Understanding the impact of hypertension medication usage on zinc status with advancing age

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Declaration

The candidate declares that the work included in this thesis is entirely my own and has not been previously submitted for any other degree and that proper acknowledgement has been provided wherever reference has been made to the work of others. This thesis was submitted as part of the requirements for the PhD at the Division of Food, Nutrition and Dietetics, School of Bioscience, University of Nottingham, Sutton Bonington Campus, Loughborough, Leicestershire, LE12 5RD. Dr Simon Welham and Dr Peter Rose have supervised this effort. Sultan Almutairi's right to be recognised as the author of this work has been asserted in under the terms of the Copyright, Designs and Patents Act 1988.

COVID-19 Pandemic Statement

The COVID-19 pandemic impacted my PhD journey – which began under the shadow of personal grief following the loss of my father, just days before I started my studies in February 2020. Just a month into my programme, the United Kingdom initiated a national lockdown – thrusting me, as an international student, into a landscape of uncertainty and challenge that demanded immense resilience and adaptability. The closure of universities and laboratories for seven months brought my research on mineral status to a complete standstill, delaying experiments and making access to vital resources difficult.

Faced with these unexpected challenges, I sought to make the best of a difficult situation by shifting my focus to alternative academic activities. During this time, I conducted a systematic review and meta-analysis of the impact of antihypertensive drugs on zinc status, which allowed me to continue engaging in my research field despite the constraints. I also maintained steady progress by attending virtual meetings with my supervisors, where we discussed strategies, refined research plans, and adjusted timelines to fit the circumstances. In addition, Moodle-based training sessions and my analysis of datasets, including the UK National Diet and Nutrition Survey, provided opportunities to expand my knowledge and skills while waiting for lab access to resume.

Participating in virtual conferences and lab meetings became a vital source of academic engagement during this period. Presenting on the topic of zinc metabolism was a pivotal moment for me – as it not only deepened my understanding of the subject but also helped me to develop my public speaking skills, boosting my confidence and fostering collaboration with

peers. These experiences were instrumental in maintaining a sense of academic community and purpose, even during prolonged isolation.

Although the disruptions caused by the pandemic were undeniably challenging, they taught me valuable lessons. The experience helped me to develop crucial skills, including adaptability, technological proficiency, and the ability to navigate a rapidly changing research environment. Looking back, this period was not just one of disruption but a transformative chapter that strengthened my resilience and enriched my academic journey, leaving me better equipped for the challenges that lie ahead.

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Abstract

Background

Zinc (Zn) is an essential trace element involved in various physiological functions, including enzymatic activity, cellular metabolism, gene expression regulation, and immune function. Adequate Zn status is crucial for maintaining overall health, particularly in older adults who are susceptible to age-related declines in Zn absorption and an increased risk of deficiency. Chronic hypertension, a prevalent condition in the ageing population, often requires long-term pharmacological intervention, which has been implicated in disrupting Zn homeostasis. Despite growing evidence suggesting an association between antihypertensive medication use and altered Zn status, the underlying mechanisms and potential health consequences remain unclear.

Aims

This thesis aims to investigate the impact of chronic antihypertensive medication use on Zn status in older adults by conducting a systematic review, secondary analysis of the UK National Diet and Nutrition Survey (NDNS), and comparative study involving older adult populations residing in Nottinghamshire.

Methods

In the initial phase of this research, a systematic review and meta-analysis were conducted in accordance with PRISMA guidelines to synthesise existing evidence regarding the relationship between antihypertensive medication use and Zn status. The review incorporated studies that assessed dietary Zn intake, serum Zn concentrations, and urinary Zn excretion. In addition, a secondary analysis of the NDNS dataset was performed to examine patterns of Zn intake and biochemical markers of Zn status among older adults prescribed antihypertensive medications. Furthermore, a cross-sectional comparative study was conducted to evaluate Zn status through dietary assessments and health-related parameters among older adults residing in care homes

and those living independently. A total of 11 participants were recruited, comprising five care home residents and six free-living individuals.

Results

Findings from the systematic review demonstrated a significant association between the use of antihypertensive medications – particularly angiotensin-converting enzyme inhibitors and diuretics – and decreased serum Zn levels, along with increased urinary Zn losses, suggesting potential disruptions in Zn homeostasis. Analysis of NDNS data corroborated these findings, indicating lower dietary Zn intake and reduced serum concentrations in older adults undergoing prolonged antihypertensive treatment, with polypharmacy exacerbating this trend. The comparative study further supported these observations, demonstrating that care home residents on multiple antihypertensive medications exhibited lower Zn status compared to their free-living counterparts.

Conclusion

The findings of this thesis highlight the potential implications of antihypertensive medication use on Zn status in older adults, underscoring the importance of regular nutritional monitoring and tailored dietary interventions to prevent deficiencies. Given the critical role of Zn in immune function and overall health, addressing potential deficiencies in hypertensive older populations is imperative. This thesis contributes to understanding the impact of chronic antihypertensive medication use on Zn status in older adults by providing evidence-based insights into the interplay between medication use, dietary intake, and Zn status. The research emphasises the need for comprehensive nutritional strategies that address the potential micronutrient imbalances induced by long-term pharmacological treatment.

The findings underscore the importance of multidisciplinary approaches, involving healthcare professionals and dietitians, to implementing targeted interventions, such as routine nutritional screening, dietary modifications, and supplementation guidelines tailored to hypertensive older

adults. Additionally, future research should focus on longitudinal studies to explore the long-term implications of antihypertensive medications on Zn homeostasis and the development of personalised nutritional recommendations to improve health outcomes in ageing populations. Furthermore, it is essential to evaluate the efficacy of Zn supplementation in mitigating the adverse effects of antihypertensive medications on Zn status.

Keywords: zinc status, hypertension, older people, antihypertensive medication, systematic review, National Diet and Nutrition Survey

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Abbreviations

ACE	Angiotensin-Converting Enzyme
AI	Adequate Intake
ARB	Angiotensin II Receptor Blocker
AT1	Angiotensin II Type 1
BMI	Body Mass Index
BP	Blood Pressure
Ca	Calcium
CCB	Calcium Channel Blocker
CI	Confidence Interval
Cl	Chloride
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
Cu	Copper
CVD	Cardiovascular Disease
dL	Decilitre
DNI	Drug-Nutrient Interaction
DNA	Deoxyribonucleic Acid
DBP	Diastolic Blood Pressure
DHSC	Department of Health and Social Care
Fe	Iron
fL	Femtolitre
FNSS	Food and Nutrition Security Survey
Folate	Folic Acid (Vitamin B9)
FFQ	Food Frequency Questionnaire

g	Grams
gCr	Grams of Creatinine
GI	Gastrointestinal
h	Hour
HCT	Haematocrit
Hgb	Haemoglobin
HTN	Hypertension
I	Iodine
I^2	I-Squared
Ibs	Pounds
IQR	Interquartile Range
K	Potassium
kcal	Kilocalories
Kg	Kilograms
L	Litre
LRNI	Lower Reference Nutrient Intake
M	Meters
MCV	Mean Cell Volume
Mcg	Micrograms
mg	Milligrams
Mg	Magnesium
MeSH	Medical Subject Headings
mmHg	Millimetres of Mercury
Mn	Manganese
MNA-SF	Mini-Nutritional Assessment Short-Form

MT	Metallothionein
Na	Sodium
Na^{+}-Cl^{-}	Sodium and Chloride
NDNS	National Diet and Nutrition Survey
NHS	National Health Service
NO	Nitric Oxide
NOS	Newcastle–Ottawa Quality Assessment Scale
ONS	Office for National Statistics
P	Phosphorus
PICO	Population, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAAS	Renin-Angiotensin-Aldosterone System
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
RNI	Reference Nutrient Intake
RNA	Ribonucleic Acid
SACN	Scientific Advisory Committee on Nutrition
SBP	Systolic Blood Pressure
SD	Standard Deviation
Se	Selenium
SOD	Superoxide Dismutase
SPSS	Statistical Package for the Social Sciences
τ^2	Tau-Squared
UK	United Kingdom
UIC	Urinary Iodine Concentration

UNICEF	United Nations International Children's Emergency Fund
µg	Micrograms
µmol	Micromoles
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organisation
Zn	Zinc
ZnD	Zinc Deficiency
ZnT	Zinc Transporter
ZIP	Zrt/Irt-Like Protein
%	Percentage

Chapter 1: Introduction and Background

1.1 Overview of Minerals

Minerals are essential inorganic elements that cannot be synthesised by the human body and must then be obtained through diet. These elements are considered essential nutrients, as small quantities are required for the body to function properly. Minerals are categorised into two groups based on their daily requirements for adults: macrominerals (major minerals), which are required in amounts greater than 100 milligrams (mg) per day, and microminerals (trace minerals), which are required in smaller amounts (Prashanth et al., 2015). Both groups play significant roles in maintaining health, and deficiencies can lead to serious health consequences (Fairweather-Tait & Hurrell, 1996; Godswill et al., 2020; Strain & Cashman, 2009). The macrominerals include calcium (Ca), potassium (K), sodium (Na), magnesium (Mg), phosphorus (P), and chloride (Cl), while microminerals include iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), iodine (I), and selenium (Se), as well as chromium, cobalt and molybdenum.

