HIGH BLOOD PRESSURE & CHOLESTEROL

Research Summary

The Hidden Inflammation Connection

For each cited study or review, it summarizes the design, main findings, and how the evidence is being used in the corresponding slide. The interpretation sections distinguish what the source directly demonstrates from the broader biological synthesis used in the video.

Evidence framework: Direct human evidence, prospective association, randomized intervention, imaging evidence, mechanistic review, condition-specific evidence, and clinical synthesis are not treated as interchangeable. A study can support biological plausibility without proving the full food → inflammation → blood-pressure / lipid pathway.

Research studies in slide order

Slide	Slide title	Study / review
5	Most high blood pressure has no single identified cause	Harrison et al., 2021
9	Nitric oxide is a blood-vessel relax signal	Rask-Madsen & King, 2007
11	Inflammation can come before the hypertension	Jayedi et al., 2019
12	Modern hypertension research explains how	Guzik et al., 2024
13	Modern hypertension research explains how	Harrison et al., 2011
19 & 21	Atherosclerosis in people who look low risk / Even very low LDL did not mean zero plaque	Fernández-Friera et al., 2017
20 & 21	Atherosclerosis in people who look low risk / Even very low LDL did not mean zero plaque	Faridi et al., 2024
22	CANTOS put the inflammation question to the test	Ridker et al. / CANTOS, 2017
24	Inflammation can change lipid metabolism	Popa et al., 2007
29	Inflammatory and metabolic diseases cross boundaries	Jess et al., 2020
32	“But my digestion is fine”	Hadjivassiliou et al., Brain 2003
32	“But my digestion is fine”	Hadjivassiliou et al., JNNP 2003
38	The 2025 IBS trial — individual reactivity studied	Singh et al., 2025

Note: Slides 34–36 are conceptual teaching slides rather than study cards; no specific paper is cited on those slides, so they are not listed as separate study entries here.

Most high blood pressure has no single identified cause

Harrison DG, Coffman TM, Wilcox CS. Pathophysiology of Hypertension: The Mosaic Theory and Beyond. Circ Res. 2021;128(7):847–863.

DOI: 10.1161/CIRCRESAHA.121.318082 PMID: 33793328

Evidence type: Authoritative pathophysiology review / clinical synthesis.

Study basics

- The review updates Irvine Page's "Mosaic Theory" of hypertension, in which multiple interacting systems rather than one lesion or one cause produce sustained high blood pressure.
- It integrates renal, vascular, autonomic, hormonal, oxidative-stress, inflammatory, genetic, sodium-homeostasis, and microbiome mechanisms.
- The review emphasizes that the relative contribution of these mechanisms can differ substantially from one person with hypertension to another.

Key results

- Primary/essential hypertension is presented as a multifactorial process rather than a disease with one identified secondary cause.
- Inflammation and oxidative stress are incorporated as interacting nodes that can affect renal, neural, and vascular control systems.
- The model supports the presentation's opening premise that conventional risk factors do not fully explain every individual case.

Interpretation for this slide: This is a review and conceptual synthesis, not a prospective trial showing that inflammation caused hypertension in a particular patient. It supports a multifactorial framework rather than assigning a single cause.

Important limitation: The slide uses the review to explain why "essential hypertension" is compatible with interacting mechanisms, including inflammation, rather than one identifiable cause.

Nitric oxide is a blood-vessel relax signal

Rask-Madsen C, King GL. Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes. Nat Clin Pract Endocrinol Metab. 2007;3(1):46–56.

DOI: 10.1038/ncpendmet0366

Evidence type: Mechanistic review of endothelial dysfunction in insulin resistance and diabetes.

Study basics

- The review examines how insulin resistance, hyperglycaemia, free fatty acids, adipose-derived cytokines, and oxidative stress alter endothelial signalling.
- It describes the endothelium as an active regulator of vascular tone rather than a passive vessel lining.
- It reviews mechanisms that impair endothelial nitric-oxide signalling and shift the vessel toward reduced vasodilation.

