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Review Article

Application and Progress of Mendelian Randomization in Intervertebral Disc Degeneration

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Abstract

Intervertebral disc degeneration (IVDD) is a prevalent degenerative disease and risk factors for it are complex and diverse. Due to limitations in observational research, identifying causal risk factors remains challenging. Mendelian randomization (MR), leveraging genetic variation as an instrumental variable (IV), has emerged as a powerful tool to study causal associations, overcoming issues of confounding bias and reverse causality. This review aims to summarise the progress of MR in exploring the causal relationship between IVDD and various associated risk factors. By summarizing 56 relevant publications retrieved from the Pubmed database, this review found significant causal links between IVDD and factors such as inflammatory cytokines, metabolism-related molecules, bacteria, smoking, and high bone mineral density. Conversely, no significant causal associations were found with LDL, total cholesterol, ApoB, serum uric acid levels, physical activity, and osteoporosis. Finally, MR not only supports observational findings but also opens new avenues for future research into IVDD causes.

Keywords

Mendelian Randomization, Intervertebral Disc Degeneration, Risk Factors, Inflammatory, Metabolic Disorders, Bacteria, Lifestyle Habits, Osteoporosis

1. Introduction

With the aging of the world's population, low back pain (LBP) has gradually become a global health problem that cannot be ignored. Among them, intervertebral disc degeneration (IVDD) has been the leading degenerative disease causing LBP [1]. According to statistics, about 5.5% of the global population suffers from IVDD accompanied by painful symptoms [2]. At the same time, IVDD-related LBP is a major cause of disability and a decline in the population's standard of living. In one study, researchers discovered that low back pain was the main cause of increased years lived with disability (YLD) in the population [3]. Most importantly, IVDD imposes a significant economic burden on society [4]. As a result, it is critical to explore the causal relationship between IVDD and other relevant risk factors in order to reveal the disease's underlying mechanism, implement effective therapies, and drive the development of scientific public health policies.

Randomised controlled trials (RCTs) have long been considered the 'gold standard' of epidemiological research [5]. However, it has several limitations, such as high time and labor costs, a lengthy study period, medical ethics, and so on, and its feasibility requirements are rather stringent [6]. Furthermore, observational studies are sometimes complicated by confounding factors and reverse causality, resulting in limits

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in their findings. With the advancement of high-throughput genomics technology, genome-wide association studies (GWAS) based on large cohorts now give adequate data for Mendelian randomisation (MR) [7]. The use of genetic variation as an instrumental variable (IV) to investigate the causal relationship between exposure and outcome is an important aspect of MR research [8]. Because of the more stable nature of the working variables used, it is well suited to overcome the constraints of RCTs and observational studies while ensuring the credibility of experimental data.

Because of the complexities of IVDD's pathogenic mechanisms, researchers continue to struggle to understand the etiology of the disease and its interaction with relevant risk factors. Because of its unique benefits, MR studies have been extensively used to explore the etiology and mechanism of IVDD in recent years, and some reliable results have been achieved, bringing new insights into the etiology of IVDD. As a result, this review discusses the use and progress of MR in the study of IVDD, with the goal of providing fresh ideas for future related research.

2. Data and Method

2.1. Literature Sources

This review searched the Pubmed database for all relevant literature up to September 2024, using the search terms 'Mendelian randomisation, Intervertebral disc degeneration, Inflammatory, Metabolic disorders, Bacteria, Smoking, Exercise, Bone mineral density, Osteoporosis'. An search of 1180 papers was conducted for this review. The titles and abstracts of these papers were briefly read and 162 papers were initially screened. Finally, 63 papers were included for further discussion after reading the whole text and applying the inclusion and exclusion criteria defined for this review.

2.2. Literature Inclusion Criteria

(i) Authoritative literature introducing background, application, and progress of MR; (ii) MR studies on the causal relationship between IVDD and associated risk factors; (iii) Correlation studies involving IVDD and related risk factors; and (iv) relevant research articles recently published in authoritative journals.

2.3. Literature Exclusion Criteria

(i) Literature that is not significantly relevant to the core themes in this review; (ii) Literature with repetitive or identical research content; (iii) Low-quality literature; and (iv) Literature that is old.