Providing an overview of both macro- and microminerals before focusing on zinc is essential, as it establishes a foundation for understanding how these elements function and interact within the body. Many minerals share intestinal uptake pathways or compete for binding sites within the gastrointestinal tract and the kidney (Fairweather-Tait & Hurrell, 1996; Goff, 2018). Calcium (Ca^{2+}), magnesium (Mg^{2+}), iron (Fe^{2+}), copper (Cu^{2+}) and zinc (Zn^{2+}) are all divalent cations that utilise overlapping transport systems in the intestinal epithelium (e.g., DMT1) and intracellular binding proteins (e.g., metallothionein). Consequently, Ca^{2+}, Mg^{2+}, Fe^{2+} and Cu^{2+} can compete with Zn^{2+} for intestinal transporters including ZIP and ZnT proteins and for binding sites in renal tissues (Miller, 2017; Jomova et al., 2022). Such interactions mean that deficiency or excess of one element can markedly influence zinc absorption and status (Sandström, 2001; Strain & Cashman, 2009; Jomova et al., 2022). Moreover, several antihypertensive medications alter zinc homeostasis indirectly by modifying renal handling of

sodium, potassium and calcium, underscoring the integrated nature of mineral metabolism (Suliburska et al., 2018; Mohn et al., 2018). A brief synthesis of these minerals therefore clarifies their interdependence and frames the rationale for a focused examination of zinc particularly in the context of hypertension and polypharmacy.

1.2 Major Minerals (Macrominerals)

1.2.1 Calcium (Ca)

Calcium is the most abundant mineral in the human body, contributing to the formation and maintenance of bones and teeth. It is also crucial for muscle contractions, nerve function, and blood clotting. Calcium deficiency can lead to osteoporosis – a condition characterised by reduced bone density, particularly in older adults (Gharibzahedi & Jafari, 2017). Calcium is primarily obtained from dairy products such as milk, cheese, and yoghurt, as well as leafy green vegetables such as kale and fish with bones (e.g. sardines and salmon; Godswill et al., 2020; Strain & Cashman, 2009). To avoid inadequate intake, calcium should be consumed through diet, with the recommended intake for older men and women being 700 mg per day (British Nutrition Foundation, 2021).

1.2.2 Potassium (K)

Potassium is essential for regulating fluid balance, nerve signals, and muscle contractions, making it critical for cardiovascular and overall health (Strain & Cashman, 2009; Zoroddu et al., 2019). Potassium is abundant in a wide range of foods, and a dietary deficiency is rare (Godswill et al., 2020). However, insufficient potassium intake can result in hypokalaemia, which is associated with cardiac disturbances (He & MacGregor, 2008; Zoroddu et al., 2019). Potassium is primarily obtained from fruits (particularly bananas, oranges, and avocados), vegetables (such as potatoes and spinach), legumes, and dairy products. Whole grains also

contribute significantly to potassium intake (Gharibzahedi & Jafari, 2017; Godswill et al., 2020; Strain & Cashman, 2009). The reference nutrient intake (RNI) for potassium for adults in the United Kingdom, including older adults, is 3,500 mg per day (British Nutrition Foundation, 2021).

1.2.3 Sodium (Na)

Sodium is widely present in most foods, and a dietary deficiency is rare. It is essential for maintaining electrolyte and fluid balance, supporting nerve function, and facilitating muscle contractions (Gharibzahedi & Jafari, 2017; Godswill et al., 2020; Strain & Cashman, 2009). Elevated sodium levels in the blood, a condition known as hypernatraemia, are characterised by symptoms such as seizures, oedema, irritability, and weakness (Godswill et al., 2020). Sodium is primarily consumed through table salt (NaCl) and processed foods, which often contain high sodium levels; bread, processed meats, and canned soups are typical contributors (Gharibzahedi & Jafari, 2017).

Although the United Kingdom's Reference Nutrient Intake (RNI) for sodium is 1,600 mg day for adults, including older adults, population intakes remain well above this benchmark (British Nutrition Foundation, 2021). The 24-hour urinary sodium survey (2018–19) reported that English adults aged 19–64 years consume, on average, 8.4 g of salt per day (≈ 3,360 mg sodium); men and women ingest 9.2 and 7.6 g/day, respectively around 40% above the Scientific Advisory Committee on Nutrition (SACN) population guideline of ≤ 6 g/day (Ashford et al., 2020). Dietary record data from the National Diet and Nutrition Survey (2019–23) indicate that adults aged ≥ 65 years obtain roughly 1,500–1,600 mg sodium/day from foods alone. Because these records exclude salt added during cooking or at the table, true intake in older adults is likely higher and may still exceed recommendations (Office for Health

Improvement & Disparities, 2025). Persistent consumption at or above these levels is a recognised risk factor for hypertension, particularly in later life.

1.2.4 Magnesium (Mg)

Magnesium is the fourth most prevalent mineral in the human body and acts as an essential cofactor in over 300 enzymatic reactions, including those involved in energy metabolism, protein synthesis, and muscle and nerve function. Additionally, it plays a vital role in regulating blood pressure (BP) and supporting immune health (DiNicolantonio et al., 2018; Gharibzahedi & Jafari, 2017; Zoroddu et al., 2019). Despite its importance, magnesium intake is frequently below the recommended levels, leading to hypomagnesaemia (DiNicolantonio et al., 2018). In the United Kingdom, the recommended daily intake is 300 mg for men and 270 mg for women (British Nutrition Foundation, 2021). Magnesium can be obtained from dietary sources such as nuts, seeds, whole grains, leafy green vegetables, legumes, and fish (Gharibzahedi & Jafari, 2017).

1.2.5 Phosphorus (P)

Phosphorus plays a key role in maintaining the structural integrity of bones and teeth and is essential for energy metabolism, as well as being a fundamental component of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (Arai & Sakuma, 2015; Gharibzahedi & Jafari, 2017). However, hyperphosphatemia is a known risk factor for chronic kidney disease and cardiovascular disease (CVD; Takeda et al., 2012). Phosphorus is abundant in protein-rich foods, including meat, poultry, fish, eggs, and dairy products. Nuts, seeds, and legumes also serve as good dietary sources (Gharibzahedi & Jafari, 2017; Takeda et al., 2012). The RNI for older men and women is 550 mg (British Nutrition Foundation, 2021).

1.2.6 Chloride (Cl)

Chloride is vital for maintaining osmotic pressure and fluid balance in the body. It is also plays an essential role as a key component of hydrochloric acid (gastric juice) in the stomach, which helps with digestion and nutrient absorption (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). Most chloride is consumed through table salt (NaCl), but it is also found in foods such as animal products, tomatoes, lettuce, and olives (Gharibzahedi & Jafari, 2017). In the United Kingdom, the RNI for chloride for adults, including older adults, is 2,500 mg (British Nutrition Foundation, 2021).

