

TEACHING MOMENTS | COMPENDIUM GENEESKUNDE | ANATOMY | MEET OUR TEAM |  
PHARMACOLOGY | ARTICLES | RADIOLOGY IMAGE | NEWS | THE EXPERT'S VIEW

**SUBJECT 101 - ANATOMY |**

MECKEL'S DIVERTICULUM:  
THE RULE OF 2S

**TEACHING MOMENTS |**

BRIDGING PERSPECTIVES:  
APPRECIATING STRENGTHS IN  
DIFFERENT SYSTEMS



# AMSj

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## Editorial

Dear readership,

On behalf of the editorial board, I have the pleasure of welcoming you to the **39th edition of the Amsterdam Medical Student Journal!** I would like to thank all the reviewers and editorial members for the effort that they have put into this edition, and congratulate them on the result!

In this edition, we bring you a range of research news, Subject 101 items, and radiology quizzes!

First, Prof. Levi shares his expert perspective on ChatGPT, with a particular focus on its current limitations, a must-read for future clinicians and researchers. Read more on page 8.

Matthijs and colleagues presented an interesting case of a delayed presentation of wrist pain after falling off a bike. Try to spot the abnormality together with a fellow medical student and refresh your knowledge of the anatomy of the carpal bones. Read more on page 5.

Selection bias and information bias may sound similar, but they are two different categories of bias. Do you know what the difference is? Flip to page 11 to find out.

On page 6, Tycho shares his reflections following a clerkship abroad in South Africa, comparing the healthcare system there with our local Dutch system. Going abroad is an enriching experience and is highly recommended!

At AMSj, we encourage students to embark on their own scientific journey—whether through research or education. We warmly invite you to submit your original work to our journal and to experience firsthand what goes into publishing scientific research. AMSj is also regularly looking for new colleagues. Are you interested in joining us as an editor or reviewer? Keep an eye on our social media channels for frequent vacancies. For general questions about AMSj, please do not hesitate to contact the Editors-in-Chief via **chief-editor@amsj.nl**; we are always happy to help.

The 39th edition of AMSj will, sadly, be the final edition for which we have had the honour of serving as Editors-in-Chief. As we move on to the next steps in our careers—combining PhD trajectories with clinical work—we will be handing over our responsibilities to the next Editors-in-Chief. We are pleased to announce that, following a rigorous selection process, from edition 39 onward, Elisha van Kouwen and Yassmina Derraze will take on this role and continue the mission of AMSj. We wish them every success and look forward to seeing AMSj continue to grow in the coming year.

Sincere greetings,

*Bobby Lam and Tina Vekua*  
**Student Editor-in-Chief**  
**Amsterdam UMC,**  
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# WHAT'S NEW

## Rethinking Opioid Use: What a Recent Systematic Review and Meta-Analysis Tells Us

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A recent systematic review and meta-analysis investigated the effectiveness and safety of opioid-free anesthesia (OFA) compared to conventional opioid-based anesthesia (OBA). This review included 42 randomized controlled trials with over 4600 patients undergoing various surgical procedures. The primary outcome was postoperative pain within the first 24 hours, and secondary outcomes included safety and adverse events. The analysis found no significant difference in postoperative pain between OFA and OBA. Evidence regarding reductions in postoperative nausea and vomiting with OFA was inconsistent, and no major safety concerns were observed for either approach.

OFA relies on the use of a combination of non-opioid medications and techniques to achieve effective analgesia and anesthesia. These alternatives include agents such as local anesthetics, alpha-2 adrenergic agonists (e.g., dexmedetomidine), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), magnesium sulfate, and nonsteroidal anti-inflammatory drugs (NSAIDs). Additionally, neuraxial blocks and regional anesthesia techniques, such as ultrasound-guided nerve blocks, play a crucial role in targeting specific areas of pain without affecting the entire body.

Clinically, the study indicates that OFA is a safe and feasible alternative to OBA, particularly in patients at high risk for opioid-related complications such as nausea, respiratory depression, or opioid tolerance. However, most included trials had moderate to high risk of bias, small sample sizes, and heterogeneous OFA protocols, which limits the certainty of these findings.

While OFA does not yet demonstrate clear superiority in analgesic outcomes, its implementation may support strategies to reduce opioid-related complications. The findings also highlight the need for standardized OFA protocols and high-quality trials to establish clear recommendations. In conclusion, this study suggests that OFA can be safely used in selected patients without compromising postoperative pain control. These findings offer more flexibility in anesthesia planning and support the practice of opioid-sparing strategies, thereby facilitating patient-centered care<sup>1</sup>.

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## Esketamine Nasal Spray versus Quetiapine in Treatment-Resistant Depression

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In major depressive disorder (MDD), 10–30% of patients develop treatment-resistant depression (TRD), defined as a non-response to two or more properly dosed and timed pharmacological therapies within the same episode. While achieving remission and preventing relapse remain central goals, many existing therapies still provide only limited benefit.

The ESCAPE-TRD study, a randomized, rater-blinded, open-label trial, compared esketamine nasal spray with quetiapine extended-release, both administered alongside an SSRI/SNRI in patients with TRD. This was the first head-to-head study directly comparing esketamine with an augmentation strategy, which is the common next step in MDD treatment protocols.

## Adrenalectomy for hypertension in patients with unilateral adrenal incidentalomas and Mild Autonomous Cortisol Secretion

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Adrenal incidentalomas, with a prevalence of 3–10% in adults, are mostly benign, yet 30–50% of these cause mild autonomous cortisol secretion (MACS). This is associated with an increased prevalence and incidence of cardiovascular risk factors, particularly hypertension<sup>1</sup>.

The CHIRACIC-study, a multicenter, superiority, open-label, randomized controlled trial, aimed to compare the proportion of patients who could reduce their standardized stepped-care anti-hypertensive treatment (SSAHT) by at least one step while maintaining blood pressure within normal ranges following adrenalectomy versus conservative management in patients with unilateral incidentalomas and MACS. In this study, with a follow-up of 13 months, 52 patients were randomly assigned to adrenalectomy (n = 26) or conservative management (n = 26), both combined with SSAHT.

Findings indicated that esketamine provided significant advantages. At week 8, 27.1% of patients receiving esketamine achieved remission (Montgomery-Åsberg Depression Rating Scale ≤10) versus 17.6% receiving quetiapine. By week 32, nearly half of patients treated with esketamine (49.7%) were in remission compared with 32.9% on quetiapine. In terms of relapse prevention, 21.7% of esketamine patients remained relapse-free compared with 14.1% of those on quetiapine. Time-to-event analyses confirmed these benefits: esketamine shortened the time to first remission and first response.

Despite limitations, such as open-label design and differences in treatment administration, results consistently favored esketamine. These findings highlight esketamine nasal spray as an effective option that not only increases remission rates, but also accelerates recovery and sustains long-term improvement in patients with TRD.<sup>1</sup>

1. Young AH, Llorca P-M, Fagioli A, Falkai P, Cardoner N, Nielsen RE, et al. Efficacy of esketamine nasal spray over quetiapine extended release over the short and long term: sensitivity analyses of ESCAPE-TRD, a randomised phase IIb clinical trial. *The British Journal of Psychiatry*. 2025;226(2):72–8. doi:10.1192/bjp.2024.124

A drug reduction in the SSATH with adequate ambulatory blood pressure measurement was achieved in 46% of patients who underwent adrenalectomy compared with 15% in the conservative group (95% CI 0.11–0.58, p=0.0038). At the end of study, MACS had disappeared in all patients who underwent adrenalectomy, whereas it persisted in all patients who were treated conservatively. This demonstrates that MACS is a cause of endocrine hypertension. Furthermore, 43% of patients who underwent adrenalectomy still required antihypertensive therapy, compared with 96% of the conservative group (95% CI –0.78 to –0.38, p <0.0001).

These findings indicate that adrenalectomy in patients with unilateral adrenal incidentalomas and MACS significantly reduces the need for antihypertensive medication. Further large-scale randomized controlled trials with longer follow-up are warranted to confirm these results and to assess long-term cardiovascular outcomes.

1. Tabarin A, Espiard S, Deutschbein T, Amar L, Vezzosi D, Di Dalmazi G, et al. Surgery for the treatment of arterial hypertension in patients with unilateral adrenal incidentalomas and mild autonomous cortisol secretion (CHIRACIC): a multicentre, open-label, superiority randomised controlled trial. *Lancet Diabetes Endocrinol*. 2025;13(7):580–90.

## Delayed Diagnosis of Wrist Fracture

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### CASE

A **29-YEAR-OLD MALE** presented two weeks after a fall from a bicycle, landing on his outstretched left hand, resulting in immediate wrist pain. He initially assumed a minor contusion and continued physical activities despite persistent discomfort. At a routine outpatient visit, examination revealed snuff-box tenderness without swelling or ecchymosis, raising suspicion for a scaphoid fracture. An X-ray of the left wrist was taken.

#### QUESTION 1

Examine the X-ray. What is the most likely abnormality, and which classification system is commonly used for this type of fracture?

- A. Vertical fracture through the scaphoid tubercle
- B. Transverse fracture through the scaphoid waist
- C. Intra-articular fracture involving the distal radius

#### QUESTION 2

What are the different management options?

#### QUESTION 3

In delayed scaphoid fractures, the risk of avascular necrosis (AVN) is highest in which anatomical location?

- A. Distal pole
- B. Waist
- C. Proximal pole
- D. Entire scaphoid equally



FIGURE 1 Oblique view of the scaphoid



FIGURE 2 Lateral X-ray of left wrist

Answer on page 29 ►

## Bridging Perspectives: Appreciating Strengths in Different Systems

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**IN THE NETHERLANDS, COMPLAINING ABOUT OUR HEALTHCARE SYSTEM ALMOST FEELS LIKE A NATIONAL PASTIME.** Waiting lists, rising insurance premiums, and staff shortages are frequent topics of discussion among patients and professionals alike. As a medical student, I have often joined these conversations, frustrated by inefficiencies that seem to undermine an otherwise well-functioning system.

