	**44.3**	13.5	**49.2**	12.9	**49.5**	15.5	**50.3**	10.9
BMI (kg/m^2)	**26.4**	4.0	**26.5**	3.8	**24.5**	4.3	**26.9**	5.1
	N	*%*	N	*%*	N	*%*	N	*%*
Age group								
≤45	15	***55.6***	28	*45.2*	16	*33.3*	15	*32.6*
>45	12	*44.4*	34	***54.8***	32	***66.7***	31	***67.4***
Smoking status								
Non-smoker	10	*37.1*	26	*41.9*	34	*70.8*	26	*56.5*
Ex-smoker	12	*44.4*	17	*27.4*	9	*18.8*	9	*19.6*
Smoker	5	*18.5*	19	*30.7*	5	*10.4*	11	*23.9*
Competitive sport	11	***40.7***	20	***32.3***	10	***20.8***	8	***17.4***
Familiar history DD	9	*33.3*	18	*29.0*	20	*41.7*	19	*41.3*
	Males				**Females**			
Class of exposure to MMH			*Exposed (N=62)*				*Exposed (N=46)*	
			N	%			N	%
Low			18	28.0			9	19.6
Intermediate			9	14.5			16	34.8
High			**35**	**56.5**			**21**	**45.6**

Prevalence of lumbar MRI findings

	Males (N=89)				Females (N=94)			
	Unexposed (N=27)		Exposed (N=62)		Unexposed (N=48)		Exposed (N=46)	
	N	%	N	%	N	%	N	%
DEBIT>1 (1, any level)	*20*	*74.1*	*46*	*74.2*	*34*	*70.8*	*35*	*76.1*
DEBIT>1 (2, any level)	*8*	*29.6*	*32*	*51.6*	*27*	*56.3*	*19*	*41.3*
DEBIT>1 (L4-L5 level)	8	29.6	33	53.2	21	43.8	21	45.7
DEBIT>1 (L5-S1 level)	**18**	**66.7**	**37**	**59.7**	**23**	**47.9**	**21**	**45.7**
Pfirrmann changes	*20*	*74.1*	*45*	*72.6*	*39*	*81.3*	*34*	*73.9*
Pfirrmann changes L4-L5	**13**	**48.2**	**30**	**48.4**	**25**	**52.1**	**26**	**56.5**
Pfirrmann changes L5-S1	16	59.3	34	54.8	33	68.8	22	47.8
Modic changes (any level)	11	40.7	32	51.6	22	45.8	21	45.7
Modic changes L4	6	22.2	16	25.8	11	22.9	14	30.4
Modic changes L5	**7**	**25.9**	**26**	**41.9**	**19**	**39.6**	**14**	**30.4**
Modic changes S1	**7**	**25.9**	**17**	**27.4**	**15**	**31.3**	**9**	**19.6**
Osteophytes (any level)	*15*	*55.6*	*47*	*75.8*	*38*	*79.2*	*35*	*76.1*
Osteophytes L4-L5	10	37.0	37	59.7	26	54.2	24	52.2
Osteophytes L5-S1	**10**	**37.0**	**32**	**51.6**	**28**	**58.3**	**21**	**45.7**

Association between lumbar spine outcomes, personal and job characteristics

Disc herniation

DEBIT (2, any level)		Univariate analysis		Multivariate model*	
	N	PR	(95%CI)	PR	(95%CI)
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	0.92	(0.58-1.45)	1.10	(0.77-1.57)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.86**	**(1.11-3.11)**	**1.85**	**(1.16-2.95)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	1.03	(0.82-1.30)	1.10	(1.03-1.17)
Intermediate	25	0.94	(0.38-2.33)	1.04	(0.48-2.28)
High	56	1.03	(0.70-1.53)	0.96	(0.70-1.32)

**Multivariate model adjusted by sex, age, BMI competitive sport*

Association between lumbar spine outcomes, personal and job characteristics

Disc herniation L4-L5

DEBIT (1, L4-L5 level)		Univariate analysis		Multivariate model[a]	
	N	*PR*	*(95%CI)*	*PR*	*(95%CI)*
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	1.03	(0.81-1.31)	1.17	(1.09 -1.25)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.41**	**(1.13-1.76)**	**1.39**	**(1.09-1.78)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	1.15	(0.85-1.55)	1.18	(1.03-1.36)
Intermediate	25	1.24	(0.81-1.89)	1.37	(0.96-1.94)
High	56	1.39	(0.97-1.97)	1.27	(0.94-1.72)