1.3 Trace Minerals (Microminerals)

1.3.1 Iron (Fe)

Iron is one of the most abundant minerals in the human body and is essential for life. It is a critical component of haemoglobin – found in red blood cells, which is responsible for transporting oxygen throughout the body – and myoglobin, located in muscle tissue. Both haemoglobin and myoglobin are iron-binding proteins (Abbaspour et al., 2014; Zoroddu et al., 2019). Additionally, iron functions as a cofactor for numerous enzymes and is crucial for their activity (Godswill et al., 2020). Iron deficiency leads to anaemia, which is characterised by fatigue and other symptoms (Gharibzahedi & Jafari, 2017). Iron is available in two forms: haem iron, derived from animal sources such as red meat, poultry, and fish, and nonhaem iron, which is found in plant-based sources such as legumes, beans, and fortified cereals (Abbaspour et al., 2014; Gharibzahedi & Jafari, 2017; Godswill et al., 2020). The RNI for iron for adults in the United Kingdom, including older adults, is 8.7 mg per day (British Nutrition Foundation, 2021).

1.3.2 Copper (Cu)

Copper plays a vital role in iron metabolism, the formation of connective tissue, and the proper functioning of the immune system (Gharibzahedi & Jafari, 2017; Godswill et al., 2020; Zoroddu et al., 2019). Dietary sources of copper include organ meats such as liver, shellfish, nuts, seeds, and whole grains, all of which contribute to maintaining adequate levels of this essential mineral (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). The RNI for copper in the United Kingdom for older adults is 1.2 mg per day (British Nutrition Foundation, 2021).

1.3.3 Manganese (Mn)

Manganese is essential for various physiological processes, including bone formation, blood clotting, and antioxidant defence. It serves as a key component of the enzyme superoxide dismutase, which plays a critical role in protecting the body against oxidative stress (Gharibzahedi & Jafari, 2017; Godswill et al., 2020; Zoroddu et al., 2019). Dietary sources of manganese include whole grains, nuts, leafy green vegetables, and tea, which contribute to maintaining adequate levels of this important mineral (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). The adequate intake (AI) for manganese in adults within the European Union is approximately 3 mg per day (EFSA NDA Panel, 2023).

1.3.4 Iodine (I)

Iodine is crucial for the synthesis of thyroid hormones, which are essential for regulating metabolism, growth, and development (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). Iodine deficiency can lead to the development of goitre and hypothyroidism, conditions that significantly affect thyroid function (Mehri, 2020). Dietary sources of iodine such as iodised salt, seafood, dairy products, and certain plants cultivated in iodine-rich soil (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). The RNI for iodine in the United Kingdom for older adults is 140 µg per day (British Nutrition Foundation, 2021).

1.3.5 Selenium (Se)

Selenium is vital for antioxidant defence and thyroid function. It also plays an important role in DNA synthesis and helps protect the body from oxidative stress (Gharibzahedi & Jafari, 2017; Godswill et al., 2020; Mehri, 2020). A lack of selenium in the diet can lead to Keshan disease, a type of cardiomyopathy (Rayman, 2012). Good dietary sources of selenium such as Brazil nuts, seafood, meats, grains, and dairy products such as eggs (Gharibzahedi & Jafari, 2017; Godswill et al., 2020). In the United Kingdom, the RNI of selenium for older adults is 75 µg per day for men and 60 µg per day for women (British Nutrition Foundation, 2021).

1.3.6 Zinc (Zn)

Zn is the second most abundant trace element in the body, after iron. Zn cannot be synthesised endogenously and must be obtained through dietary sources to maintain optimal levels (Sangeetha et al., 2022). It is an essential trace mineral fundamental to human nutrition and health due to its wide-ranging structural, enzymatic, and regulatory roles within biological systems (King et al., 2016). Nutritionally, Zn acts as a cofactor for over 300 enzymes and 2,000 transcription factors, supporting processes such as protein synthesis, nucleic acid metabolism, and gene transcription (Chasapis et al., 2012; Kiouri et al., 2024). Zn serves as a vital cofactor in numerous metabolic processes, including bone metabolism via alkaline phosphatase and protein digestion through carboxypeptidase (Clemens, 2022). Additionally, Zn plays a vital role in bone health, acting as a structural component involved in collagen matrix synthesis, mineralisation, and bone turnover, highlighting its importance in skeletal development and maintenance (King et al., 2016). Zn is equally critical for immune functionality, as it modulates intracellular signalling pathways in innate and adaptive immune cells. It influences immune responses – involving antibody production, inflammatory signalling, and lymphocyte differentiation, underscoring its role in enhancing immune resilience and reducing susceptibility to infections (Bonaventura et al., 2015; Chen et al., 2024).

Zn deficiency in humans was identified in 1961 when a man subsisting on a diet of unrefined flatbread, potatoes, and milk was found to suffer from a syndrome characterised by anaemia, hypogonadism, and dwarfism, a discovery reported by Prasad et al. (1963). This marked a pivotal moment in nutritional science, sparking extensive research into the role of Zn in human health. This finding transformed previous perceptions of Zn, with subsequent studies establishing it not as a toxic transition metal but as a nutritionally essential element critical for numerous physiological functions and overall health (Jarosz et al., 2017; Roohani et al., 2013).

1.3.6.1 Dietary Sources and Requirements of Zn

Zn is a vital trace element found in various foods, with dietary intake being the primary source for maintaining Zn homeostasis (Hambidge et al., 2010; Sangeetha et al., 2022). The relationship between Zn intake and absorption is inversely proportional: The body enhances Zn absorption during periods of deficiency and reduces it when intake is excessive to prevent toxicity (Hambidge et al., 2010; Szabo et al., 2021). However, the availability of Zn from different dietary sources varies significantly due to differences in bioavailability and food composition.

The RNI and lower RNI for Zn, as established by the British Nutrition Foundation (2023), provide standards for assessing dietary Zn adequacy across population groups. These values are detailed in **Table 1.1** and summarise the recommended intake values necessary to prevent deficiency and maintain optimal health.

Foods rich in protein are significant sources of dietary Zn, whereas those primarily composed of carbohydrates generally contain much lower Zn levels (Osis et al., 1972). Zn-rich foods can be categorised into several groups, with oysters recognised as the most Zn-abundant food source. However, in typical dietary patterns, the primary contributors to Zn intake are meat and meat products, including beef, pork, lamb, and processed meats. Additional significant sources include cereals, grains, milk, and dairy products, which together form a substantial part of dietary Zn intake (Deshpande et al., 2013; Forouzesh et al., 2022). Within the meat category, red meat, such as beef, provides higher Zn levels compared to white meat (e.g. chicken) or fish, making it a more reliable and concentrated source of dietary Zn (Awad & Ali, 2023).

Table 1.1 UK zinc RNI and LRNI values by age and sex

(Department of Health and Social Care; on SACN advice).

Group	RNI	LRNI
Infants (0–3 months)	4.0 mg/day	2.5 mg/day
Infants (4–6 months)	4.3 mg/day	2.8 mg/day
Infants (7–12 months)	5.0 mg/day	3.3 mg/day
Children (1–3 years)	5.0 mg/day	3.0 mg/day
Children (4–6 years)	6.5 mg/day	4.0 mg/day
Children (7–10 years)	7.0 mg/day	4.5 mg/day
Adolescents (11–14 years)	9.0 mg/day (boys), 7.0 mg/day (girls)	5.5 mg/day (boys), 4.5 mg/day (girls)
Adolescents (15–18 years)	9.5 mg/day (boys), 7.0 mg/day (girls)	6.0 mg/day (boys), 4.5 mg/day (girls)
Adults (19–50 years)	9.5 mg/day (men), 7.0 mg/day (women)	6.0 mg/day (men), 4.5 mg/day (women)
Adults (50+ years)	9.5 mg/day (men), 7.0 mg/day (women)	6.0 mg/day (men), 4.5 mg/day (women)
Pregnant women	7.0 mg/day	5.0 mg/day
Lactating women	7.0 mg/day	5.0 mg/day

This table represents the Reference Nutrient Intakes (RNIs) and Lower Reference Nutrient Intakes (LRNIs) for zinc in the UK, as outlined by the Department of Health. The RNI is defined as the amount of zinc sufficient to meet the nutritional needs of almost all (97.5%) individuals in a specific group, ensuring optimal health and functionality. The LRNI, on the other hand, represents the minimum amount of zinc required to meet the needs of only a small proportion (2.5%) of individuals with lower nutritional requirements, indicating that most people would require greater amounts of zinc for adequate nutrition. These values provide essential guidance for assessing dietary zinc intake and preventing deficiencies or excess.