Key results

- Pro-inflammatory cytokines and oxidative stress can alter endothelial cell signalling and the release or availability of endothelium-derived relaxing factors.
- Impaired nitric-oxide bioavailability is a central mechanism of endothelial dysfunction and reduced vasodilatory capacity.

- The review connects metabolic and inflammatory abnormalities with functional changes in the arterial wall.

Interpretation for this slide: This is a mechanistic review focused largely on insulin resistance and diabetes. It supports the nitric-oxide/endothelial pathway but does not show that inflammation is the cause of all hypertension.

Important limitation: The slide uses this review for the simple physiology: healthy endothelial signalling promotes nitric-oxide-mediated relaxation; inflammatory/oxidative stress can reduce that relaxation signal and leave vessels functionally tighter.

Inflammation can come before the hypertension

Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S. Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. Heart. 2019;105(9):686–692.

DOI: 10.1136/heartjnl-2018-314216 PMID: 30700522

Evidence type: Meta-analysis of longitudinal cohort and nested case-control studies.

Study basics

- Included 21 studies with 142,640 participants and 20,676 incident hypertension cases.
- Evaluated circulating CRP, hs-CRP, IL-6, and IL-1β measured before the development of hypertension.
- Compared higher versus lower circulating inflammatory-marker groups and also examined dose-response relationships.

Key results

- CRP: highest versus lowest tertile RR 1.23 (95% CI 1.11–1.35).
- hs-CRP: RR 1.20 (95% CI 1.02–1.37).
- IL-6: RR 1.51 (95% CI 1.30–1.71), the ~51% higher-risk figure highlighted in the deck.
- IL-1β was not significantly associated with future hypertension (RR 1.22; 95% CI 0.92–1.51).
- The CRP association persisted after adjustment for BMI, and risk rose with increasing inflammatory-marker levels.

Interpretation for this slide: This is the strongest prospective evidence in the deck for timing: inflammatory markers were elevated before hypertension developed. It supports inflammation as a possible upstream contributor rather than only a consequence of established high blood pressure.

Important limitation: Observational prospective evidence establishes association and temporality, not causation. Elevated markers may reflect other upstream processes that themselves contribute to hypertension.

Modern hypertension research explains how — vascular mechanisms

Guzik TJ, Nosalski R, Maffia P, Drummond GR, et al. Immune and inflammatory mechanisms in hypertension. Nat Rev Cardiol. 2024;21:396–416.

DOI: 10.1038/s41569-023-00964-1

Evidence type: Contemporary mechanistic review of immune and inflammatory pathways in hypertension.

Study basics

- Reviews evidence implicating T cells, monocytes/macrophages, dendritic cells, B cells, natural killer cells, cytokines, chemokines, neoantigens, inflammasome activation, high salt, and sympathetic signalling.

- Integrates inflammatory mechanisms across the vasculature, kidney, nervous system, and other BP-control pathways.
- Focuses on disease initiation and progression rather than treating inflammation as a passive biomarker.

Key results

- Inflammatory mediators can reduce nitric-oxide availability and promote endothelial dysfunction and vascular reactivity.
- Immune activation can affect renal sodium/water handling and promote vascular fibrosis and remodelling.
- The review presents hypertension as having a substantial immune/inflammatory component in experimental and human evidence, while recognizing heterogeneity.

Interpretation for this slide: This review supports the presentation's "three control systems" concept: inflammatory signalling can affect vascular tone, kidney function, and neurohormonal control. It provides mechanistic coherence for the prospective association shown on the preceding slide.

Important limitation: A review integrates evidence from many experimental and human studies; it is not one intervention trial proving that suppressing these pathways will lower blood pressure in all patients.

Modern hypertension research explains how — kidney and immune mechanisms

Harrison DG, Guzik TJ, Lob HE, Madhur MS, Marvar PJ, Thabet SR, Vinh A, Weyand CM. Inflammation, immunity, and hypertension. Hypertension. 2011;57(2):132–140.