**Multivariate model adjusted by sex, age, BMI competitive sport*

Association between lumbar spine outcomes, personal and job characteristics

Disc herniation L5-S1

DEBIT (1, L5-S1 level)		Univariate analysis		Multivariate model*	
	N	PR	(95%CI)	PR	(95%CI)
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	1.32	(0.92-1.89)	1.45	(1.03 -2.04)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	1.00	(0.90-1.11)	1.01	(0.95-1.08)
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	0.88	(0.56-1.39)	0.81	(0.54-1.20)
Intermediate	25	1.02	(0.93-1.13)	1.02	(0.99-1.05)
High	56	1.01	(0.72-1.43)	0.89	(0.60-1.30)

**Multivariate model adjusted by sex, age, BMI competitive sport*

Association between lumbar spine outcomes, personal and job characteristics

Vertebral endplate and Bone marrow changes

Modic changes		Univariate analysis		Multivariate model*	
	N	PR	(95%CI)	PR	(95%CI)
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	1.06	(0.62-1.79)	1.26	(0.70-2.25)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.97**	**(1.75-2.23)**	**1.89**	**(1.85-1.92)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	0.76	(0.60-0.95)	0.78	(0.65-0.94)
Intermediate	25	1.09	(0.94-1.27)	1.13	(0.91-1.40)
High	56	**1.30**	**(1.07-1.58)**	1.13	(0.94-1.35)

*Multivariate model adjusted by sex, age, BMI competitive sport

Association between lumbar spine outcomes, personal and job characteristics

Vertebral endplate and Bone marrow changes

Modic changes L5		Univariate analysis		Multivariate model[a]	
	N	*PR*	*(95%CI)*	*PR*	*(95%CI)*
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	1.06	(0.66-1.70)	1.24	(0.86 -1.78)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.81**	**(1.74-1.88)**	**1.63**	**(1.59-1.67)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	0.85	(0.45-1.63)	0.90	(0.58-1.39)
Intermediate	25	0.92	(0.71-1.21)	0.92	(0.62-1.35)
High	56	1.24	(0.61-2.50)	1.06	(0.64-1.75)

*Multivariate model adjusted by sex, age, BMI competitive sport

Associations between lumbar spine outcomes and personal characteristics

Bone spurs

Osteophytes		Univariate analysis		Multivariate model*	
	N	PR	(95%CI)	PR	(95%CI)
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	0.90	(0.84-0.96)	1.00	(0.94-1.06)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.87**	**(1.58-2.21)**	**1.77**	**(1.54-2.04)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	1.00	(0.81-1.22)	1.07	(0.98-1.17)
Intermediate	25	1.02	(0.75-1.39)	1.02	(0.84-1.24)
High	56	**1.14**	**(1.04-1.24)**	1.04	(0.95-1.15)

** Multivariate model adjusted by sex, age, BMI competitive sport*

Association between lumbar spine outcomes, personal and job characteristics

Intervertebral disc changes

Pfirrmann changes		Univariate analysis		Multivariate model+	
	N	PR	(95%CI)	PR	(95%CI)
Sex					
Female	94	1.00	(Ref.)	1.00	(Ref.)
Male	89	0.94	(0.86-1.03)	1.08	(0.94-1.23)
Age (years)					
≤45	74	1.00	(Ref.)	1.00	(Ref.)
>45	109	**1.36**	**(1.10-1.68)**	**1.33**	**(1.10-1.61)**
Class of exposure to MMH					
No exposure		1.00	(Ref.)	1.00	(Ref.)
Low	27	0.94	(0.61-1.44)	0.97	(0.71-1.34)
Intermediate	25	0.97	(0.69-1.34)	1.00	(0.65-1.53)
High	56	0.91	(0.54-1.52)	0.85	(0.50-1.44)

** Multivariate model adjusted by sex, age, BMI competitive sport*

Pfirrmann Grade (0. grade I and II; 1. grade III; 2. grade IV and V) spt. 1 & 2, 30% cad

Fractions of cases attributable to each risk factor in the study population

DEBIT changes >2 levels, Modic changes (any level) and osteophytes, about 30% cases could be attributed to **age >** 45 years. The contribution of age seems to be prevalent in L4 L5.