1.3.6.2 Factors Inhibiting Zn Absorption

Zn bioavailability, defined as the proportion of Zn that can be absorbed and utilised by the body, is a critical factor in maintaining overall health (Stiles et al., 2024). Zn absorption is significantly influenced by dietary components. For example, phytates found in grains, seeds, and legumes can bind with Zn in the gastrointestinal (GI) tract and inhibit its absorption (Bel-Serrat et al., 2014; Hambidge et al., 2010). However, certain food processing methods, such as soaking and fermenting, have been demonstrated to reduce phytate levels and thereby enhance Zn bioavailability (Singh & Prasad, 2023). Moreover, proteins, particularly those derived from dairy products, can facilitate Zn absorption by mitigating the inhibitory effects of phytates (Shkembi & Huppertz, 2021). On the other hand, polyphenols, commonly present in tea and certain fruits, can significantly impair Zn absorption by forming insoluble complexes with Zn, reducing its bioavailability (Singh & Prasad, 2023). Additionally, the presence of other minerals can affect absorption rates; high calcium intake may compete with Zn for absorption sites in the GI tract, potentially leading to decreased Zn bioavailability (Bel-Serrat et al., 2014; Krebs, 2000). Research has indicated that certain antihypertensive drugs can significantly influence Zn absorption and metabolism (see **Figure 1.1**). Antihypertensive medications, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs), impact Zn status by altering renal excretion and GI absorption. For instance, diuretics have been demonstrated to increase Zn excretion via urine, thereby reducing overall Zn levels in the body (Chiba et al., 2013). Similarly, calcium antagonists have been reported to reduce erythrocyte Zn levels, while ACE inhibitors lower serum Zn concentrations (Suliburska et al., 2018). Furthermore, supplementation with Zn in indapamide-treated rats improved mineral homeostasis and enhanced the antihypertensive efficacy of the drug (Suliburska et al., 2014).

The widespread use of antihypertensive medications presents a significant public health challenge, particularly due to their potential impact on Zn absorption (Braun & Rosenfeldt, 2013; Mohn et al., 2018). The intersection of high hypertension prevalence, reliance on pharmacological interventions, and Zn absorption inhibition raises serious concerns about the broader implications for population health. Addressing this issue is crucial to developing strategies that mitigate Zn deficiency risks among individuals undergoing hypertension (HTN) management, thereby improving overall health outcomes.

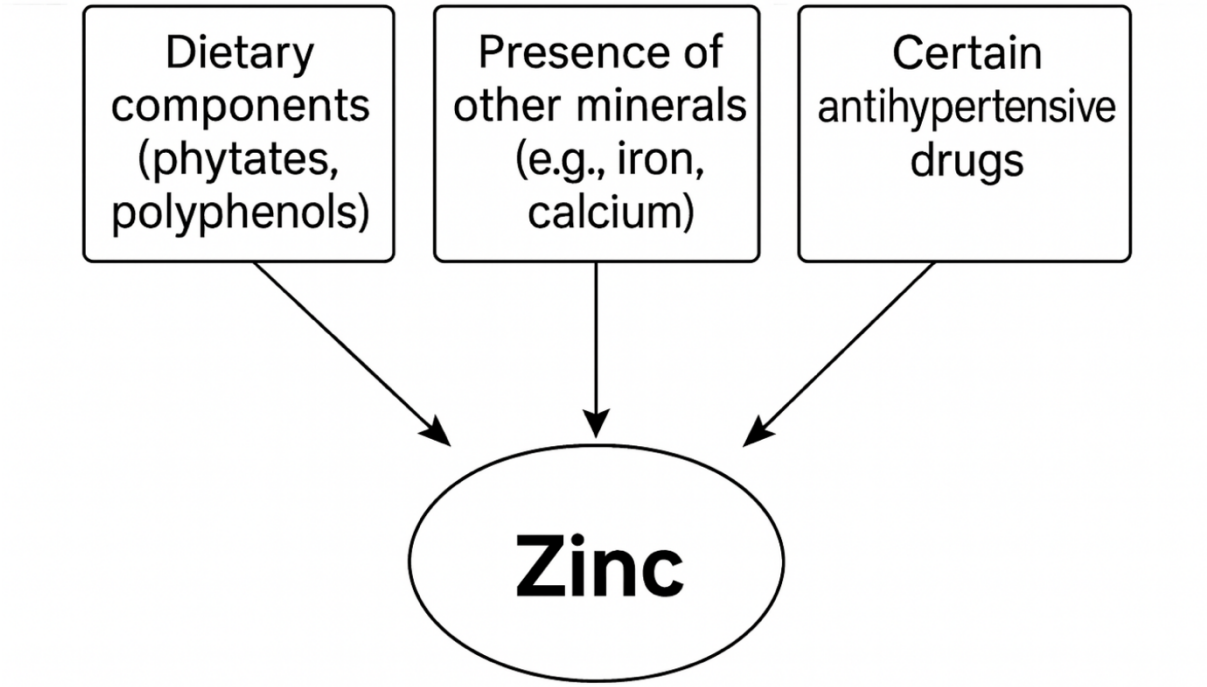


Figure 1.1 Factors influencing zinc status

1.4 Physiological Mechanisms of BP Regulation

Blood pressure (BP) regulation is a complex process that ensures adequate perfusion of tissues and organs by maintaining BP. It involves the interaction of several systems – including the neural, vascular, endocrine, renal, and local tissue control mechanisms, working through short-term (effective over a period of seconds to hours), as well as mid- and long-term processes (operate over days to weeks; Guyton, 2006; Hall et al., 2012; Porth, 2009; Saugel & Sessler, 2020; see **Figure 1.2**).

1.4.1 Neural Mechanisms

The nervous system is critical for short-term BP regulation – primarily through the autonomic nervous system, specifically the baroreceptor reflex (Japundzic-Zigon, 1998). Baroreceptors, which are most abundant in the carotid sinus and aortic arch, play a central role in this process (Guyton, 2006). The sympathetic and parasympathetic branches of the autonomic nervous system work in opposition to control vascular tone and heart rate. When BP rises, baroreceptors are activated, increasing parasympathetic activity and suppressing sympathetic output. This leads to vasodilation and a slower heart rate. In contrast, when BP drops, sympathetic activity is stimulated, causing vasoconstriction, a faster heart rate, and stronger heart contractions (Salah et al., 2024). The sympathetic nervous system is particularly effective in making rapid BP adjustments via adrenergic pathways. Activation of alpha-1 adrenergic receptors causes vasoconstriction, while beta-adrenergic receptors increase both heart rate and cardiac contractility. Together, these mechanisms help stabilise BP in the short term (Touyz et al., 2018; Triposkiadis et al., 2009).

1.4.2 Vascular Mechanisms

The vascular system plays a key role in regulating BP by coordinating the actions of endothelial cells and vascular smooth muscle (Pintérová et al., 2011). Endothelial cells release nitric oxide (NO), which helps relax blood vessels and promotes vasodilation, while endothelin causes vasoconstriction to maintain vascular tone (Sandoo et al., 2010). Calcium ions are also critical for smooth muscle contraction, and medications such as calcium channel blockers (CCBs) are often used to treat HTN. These drugs work by reducing calcium entry into muscle cells, leading to relaxed blood vessels and lower BP (Touyz et al., 2018).

1.4.3 Endocrine Mechanisms

The endocrine system plays a key role in regulating BP by producing hormones that affect vascular tone and fluid balance (Touyz et al., 2018). A key pathway involved in long-term regulation is the renin-angiotensin-aldosterone system (RAAS), which is triggered when renal perfusion or sodium levels drop. In response, the kidneys release renin, an enzyme that converts angiotensinogen into angiotensin I from juxtaglomerular cells (Chopra et al., 2011). Angiotensin I is then converted into angiotensin II by ACE. Angiotensin II is a potent vasoconstrictor that increases BP (Cowley, 1992; Gordan et al., 2015). Angiotensin II also stimulates the adrenal glands to produce aldosterone, a hormone that promotes sodium and water retention. This increases blood volume and pressure, further supporting long-term regulation (Chopra et al., 2011; Gordan et al., 2015). Other hormones, such as vasopressin (antidiuretic hormone) and atrial natriuretic peptide, also play a role by controlling fluid levels and vascular tone, helping to modulate BP regulation (Chopra et al., 2011).