That perspective began to shift during my surgical clerkship at Steve Biko Academic Hospital in South Africa. My first patient handed me a stack of paper records after waiting five months for pathology results that would determine their treatment. Some aspects of the hospital environment reflected the resource constraints that are part of the South African public sector: shortages of supplies, long queues, and infrastructure under pressure.<sup>1,2</sup>

**But what stood out even more were the strengths of the system and the professionals working within it.**

The expected clinical knowledge of the South African medical students, and their ability to formulate precise differentials from history and examination alone, often exceeded what is typically expected of students at a comparable stage in the Netherlands. Decisions about additional testing were made carefully and consciously, with attention to cost-effectiveness and patient context. In a setting where inequality in access to care is a daily reality, their ability to deliver high-quality tertiary

care was inspiring rather than discouraging.

Back in the Netherlands, I began to see our system differently. Yes, it is imperfect. But it is also mostly safe, equitable, and remarkably efficient. Patients rarely face catastrophic delays or financial barriers that affect their outcomes.

**Seeing how care is delivered in different contexts helped me understand the strengths of each system and what can be learned from both.**

It is easy to critique what we know, and it is harder to appreciate what quietly works well. The 2024 World Index of Healthcare Innovation ranked the Netherlands fourth globally.<sup>3</sup> Based on 48 indicators, the Dutch healthcare system is currently ranked second in Europe.<sup>4</sup> It is a privilege to practice medicine in a system that is largely safe and efficient, while also learning from the clinical expertise and medical proficiency elsewhere.

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# MEET OUR TEAM

Hi everyone,

My name is Yassmina Derraze, and I am one of the new Editors-in-Chief VUmc. I am a 23-year-old medical student, currently completing my clinical clerkships.

In my role as Editor-in-Chief, I oversee the peer-review process, serve as a point of contact for our reviewers, and maintain close communication with the General Board of AMSJ. Having previously worked as a reviewer myself, I am familiar with both perspectives within the journal and understand the challenges that come with each role.

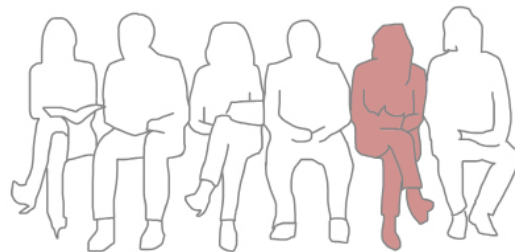
In addition, I have been actively involved in scientific research driven by my own interests, including gastrointestinal surgery, lung oncology, and plastic surgery. Through these projects, I have contributed to several peer-reviewed publications. I hope to use this experience to support student reviewers in improving their scientific writing skills through initiatives such as 'How To Write Your Thesis' and our yearly Journal Clubs.

Over the coming year, I aim to fully engage with all aspects of my position. My goal at AMSJ is to create an environment in which students feel supported and confident to engage with scientific research. I want reviewers to perceive the publication process not as distant or intimidating, but as an accessible and rewarding opportunity for academic growth.

Yours sincerely,  
Yassmina Derraze



**Yassmina Derraze,  
Editor-in-Chief VUmc**



## Is artificial intelligence a blessing or a threat for science?

MARCEL LEVI<sup>1</sup>

*1 President Dutch Research Council (NWO) and Professor of Medicine, University of Amsterdam and University College London*



IN THE 1950'S ISAAC ASIMOV PUBLISHED A SERIES OF SCIENCE FICTION NOVELS TITLED "I, ROBOT", in which the world is gradually being taken over by robots. They are slowly but surely pushing humans aside, even though their initial purpose was to help them. A recent development in artificial intelligence brings Isaac Asimov's world alarmingly closer and an increasing group of people seem to believe that subjugation by computers is imminent.

The fear is sparked by ChatGPT and similar computerized large language systems: impressive machine learning programs with autonomous algorithms that continuously analyze billions of texts and learn how words and sentences are related. This results in a system that, based on simple questions, generates elaborate essays and erudite treatises. By simply typing terms like "climate change" or "a cure for cancer", well-researched texts appear that wouldn't be out of place in a university student's essay or even a bachelor thesis. Last year, the program even passed a Master of Business Administration (MBA) exam.

At first glance, ChatGPT is astonishing, and the texts it generates are virtually indistinguishable from human-written publications.

Of fifty summaries generated by ChatGPT based on information gathered from leading medical journals, only half were identified by scientific experts as computer-generated.

So many researchers ask themselves whether ChatGPT and its ultrarapid analytic capabilities and skillful writing properties could be a blessing for science. Others are more pessimistic

and see major disadvantages, leading to their conviction that the use of ChatGPT should be banned from research grant proposals and scientific publications.

There are certainly issues. In the first place, ChatGPT's "intelligence" is—at least currently—not so gifted as it looks at first sight. In texts on a topic you know a little more about, incorrect conclusions are drawn due to misinterpretation of word patterns, superficial conclusions, and the use of irrelevant or incorrect references. ChatGPT clearly cannot distinguish between old, outdated information and more recent knowledge.

Nevertheless, the convincing and often error-free style makes it difficult for a casual reader to see through the lack of accurate information.

Also, everything ChatGPT is doing is based on earlier ideas and published texts. It is hardly capable of generating or judging original ideas, and that is often just the quintessence of scientific work and writing. Hence, the concern that ChatGPT should not be used for reviewing grants or science papers is justified as it would likely not give appropriate merit to highly innovative and creative thoughts.

On the other hand, one can also view that if ChatGPT or similar models are capable of doing exams, writing research proposals or (parts of) scientific articles, it may also mean that these texts are just too simple and may even be of questionable quality. In that case ChatGPT teaches us—just like Isaac Asimov's stories—**THAT MACHINES AND ROBOTS WILL ONLY WIN OVER US IF WE LOWER OURSELVES TO THE LEVEL OF UNIMAGINATIVE AND UNINSPIRED BEINGS.**

## Meckel's Diverticulum: The Rule of 2s

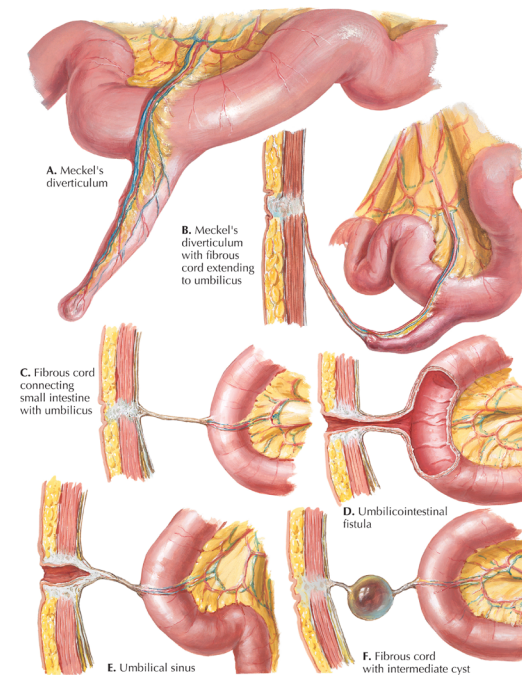
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A 2-YEAR-OLD BOY is brought to the Emergency Department by his worried parents after passing red blood in his stool. The bleeding is painless but substantial enough to soak his diaper. The child appears pale but hemodynamically stable, with no abdominal tenderness on examination. His parents mention he has had similar, smaller episodes over the past months that resolved spontaneously. Laboratory results show iron deficiency anemia. The doctor orders an abdominal ultrasound which reveals a small outpouching in the distal ileum: a **Meckel's diverticulum**.<sup>1</sup>



**FIGURE 1** Meckel's diverticulum.  
Netter's Atlas of Human Embryology, Larry S. Cohard, Icon Learning Systems 2002.

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, representing a persistent remnant of embryonic development. This small pouch protrudes from the wall of the small intestine.<sup>1,2</sup> The congenital anomaly results from incomplete obliteration of the **vitelline (omphalomesenteric) duct** during the 5th–7th week of gestation.<sup>3</sup> This duct normally connects the primitive midgut to the yolk sac and involutes by week 7. Failure of involution produces a true diverticulum on the antimesenteric border of the ileum, containing all intestinal wall layers.<sup>2,3</sup>

The characteristic features of Meckel's diverticulum can be remembered through the mnemonic *'the rule of 2s'*:

- Occurs in 2% of the population
- Located 2 feet from the ileocecal valve
- Approximately 2 inches long
- May contain 2 types of ectopic mucosa (gastric, pancreatic)
- 2:1 male-to-female ratio for complications
- Often symptomatic before the age of 2<sup>4</sup>

Most cases remain silent and are found incidentally. Symptomatic presentations fall into three main groups:

- Bleeding: from ulceration due to ectopic gastric mucosa, classically painless in toddlers
- Obstruction: through intussusception with the diverticulum as lead point, or volvulus around fibrous bands
- Inflammation: diverticulitis mimicking acute appendicitis, sometimes only recognized during appendectomy<sup>1,4</sup>

Ultrasound can suggest the diagnosis, while a **technetium-99m pertechnetate scintigraphy**, also known as the *'Meckel scan'*, has high specificity and sensitivity. This scan localizes ectopic gastric mucosa and typically reveals focal uptake in the right lower quadrant corresponding to the diverticulum.<sup>4</sup>

This congenital anomaly is named after **Johann Friedrich Meckel the Younger** (1781–1833), a German anatomist from an illustrious medical family. At only 24 years old he became professor of anatomy in Halle, and in 1809 he published his description of the diverticulum ilei, recognizing it as a remnant of the omphalomesenteric duct.<sup>6</sup> Though first observed by Fabricius Hildanus in 1598, Meckel's embryologic explanation and systematic analysis secured his name in medical history.<sup>2</sup>

Meckel's diverticulum, though often asymptomatic, serves as a classic illustration of how embryology meets clinical medicine. The rule of 2s is a useful guide, but variation is common; in young children with painless lower gastrointestinal bleeding, early consideration of Meckel's diverticulum and a timely *'Meckel scan'* is key to achieving a definitive diagnosis and preventing recurrent complications.<sup>1,5</sup>

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JOHANN FRIEDRICH MECKEL  
THE YOUNGER (1781–1833)

What inspired you and what did you learn? Inspire other students. See guidelines for submitting on amsj.nl



## Selection Bias versus Information Bias: A Practical Overview

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### INTRODUCTION

Bias threatens the validity of epidemiological research. Two major forms of bias are selection bias and information bias. Although they arise through different mechanisms, each can distort study findings substantially. Recognising how these biases occur is crucial for evaluating study quality and determining whether results can be applied to both the study population and the broader target population. For a more detailed explanation of these populations, see our earlier review, *Distinguishing Study Population from Target Population in Epidemiological Research*<sup>1</sup>.