Male gender contributed to 10% or 17% of Modic changes and DEBIT L5-S1,

Table 4 Population attributable fractions (%) of lumbar spine outcomes. Maximum likelihood estimates from the multivariate models presented in tables 3A and B

	DEBIT (1, any level)		DEBIT (2, any levels)		DEBIT (1, L4-L5 level)		DEBIT (1, L5-S1 level)		Pfirrmann changes		Pfirrmann changes L4-L5		Pfirrmann changes L5-S1	
Characteristics	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %
Male gender	5	(0 to 9)	4	(–13 to 19)	7	(4 to 10)	17	(0 to 32)	3	(–3 to 9)	2	(–7 to 10)	6	(–10 to 19)
Age above 45 years	8	(3 to 13)	34	(6 to 53)	19	(5 to 31)	1	(–3 to 4)	17	(5 to 27)	26	(6 to 42)	16	(–1 to 30)
Exposure to MMH	2	(–1 to 7)	1	(–22 to 19)	14	(–1 to 26)	–7	(–15 to 1)	–6	(–35 to 18)	1	(–21 to 18)	–17	(–57 to 13)

	Modic changes		Modic changes L4		Modic changes L5		Modic changes S1		Osteophytes		Osteophytes L4-L5		Osteophytes L5-S1	
Characteristics	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %	PAF %	(95% CI) %
Male gender	10	(–20 to 33)	6	(–15 to 23)	10	(–9 to 25)	10	(–13 to 29)	1	(–3 to 3)	6	(–1 to 11)	3	(–12 to 15)
Age above 45 years	35	(33 to 37)	58	(20 to 78)	28	(26 to 30)	23	(2 to 42)	32	(24 to 39)	43	(–4 to 69)	27	(21 to 32)
Exposure to MMH	3	(–9 to 13)	11	(–11 to 28)	–1	(–32 to 23)	–18	(–56 to 10)	3	(1 to 4)	6	(4 to 8)	-4	(–12 to 2)

PAF, population attributable fraction; DEBIT, disc extension beyond the interspace; MMH, manual material handling.

Based on the multivariate risk estimates

Study limitations

- Cross-sectional design
- Work history + risk assessment based on retrieval of information from the past: self-reported exposure is usually employed and is considered a source for recall bias and possibly overestimation of exposure (Kuijer et al., *Neurology* 2018)
- Only patients referred for MRI
- Misclassification of exposure or misclassification of the outcome

Discussion

- The main result of this study is a lack of difference in the prevalence of lumbar vertebral body and disc changes between subjects exposed to significant MMH and those unexposed

- A consistent association found was between age above 45 years and disc changes

Conclusion

- Multifactorial nature of disc pathology
- Although a positive dose-response relationship between cumulative occupational lumbar load and lumbar disc herniation/narrowing has been reported in literature
- We observed that age, and not manual material handling, seems to primarily affect the presence of lumbar intervertebral disc changes
- Need for: enlarge sample size, prospective studies to explore the level and characteristic of disc pathology and its relation to lumbar load

Rustenburg et al. ***Prognostic factors in the progression of intervertebral disc degeneration:*** *Which patient should be targeted with regenerative therapies? JOR Spine.* ***2019*** *Sep 21;2(3):e1063*

Limited conflicting evidence for most of the prognostic factors, due to diversity in determinants and outcome parameters between the included studies

It is difficult to predict any risk factors for the progression of DD

The current definition of DD is not on-point

The natural history of DD is unclear

TABLE 5 Best-evidence synthesis of prognostic factors in the progression of DD

	Associated with progression	Associated with no progression	Not-associated with progression
Strong evidence (Consistent (>75%) findings in multiple (≥2) high-quality studies)	Disc herniation		Age, gender, body weight, BMI, smoking, car driving, occupation, recreational activities at leisure time
Moderate evidence (Findings in one high-quality study and consistent (>75%) findings in ≥2 low-quality studies)			

OCCUPATION
working as a nurse or construction, carpenter

	Insufficient evidence for association with progression	Insufficient evidence for association with no progression	Insufficient evidence for no association with progression
Limited evidence (Findings in one high-quality study or consistent (>75%) findings in ≥ 3 low-quality studies)	Heritability, genetic risk factors (ie, T-allele IL1A rs1800587 female), fast bowling, weight lifted at work, work schedule, lack of sports activities, number of degenerated discs, presence and change of Modic type I, radial tears	Genetic risk factor (ie, IL6 rs1800795 genotype G/C male)	Obesity, pregnancy, DM, hypertension, back injuries, working style, disc level
Inconclusive evidence (Findings found in < 3 low-quality studies)	American Football position played during career, lumbar lordosis, endplate degeneration, Schmorl nodes		American Football playing career, sacral slope, scoliosis, listhesis
Conflicting evidence (<75% of the studies reported consistent findings)	Overweight, resistance training, lifting weight, annulus tear		