1.4.4 Renal Mechanisms

The kidneys are fundamental to long-term BP regulation, primarily through their role in managing fluid and electrolyte balance. By adjusting sodium excretion and urine output, they control blood volume, which directly affects BP (Cowley, 1992; Hall et al., 2012; Van Beusecum & Inscho, 2015). In the 1960s, Guyton demonstrated that the kidneys are central to maintaining long-term BP, highlighting their control over mean arterial pressure through fluid balance. Later, in 1969, Guyton and colleagues identified the key link between BP and sodium excretion, known as the 'pressure-natriuresis relationship' (Van Beusecum & Inscho, 2015). This relationship ensures that when arterial pressure increases, sodium and water excretion are enhanced, leading to reduced blood volume and lower BP. Conversely, when arterial pressure drops, sodium retention increases, conserving blood volume and raising pressure to restore balance (Cowley, 1992; Hall et al., 2012; Van Beusecum & Inscho, 2015).

The physiological mechanisms that regulate BP are also influenced by external factors such as physical activity and stress (Cowley, 1992; Hall et al., 2024; Touyz et al., 2018). Physical activity, for instance, has been demonstrated to improve vascular function and BP regulation through mechanisms involving NO and other vasodilatory factors. In contrast, stress can lead to activation of the sympathetic nervous system and RAAS, which may contribute to HTN progression (Bakris & Mensah, 2002; Guyton, 2006; Touyz et al., 2018).

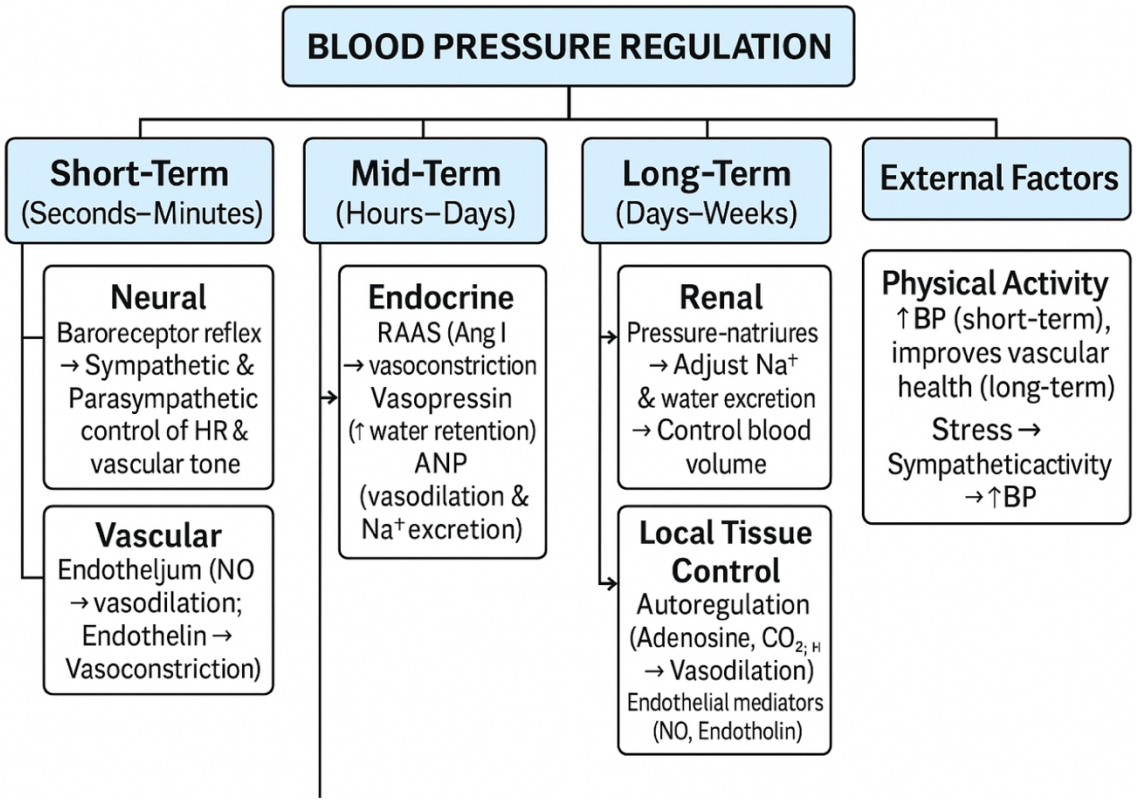


Figure 1.2 Factors Influencing BP regulation

1.5 Hypertension and Consequences

Healthcare research and treatment represent one of the most significant financial challenges globally (Rudan, 2023). Despite the presence of numerous research centres worldwide, there are still conditions that remain without definitive cures, continuing to contribute to patient suffering (Mucke, 2024). Hypertension (HTN), commonly referred to as high BP, is one of the most widespread medical conditions globally, defined in adults as a persistent elevation in systolic BP (≥140 mmHg) and/or diastolic BP (≥90 mmHg), and it contributes significantly to global morbidity and mortality (Charchar et al., 2024). Systolic BP represents the peak pressure exerted on arterial walls during the contraction phase of the heart (systole), specifically when the ventricular muscles contract to pump blood into the pulmonary artery and aorta. In contrast, diastolic BP measures the baseline pressure in the arteries during the relaxation phase of the heart (diastole), when the heart cavities dilate and fill with blood. These parameters are central to HTN assessment and management (Janjua, 2021; Messerli et al., 2007).

The challenges of maintaining a healthy lifestyle, including a proper diet and regular physical activity, have contributed to increasing HTN incidence. With an estimated 1.3 billion individuals globally affected by HTN, particularly among older adults (Richardson et al., 2024). Global cases are projected to exceed 1.5 billion by 2030 (Jafar et al., 2016). The overall prevalence of HTN in the UK is estimated to be between 30% and 45% among adults, increasing significantly among older people (NHS Digital, 2023; Tapela et al., 2021).

It is additionally classified into primary (essential) HTN, which accounts for 95% of cases, and secondary HTN, which makes up the remaining 5% (Hall et al., 2012; Poulter et al., 2015). The exact aetiology of primary HTN remains elusive and a range of intertwined environmental, genetic and lifestyle factors influence the disease incidence (Carretero & Oparil, 2000). On the

contrary, secondary HTN has defined identifiable causes, such as the narrowing of kidney arteries, chronic kidney disease and endocrine disorder (Poulter et al., 2015).

HTN (the silent killer) is recognised by the World Health Organisation (WHO) as a leading risk factor for CVD, which constitutes one of the primary causes of mortality globally (Mendis, 2013). HTN is particularly harmful, as it significantly increases the risk of life-threatening complications such as stroke, heart attack, and chronic kidney disease (Unger et al., 2020). Additionally, CVD, for which HTN is a major risk factor, results in approximately one million hospital admissions each year in England, contributing to healthcare costs estimated at £7.4 billion annually (Public Health England, 2020). This chronic condition is caused by various factors, including genetic predisposition, obesity, high salt intake, and prolonged stress (Masenga & Kirabo, 2023). According to the 2023 guidelines of the International Society of Hypertension (endorsed by the World Hypertension League and the European Society of Hypertension), lifestyle modifications are advocated as the primary intervention for the prevention and initial management of hypertension (HTN). Evidence-based measures, including the reduction of dietary sodium intake, weight management, and regular engagement in physical activity, are highlighted for their capacity to mitigate the risk of developing HTN and lower associated cardiovascular risks. Nevertheless, following a confirmed HTN diagnosis, the initiation of antihypertensive pharmacotherapy becomes imperative. Such interventions are essential for achieving effective BP control and minimising the risk of HTN-related complications, aligning with contemporary global clinical guidelines on cardiovascular health (Charchar et al., 2024). Moreover, studies on dietary modifications, such as the Dietary Approaches to Stop Hypertension, have indicated that adopting a nutritious diet rich in fruits, vegetables, low-fat dairy, and plant-based proteins from legumes and nuts can effectively lower high BP (Patel et al., 2020; Strilchuk et al., 2020).