DOI: 10.1161/HYPERTENSIONAHA.110.163576 PMID: 21149826

Evidence type: Mechanistic review emphasizing experimental immune pathways in hypertension.

Study basics

- The review synthesizes experimental work showing that hypertensive stimuli such as angiotensin II and salt can activate immune pathways.
- It describes T-cell activation and migration into the kidney and vasculature, followed by recruitment of macrophages and other inflammatory cells.
- It highlights cytokines such as IL-17 as mediators linking immune activation to vascular and renal dysfunction.

Key results

- The proposed model links immune-cell infiltration with cytokine release, vasoconstriction, and enhanced sodium/water retention.
- Kidney and vascular inflammation are presented as mutually reinforcing contributors to sustained blood-pressure elevation.
- The paper helped establish the immune/inflammatory paradigm that later reviews expanded with additional human evidence.

Interpretation for this slide: The slide uses this source to show how immune signalling can influence sodium regulation, renal blood flow, and vascular tone — mechanisms capable of raising pressure without one single structural lesion.

Important limitation: Much of the causal evidence available when this review was written came from animal and experimental models. The authors themselves noted that direct proof of inflammatory causation in human hypertension was limited at that time.

Atherosclerosis in people who look low risk — PESA

Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors. J Am Coll Cardiol. 2017;70(24):2979–2991.

DOI: 10.1016/j.jacc.2017.10.024 PMID: 29241485

Evidence type: Cross-sectional imaging analysis within the PESA cohort.

Study basics

- Analyzed 1,779 middle-aged adults from PESA who had no conventional cardiovascular risk factors by the study's definitions.
- Participants were nonsmokers without hypertension, diabetes, or dyslipidaemia and were not receiving treatment for those conditions.
- Subclinical atherosclerosis was assessed by vascular ultrasound and coronary artery calcium imaging across multiple vascular territories.

Key results

- 49.7% of the conventionally risk-factor-free participants had subclinical atherosclerosis.
- Among the more stringently defined "optimal" subgroup, 37.8% still had evidence of atherosclerosis.
- LDL-C was independently associated with presence and extent of atherosclerosis.
- Plaque prevalence rose from about 11% at LDL-C 60–70 mg/dL to 64% at 150–160 mg/dL.

Interpretation for this slide: The slide uses PESA to make two simultaneous points: a normal-looking conventional risk profile does not guarantee plaque-free arteries, and LDL still matters strongly even within the "normal" range. This supports a more complete model rather than an "LDL versus inflammation" model.

Important limitation: This is imaging-based observational evidence, not a randomized causal experiment. "Risk-factor free" depends on threshold definitions, and the findings do not identify inflammation as the explanation for plaque in those participants.

Atherosclerosis in people who look low risk — Miami Heart

Faridi KF, Lahan S, Budoff MJ, et al. Serum Lipoproteins Are Associated With Coronary Atherosclerosis in Asymptomatic U.S. Adults Without Traditional Risk Factors. JACC Adv. 2024;3(7 Pt 1):101049.

DOI: 10.1016/j.jacadv.2024.101049

Evidence type: Cross-sectional coronary CT angiography analysis from the Miami Heart Study.

Study basics

- Included 1,033 asymptomatic adults aged 40–65 years who were not taking lipid-lowering therapy and had no hypertension, diabetes, or active tobacco use.
- 86.3% had an estimated 10-year ASCVD risk below 5%.
- Coronary atherosclerosis was assessed directly by coronary CT angiography (CCTA).

Key results

- 35.9% had coronary atherosclerosis on CCTA.
- At LDL-C <70 mg/dL, 13.2% still had coronary atherosclerosis.
- At LDL-C ≥160 mg/dL, prevalence was 48.2%.
- Each 10 mg/dL higher LDL-C was associated with higher adjusted odds of plaque (aOR 1.13; 95% CI 1.08–1.18).