### SELECTION BIAS

Selection bias arises when individuals who are included in a study differ systematically from those who are not, in ways related to both the exposure and the outcome<sup>2</sup>. As a result, the final study sample no longer represents the population the researchers intended to examine (target population). This often occurs through differential loss to follow-up: when the likelihood of remaining in the study depends on both exposure and outcome, the observed association becomes distorted<sup>2</sup>. For example, if only participants who completed follow-up are analysed, and completion is influenced by their exposure and disease severity, the resulting sample becomes unbalanced. The analysis may then suggest an association that does not exist, or fail to detect one that does<sup>2</sup>. The LIFE-Adult Study provides a clear illustration of selective participation at baseline (the ‘‘healthy participant effect’’)<sup>3</sup>: Only 31% of invited Leipzig residents participated in the baseline assessment, and comparison with nonparticipants showed systematic differences. Participants were more often highly educated, employed, and married, and reported a lower prevalence of major health conditions than the general

Leipzig population. These patterns show that the study population differs meaningfully from the intended target population.

### INFORMATION BIAS

Information bias arises when there are systematic errors in the way exposure, outcome, or other variables are measured<sup>4,5</sup>. This type of bias occurs when the information collected from participants does not accurately reflect the truth<sup>4,5</sup>. The problem lies not in who is included in the study, but in the accuracy and consistency of the measurements itself. A central mechanism is misclassification, which occurs when individuals are assigned to the wrong exposure or outcome category<sup>4,5</sup>. This may happen for various reasons: participants may not remember past events accurately, measurement tools may lack precision, or observers may record information differently depending on what they already know about a participant<sup>4,5</sup>. Misclassification can take different forms **FIGURE**<sup>4,5</sup>. When measurement errors occur equally across comparison groups, the misclassification is considered non-differential. This tends to weaken true differences between groups, often resulting in an association towards the null **FIGURE**<sup>4,5</sup>. In contrast, when errors differ between groups, such as when people with a disease recall past exposures more thoroughly than those without the disease, the misclassification becomes differential. Differential errors can bias results in any direction, potentially exaggerating a true association or obscuring one that exists **FIGURE**<sup>4,5</sup>. Common examples of information bias include recall bias in case-control studies, where cases may reflect more carefully on past exposures than (healthy) controls, and observer bias, in which outcome assessors score participants differently based on their knowledge of exposure status<sup>4,5</sup>.

Inaccurate self-reported behaviors, such as physical activity or alcohol use, also fall into this category<sup>4,5</sup>. Because information bias affects the accuracy of the collected data rather than the process of selecting participants, it can distort study findings even when the study population perfectly represents the target population.

### CONCLUSION AND WAYS TO REDUCE BIAS

Selection bias and information bias affect epidemiological research in fundamentally different ways. Selection bias alters the composition of the study population, meaning that the individuals included in the analysis may no longer represent the target population. Information bias, on the other hand, arises from inaccurate or inconsistent measurements, leading to incorrect classification of exposures or outcomes. **Recognising which type of bias is present is essential for choosing appropriate prevention strategies.** To reduce selection bias, researchers can aim to maximise participation at baseline, monitor and describe nonresponders, minimise loss to follow-up, and routinely assess whether the study population still resembles the intended target population, as illustrated in the LIFE-Adult Study<sup>3</sup>. To reduce information bias,

it is important to use validated and reliable measurement tools, standardised data collection procedures, blind outcome assessors when possible, as well as avoiding heavy reliance on participant recall. **Distinguishing between these two forms of bias strengthens our ability to judge whether study findings accurately reflect reality and whether they can be applied to the broader target population.**

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### Differential & Non-differential misclassification

#### Non-differential error misclassification

- Similar error across groups
- Typically weakens the association (bias toward the null)



#### Differential error misclassification

- Error differs by group
- Can bias the association in either direction (toward or away from the null)



**FIGURE** Differential versus non-differential misclassification. Non-differential misclassification often weakens associations toward the null, whereas differential misclassification can bias estimates in either direction.

# Breaking the Shackles of Rheumatoid Arthritis with Physical Exercise: A Promising Avenue for Improved Health

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## ABSTRACT

**INTRODUCTION** Rheumatoid arthritis (RA) is a chronic inflammatory disease in which patients have significant joint inflammation with functional impairment, pain, fatigue, and sleep disturbances, all leading to poor health. Studies have proven that most people with RA avoid doing physical activities out of fear that it may worsen the pain or cause joint damage, resulting in decreased muscle strength and ultimately leading to disability and impaired quality of life (QoL). Investigating the effects of physical exercise on major outcome measures in RA is essential to inform clinicians as well as patients about the importance of physical exercise to improve the course and outcome of RA. Major outcome measures in RA include disease activity, joint damage, disability, aerobic capacity, muscle strength, and body composition. The aim of this study was to review the scientific evidence for the effectiveness of physical exercise on major outcome measures in patients with RA.

**METHODS** An advanced literature search was conducted across PubMed, Cochrane Library, Web of Science, Wiley Online Library, and Google Scholar. Original studies from the past ten years (2013–2023) examining physical exercise and major outcome measures in RA were selected. Relevant data were extracted and critically reviewed.

**RESULTS** Eighteen clinical trial articles were included. Their findings show that physical exercise improves disease activity, functional ability, aerobic capacity, muscle strength, body composition, fatigue, sleep, stiffness, pain, and QoL in RA patients. All studies confirmed that physical exercise is safe for RA patients. However, none examined its effect on joint damage.

**CONCLUSION** Physical exercise is safe for RA patients and correlates with the improvement and maintenance of many of the major outcome measures in RA, both physically and mentally. RA patients should be better informed and encouraged by health care professionals to perform physical exercise according to the international recommendations.

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease and among the most common chronic inflammatory conditions<sup>1</sup>. Its primary symptom is symmetrical polyarthritis, but other features include lung involvement, vasculitis, and systemic symptoms<sup>1</sup>. In 2017, there were nearly 20 million RA cases worldwide - a 7.4% increase since 1990<sup>2</sup>. RA is more common in women, typically between ages 50–60<sup>3</sup>. Pain, fatigue, and joint deformities impair body composition, muscle strength, and quality of life (QoL)<sup>4</sup>.

Treatment involves DMARDs, non-drug therapies, and lifestyle advice, including physical activity<sup>5</sup>. Yet, patients often receive little guidance on how exercise can affect their disease<sup>5</sup>.

Many remain inactive due to pain, fatigue, or fear of joint damage<sup>6–8</sup>, which worsens symptoms<sup>9</sup>. Despite believing they are active enough, most fall short of activity guidelines<sup>10</sup>. Exercise is feasible and beneficial for RA patients<sup>11,12</sup>, including aerobic, strength, combined, aquatic, and stretching routines<sup>13</sup>. Inactivity rates range from 42% to 80% globally<sup>14,15</sup>.

Major RA outcome measures include disease activity, disability, joint damage, pain, physical fitness (aerobic capacity, muscle strength), body composition, fatigue, sleep, and QoL<sup>13,16</sup>. This review aims to assess the evidence on how physical exercise affects these outcomes in RA patients.

## METHODS

An advanced literature search was conducted across PubMed, Cochrane Library, Web of Science, Wiley Online Library, and Google Scholar using relevant MeSH and tiab terms (shown in the table below). Boolean operator “AND” was used to combine these terms, and filters excluded reviews and meta-analyses, limiting results to original studies published between 2013 and 2023. This yielded a total of 2642 articles.

Rheumatoid arthritis	"Arthritis, Rheumatoid"[Mesh] OR rheumatic disorders*[tiab] OR Rheumatic Diseases*[tiab] OR arthritis*[tiab] OR rheumatoid arthritis*[tiab] OR rheumatic*[tiab]
Physical exercise	"Exercise"[Mesh] OR exercising*[-tiab] OR physical activity*[tiab] OR training*[tiab] OR physiotherapy*[-tiab] OR movement*[tiab]
Effectiveness	"Comparative Effectiveness Research"[Mesh] OR "Treatment Outcome"[Mesh] OR "Pragmatic Clinical Trials as Topic"[Mesh] OR "Pragmatic Clinical Trial"[Publication Type] OR impact*[tiab] OR influence*[tiab] OR efficiency*[tiab] OR usefulness*[tiab] OR value*[tiab] OR efficacy*[tiab] OR effect*[tiab] OR effective*[tiab] OR efficient*[tiab] OR effectivity*[tiab] OR benefit*[tiab]

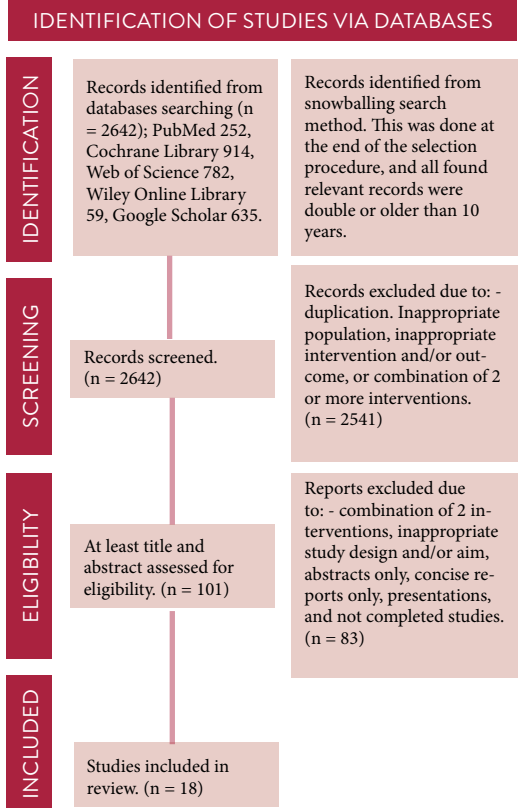
For this review, data extracted per article included study design, number of RA patients and controls, type, duration, and weekly frequency of exercise intervention, and RA outcome measures.