WEIGHT LIFTED AT WORK

Macedo and Battié *BMC Musculoskeletal Disorders* (2019) 20:489
https://doi.org/10.1186/s12891-019-2835-2

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

The association between occupational loading and spine degeneration on imaging – a systematic review and meta-analysis

Luciana G. Macedo[1*] and Michele C. Battié[2]

2019

Abstract

Background: There are inconsistencies in findings regarding the relationship of occupational loading with spinal degeneration or structural damage. Thus, a systematic review was conducted to determine the current state of knowledge on the association of occupational loading and spine degeneration on imaging.

Methods: We performed electronic searches on MEDLINE, CINAHL and EMBASE. We included cross-sectional, case control and cohort studies evaluating occupational loading as the exposure and lumbar spine structural findings on imaging as the outcomes. When possible, results were pooled.

Results: Seventeen studies were included in the review. Ten studies evaluated the association of occupational loading with disc degeneration (signal intensity), four of which were pooled into a meta-analysis. Of the 10 studies, only two did not identify a relationship between occupation loading and disc degeneration. A meta-analysis including four of the studies demonstrated an association between higher loading and degeneration for all spinal levels, with odds ratios between 1.6 and 3.3. Seven studies evaluated disc height narrowing and seven evaluate disc bulge, with six and five identifying an association of loading and with imaging findings respectively. Three studies evaluated modic changes and one identified and association with occupational load.

Conclusions: There was moderate evidence suggesting a modest association between occupational loading and disc degeneration (signal intensity), and low-quality evidence of an association between occupational loading and disc narrowing and bulging.

Keywords: Occupational load, Spine degeneration, Disc degeneration, Disc height, Imaging, Magnetic resonance imaging, X-ray

Systematic review

- Disc height (7 studies)
- Disc bulge or herniation (7 studies)
- Modic changes (3 studies)
- Endplate abnormalities (2 studies)