3. Results

3.1. Introduction of MR

3.1.1. The Development of MR

In the 19th century, Mendel, an Austrian biologist, uncovered the fundamental laws of heredity through pea hybridization experiments, laying the theoretical groundwork for genetic study. Katan first introduced the MR method to research in 1986 [9]. Drawing on Mendel's law of independent assortment, he proposed using genetic variation as an IV to explore relationships with disease. The IV is unaffected by external factors such as acquired environmental, social, economic, and behavioral variables, and it can greatly reduce confounding bias. The fact that their traits are innate assures a precise temporal sequence between them and the outcome, essentially eliminating the possibility of reverse causality. George et al. published the first Mendelian randomisation article in 2003, highlighting the capabilities of this research methodology in exploring the impact of environmental variables on disease and, as a result, proposing a research framework [10]. In 2005, studies using GWAS data on age-related macular degeneration (AMD) became frequently reported [11, 12]. These research established the possibility of using GWAS data to explore genetic factors in complicated diseases, and they also encouraged the development of later GWAS data, which offered significant data support for MR. To date, MR have been widely employed to examine the causal relationship between various diseases and exposures, including neoplasms, chronic diseases, and genetic diseases.

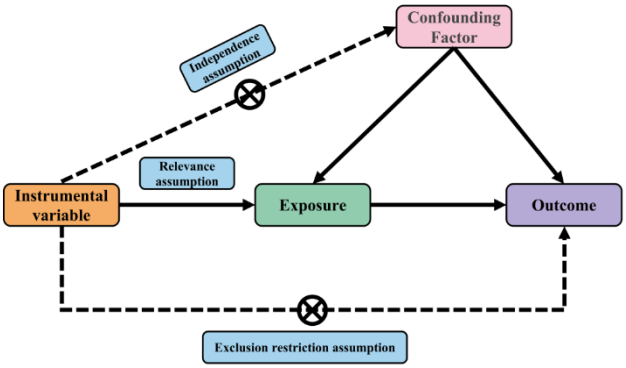

Figure 1. *The unit of MR analysis and the three key assumptions.*

3.1.2. Three Key Assumptions of MR

The selection of relevant genetic variations as IV is critical to MR studies, and the chosen IV must satisfy all three fundamental requirements at the same time [13]. (i)Relevance assumption, which means there must be a substantial relationship between IV and exposure. This suggests that variations in the IV can have a realistic effect on the exposure. (ii)

Independence assumption, which means that IV cannot directly or indirectly alter the relationship between exposure and outcome. To reduce confounding bias, IV should have no influence on the outcome other than through exposure. (iii) Exclusion restriction assumption, which means that the only way IV can influence outcome is by influencing exposure. This ensures IV's effectiveness during the regulatory process. If the selected IV does not adhere to any of the aforementioned principles, it may result in biased studies, lowering the dependability of causality estimates. Specific relationships are shown in Figure 1.

3.1.3. Types of MR

There are two basic types of MR: one-sample and two-sample [14]. The main feature of one-sample MR is that the IV, exposures, and outcomes used in the analysis are all derived from the same dataset. One-sample MR has been recognized as the most basic type of MR due to its single source of data and ease of analysis. The two-sample MR uses two datasets from two separate sources to validate IV-exposure and IV-outcome correlations, respectively, in order to infer causation between exposure and outcomes. Two-sample MR improves the reliability and generalizability of the results compared one-sample MR because it includes data from multiple sources. However, it does make analysis more complex. In addition, bidirectional mendelian randomization (BMR) of the highest order type is commonly used [15]. It is possible to reveal a bidirectional relationship between exposure and outcome by conducting two two-sample MR analyses in opposite directions. This study summarises the principles, methods and advantages and disadvantages of the above types of MR, as shown in Table 1.