## RESULTS

### 3.1 SELECTION OF ARTICLES AND PARTICIPANTS

Exclusion criteria included reviews, case reports, guidelines, non-English articles, studies on non-RA rheumatic diseases, non-exercise interventions, and outcomes unrelated to major RA measures. The selection process is shown in Figure 1.

Most RA patients were recruited from rheumatology outpatient clinics at (large) teaching or academic hospitals, or from existing clinical databases. One study recruited participants via a local newspaper advertisement<sup>17</sup>.



**FIGURE 1** The flow chart of the selection procedure. From: Page MJ, Mulrow CD, et al.

### 3.2 THE EFFECTS OF PHYSICAL EXERCISE ON RA MAJOR OUTCOME MEASURES

The intervention programs were well described but varied in exercise type (aerobic, strength, or both), duration, intensity, and frequency.

Bartlett et al.<sup>18</sup> examined a 10-week aerobic program (3 × 30 min/week), which led to a clinically significant reduction in disease activity (p = 0.001). Both relative and absolute cardiorespiratory fitness also improved (both p < 0.001). Katz et al.<sup>19</sup> conducted a 21-week, three-arm study: a control group (EDU) received education on daily physical activity, while PED and PED+ groups received pedometers, step diaries, and varying coaching levels. Physical function (PED p = 0.01; PED+ p = 0.002) and fatigue (PED p = 0.02; PED+ p = 0.0002) improved significantly, along with self-reported disease activity in both intervention groups.



Azeez et al.<sup>20</sup> implemented a 3-month individualized exercise program (cardio and strength training), with physiotherapist follow-ups every 4 weeks to adjust intensity. The control group received standard care with general exercise advice. Significant improvements were observed in functional capacity, body composition, aerobic capacity, grip strength, cognition, and fatigue. Similar results were reported by Morsley et al.<sup>21</sup>, and Lourenzi et al.<sup>22</sup> found that a 12-week resistance program significantly improved physical function, grip and muscular strength ( $p = 0.03$ ).

Durcan et al.<sup>23</sup> studied a 6-week home-based program of strengthening, stretching, and walking. The control group received only exercise advice. The intervention led to significant improvements in functional disability, pain, stiffness, fatigue, and sleep quality. Thomsen et al.<sup>24</sup> conducted a 16-week behavioral intervention to reduce sedentary time and promote light physical activity. The control group maintained usual routines. Significant improvements were observed in physical function, fatigue, pain, quality of life, and self-efficacy in the intervention group.

In three trials<sup>25-27</sup>, intervention included 20 weeks of supervised, gym-based moderate- to high-intensity aerobic and resistance exercise (3x/week), as well as home-based sessions. Control groups received one physiotherapist visit and home exercise instructions. Lange et al.<sup>25</sup> showed significant improvements in aerobic capacity, endurance, strength, and balance in older RA patients, partly maintained at 1-year follow-up. Sul et al.<sup>28</sup>, Andersson et al.<sup>26</sup>, and Joo et al.<sup>29</sup> confirmed strength gains. Kucharski et al.<sup>27</sup> found greater reductions in physical ( $p = 0.002$ ) and mental fatigue ( $p = 0.048$ ). Reduced depression symptoms were observed at 20 weeks ( $p = 0.039$ ), though these were not sustained at 52 weeks.

Loeppenthin et al.<sup>30</sup> studied 6 weeks of aerobic training (3x/week), while the control group received standard care. No significant effect on objectively measured sleep efficiency was found, but fatigue and depressive symptoms were significantly reduced. Feldthusen et al.<sup>31</sup> showed that 12 weeks of moderate aerobic activity (>30 min, 5x/week) significantly reduced fatigue. Zippenfening et al.<sup>32</sup> found that 6 months of aerobic training (45

min, 3–5x/week) significantly improved physical and mental health ( $p < 0.05$ ). Jahanbin et al.<sup>33</sup> reported that 8 weeks of aerobic and strength training significantly improved health status and pain scores ( $p < 0.001$ ). Ohenewa et al.<sup>34</sup> and Baxter et al.<sup>17</sup> found that aerobic exercise (mainly walking and cycling) enhanced physical function, self-efficacy, and overall well-being.

DISCUSSION

A key finding of this review is that one study<sup>18</sup> showed that various forms of physical activity—especially strengthening exercises—significantly reduced RA disease activity, aligning with earlier research<sup>35,36</sup>. In contrast, five studies<sup>20, 22, 26, 27, 32</sup> showed no effect. Pain, joint swelling, and other disease activity markers affect function, joint damage, and raise cardiovascular and infection risks<sup>37</sup>.

Six studies<sup>19-23, 26</sup> reported significant improvements in physical function and fatigue, consistent with prior findings<sup>38</sup>. Fatigue, common in RA, greatly impacts QoL, making its reduction important for patients and society<sup>39</sup>. Despite its relevance, none of the reviewed studies assessed joint damage, a core RA outcome per the World Health Organization and the International League of Associations for Rheumatology<sup>40</sup>.

Four studies<sup>20, 21, 25, 26</sup> found that aerobic and strength training improved body composition and aerobic capacity, which is crucial for cardiovascular health<sup>41, 42</sup>. Four studies<sup>20-22, 26</sup> also showed increased grip and muscle strength, reducing disability, fall risk, and work limitations<sup>35, 43</sup>. These gains support improved function, QoL, and well-being.

Exercise interventions were also associated with better sleep, mood, and health-related outcomes<sup>21, 27, 28, 30, 32, 33</sup>, aligning with previous evidence<sup>44</sup>. Sleep disturbance is common in RA and hampers daily life<sup>14</sup>, making exercise a valuable management tool.

As RA symptoms relate to higher mortality and healthcare use, integrating physical activity into care is essential<sup>46</sup>. However, some interventions were resource-intensive and logistically challenging, which may limit implementation. Environmental and cultural barriers should also be considered in practice and future research.

TABLE 1 Overview of the most relevant study characteristics

AUTHOR (YEAR)	STUDY POPULATION(S) CHARACTERISTICS	STUDY DESIGN	INTERVENTION TYPE IG VS CG IF PRESENT	MAIN RESULTS
Azeez et al. (2020) [20]	IG: N = 33. CG: N = 33. Age 18-75 yrs. 84.5% female	RCT	Aerobic and strength exercise vs Standard care.	Significant improvement: disability, waist circumference, VO2max, grip strength, fatigue, truncal fat.
Lourenzi et al. (2017) [22]	IG: N=27. CG: N=33. Age 18-65 yrs. 92% female	RCT	Strength exercise vs Standard care	No effect: disease activity.
Lange et al. (2018) [25]	IG: N=36. CG: N=38. Age 65-75 yrs. 75.5% females.	RCT	Aerobic, resistance exercise and home-based exercise vs Same home-based exercise of the CG.	Significant improvement: disability, functional capacity, pain, muscle strength.
Durcan et al. (2014) [23]	IG: N=40. CG: N= 38. Age 60 yrs. 65% female	RCT	home-based strengthening, stretching, and walking exercises program vs Advice only on the benefits of exercise in RA.	No effect: disease activity.
Loeppenthin et al. (2022) [30]	CG: N=17. CG: N= 21. Mean age 55 ± 9 yrs. 86% female.	RCT	Aerobic exercise vs Standard care.	Significant improvement: aerobic capacity and physical fitness.
Feldthusen et al. (2016) [31]	IG: N=36. CG: N= 34. Age 20-65 yrs. 89% female	RCT	A person-centered physical therapy with focus on physical activity vs Usual care	No effect: disabilityv
Andersson et al. (2020) [26]	IG: N= 36. CG: N= 34. Age 20-65 yrs. 82% female	RCT	Aerobic, resistance exercise and home-based exercise vs Same home-based exercise of the CG.	Significant improvement: disability, pain, sleep, fatigue.
Thomsen et al. (2017) [24]	IG: N=75. CG: N=75. Mean age 60 yrs. 81% female	RCT	Behavioral intervention aiming to increase physical activity through reduction of sedentary behavior vs Usual care	significant improvement: fatigue, depression.
Zippenfening et al. (2014) [32]	IG: N=10. CG: N=12. Age 55-80 yrs. 87% female	RCT comparative study	Aerobic exercise program vs No intervention	No effect: sleep, VO2max, pain, physical function.
Sul et al. (2020) [28]	IG: N=20. CG: N=20. Age >18 yrs. Only female	prospective,	Resistance exercises program vs Usual care.	significant improvement: fatigue, strength, anxiety.
Kucharski et al. (2019) [27]	IG: N=36. CG: N=38. Age 65-75 yrs. 75.5% females.	intervention CT	Aerobic, resistance, and home-based exercise for 20 weeks vs Same home-based exercise of CG.	Significant improvement: aerobic capacity, muscle strength.
Jahanbin et al. (2014) [33]	IG: N=33. CG: N= 33. Age 23-63 yrs. 100% female	RCT	Aerobic, isometric, and	No effect: disease activity, disability.
Morsley et al. (2017) [21]	Average age 51 yrs. N = 83	RCT	isotonic exercises vs home training booklet	Significant improvement: fatigue, pain, physical function, QoL.
Bartlett et al. (2018) [18]	Age 55-70 yrs. N = 12	CT	Resistance training.	Significant improvement: physical and mental health (SF-36), QoL.
Katz et al. (2017) [19]	IG1: N = 34. IG2: N =34. CG: N = 28. Age 54 ± 13.4 yrs.	CT	Aerobic exercise.	No effect: disease activity, pain.
Ohenewa et al. (2021) [34]	IG: N=30. CG: N=30. age 18-65 yrs. 80% female	RCT	Provision of pedometers and daily step-monitoring diaries to increase physical activity level vs only education.	Significant improvement: lower extremity muscle strength, mental health.
Baxter et al. (2015) [17]	IG: N=11. CG: N 22. age >20 yrs. 75% female	Quasi experimental study	Moderate intensity aerobic exercises vs Usual care.	No effect: upper extremity muscle strength, physical function.
Joo et al. (2022) [29]	IG: N = 28. CG: N 14. Age 18-65 yrs. Only female	RCT	Walking program vs Usual care.	Significant improvement: fatigue, depression.