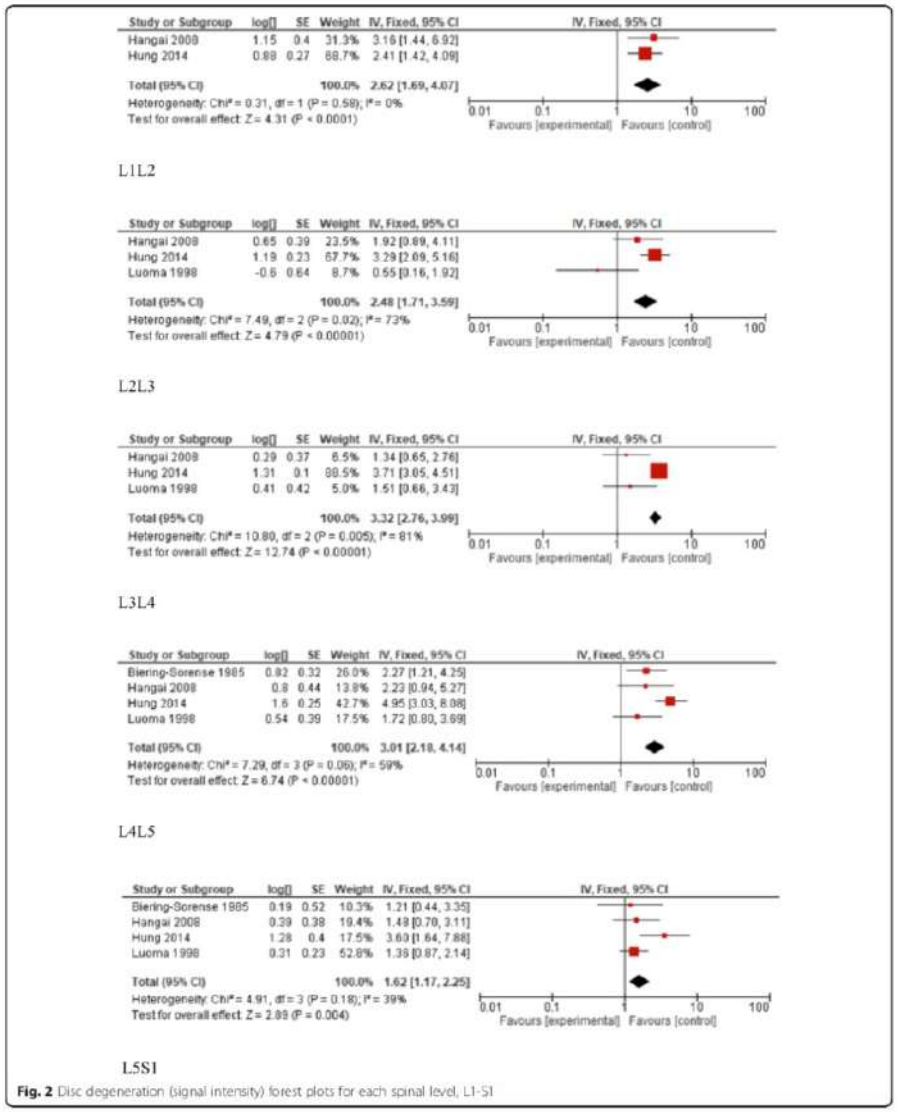


Fig. 2 Disc degeneration (signal intensity) forest plots for each spinal level, L1-S1

Results

⇐ **Moderate grade** evidence of an association between occupational loading and **disc degeneration** in terms of **signal intensity** (FIG.)

- *Low quality grade evidence between loading and **disc height**, with inconsistent results between levels.*
- *Low quality evidence for an association of **disc bulging** with occupational loading, again with inconsistent results among spinal levels.*
- *Low quality evidence of an association between occupational loading and **osteophytes, Modic changes, Schmorl's nodes and other endplate abnormalities**.*

Macedo and Battie, 2019

ORIGINAL ARTICLE

Journal of Occupational Health WILEY

Association between severe lumbar disc degeneration and self-reported occupational physical loading

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Abstract

Objectives: Occupational physical loading has been reported to be associated with intervertebral disc degeneration. However, previous literature reports inconsistent results for different vertebral levels. The aim of our study was to investigate the association between lumbar disc degeneration (LDD) at different vertebral levels and the self-reported physical loading of occupation.

Methods: The study population consisted of 1,022 postmenopausal women and was based on the prospective Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study cohort. The severity of LDD was graded from T2-weighted MRI images using the five-grade Pfirrmann classification. Five intervertebral levels (L1–L2 to L5–S1) were studied (total 5110 discs). The self-rated occupational physical loading contained four groups: sedentary, light, moderate, and heavy.