1.5.1 Medication Use in HTN Management

Pharmacological interventions remain central to HTN management, effectively lowering BP and reducing the risk of adverse cardiovascular outcomes (Rahimi et al., 2021). HTN management typically begins with the initiation of first-line antihypertensive medications, which can be administered either as monotherapy or in combination (Garjon et al., 2020). For patients presenting with significantly elevated baseline BP, combination therapy is often the preferred strategy to achieve more effective and timely BP control. The five major primary classes of medications frequently prescribed for HTN are thiazide diuretics (introduced in 1958), beta-blockers (1973), CCBs (1977), ACE inhibitors (1977), and ARBs, the latest first-line therapy introduced to the market in 1993 (Laurent, 2017; Rouette et al., 2022). The choice of treatment should be tailored to efficacy and tolerability (Cuspidi et al., 2018). These evidence-based classes remain the foundation of HTN management worldwide. These drugs are well regarded not only for their ability to lower BP but also for their effectiveness in reducing associated health risks (Laurent, 2017).

A population-based cohort study of 2.7 million UK primary care patients over 31 years (1988–2018) found a notable rise (7.8%–21.9%) in the proportion of patients prescribed antihypertensive medications. During this period, the use of angiotensin-converting enzyme (ACE) inhibitors increased from 0.4% to 9.3%, angiotensin receptor blockers (ARBs) increased from 0% to 4%, calcium channel blockers (CCBs) rose from 1.4% to 8.7% and beta-blockers increased from 2.6% to 8.6%. Conversely, the prevalence of thiazide diuretics declined after reaching a peak in 2005 (7.3% down to 3.8%). By 2018, the relative proportions of these prescriptions were as follows: ACE inhibitors (24.5%) followed by CCBs (22.9%) and beta-blockers (22.5%), each category representing a specific share of the total antihypertensive prescriptions (Rouette et al., 2022).

1.5.2 Mechanistic Insights into Drug Efficacy and Safety

Each pharmacological class is designed to target distinct mechanisms for effective BP regulation (see **Table 1.2**).

Table 1.2 Pharmacological agents and mechanisms of action of antihypertensive drugs (Source: Laurent, 2017).

Target Organ/System	Pharmacological Class	Examples	Mechanism of Action
Brain	Centrally Acting Agents	Clonidine, Rilmenidine	↓ Sympathetic tone (α2-adrenergic receptors, imidazoline receptors)
Heart	Betablockers	Atenolol, Metoprolol	↓ HR (bradycardia) by blocking β1-adrenergic receptors → ↓ cardiac output
	Non-DHP CCBs	Verapamil, Diltiazem	Block L-type Ca^{2+} channels → ↓ HR & contractility
Blood Vessels	DHP-CCBs	Amlodipine, Nifedipine	Vasodilation via L-type Ca^{2+} channel blockade
	ACE Inhibitors	Enalapril	↓ Ang II → Vasodilation
	ARBs	Losartan	Block Ang II receptor → Vasodilation
	Alpha-1 Adrenergic Antagonists	Prazosin	Block α1-receptors → Vasodilation
	Direct Vasodilators	Minoxidil, Hydralazine	Direct smooth muscle relaxation
Kidneys	Diuretics	Loop (Furosemide), Thiazides	↑ Na^{+} excretion → ↑ diuresis → ↓ extracellular fluid volume
	Renin Inhibitors	Aliskiren	↓ Renin activity
	Betablockers	Atenolol, Metoprolol	↓ Renin secretion

1.5.2.1 ACE Inhibitors

ACE inhibitors, a pivotal class of antihypertensive medications, function primarily by targeting the Renin-Angiotensin-Aldosterone System (RAAS), a critical regulator of vascular resistance and fluid homeostasis. These drugs inhibit ACE, responsible for the conversion of angiotensin I to the potent vasoconstrictor angiotensin II. This inhibition reduces systemic vascular resistance, arteriolar vasoconstriction, and aldosterone secretion, thereby decreasing sodium and water retention. Additionally, ACE inhibitors prevent the degradation of bradykinin (a vasodilatory peptide), further contributing to their antihypertensive effect (Brown & Vaughan, 1998; Cutrell et al., 2023; Laurent, 2017). The therapeutic utility of ACE inhibitors extends beyond HTN management – demonstrating substantial efficacy in patients with heart failure, diabetes, and chronic kidney disease, where they provide critical clinical benefits (Laurent, 2017).

The commonly used ACE inhibitors include benazepril, captopril, cilazapril, enalapril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril, which have demonstrated efficacy in reducing cardiovascular morbidity and mortality (Brown & Vaughan, 1998). Based on their binding with ACE, ACE inhibitors are structurally classified into sulfhydryl-containing inhibitors (e.g. captopril), dicarboxyl-containing inhibitors (e.g. perindopril, enalapril, and ramipril), and phosphonate-containing inhibitors (e.g. fosinopril). However, the use of ACE inhibitors is associated with notable adverse effects, such as a persistent dry cough due to bradykinin accumulation, and rare but severe events, such as angioedema (Cutrell et al., 2023; Laurent, 2017). Despite certain limitations, ACE inhibitors remain integral to HTN treatment, underpinned by their proven efficacy and significant therapeutic benefits when appropriately prescribed (Izzo & Weir, 2011; Williams et al., 2004).

1.5.2.2 ARBs

ARBs, also known as sartans, are a class of antihypertensive medications that also target the RAAS. Unlike ACE inhibitors, which prevent the conversion of angiotensin I into the potent vasoconstrictor angiotensin II, ARBs act by selectively blocking angiotensin II type 1 (AT1) receptors, thereby inhibiting the effects of angiotensin II at its target sites in tissues. This mechanism results in BP reduction by counteracting the vasoconstrictive and hypertensive actions of angiotensin II (Burnier, 2001; Laurent, 2017). ARBs are particularly advantageous for patients who experience intolerance to ACE inhibitors, such as those with a persistent cough. Additionally, ARBs are often prescribed as first-line treatments for new HTN cases or when ACE inhibitors are contraindicated (Karunarathna et al., 2024; Ojha et al., 2022).

Several ARBs, including losartan, valsartan, and candesartan, are not only used for managing HTN but also approved for treating heart failure, providing a versatile therapeutic option for a range of cardiovascular conditions (Laurent, 2017; Ojha et al., 2022). Despite their favourable safety profile and tolerability, ARBs are not devoid of adverse effects, including dizziness, headache, and hyperkalaemia (Ojha et al., 2022). Nevertheless, their proven efficacy and ability to target the RAAS make them a vital option in the treatment of HTN and related comorbidities.

1.5.2.3 Beta-Adrenergic Blockers (Beta-Blockers)

Beta-blockers, such as atenolol, bisoprolol, and metoprolol, function by antagonising beta-adrenergic receptors, thereby inhibiting the actions of catecholamines (including adrenaline and noradrenaline) on the cardiovascular system (Taddei et al., 2024). This action reduces heart rate and myocardial contractility – resulting in a decrease in cardiac output and, consequently, BP reduction (Frishman, 2008; Laurent, 2017). Beta-blockers are particularly effective in HTN management in patients with coexisting conditions – such as heart failure, obstructive

cardiomyopathy, or specific arrhythmias, where their cardioprotective properties confer significant clinical advantages (Bangalore et al., 2007). However, the use of beta-blockers is not without adverse effects. Bradycardia is a frequently observed side effect, arising from beta-blockers' negative chronotropic effects, while fatigue and diminished exercise tolerance are commonly reported and attributed to cardiac output reductions (Karunarathna et al., 2024). Despite these limitations, beta-blockers remain an important therapeutic option in HTN management, particularly for patients with relevant comorbidities.

1.5.2.4 CCBs

CCBs, also known as calcium antagonists, represent a class of drugs that inhibit the movement of calcium ions through calcium channels in vascular smooth muscle cells and cardiac myocytes. This mechanism reduces intracellular calcium levels, leading to the relaxation of vascular smooth muscle, vasodilation, and BP reduction (Elliott & Ram, 2011). These effects make CCBs highly effective in HTN management, particularly in combination with other antihypertensive agents (Karunarathna et al., 2024). Dihydropyridine CCBs, such as amlodipine and nitrendipine, primarily act as potent vasodilators and are effective in lowering BP, whereas nondihydropyridine CCBs, including diltiazem and verapamil, also exert negative chronotropic and inotropic effects on the heart, making them particularly useful for patients with angina, atrial fibrillation, or other supraventricular arrhythmias (Elliott & Ram, 2011; Laurent, 2017).