Table 1. *Principles, methods, advantages and disadvantages of common MR types.*

Type	Principle	Method	Advantages	Disadvantages
One-sample MR	Causal analyses using genetic variation in the same dataset as an instrumental variable	(i) Validating the association between genetic variation and exposure; (ii) Validating the association between exposure and outcome	(i) Simple to operate; (ii) Suitable for analysing a single exposure factor and a single outcome; (iii) No need for additional external data sources	(i) Possible weak instrumental bias; (ii) Possible interference from horizontal pleiotropy; (iii) Relatively weak generalisability of results
Two-sample MR	Causality analysis using two datasets from different sources	(i) Applying dataset one to validate the association between genetic variation and exposure; (ii) Applying dataset two to validate associations between genetic variation and outcome; (iii) Validating the association between exposure and outcome	(i)More diverse data sources;(ii)Effects due to group factors can be attenuated;(iii)Horizontal pleiotropy can be controlled	(i) Need to obtain data sets from two independent sources; (ii) Selection bias may be introduced
Bidirectional MR	Analysing the bidirectional relationship between exposure and outcome	A variant of the two-sample MR, containing two two-sample MR analyses	Bidirectional validation was carried out, providing causal information in different directions	(i) More data and statistical analyses are needed; (ii) All of the working variables for both analyses need to satisfy the three key assumptions of MR

3.2. MR in Studies of IVDD and Its Applications

MR, as a causality research method with advantages over observational studies, is currently widely used to explore risk factors for IVDD. This review will discuss the findings of MR in IVDD research in terms of cellular inflammatory factors, metabolism, bacteria, lifestyle habits, and osteoporosis.

3.2.1. Cellular Inflammatory Factors and IVDD

Inflammation is directly associated to IVDD and one of the key factors underlying its development. Inflammation-induced IVDD involves multiple signaling pathways, including NF-KB pathways, TLR pathways and JNK pathways [16-18] and pro-inflammatory chemicals such IL-1β, IL-6, and NLRP3 [19-21]. In addition, inflammatory reaction that occurs in the intervertebral disc greatly upregulates NGF, BDNF, and other associated proteins to increase nerve development in the disc tissue and surrounding tissues, hence causing severe LBP [22]. A two-sample MR study by Gao F et al. indicated that IFN-γ and IL-18 had a significant causative relationship with IVDD [23]. In addition, it was found

that reducing IFN-γ and IL-18 expression levels may increase the risk of IVDD. A study by Xu T et al [24] indicated that six inflammatory cytokines, including GCSF, IFN-γ, IL-1β, SDF1a, IL-4, and IL-18, are causally related with IVDD. IFN-γ, IL-1β, IL-4, IL-18, and GCSF were found to reduce the risk of IVDD, but SDF1a raised the risk. Chen ZX et al used a BMR study to explore the bidirectional relationship between IVDD and cellular inflammatory factors [25]. The study found that IFN-γ and MIP-1β had a causal relationship with IVDD and lower the probability of development. The results of the reverse causality analysis revealed a connection between IVDD and lower levels of IL-13.

These studies not only highlight the complexity of inflammation in the development of IVDD and the diversity of cytokines involved, but also suggest that different inflammatory cytokines may have varied effects on IVDD. It emphasizes that inflammation-induced IVDD is caused by the combination of multiple inflammatory cytokines and should not be considered in isolation. Notably, several MR studies have demonstrated that IFN-γ is associated with a lower incidence of IVDD. Previous studies confirm that IFN-γ can perform an anti-inflammatory and reparative role by reducing T cell proliferation [26, 27]. IFN-γ may be a key target for influencing inflammation-induced IVDD.

3.2.2. Metabolism and IVDD

Among the metabolic processes in the body, the relationship between lipid metabolism disorders and IVDD has been a popular research issue. Lipid metabolism disorders can activate a variety of processes that promote the development of IVDD, including oxidative stress, endoplasmic reticulum stress, autophagy, and apoptosis [28]. Among them, lipid metabolism disorders induce IVDD mainly due to their production of large amounts of reactive oxygen species (ROS) triggering oxidative stress [29]. Important relationship between disorders of lipid metabolism and IVDD has also been found in many observational studies. Shi S et al discovered that IVDD was associated with increased triglycerides (TG) and waist to hip ratio (WHR) [30]. Meanwhile, Yuan L et al discovered that total cholesterol (TC) and low-density lipoprotein (LDL) are also risk factors for the development of IVDD [31]. In a BMR study by Guo W et al, they found that high-density lipoprotein(HDL), TG, and ApoA-I were associated with IVDD, with HDL and ApoA-I also having bidirectional causal relationship with IVDD [32]. Furthermore, the findings revealed that LDL, TC, and ApoB were not associated with IVDD.