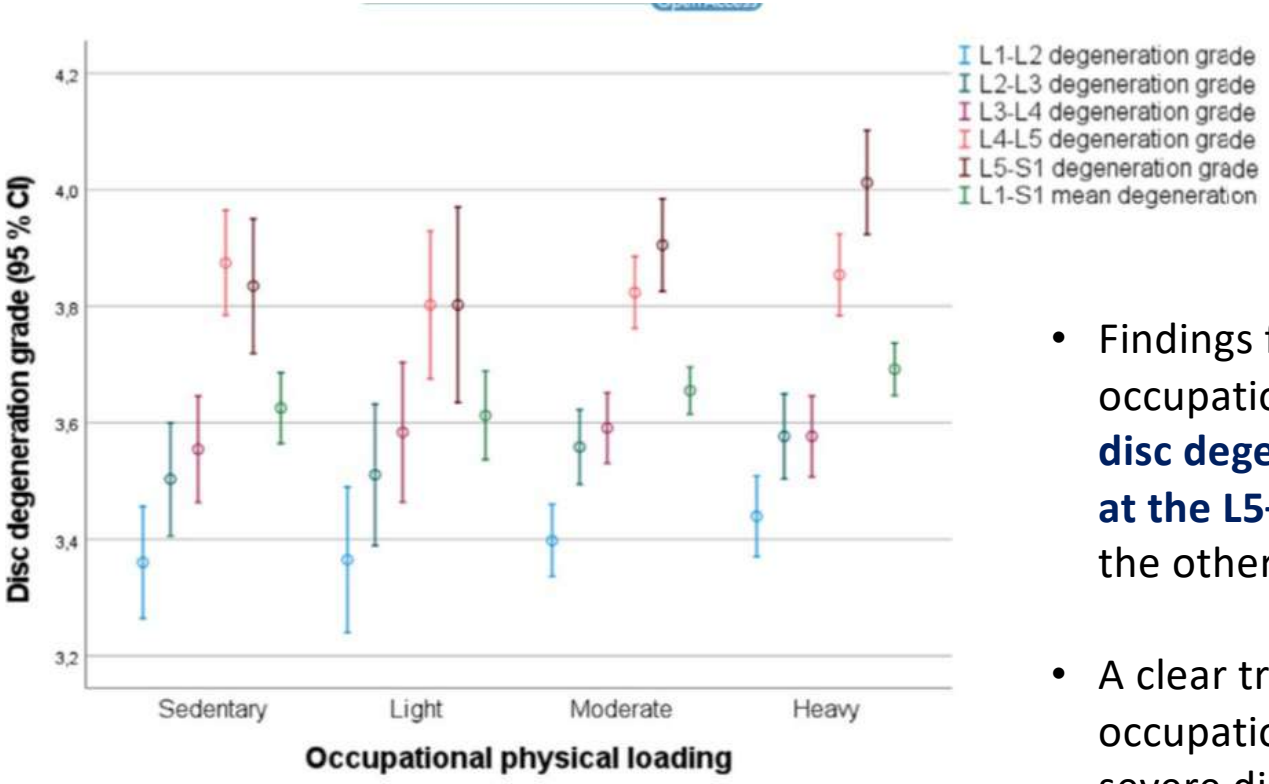
Results: The heavy occupational physical loading group had higher odds for severe LDD at the L5–S1 vertebral level (OR 1.86, 95% CI: 1.19–2.92, $p = .006$) in comparison with the sedentary work group. A clear trend of increasing disc degeneration with heavier occupational loading was also observed at the L5–S1 level. Age, smoking, and higher body mass index (BMI) were associated with more severe LDD. Leisure-time physical activity at the age of 11–17 years was associated with less severe LDD. Controlling for confounding factors did not alter the results.

Conclusions: There appears to be an association between occupational physical loading and severe disc degeneration at the lower lumbar spine in postmenopausal women. Individuals in occupations with heavy physical loading may have an increased risk for work-related disability due to more severe disc degeneration.

KEYWORDS
intervertebral disc degeneration, lumbosacral region, occupational exposure, postmenopause, spine, women's health

2022

- To investigate the association between occupational physical loading and lumbar disc degeneration in **1022 Finnish postmenopausal women** using a five-grade Pfirrmann disc degeneration classification system.
- All MRI scans were performed due to any clinical indication for an MRI scan of the lumbar spine (back pain or back pain and earlier cancer diagnosis, neurological symptoms of the lower legs, and spinal claudication or stenosis symptoms ..)
- Mean age at the time of the MRI scan 73.0 years (SD 4.4).
- Time from answering the questionnaire on occupational physical loading to the date of MRI scan was, on average, 15.9 years (SD 3.7).
- For some largest occupational classes, a comparison to FINJEM data was done (similar results)
- The majority of the discs (97.9%) were within the higher degeneration groups 3–5 Pfirrmann
- Age, smoking, and higher body mass index (BMI) were associated with more severe LDD



- Findings for the association between occupational physical loading and **severe disc degeneration** were **significant only at the L5–S1** vertebral level and not at the other lumbar vertebral levels.

- A clear trend between greater occupational physical loading and more severe disc degeneration was found at most of the vertebral levels.

Salo et al., **2022**

SOCIETÀ ITALIANA DI MEDICINA DEL LAVORO
Fondata nel 1929
SIML

WHAT'S NEXT

I NETWORK NELLA RICERCA IN MEDICINA DEL LAVORO:
UNA PRATICA OBBLIGATA PER LA CRESCITA COMPLESSIVA DELLA NOSTRA DISCIPLINA

2020
Aumentare il numero di centri partecipanti

... *Pandemia* ..

Replicare lo stesso studio?

Necessario rivalutare protocollo?