This review draws strength from its analysis of 18 recent trials, though limitations include language bias and the exclusion of alternative exercise forms (e.g., yoga, Tai Chi). Differences in intervention type, duration, intensity, and setting were not deeply explored, though higher-intensity, frequent programs are known to yield better results<sup>46</sup>.

Trial participants often had milder disease and fewer comorbidities, limiting generalizability. Supervised and group-based settings may boost motivation and social support, potentially influencing outcomes like mood and depression.

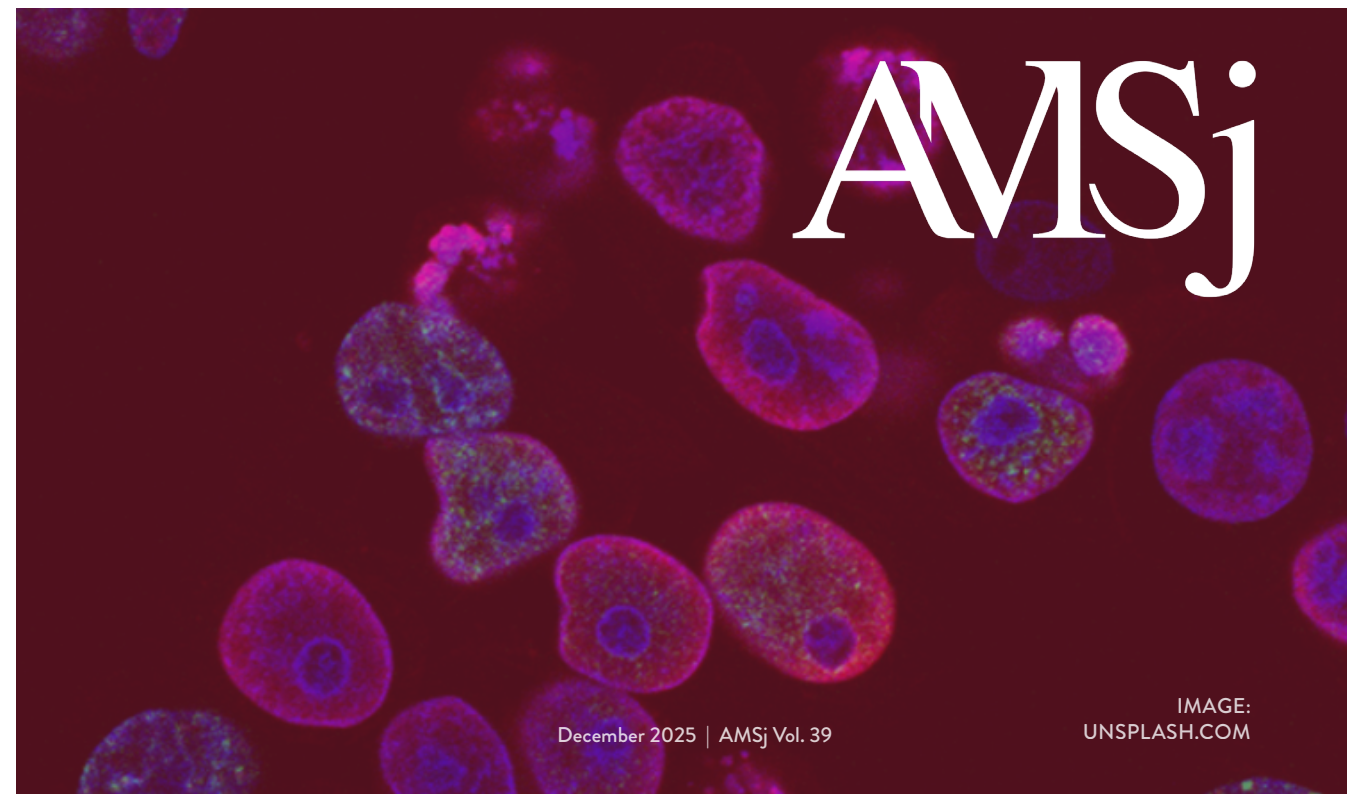
In conclusion, physical exercise is safe and beneficial for RA patients, improving physical fitness, function, disease activity, body composition, pain, fatigue, sleep, and QoL. The main challenge now is integrating these findings into everyday care—how can we motivate RA patients to stay active for life?

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## Displaced distal radius fractures in the elderly: To operate or not to operate?

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**IN THE NETHERLANDS**, distal radius fractures are observed commonly and the incidence is increasing.<sup>1</sup> Moreover, there is an increasing trend for surgical management with plate fixation of these fractures.<sup>1</sup> While surgery for these fractures in the elderly does not seem beneficial after one year when compared to non-operative management, outcomes may be in favour of the latter on the short-term (3 months).<sup>2</sup> In line with these findings, the Dutch guidelines recommend operative treatment after a displaced distal radius fracture in healthy older adults, resulting in swift return to normal wrist function and daily activities.<sup>3</sup>

Recently, a Dutch randomised controlled trial was conducted, investigating non-inferiority of casting versus surgery in displaced distal radius fractures (i.e. the more severe cases) in patients aged 65 years or older.<sup>4</sup> This multicentre study across 19 Dutch hospitals included 69 patients in each group and the intention-to-treat analysis was inconclusive at the one-year mark. However, after covariate adjustment for baseline variables (such as frailty, comorbidities and grip strength), casting was non-inferior to plate fixation. Operative treatment resulted in better early functional outcomes, but reoperation rates were higher. Moreover, subanalyses suggest that healthy patients do benefit from operative treatment, whereas more frail patients do not.<sup>4</sup>

These findings highlight the need for an individualised approach towards surgical decision-making for displaced distal radius fractures. As of now, the guidelines only recommend casting in patients with incapability of wrist movement, dementia, or high age.<sup>3</sup> The study's results highlight the heterogeneity of older adults, and more factors than currently described may be relevant for surgical decision-making in this population. Chronological age, often used as a benchmark for non-operative treatment recommendation, is not generalizable to all patients. Furthermore, it stresses the importance of shared decision-making be-

tween patients and surgeons, as every individual has different goals and expectations.

In conclusion, this study shows us that an individualised approach is paramount when counselling patients on operative or non-operative treatment after a substantially displaced intra-articular distal radius fracture. Healthy patients can be counselled on operative treatment for quick functional recovery, whereas non-operative treatment may be more beneficial for frail patients. The findings also stress the heterogeneity in this patient population and the current proxies for non-operative recommendation may not cover the complete shared decision-making progress. We should not ask ourselves the question whether to operate or not. Rather, we should focus on who we operate, and why.

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## MEET OUR TEAM



**Elisha van Kouwen,  
Editor-in-Chief AMC**

Hi! My name is Elisha, and I am the new Editor-in-Chief representing the AMC.

Throughout my bachelor's and master's in Medicine, the AMSj has been a journal I've always enjoyed reading. It has inspired me and offered valuable insight into the diverse research projects fellow students are involved in.

Over time, my own interest in research has grown. I've come to appreciate not only the excitement of exploring clinical questions, but also the essential role research plays in advancing medical practice and improving patient care.

Through the AMSj, I hope to spark that same sense of curiosity and enthusiasm in other students. By highlighting the work of our peers, I aim to make research feel accessible, motivating, and meaningful. I'm excited to contribute to a journal that has inspired me for so many years and to help others discover what makes research such a vital part of medicine.



What inspired you and what did you learn? Inspire other students. See guidelines for submitting on [amsj.nl](https://amsj.nl)

## Peptides that beat the first-pass effect

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Peptides are increasingly used in contemporary pharmacotherapy. Well-known examples include GLP-1-agonists for type 2 diabetes, teriparatide for osteoporosis, and GnRH-agonists for hormone-sensitive malignancies. Peptides are often large, highly hydrophilic molecules and, being composed of amino acids, are prone to hydrolysis by bacterial, gastrointestinal and liver peptidases. It is therefore no surprise that peptides are usually administered by injection. However, injectable formulations are often less patient-friendly, more expensive, and require special storage conditions compared to their oral counterparts. Over the years, researchers have developed some notable examples of “rule-breaking” peptides to address these issues.<sup>1</sup>

For an orally administered drug to become systemically available, it must dissolve in luminal fluid and then cross the membranes of the gut wall. To achieve this, the drug must be moderately lipophilic and small, preferably no heavier than 500 g/mol. Moreover, the drug should circumvent various threats to its integrity collectively known as the first-pass effect. Beyond the literal “first pass” by portal venous blood to the liver, some definitions also include the first pass through the gastrointestinal tract itself, in which bacterial enzymes may process the drug before it reaches its systemic destination. In the first pass over the gastrointestinal epithelium, the drug may already be metabolized or excreted backward.<sup>2</sup> The first-pass effect is especially harsh on peptides, since their amino acids are nutritious to both humans and microbes.