Interpretation for this slide: This corroborates the PESA message using direct coronary imaging: very low LDL and low calculated conventional risk do not guarantee the absence of plaque, while progressively higher LDL remains associated with substantially more plaque.

Important limitation: Cross-sectional association cannot establish why plaque developed or assign unmeasured inflammation as the cause. The study primarily strengthens the importance of atherogenic lipoproteins even in otherwise low-risk adults.

CANTOS put the inflammation question to the test

Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119–1131.

DOI: 10.1056/NEJMoa1707914 PMID: 28845751

Evidence type: Large randomized, double-blind, placebo-controlled cardiovascular outcomes trial.

Study basics

- Randomized 10,061 people with prior myocardial infarction and hs-CRP ≥2 mg/L.
- Participants received placebo or canakinumab 50 mg, 150 mg, or 300 mg subcutaneously every 3 months.
- Canakinumab targets IL-1β, allowing inflammatory signalling to be modified without directly lowering lipids.

Key results

- Canakinumab lowered hs-CRP and IL-6 without significantly lowering LDL-C, HDL-C, or triglycerides.
- The 150-mg dose reduced the primary composite cardiovascular endpoint by about 15% versus placebo (HR 0.85; 95% CI 0.74–0.98).
- The trial therefore demonstrated cardiovascular benefit from targeting an inflammatory pathway independently of lipid lowering.
- Serious/fatal infection risk was higher, and all-cause mortality was not significantly reduced.

Interpretation for this slide: This is the deck's strongest randomized evidence that inflammatory signalling is not merely a bystander in atherosclerotic disease. Inflammation changed, lipids did not meaningfully change, yet cardiovascular event risk changed.

Important limitation: This was secondary prevention in patients with previous MI and elevated hs-CRP. It does not show that food caused the inflammation, does not establish canakinumab as appropriate general therapy, and does not make LDL or other risk factors irrelevant.

Inflammation can change lipid metabolism

Popa C, Netea MG, van Riel PLCM, van der Meer JWM, Stalenhoef AFH. The role of TNF-alpha in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. J Lipid Res. 2007;48(4):751–762.

DOI: 10.1194/jlr.R600021-JLR200 PMID: 17202130

Evidence type: Mechanistic and clinical review of TNF-α, inflammation, lipid metabolism, and glucose regulation.

Study basics

- Reviews evidence from acute and chronic inflammatory diseases in which TNF-α concentrations are elevated.
- Examines effects of inflammatory signalling on intermediary metabolism, insulin action, and lipoprotein patterns.
- Includes clinical observations from chronic inflammatory diseases and studies of TNF-α blockade.

Key results

- Chronic inflammatory states can be accompanied by impaired glucose tolerance and shifts toward a more atherogenic lipid profile.
- TNF-α is implicated in insulin resistance, triglyceride metabolism, lipoprotein production/composition, and cholesterol handling.
- Available anti-TNF studies reviewed by the authors suggested potential improvements in insulin resistance and lipid profiles in some chronic inflammatory diseases.

Interpretation for this slide: This review supports the slide's narrower mechanism: inflammatory cytokines can influence the lipid panel itself, not only the artery wall. That makes it biologically plausible for inflammation to contribute to both dyslipidaemia and vascular dysfunction.

Important limitation: This is a review across heterogeneous inflammatory diseases and interventions. Lipid changes can differ by disease and therapy, and the paper does not show that inflammation is the sole cause of dyslipidaemia in the general population.

Inflammatory and metabolic diseases cross boundaries

Jess T, Jensen BW, Andersson M, Villumsen M, Allin KH. Inflammatory Bowel Diseases Increase Risk of Type 2 Diabetes in a Nationwide Cohort Study. Clin Gastroenterol Hepatol. 2020;18(4):881–888.e1.

DOI: 10.1016/j.cgh.2019.07.052 PMID: 31394285

Evidence type: Nationwide population-based cohort study in Denmark.