Hyperglycemia, a direct result of glucose metabolism disorders, can cause IVDD by increasing processes such as proteoglycan degradation, apoptosis, and cellular senescence in intervertebral disc tissues [33, 34]. Diabetes mellitus is a common example of a glucose metabolism disorders that is thought to be a significant risk factor for developing IVDD. A retrospective study based on MRI imaging data found that patients with persistent hyperglycemia had a more severe IVDD than the healthy population [35]. In addition, a meta-analysis confirmed significant correlation between diabetes mellitus and IVDD in adults, which was unaffected by age [36]. In a MR study from Jin P et al, they discovered that type 2 diabetes (T2D) patients developed IVDD 6.9% more frequently than non-T2D patients [37]. In a BMR study mentioned above, it showed that T2D is significantly related with a high prevalence of IVDD, and increased fasting glucose and glycated haemoglobin levels may also greatly increase the incidence of IVDD [32].

In addition to lipid and glucose metabolism, other metabolites, such as uric acid, are known to contribute to IVDD. Uric acid levels were found to be a risk factor for IVDD in a retrospective study, implying that either high or low uric acid levels may raise the risk of the condition [38]. Interestingly, a two-sample MR study by Cai YT et al reported no significant connection between higher uric acid levels and IVDD [39]. This finding was validated in sensitivity analyses, thus enhancing the reliability of the results.

3.2.3. Bacteria and IVDD

There are various theoretical hypotheses in the academic community about the effect of bacteria on IVDD. In one study, microbiological culture and PCR were used to detect the growth of a range of bacteria in IVDD tissues, with Propionibacterium acnes (P. acnes) having the highest positive rate at 28.7% and therefore being regarded the most important causal organism [40]. Other studies validated this finding [41, 42]. Another study used 16sRNA sequencing to identify the same 52 bacteria in IVDD tissues and intestines, leading to a theory of gut-spine axis regulation [43]. This shows that P. acnes and the gut microbiota have a role in the development of IVDD.

In a two-sample MR study, Jia Y et al discovered that P. acnes was related with lower incidence of IVDD [44]. This result seems to differ dramatically from the results of previous studies, but it goes some way to supporting the possibility of the contamination theory that P. acnes was brought into the disc tissue because of surgical and sampling contamination. In a two-sample MR study, Zheng D et al. discovered ten bacterial species that were causally related with IVDD, two of which were positively associated with the disease (*Eubacterium brachy* and *Marvinbryantia*) and the other eight were negatively associated [45]. In addition, another BMR study also found the causal relationship between nine bacterial species and IVDD [46]. Based on the above findings, it is indicated that there is a clear causal association between intestinal flora and IVDD, lending support to the gut-spine theory. It is worth noting that, due to the diversity of intestinal flora and the complexity of the microenvironment, flora interact in complicated ways [47]. Current MR studies do not take into account the potential impact of inter-flora interactions on the final output. As a result, more extensive research should be conducted in the future to validate these findings.

3.2.4. Lifestyle Habits and IVDD

Smoking, as a high-risk lifestyle habit, is closely linked to the development of a variety of diseases. A retrospective study found that smokers had a higher level of IVDD than nonsmokers, and the associated LBP were more severe [48]. Furthermore, some retrospective studies have found that smoking may increase the risk of IVDD recurrence and postoperative pain [49, 50]. In a two-sample MR analysis by Han Z et al, the study demonstrated a causal relationship between smoking and IVDD, between serum IL-1β and IVDD, and between smoking and serum MCP-3, respectively [51]. By integrating with basic medical theories, The study found that continuous smoking increases serum MCP-3 levels, which promotes macrophage activation and IL-1β release, aggravating the progression of IVDD. This is an innovative application of MR study results combined with basic medical theory, which provides inspiration for the application of MR to further reveal disease mechanisms in the future.

Physical activity can have both positive and negative effects on physical health. Light, moderate physical activity promotes adjustment and functional recovery, but excessive, severe physical activity frequently causes injury. As an important structure for weight bearing and decompression of the spine, degeneration and injury of the intervertebral disc are also closely related to physical exercise. Previous research has found that excessive or high-load activity, as well as a lack of exercise, can harm the intervertebral discs, particularly high-load exercise, which is more likely to cause acute injuries due to the increased stress it places on the discs [52, 53]. In a two-sample MR study, it was reported that there was a negative causal relationship between mean exercise level and LBP, whereas vigorous activity and LBP were positively related [54]. However, no direct causal relationship with IVDD was found regardless of the level of exercise. It is worth noting that the study used energy expenditure as the basis for categorising exercise intensity, whereas the data was intended to be measured over a short timeframe. As a result, studies of chronic conditions such as IVDD may require more suitable criteria for determining exercise intensity levels.