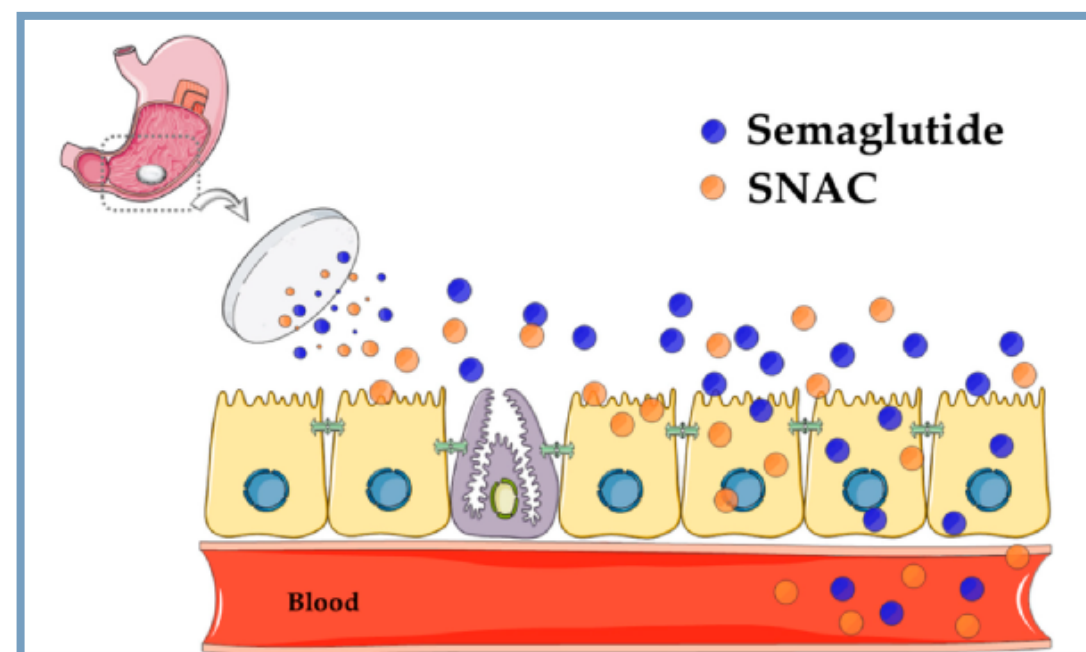
One way for a peptide drug to overcome this is to increase the oral dose to a level so high that, even if only a fraction is absorbed, sufficient systemic exposure is achieved. Desmopressin (1069 g/mol) is a vasopressin analogue used to treat central diabetes insipidus. If administered in tablet form, up to a thousandfold increase of the equivalent IV dose may be necessary. Another ‘intermediate’ route of administration is via a nasal spray. The venous drainage of the nasal mucosa bypasses the liver. Even so, the equivalent dose increase is about ten- to hundredfold.<sup>3</sup> Another approach is to improve uptake by adding adjuvants to the tablet. A prime example is Rybelsus® (semaglutide, 4114 g/mol), the oral form of Ozempic®. Its formulation contains salcaprozate sodium (SNAC), an absorption enhancer thought to inhibit pepsin, raise the local pH, and form a protective cover around semaglutide **FIGURE 1**.<sup>4</sup> Nevertheless, bioavailability is highly variable, and 2-4% of patients are not exposed to semaglutide at all.

Recently, researchers have devised a particularly resourceful method for a peptide to stay under the radar of proteolytic enzymes. The amyloid  $\beta$ -disassembling peptide PRI-002 (1599 g/mol) is designed solely with d-amino acids.<sup>5</sup> This

means that it functions as a mirror image of its ‘natural’ l-form, making it considerably less likely to be bound by proteases. An oral formulation is currently in development in the phase II PRImus-AD trial for treating mild Alzheimer’s disease. Through innovations like these, prescribers may become less reliant on injectable peptides, so look out for oral alternatives the next time you encounter a peptide drug.

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**FIGURE 1** SNAC enhances semaglutide absorption<sup>4</sup>



## Subject 101: “Tests of hemostasis”

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### HEMOSTASIS

After injury, vasoconstriction reduces blood flow, initiating hemostasis. Then, von Willebrand Factor (vWF) binds to collagen exposed on the damaged endothelium and to glycoprotein Ib-IX (GPIb-IX) on platelets, leading to platelet adhesion, activation, and aggregation, forming a temporary plug. Meanwhile, secondary hemostasis initiates the coagulation cascade, resulting in a stable fibrin-rich clot, after which tissue repair begins. Laboratory tests assessing hemostasis can provide clues as to whether a patient has a bleeding disorder or, conversely, a tendency toward excessive clotting.

### PRIMARY HEMOSTASIS

#### PLATELET COUNT

Platelet counts (normally  $150\text{--}400 \times 10^9/\text{L}$ ) may be falsely low when patient-derived agglutinating antibodies cause EDTA-induced platelet clumping. The platelet aggregate is counted as a single platelet, resulting in a spuriously low platelet count. To overcome this problem, known as “pseudothrombocytopenia”, repeat the test using a different anticoagulant such as citrate<sup>1</sup>.

True thrombocytopenia can manifest as a bleeding tendency, as in immune thrombocytopenia (ITP), where thrombocytes are attacked by the immune system, or due to blood loss. Surgery becomes risky when the platelet count drops below  $50 \times 10^9/\text{L}$ , and spontaneous bleeding may occur below  $10 \times 10^9/\text{L}$ .

Low platelet count can coexist with increased hemostasis, as in disseminated intravascular coagulation (DIC). During sepsis, the coagulation system is activated, leading to microvascular clotting and consumption of platelets and coagulation factors, causing thrombocytopenia, prolonged clotting times, low fibrinogen, and markedly elevated D-dimer levels.

In thrombotic thrombocytopenic purpura (TTP), low ADAMTS13 levels result in large vWF multimers that trap and aggregate platelets in small vessels. Although it appears to be a bleeding diathesis, patients primarily suffer from ischemia due to microcirculatory obstruction (renal failure/neurological symptoms). Schistocytes and signs of (Coombs negative) hemolysis may be seen on the blood smear, and low ADAMTS13 activity confirms the diagnosis<sup>2</sup>.

Whereas reactive thrombocytosis (platelets  $>400 \times 10^9/\text{L}$ ) occurs with inflammation (e.g., IBD), malignancy, surgery, or iron deficiency, driven by interleukin-mediated megakaryocyte stimulation and increased thrombopoietin. It is usually transient and carries a low thrombotic risk. Essential thrombocythemia (ET), a myeloproliferative disease, causes persistent platelet overproduction and increased thrombosis risk, with JAK2 V617F testing supporting the diagnosis<sup>3</sup>.

#### VWF

When a disturbance in primary hemostasis is suspected (spontaneous or mucocutaneous bleeding) and the platelet number is normal, consider von Willebrand disease (vWD)<sup>4</sup>. Laboratory findings may include reduced vWF levels (though not always), decreased vWF-activity, and reduced factor VIII activity (as vWF carries factor VIII).

#### PLATELET FUNCTION

Platelet function can be assessed using a platelet function analyzer (PFA)<sup>5</sup>. Results, however, are nonspecific and may be difficult to interpret. Blood is aspirated through a small aperture coated with collagen and ADP or adrenaline<sup>6</sup>, and the time required to occlude the aperture is measured. Thrombocytopathies may be caused by medication (e.g., NSAIDs), uremia, or inherited disorders such as Bernard-Soulier syndrome or Glanzmann thrombasthenia.

### SECONDARY HEMOSTASIS

#### PT-INR

Prothrombin time (PT-INR) evaluates the extrinsic and common pathway. Blood is collected in a citrate tube, which chelates calcium and prevents coagulation. Plasma is then separated, and tissue factor plus calcium are added to activate coagulation. The time required to form a clot is the PT. Because PT values vary slightly between laboratories, results are standardized and reported as the “International Normalized Ratio (INR)”.

Elevated INR values indicate the use of a vitamin K antagonist, vitamin K deficiency, liver disease, factor VII deficiency, massive bleeding, or DIC.

#### APTT

Activated partial thromboplastin time (aPTT) assesses the intrinsic and common pathway, primarily evaluating factors II, V, VIII-XII, and fibrinogen. After plasma is separated from cells, phospholipids, kaolin or silica and calcium are added to initiate coagulation<sup>7</sup>. The time required to form a fibrin clot is the aPTT.

Prolonged aPTT may result from loss of clotting factors (e.g., massive bleeding), factor VIII or IX deficiency (haemophilia A/B), and is used to monitor unfractionated heparin therapy. Prolongation may also occur in hypercoagulable states such as DIC or antiphospholipid syndrome (APS). In APS, lupus anticoagulant (LAC) binds phospholipids, prolonging aPTT in vitro, while paradoxically promoting thrombosis in vivo, which can lead to venous thromboembolism and arterial events such as premature stroke.

#### MIXING STUDIES

An elevated aPTT may be caused by a factor deficiency or antibodies (e.g., factor VIII inhibitor or LAC). These can be differentiated using a mixing study<sup>9</sup>, in which patient plasma (with prolonged aPTT) is mixed 1:1 with normal plasma. If clotting times normalize, a factor deficiency is likely. If clotting times remain prolonged, an inhibitory process (such as a factor VIII inhibitor or LAC) is more probable.

#### INDIVIDUAL CLOTTING FACTORS

Clotting factors can be measured individually. For example, DIC is typically associated with very low fibrinogen (factor I), which is an important diagnostic clue. In liver failure, low factor V levels indicate prognosis and may guide urgency of liver transplantation. In haemophilia, the percentage activity of the deficient factor reflects disease severity:  $<1\%$  indicates severe haemophilia,  $1\text{--}5\%$  moderate, and  $5\text{--}40\%$  mild.