Despite their efficacy, CCB usage is associated with a range of adverse effects. Peripheral oedema is dose related, caused by arteriolar vasodilation (Karunarathna et al., 2024). Other side effects include headaches, flushing, and in the case of verapamil, constipation (Eisenberg

et al., 2004). Nevertheless, CCBs remain an integral component of antihypertensive therapy, offering significant benefits in both BP control and cardiovascular risk reduction.

1.5.2.5 Diuretics

Diuretics are foundational and widely used as first-line antihypertensive medications. Their primary function is to promote the excretion of water through the kidneys, a process that reduces extracellular fluid volume, decreases cardiac output, and lowers BP (Laurent, 2017; Pandey et al., 2022).

Diuretics are broadly classified into three main categories: thiazide, loop, and potassium-sparing diuretics, each with distinct mechanisms of action and therapeutic indications (Ellison, 2019; Laurent, 2017).

• Thiazide diuretics, such as hydrochlorothiazide, chlortalidone, indapamide, and xipamide, are among the most commonly prescribed diuretics for HTN (Morales-Olivas, 2024). These agents act on the distal convoluted tubule of the nephron – inhibiting the Na^+Cl^- cotransporter, which reduces sodium and chloride reabsorption. This action increases urinary sodium and water excretion, leading to a reduction in plasma volume, extracellular fluid, and ultimately, peripheral vascular resistance. Additionally, thiazides retain calcium while promoting potassium loss. They are often used in combination with other antihypertensive agents, such as ACE inhibitors (Frank, 2008; Laurent, 2017; Morales-Olivas, 2024).

• Loop diuretics, such as furosemide, bumetanide, and torasemide, exert their mechanism of action by inhibiting the sodium, chloride, and potassium cotransporter located in the thick ascending limb of the loop of Henle, from which their classification derives (Laurent, 2017; Morales-Olivas, 2024; Wu et al., 2024). This results in significant sodium, chloride, and

potassium excretion, accompanied by increased water loss. Loop diuretics exhibit a more potent diuretic effect compared to thiazides but are less effective as standalone antihypertensive agents (Wu et al., 2024). They are primarily indicated for conditions requiring rapid fluid removal, such as heart failure and pulmonary oedema (Morales-Olivas, 2024). However, their use is associated with potential side effects, including severe electrolyte imbalances (e.g. hypokalaemia, hypomagnesaemia, hypochloraemia, and hyponatraemia) and ototoxicity, particularly at high doses (Karunarathna et al., 2024; Wu et al., 2024).

•Potassium-sparing diuretics, such as amiloride, spironolactone, and triamterene, provide a diuretic effect by either antagonising the sodium-potassium exchange in the distal convoluted tubule or acting as aldosterone receptor antagonists (Ellison, 2019; Laurent, 2017; Morales-Olivas, 2024). These agents promote sodium and water excretion while conserving potassium, thus reducing the risk of hypokalaemia (Pandey et al., 2022). However, excessive potassium retention may result in hyperkalaemia – necessitating cautious use, especially in patients with renal impairment or when combined with other potassium-sparing medications (Ellison, 2019; Laurent, 2017). Despite these limitations, diuretics remain a cornerstone in the management of HTN and fluid overload disorders, owing to their efficacy and versatility.

1.6 Antihypertensive Drug Impact on Zn Status

The interaction between drugs and nutrients involves physical, chemical, or biological mechanisms that can lead to significant pharmacological or nutritional effects (Mohn et al., 2018). Such interactions are characterised by unexpected outcomes resulting from the concurrent administration of medications and dietary components (Bushra et al., 2011; Prescott et al., 2018). Drug-nutrient interactions (DNIs) can be broadly categorised into four main types: (1) bioinactivation, (2) altered absorption, (3) changes in pharmacological activity, and (4) modified excretion (Prescott et al., 2018; Renaud et al., 2024). These interactions occur when drugs and nutrients compete for shared metabolic or transport pathways, thereby influencing pharmacokinetics or nutritional status at various stages, including absorption, distribution, metabolism, and excretion (Prescott et al., 2018). Of particular interest is the impact of DNIs on Zn metabolism, given Zn's vital role in cardiovascular health, enzymatic processes, and immune function (Chasapis et al., 2020).

ACE inhibitors, such as captopril and enalapril, have been demonstrated to disrupt Zn homeostasis. These drugs contain functional groups capable of chelating Zn ions, which may reduce Zn status and lead to hypozincaemia (Koren-Michowitz et al., 2005; Nakamura et al., 2021). This chelation effect raises clinical concerns because Zn deficiency is associated with adverse health outcomes, including impaired immune function and delayed wound healing (Nakamura et al., 2021). The structural properties of ACE inhibitors influence their pharmacological activity and interactions with Zn. For instance, sulfhydryl-containing inhibitors, such as captopril, exhibit a pronounced capacity to bind Zn, thereby altering its status (Brown & Vaughan, 1998; Ondetti, 1988). Similarly, dicarboxyl-containing inhibitors, including enalapril and lisinopril, may increase Zn excretion and impair absorption through mechanisms related to their chemical structure. The thiol group present in certain ACE

inhibitors plays a key role in mediating these interactions, which not only affect Zn status but may also impact the overall efficacy of the medications (Ondetti, 1988).

Additionally, thiazide diuretics have been reported to increase urinary Zn excretion, potentially resulting in a gradual depletion of Zn stores (Mohn et al., 2018). Long-term use of these diuretics may contribute to symptoms of Zn deficiency, particularly in individuals with suboptimal dietary Zn intake (Braun & Rosenfeldt, 2013). Thiazide diuretics, such as hydrochlorothiazide, warrant particular attention due to their significant impact on Zn levels. These medications enhance renal Zn excretion, potentially leading to Zn depletion over prolonged use (Jo et al., 2023). Zn deficiency resulting from diuretic therapy has been linked to reduced immunity, impaired wound healing, and diminished taste perception (Ruz et al., 2020). Furthermore, Zn's role in maintaining endothelial integrity and mitigating oxidative stress is critical for cardiovascular health, making the effects of Zn depletion particularly concerning in hypertensive patients (Chasapis et al., 2020).

Other antihypertensive drug classes, including beta-blockers and CCBs, may indirectly influence Zn metabolism. Beta-blockers have been implicated in altering metabolic pathways that affect Zn homeostasis, while CCBs have been indicated to modulate mineral handling in the kidneys, albeit to a lesser extent than diuretics (Mohn et al., 2018). Although these interactions are subtler, they underscore the necessity of maintaining adequate Zn levels in patients undergoing antihypertensive therapy.

1.7 Zn Homeostasis in the Human Body

Zn distribution in the human body is meticulously regulated to align with the functional demands of various tissues (see **Figure 1.3**). Zn is distributed across the body – with most found in skeletal muscles (50%–60%) and bones (20%–30%), reflecting their high metabolic demand (Chasapis et al., 2012; Kambe et al., 2014; Willekens & Runnels, 2022). In skeletal muscles, Zn supports muscle repair and metabolism, whereas in bones, it enhances osteoblastic activity and contributes to bone mineralisation by activating enzymes such as alkaline phosphatase (O'Connor et al., 2020). The liver, which accounts for approximately 5%–6% of the body's Zn content, plays a central role in regulating Zn metabolism, including its storage and redistribution (O'Connor et al., 2020; Willekens & Runnels, 2022). Zn is also critical for pancreatic function, particularly in insulin storage and secretion. The brain, although containing a smaller proportion of Zn (approximately 1%), utilises it for essential functions such as synaptic transmission and neurogenesis, with the hippocampus being a region of high Zn concentration (Willekens & Runnels, 2022). Zn is also present in the skin and hair, where it supports keratinocyte proliferation, wound healing, and hair follicle health (Al-Khafaji et al., 2022).