Denominazione struttura	Unità Operativa
Promotore Azienda Ospedaliero-Universitaria di Bologna - Policlinico Sant'Orsola-Malpighi	UO Proponente: U.O. Medicina del Lavoro (Centro coordinatore) U.O Radiologia (collabora)
Bari Dipartimento Interdisciplinare di Medicina (DIM) - Università degli Studi di Bari Aldo Moro	Sezione di Medicina del Lavoro 'EC Vigliani' -
Bergamo - Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII	UOC Medicina del Lavoro UOC Radiologia diagnostica per immagini 2-Neuroradiologia
Brescia - Azienda Socio-Sanitaria Territoriale degli Spedali Civili	UOC Medicina del Lavoro, Igiene, Tossicologia e Prevenzione Occupazionale UO Diagnostica per immagini - Neuroradiologia
Genova - Ospedale Policlinico San Martino IRCCS di Genova	UO Medicina del Lavoro UOS Sorveglianza Sanitaria Personale Universitario
Messina - AOU Policlinico "G. Martino"	UO Medicina del Lavoro
Napoli - Azienda Ospedaliero Universitaria Federico II	UOC di Medicina del Lavoro
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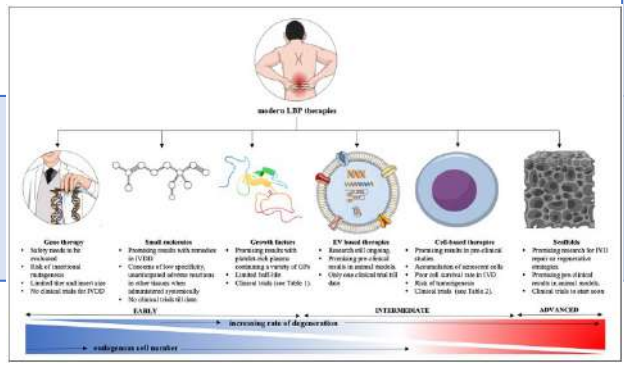
Pisa - Azienda Ospedaliero Universitaria Pisana	SOD Medicina del lavoro
Roma - Fondazione Policlinico Tor Vergata.	UOSD Medicina del Lavoro UOC Diagnostica per immagini
Torino - Azienda Ospedaliero Universitaria Città della Salute e della Scienza	SCU Medicina del Lavoro - Rischio Occupazionale
Trieste - Azienda Sanitaria Universitaria Giuliano Isontina	Uco Medicina del Lavoro Uco di Radiologia Diagnostico Interventistica -

Limitations		
Recruitment in clinical setting (hospital**)**	Mainly symptomatic and more severe cases (pain, trauma, surgery) i.e. generally accepted indications for magnetic resonance imaging	
Study design: only a small portion assessing disc degeneration longitudinally	Limits interpretation regarding the progression of spine degeneration	
Self reported exposure assessment	Recall bias and possibly overestimation of exposure	
Heterogeneity of **outcome definition**	Lack of comparability	
Heterogeneity of **imaging technique** and **classification** of radiological outcome	Lack of comparability	
MRI **Costs** 💰 **MRI is the gold standard imaging modality for the evaluation of IVD pathologies.**	MRI allows for the qualitative and quantitative analysis of degenerative changes in the IVD such as disc dehydration, proteoglycan loss, and collagen breakdown. In addition, it provides detailed information about the other structures related to IVDs, including endplates, facet joints, ligaments, and nerves)	

Occupational setting **Health surveillance**	**Limitations to overcome** **New proposals**	**Clinical setting**
Workers who underwent MRI of the lumbar spine. Less severe cases (?)	**Recruitment strategy**	Patients referred for MRI of lumbar spine. Severe cases.
Retrospective/Prospective follow-up. Repeated imaging. Available digital images.	**Study design**: only a small portion assessing disc degeneration longitudinally	Retrospective/Prospective follow-up. Repeated imaging in the same centre (or in other centres)
More detailed exposure assessment: observed/measured not only self reported	**Self reported exposure assessment**	Questionnaire self-reported exposure assessment
Study protocol: Reach a consensus on outcome definition	Heterogeneity of **outcome definition**	Study protocol: Reach a consensus on outcome definition
Study protocol: Reach a consensus on radiological outcome definition	Heterogeneity of **imaging technique** and **classification** of radiological outcome	Study protocol: Reach a consensus on radiological outcome definition
	MRI is the gold standard imaging modality for the evaluation of IVD pathologies 💰	
	Inflammatory biomarkers / Genetic profile **Intervertebral disc degeneration-** **New therapeutic options and challenges**	

Samanta A eta l. Intervertebral disc degeneration-Current therapeutic options and challenges. Front Public Health. 2023 Jul 6;11:1156749

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