3.2.5. Osteoporosis and IVDD

Most previous studies have found a possible causal relationship between osteoporosis, particularly vertebral osteoporosis, and IVDD; nevertheless, there is still academic debate about whether this correlation is positive or negative [55]. A study of postmenopausal women indicated that high bone mineral density (BMD) in the lumbar spine was strongly associated with the severity of IVDD [56, 57]. On the contrary, animal studies have shown that vertebral osteoporosis may contribute to the development of IVDD by damaging endplate architecture, increasing the expression of catabolic proteins, and accelerating extracellular matrix degradation [58]. In a MR study by Li L et al, after adjusting for removal of factors that could have an effect on the outcome, the final results found that heel BMD, lumbar spine BMD and whole body BMD were causally related to disc degeneration, whereas femoral neck BMD was not causally related to disc degeneration [59]. Similar results to those of the above study were obtained in BMR study by Liu G et al [60]. The difference is that this study determined that femoral neck BMD had a possible causal link with IVDD. The variation in the outcomes of the aforementioned two MR investigations could be attributed to the varied selection of confounders that need to be removed. Because, before adjusting for confounders, the first study showed an association between femoral neck BMD and IVDD as well [59]. In conclusion, both studies illustrate the increased risk of IVDD with high BMD, but the exact mechanism of its effect remains to be investigated further.

4. Conclusion

IVDD is a chronic degenerative disease affecting the intervertebral discs. Because the pathogenic mechanism of IVDD is complex, the causal relationship between it and related risk factors is still not entirely understood. MR is a analytical methods of causality using genetic variation as IV, and relying on the vast data resources of the GWAS database, it has now shown great potential in studies exploring risk factors for IVDD. Existing MR studies on IVDD show that cellular inflammatory factors such as IL-18, IFN-γ, IL-1β, Apo a-I, T2D, fasting blood glucose, glycosylated hemoglobin, bacterial microorganisms, smoking, and high BMD are causally associated with IVDD, while LDL, TC, Apo B, serum uric acid levels, physical activity, and osteoporosis are not. However, MR studies still have some limitations. First, study data may be selectively biased. The majority of the data used for analysis in the GWAS database comes from European populations, which may make the results less generalizable. This requires that the GWAS database continually improve its data structure, or that researchers include data from richer sources into these studies. Second, MR has not yet created a standardized research framework. There have been MR studies on IVDD in which researchers use different criteria for screening IVs due to the variety of data sources, different types of MR, and so on. However, this may introduce the problem of weak instrumental variables, leading to discrepancies between study results. This necessitates the development of uniform screening IV criteria, which will increase the reliability of results and their comparability. Finally, the ability to reveal pathogenic mechanisms is limited. MR studies can make correct judgments about the causal relationship between exposure and outcome, but revealing the mechanism of action between the two is insufficient. Researchers must be able to combine histology data and basic studies in order to validate the results of MR studies, which will aid in the discovery of potential complex disease mechanisms. In conclusion, MR, as an emerging research method, has demonstrated unique advantages for exploring disease causality. It not only complements the findings of previous observational studies, but also provides a new direction for

future research on IVDD-related risk factors. It is believed that with the continuous development of MR, it will become a strong link between causal evidence of traditional clinical studies and basic research in the future.

Abbreviations

IVDD	Intervertebral Disc Degeneration
MR	Mendelian Randomization
IV	Instrumental Variable
LBP	Low Back Pain
YLD	Years Lived with Disability
RCTs	Randomised Controlled Trials
GWAS	Genome-wide Association Studies
AMD	Age-related Macular Degeneration
BMR	Bidirectional Mendelian Randomization
ROS	Reactive Oxygen Species
TG	Triglycerides
WHR	Waist to Hip Ratio
TC	Total Cholesterol
LDL	Low-density Lipoprotein
HDL	High-density Lipoprotein
T2D	Type 2 Diabetes
P. acnes	Propionibacterium Acnes
BMD	Bone Mineral Density

Author Contributions

Weichao Yang: Resources, Visualization, Writing – original draft

Dongping Ye: Conceptualization, Funding acquisition, Supervision, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Fields

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