Study basics

- Population base included 6,028,844 people followed from 1977 through 2014.
- Compared people with inflammatory bowel disease (Crohn's disease or ulcerative colitis) with the general population.
- Type 2 diabetes incidence was evaluated using national registry data.

Key results

- 3,436 people with IBD developed type 2 diabetes versus 2,224 expected: SIR 1.54 (95% CI 1.49–1.60), approximately 54% higher than expected.
- Risk was elevated in both ulcerative colitis and Crohn's disease.
- Risk was highest in the first year after IBD diagnosis but remained elevated 20+ years later (SIR 1.26; 95% CI 1.16–1.38).
- The increased risk was not explained by healthcare-contact frequency or corticosteroid exposure in the authors' analyses.

Interpretation for this slide: The slide uses this large cohort as a tangible example that inflammatory disease centred in the gut can be associated with later metabolic disease outside the gut. It supports the idea that inflammatory physiology can cross organ-system boundaries.

Important limitation: Observational cohort evidence cannot prove that IBD-related inflammation directly caused diabetes in an individual. Shared genetics, medications, behaviour, microbiome factors, and other confounders can also contribute.

“But my digestion is fine” — gluten ataxia without prominent gut disease

Hadjivassiliou M, Grünewald R, Sharrack B, et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. Brain. 2003;126(Pt 3):685–691.

DOI: 10.1093/brain/awg050 PMID: 12566288

Evidence type: Clinical cohort / case-series characterization with serologic screening and controls.

Study basics

- Screened 224 patients with various ataxias in North Trent, an additional 44 patients with sporadic idiopathic ataxia in London, and 1,200 healthy controls for antigliadin antibodies.
- Clinical characteristics were described in 68 patients considered to have gluten ataxia.
- The study specifically examined whether gluten sensitivity could present neurologically rather than as classic intestinal disease.

Key results

- Gastrointestinal symptoms were present in only 13% of the gluten-ataxia group.
- Gluten-sensitive enteropathy was found in only 24%.
- Antigliadin antibodies were much more common in the sporadic idiopathic ataxia groups than in controls.
- The cohort therefore contained many patients with a neurological presentation despite little or no clinically obvious gut disease.

Interpretation for this slide: This is used as proof of principle for the slide’s narrow claim: a food-related immune condition does not have to present with digestive symptoms, and the clinically affected organ can be distant from the gut.

Important limitation: Antigliadin antibodies are not highly specific, the disease entity and diagnostic boundaries have been debated, and this observational study does not establish that similar mechanisms cause hypertension or dyslipidaemia.

“But my digestion is fine” — response to gluten withdrawal

Hadjivassiliou M, Davies-Jones GAB, Sanders DS, Grünewald RA. Dietary treatment of gluten ataxia. J Neurol Neurosurg Psychiatry. 2003;74(9):1221–1224.

DOI: 10.1136/jnnp.74.9.1221 PMID: 12933922

Evidence type: Prospective dietary treatment study with a non-randomized comparison group.

Study basics

- 43 patients with gluten ataxia were offered a strict gluten-free diet and followed for one year.
- 26 adherent patients who eliminated antigliadin antibodies formed the treatment group; 14 who refused the diet served as controls; 3 with persistently elevated antibodies were excluded from analysis.
- Ataxia was assessed using a battery of objective tests at baseline and after one year.

Key results

- The treatment group improved across the ataxia tests after one year, significantly compared with controls.
- Improvement occurred irrespective of whether enteropathy was present.
- The authors concluded that gluten ataxia can respond to strict gluten withdrawal even in the absence of enteropathy.

Interpretation for this slide: Together with the Brain cohort, this strengthens the “gut is not necessarily the target organ” teaching point: removing the food antigen improved a neurologic disorder even in patients without demonstrable intestinal enteropathy.