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# Application of DNA Analysis in Tracing the Geographical Origin of *Salmonella* spp.

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## ABSTRACT

**INTRODUCTION** *Salmonella* is a major global cause of foodborne infections, and increasing globalization of the food supply chain facilitates the spread of strains across borders. Outbreaks originating in one region can rapidly affect populations elsewhere, highlighting the importance of fast and accurate source attribution. DNA-based analytical methods, particularly whole genome sequencing (WGS), offer high-resolution genetic information that can support identification of the geographical origin of *Salmonella* strains.

**METHODS** This review summarizes recent studies that examined the use of WGS and other genetic subtyping methods, including multilocus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), and core genome MLST (cgMLST), for determining relationships between *Salmonella* isolates. Literature was identified through academic databases and selected based on relevance to geographic tracing and outbreak investigation.

**RESULTS** WGS and related subtyping approaches can detect small genetic differences between strains, which may correspond to geographical clustering. Machine learning models have demonstrated high accuracy in assigning strains to specific regions based on genomic features. Outbreak investigations have shown that WGS and cgMLST can link clinical isolates to contaminated food products, including imported items, enabling more targeted public health interventions.

**CONCLUSION** DNA-based methods, particularly WGS, offer powerful tools for geographical source attribution of *Salmonella*, especially when combined with epidemiological data. However, their effectiveness depends on genetic diversity and the availability of well-curated reference databases. Continued development of analytical approaches and expansion of global genomic resources will strengthen the use of DNA analysis in outbreak source tracing.

## INTRODUCTION

*Salmonella* is a globally prevalent cause of foodborne disease, responsible for significant morbidity and mortality. Non-typhoidal *Salmonella* infections are estimated to cause approximately 94 million cases and 155,000 deaths annually, disproportionately affecting low- and middle-income regions.<sup>1</sup> With the increasing globalization of food production and distribution systems, contaminated food products and infected individuals travel widely, facilitating the international spread of *Salmonella* strains.<sup>2</sup> An example of this phenomenon is the globally disseminated extensively drug-resistant *Salmonella* Typhi lineage emerging from Pakistan, linked to international travel.<sup>3</sup>

This globalized pattern of transmission is illustrated in **Figure 1**, which shows how *Salmonella* may

disperse internationally through food trade and human mobility. Such cross-border spread underscores the necessity for surveillance tools capable of identifying not only the bacterial strain involved in an outbreak, but also its potential geographical origin.

Rapid and accurate identification of contamination sources is critical for outbreak control. Traditional serotyping and epidemiological tracing can be slow or insufficiently specific in complex supply chains. DNA-based methods, particularly whole genome sequencing (WGS), now allow for highly resolved comparison of bacterial isolates. When supported by reference genomic databases and epidemiological metadata, such methods may help determine geographical origin, clarify transmission pathways and improve targeted control measures.

**OBJECTIVE:** This systematic review evaluates the role of DNA analysis, especially WGS and genetic subtyping, in determining the geographical origin of *Salmonella* strains and tracing contamination sources during outbreaks.

## METHODS

### STUDY DESIGN

A systematic review of peer-reviewed literature was conducted, focusing on the use of DNA-based analytical methods to support geographical source attribution of *Salmonella*.

### SEARCH STRATEGY

Searches were performed in PubMed, Google Scholar, ScienceDirect, and the University of Amsterdam online library. Search terms included combinations of:

- “*Salmonella*” AND “geographic origin” AND “whole genome sequencing”
- “source tracking” AND “genetic subtyping”
- “DNA analysis” AND “outbreak investigation”

### INCLUSION CRITERIA

Published 2010–2025

- Investigated *Salmonella enterica*
- Applied WGS, MLST, PFGE, cgMLST, or comparable genomic methods
- Reported outbreak investigations or evidence of geographic clustering

### EXCLUSION CRITERIA

- Studies lacking genomic analysis
- Reviews without primary data
- Non-English publications

### DATA EXTRACTION

Data extracted included study setting, strain origin, genomic method, evidence for geographic clustering, and relevance for outbreak tracing. Where reported, links to food sources or supply-chain tracing were noted.

## RESULTS

### GENOMIC ANALYSIS IN OUTBREAK SOURCE TRACING

Integrated WGS surveillance systems allow high-resolution comparison of isolates from patients, foods, and environments. A retrospective and prospective WGS program in China enabled discrimination of outbreak-related *Salmonella*

Enteritidis strains from sporadic isolates using single nucleotide polymorphism (SNP) analysis.<sup>4</sup> Similarly, genetic identity between isolates from patients and contaminated poultry products confirmed the source of an outbreak in Shenzhen.<sup>5</sup>

In Europe, cgMLST confirmed genetic matches between cases and contaminated baby spinach, identifying a specific supplier within the distribution chain.<sup>6</sup> These examples demonstrate that genomic comparison can guide precise recall actions and limit spread.

Multiple studies show that genomic variation among *Salmonella* strains can reflect geographic origins. In *Salmonella* Enteritidis, WGS revealed subtle SNP patterns associated with regional distribution.<sup>7</sup> In Turkey, MLST and PFGE of *Salmonella* Typhimurium demonstrated regional clustering, suggesting localized transmission lineages.<sup>8</sup>

A hierarchical machine learning approach trained on WGS data classified *Salmonella* Enteritidis isolates to likely geographic origin with >90% accuracy at continental level, supporting the feasibility of predictive source attribution models.<sup>9</sup>

### WGS AS AN ALTERNATIVE TO TRADITIONAL SEROTYPING

Traditional serotyping may be slow or insufficient for rare variants. WGS-based serotype prediction tools, such as SeqSero2 and SISTR, demonstrated high accuracy in multiple studies and additionally identified virulence and resistance genes.<sup>10,11</sup> These capabilities make WGS a powerful dual-purpose tool for both serotyping and outbreak tracing.

### TRACING IMPORTED FOOD-ASSOCIATED OUTBREAKS

WGS confirmed the link between a U.S. outbreak and tuna imported from India, demonstrating international contamination spread.<sup>12</sup> Another outbreak linked to imported eggs in England was similarly supported by cgMLST analysis combined with supply chain information.<sup>13</sup>

## DISCUSSION

DNA-based analytical techniques, particularly WGS, substantially enhance the ability to trace *Salmonella* transmission pathways. Evidence from multiple regions demonstrates that genetic variation among strains can provide geographically informative patterns. Machine learning models further improve predictive accuracy by integrating genomic signatures across large datasets.<sup>9</sup>



However, the effectiveness of geographical attribution varies by context. Interpretation is limited when genetic diversity between regions is low, reference genome libraries are incomplete, or sampling is biased toward outbreak-heavy regions.<sup>14</sup> Furthermore, WGS alone rarely determines geographic origin without supporting epidemiological and supply-chain data.

Strengths of this review include its systematic approach and inclusion of diverse geographic contexts. Limitations include variability in reporting detail across studies and uneven availability of publicly accessible genomic databases.

## CONCLUSION

WGS and related DNA-based methods are powerful tools for tracing Salmonella outbreaks and can provide meaningful insights into geographical origin when supported by high-quality reference data. Implementation of standardized global genomic surveillance networks and expansion of reference databases will improve accuracy and utility. Integration of genomic, epidemiological, and supply-chain data remains essential for effective outbreak response and prevention.

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## The Changing Face of Liver Disease: Practical Guidance from the Pocket Gastroenterology & Hepatology

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Within the field of Gastroenterology & Hepatology, liver transplantation is among the treatment options with the highest life-saving potential. A significant global shift is occurring in the most common indications for this procedure<sup>1</sup>. Viral hepatitis had long been leading this list, but its position is now being taken over by steatotic liver disease. While alcohol-related liver disease is the prognostically most severe phenotype, metabolic dysfunction-associated liver disease has seen the sharpest increase in disease burden. Strikingly, the largest portion of newly diagnosed liver cancers today are preventable<sup>2</sup>. Engage in the real-life example below and find out for yourself!

**A 68-YEAR OLD FEMALE**, presenting with peripheral edema and abdominal distension, was admitted to the emergency department. Her medical history included suboptimally managed type 2 diabetes mellitus, moderate alcohol use, and hypothyroidism. Cardiac and nephrotic etiologies were excluded, and you are consulted next. What differential diagnosis is at the top of your list? Exactly: hepatic decompensation. After stabilization of the patient, laboratory evaluation revealed increased liver enzymes and low platelets. Upper endoscopy showed small esophageal varices with no signs of (recent) bleeding, and a spontaneous bacterial peritonitis was ruled out via paracentesis. One important question remains: what are the most likely underlying causes of this patient's liver cirrhosis? The answer can be found in the paperback.

To provide students and young doctors with practical tools, we have contributed several chapters to the Gastroenterology and Hepatology pocketbook covering chronic liver disease and common causes of liver cirrhosis. We provide a comprehensive guide to prevention and incorporate the updated clinical framework for metabolic dysfunction-associated steatotic liver disease. In addition, we address acute complications and alcohol-related conditions, including suspected variceal haemorrhage and the management of alcohol withdrawal symptoms. All in all, we offer practical guidance that spans for both acute scenarios and chronic disease management.

The latest addition to the 'Compendium Medicine' series is designed for students, doctors, and healthcare professionals in Gastroenterology and Hepatology. The team behind this paperback includes students, doctors and specialists from hospitals around the world. Multidisciplinary collaboration is a cornerstone of Gastroenterology and Hepatology. For this reason, the project involved close collaboration with colleagues from microbiology, radiology, hospital pharmacy, surgery, internal medicine and more.

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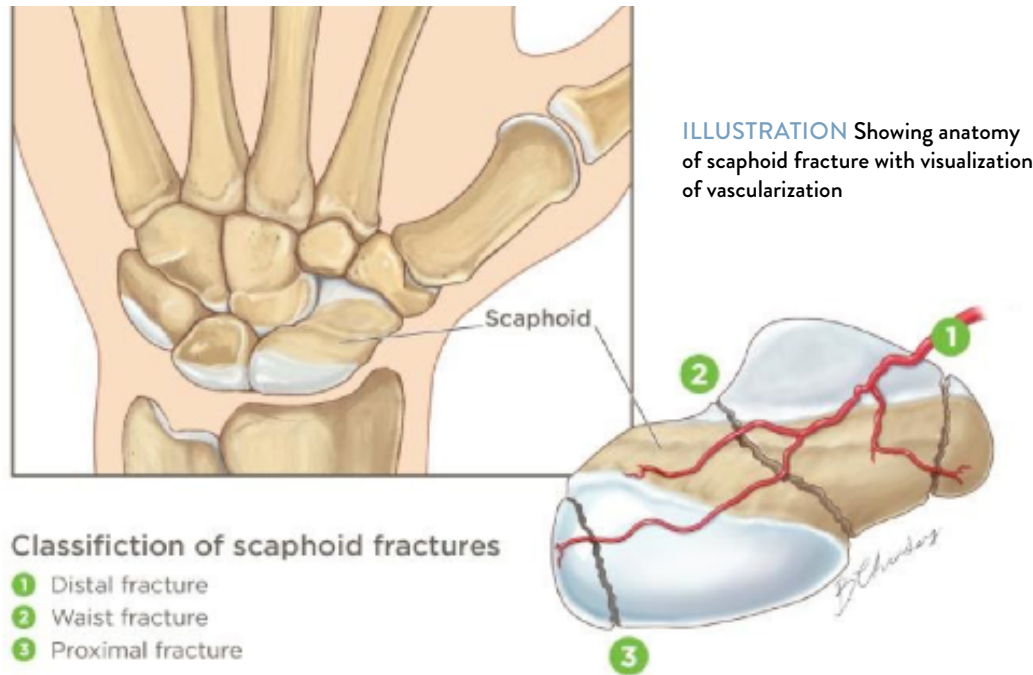
**Compendium**  
Geneeskunde

## Answers 'Delayed Diagnosis of Wrist Fracture'

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**Correct answers: Q1-A, Q3-C**

### EXPLANATION

The scaphoid is involved in 90% of all carpal fractures, making it the most commonly fractured carpal bone. This fracture typically occurs after a fall on an outstretched hand (FOOSH) or forced wrist extension.<sup>1</sup>

On imaging, a vertical fracture through the scaphoid tubercle was identified, consistent with a Herbert type A1 fracture, representing an acute stable injury. The Herbert classification differentiates acute stable (A), acute unstable fracture (B), delayed union (C) and nonunion (D) fractures. In this case, CT confirmed an intra-articular gap <1 mm with preserved alignment.

Clinical features include persistent pain and tenderness in the anatomical snuffbox, swelling, limited wrist or thumb motion, reduced grip strength, and pain during lifting or squeezing.<sup>2</sup> Scaphoid fractures predominantly affect young adults, more commonly men (107-151 per 100,000) than women (14-46 per 100,000), with peak incidence between 20-29 years in men 10-19 years in women.<sup>1,3</sup> In the Netherlands, 20,000-24,000 cases occur annually.<sup>4</sup>

Early diagnosis and adequate treatment are essential to prevent complications such as delayed consolidation, nonunion, malunion, AVN and long-term osteoarthritis. These complications can impair function, quality of life, and workforce participation.<sup>1</sup>

Non-displaced or minimally displaced fractures are managed non-operatively with immobilization in a cast or splint, as in this case: a

total of four weeks of casting (one week splint followed by three weeks circular cast), then two weeks of activity-specific bracing. Patients are generally advised to avoid contact sports for 2-3 months. Displaced or unstable fractures, fractures of the proximal pole, or cases with nonunion or AVN may require surgical fixation.

AVN risk is highest in the proximal pole due to retrograde blood flow from the dorsal carpal branch of the radial artery. The distal pole receives direct perfusion from the volar radial artery, making it less vulnerable. Fractures at the waist or proximal segment can disrupt retrograde supply, placing the proximal pole at the highest risk for avascular necrosis.<sup>5</sup>

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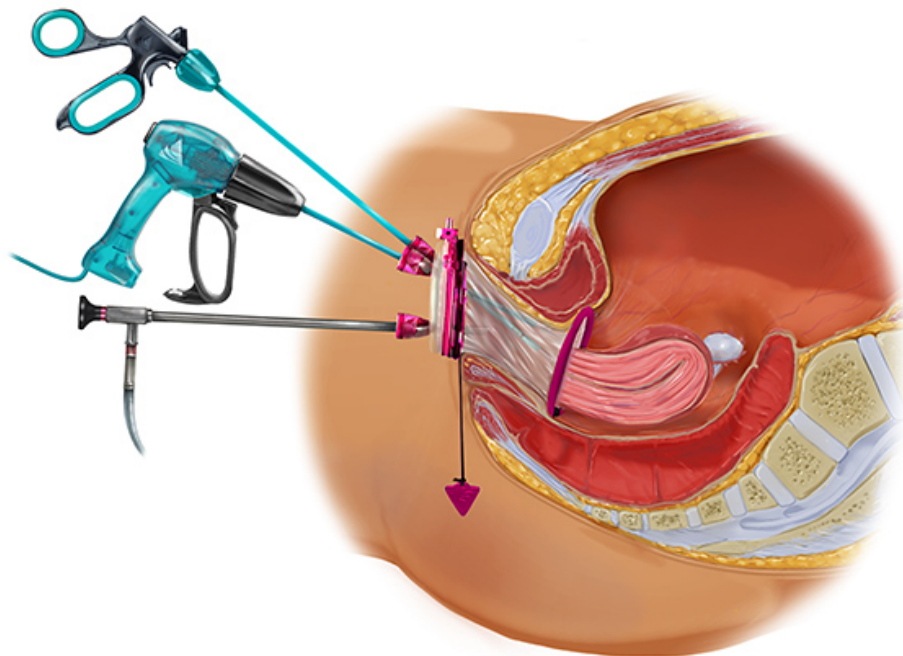


# Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES): Advancing Minimally Invasive Gynaecologic Surgery

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**FIGURE 1** Vaginal natural orifice transluminal endoscopic surgery (vNOTES) hysterectomy. Schematic illustration of transvaginal access to the peritoneal cavity via the posterior fornix. An Alexis Contained Extraction System (CES) is placed to facilitate access, followed by the GelPOINT V-Path® to establish and maintain pneumoperitoneum. Endoscopic and laparoscopic instruments are introduced through the port allowing visualization, dissection, coagulation and removal of the uterus.<sup>6,7</sup>

Vaginal natural orifice transluminal endoscopic surgery (vNOTES) was first introduced by Belgian gynaecologist Jan Baekelandt in 2014. The procedure utilized the natural vaginal route to perform endoscopic gynaecologic surgery without creating abdominal wall incisions promoting a minimally invasive procedure. By introducing a specialized Alexis retractor and laparoscopic instruments transvaginally, access to the peritoneal cavity is gained while maintaining full endoscopic visual-

ization.<sup>1</sup> This approach progressively evolved from a single-side surgery into an entirely transvaginal procedure. vNOTES has proven to be effective for a wide spectrum of gynaecological operations, including hysterectomies, salpingectomies, oophorectomies, ovarian cyst resections, and myomectomies. In addition, it may even be utilized for complex operations such as lymphadenectomy, tumor staging surgery, and sacral colpopexy.<sup>2</sup>

There is a growing demand for less invasive approaches in surgery, including gynaecology, driven by a focus on minimizing postoperative pain, reducing recovery times and optimizing cosmetic outcomes. Patients benefit from faster recovery and return to daily activities along with reducing postoperative pain and use of analgesics compared to conventional laparoscopic surgery.<sup>3</sup> With the absence of abdominal incisions and thereby avoiding visible scars, vNOTES satisfies the cosmetic demand.

The recent systematic review and meta-analysis of Marchand et al. (2024) reported a reduction in operative time, length of hospital stay and postoperative pain in vNOTES compared to laparoscopic hysterectomy. However, there were no significant differences in intraoperative complications, estimated blood loss or conversion rate.<sup>4</sup> These findings emphasize the safety and feasibility of vNOTES as an alternative for the laparoscopic approach for benign gynaecologic procedures.

Obese patients, patients with large uteri, and patients with lower abdominal adhesions have the highest potential to benefit from vNOTES.<sup>3</sup> However, patients with endometriosis are not suitable for vNOTES due to obliteration of the pouch of Douglas, which raises concerns about the safety of posterior colpotomy and increasing the risk of visceral injury. This also applies to women with an history of pelvic inflammatory disease or pelvic abscesses as these conditions elevate the risk of infectious complications when residual infection or dense inflammatory adhesions are present.<sup>3</sup>

Although the learning curve for vNOTES is reported to be relatively short, Dr. Baekelandt stresses the value of formal training and starting with less complex cases to gradually develop skill and confidence with the procedure. He emphasizes that the best surgical technique is the one that allows the surgeon to feel assured while ensuring patient safety.<sup>5</sup>

In conclusion, vNOTES is a promising minimally invasive approach that contributes to faster postoperative recovery enabling patients to resume their daily activities sooner in comparison with conventional techniques. In addition, it offers cosmetic benefits by avoiding visible abdominal scars and a significant reduction in postoperative pain and analgesics use. Therefore, vNOTES had the potential to evolve into a new standard of care in gynaecologic surgery.

## CENTRAL MESSAGE

vNOTES enables minimally invasive gynaecologic surgery without abdominal incisions. Patients benefit from faster recovery and reduced postoperative pain. Together with preferable cosmetic outcomes it makes vNOTES a potential new standard.

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