Important limitation: The study was small, not randomized, and not blinded; adherence determined group membership, creating potential selection and expectation bias. It is condition-specific evidence, not direct evidence for cardiovascular or metabolic disease.

The 2025 IBS trial — individual reactivity studied

Singh P, Chey WD, Takakura W, et al. A Novel, IBS-Specific IgG ELISA-Based Elimination Diet in Irritable Bowel Syndrome: A Randomized, Sham-Controlled Trial. Gastroenterology. 2025;168(6):1128–1136.e4.

DOI: 10.1053/j.gastro.2025.01.223 PMID: 39894284

Evidence type: Multicentre randomized, double-blind, sham-controlled dietary trial.

Study basics

- 238 participants with IBS were randomized at 8 centres; 223 were included in the modified intention-to-treat analysis.
- Participants were positive to at least one food on an 18-food IBS-specific IgG assay and were assigned to an antibody-guided elimination diet or a sham diet for 8 weeks.
- Primary efficacy outcome was an abdominal-pain-intensity responder endpoint.

Key results

- Primary endpoint response was 59.6% with the guided diet versus 42.1% with sham (P = .02).
- Exploratory subtype results were particularly strong in constipation-predominant IBS: 67.1% versus 35.8%.
- In mixed-bowel-habit IBS, response was 66.0% versus 29.5%.
- The trial demonstrated that this specific individualized IgG-guided selection method could outperform a matched sham diet under blinded randomized conditions.

Interpretation for this slide: This is the presentation's strongest controlled evidence for the narrower concept of individualized food reactivity: personalized food selection based on a specific immune assay produced different outcomes from sham selection.

Important limitation: This was an IBS trial, not a hypertension, cholesterol, or metabolic-syndrome trial. It does not validate every commercial IgG panel, prove that IgG itself is the causal mechanism, or establish IgG-guided elimination as cardiovascular treatment.

Overall evidence summary

What is directly supported: Prospective human evidence shows that higher CRP/hs-CRP/IL-6 can precede the development of hypertension. Randomized CANTOS evidence shows that modifying an inflammatory pathway can reduce recurrent cardiovascular events without lowering lipids. Imaging studies show that plaque can exist in conventionally low-risk people and even at very low LDL levels, while also showing a strong graded relationship between higher LDL and more plaque.

What is supported mechanistically: Contemporary hypertension and endothelial reviews describe plausible pathways through which immune cells, cytokines, oxidative stress, nitric-oxide impairment, vascular tone, renal sodium handling, and neurohormonal systems can interact. The TNF-α review supports the additional concept that inflammatory signalling can influence lipid and glucose metabolism.

What the cross-boundary studies add: The Danish IBD cohort shows that a chronic inflammatory disease in one organ system is associated with later metabolic disease in another. The gluten-ataxia studies show that food-related immune disease can present outside the gut and can improve with antigen removal even when enteropathy is absent.

What the food trial adds: The 2025 IBS randomized sham-controlled trial shows that one assay-specific, individualized IgG-guided elimination strategy can outperform sham selection for IBS pain. This supports the narrower proposition that individualized immune-related food reactivity can be investigated rigorously.

What is not directly proven: No study in this presentation directly demonstrates that a delayed food-specific immune reaction causes essential hypertension, dyslipidaemia, atherosclerosis, or metabolic syndrome in the general population. The aging/hormone illustration is also presented as one plausible example of changing inflammatory balance, not as a single-study causal conclusion.

The synthesis used in the video: The combined evidence supports chronic inflammation as one biologically credible contributor to vascular dysfunction, atherosclerotic risk, blood-pressure regulation, insulin resistance, and lipid metabolism. In a susceptible individual, a persistent inflammatory food reaction is biologically plausible as one possible source of that inflammatory load. The full pathway — food antigen → individual immune response → chronic inflammatory signalling → metabolic / vascular expression — is a synthesis of prospective, randomized, imaging, mechanistic, and condition-specific evidence rather than the result of one definitive trial.