This strategic distribution ensures that Zn reservoirs can be efficiently mobilised to maintain systemic homeostasis, especially during periods of physiological stress or dietary insufficiency (Kambe et al., 2014; O'Connor et al., 2020). The intricate regulation, distribution, and utilisation of Zn within the body reaffirm its status as an indispensable micronutrient. Through its involvement in enzymatic activities, cellular signalling, immune responses, and tissue integrity, Zn supports a broad range of biological processes. As both a deficiency and an excess pose health risk, maintaining Zn homeostasis is essential for promoting optimal health and preventing disease.

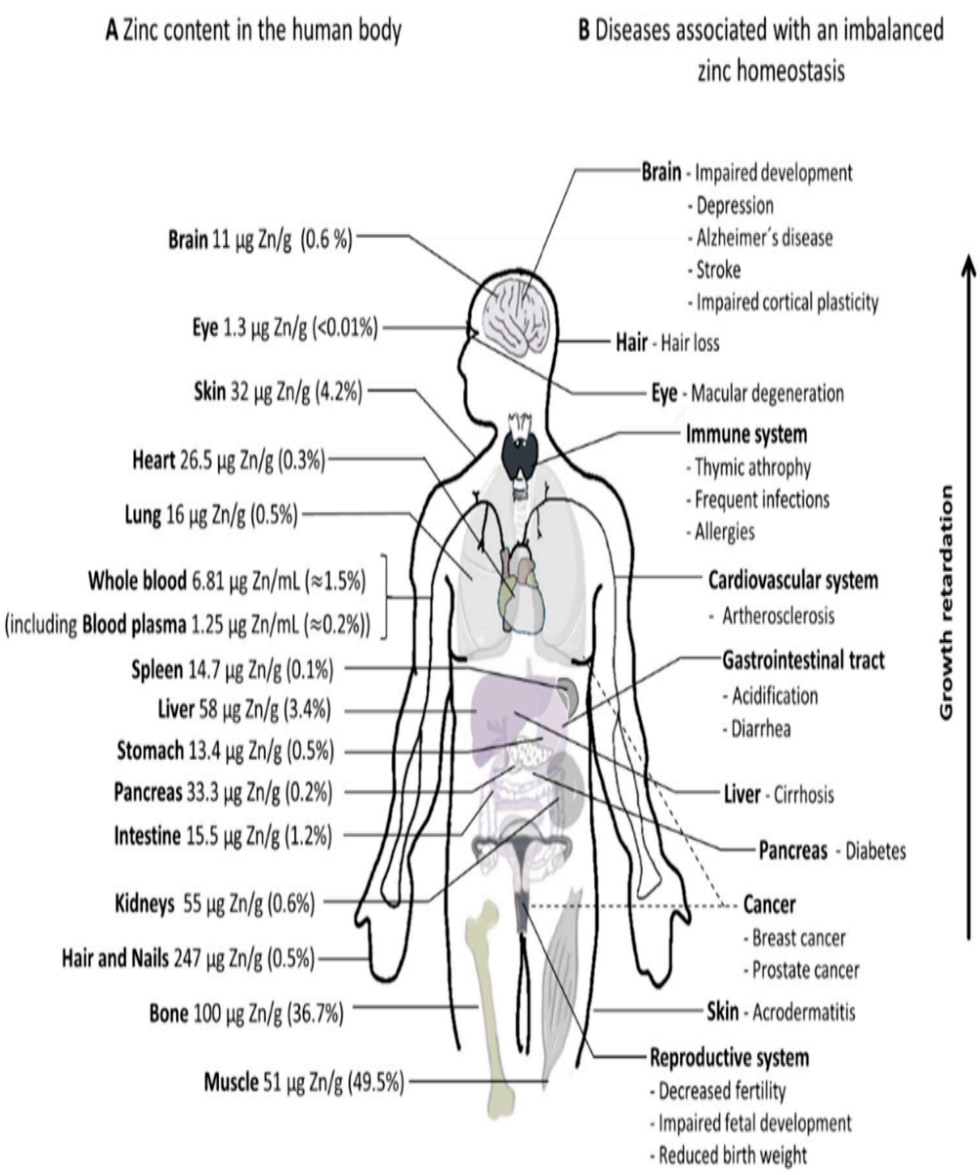


Figure 1.3 Zinc distribution and its clinical implications in human health

(Source: Maares & Haase, 2020).

Zn homeostasis involves maintaining stable Zn levels within body fluids, tissues, and organs, primarily regulated through the processes of Zn uptake and excretion (Cummings & Kovacic, 2009). Zn homeostasis is a tightly regulated process that ensures adequate Zn levels are maintained to support essential functions while preventing toxicity (Hambidge et al., 2010; Kambe et al., 2014; O'Connor et al., 2020). This regulation involves coordinated mechanisms of absorption, transport, storage, and excretion, mediated by a network of Zn-binding proteins, transporters, and cellular signalling pathways (Kambe et al., 2014). Unlike many other essential trace elements, the human body lacks specialised Zn storage systems, making regular dietary intake vital for maintaining optimal Zn levels (Chasapis et al., 2020). The total body Zn content in an average adult weighing approximately 70 kg is estimated to be between 1.4 and 2.3 g (Chasapis et al., 2012; Chen et al., 2024; McCance & Widdowson, 1942).

1.7.1 Zn in BP Regulation

The relationship between Zn and BP is complex, involving various interconnected physiological pathways and mechanisms. Zn plays a critical role in oxidative stress management, vascular function, and RAAS regulation, all of which are key to BP control (Carpenter et al., 2013). As a cofactor for copper-Zn superoxide dismutase, Zn mitigates oxidative stress, a major contributor to HTN, by neutralising reactive oxygen species (Chasapis et al., 2020). Zn deficiency reduces ACE activity, leading to RAAS dysregulation and elevated BP (Tubek, 2006). Additionally, Zn is essential for the synthesis of NO, a molecule critical for vascular relaxation and BP regulation (Ozyildirim & Baltaci, 2023). Zn deficiency decreases NO synthase expression and activity, thereby reducing NO availability and increasing vascular resistance (Chasapis et al., 2020). Zn also regulates sodium retention through its influence on the Na^+-Cl^- cotransporter – where deficiency upregulates the cotransporter's expression, contributing to sodium retention and HTN (Williams et al., 2019).

1.7.2 Zn Absorption and the GI System

The GI system plays a pivotal role in Zn absorption and homeostasis. Dietary Zn is predominantly absorbed in the small intestine, particularly in the duodenum and jejunum, via a carrier-mediated mechanism and, less frequently, through passive diffusion (Jarosz et al., 2017; Willekens & Runnels, 2022). Once Zn enters the small intestine, it transitions into the bloodstream within approximately three hours (Jarosz et al., 2017). Daily replenishment of Zn through dietary sources constitutes about 0.1% of the body's total Zn content, underscoring the importance of dietary adequacy (Willekens & Runnels, 2022).

1.7.3 The Role of Zinc Transporters in Homeostasis

The regulation of Zn homeostasis in mammals is dependent on the coordinated actions of several proteins – including the Zrt/Irt-like protein (ZIP) and zinc transporter (ZnT) families, which manage systemic and cellular Zn balance (Kambe et al., 2014; Szabo et al., 2021). These transporters facilitate Zn absorption, distribution, and cellular storage, ensuring adequate availability for various physiological functions. Unlike iron metabolism, which is regulated by the peptide hormone hepcidin acting as a humoral mediator to coordinate systemic distribution, no equivalent signalling molecule has been identified in Zn metabolism (Szabo et al., 2021). This lack of an interorgan communication mechanism represents a fundamental difference in the homeostatic control of these essential trace elements (Taylor, 2005). Despite this, the body efficiently regulates Zn through its transport proteins and binding molecules, maintaining balance across various physiological compartments. Specifically, ZIP4, a member of the ZIP14 family, plays a crucial role in Zn uptake into enterocytes from the intestinal lumen. Once inside enterocytes, ZnT1, a member of the ZnT10 family, mediates the export of Zn into the bloodstream, facilitating systemic distribution (Kambe et al., 2014; Szabo et al., 2021). Dysregulation of Zn homeostasis can lead to both deficiency and toxicity, with significant health implications (Kambe et al., 2014).

1.7.4 Zn Deficiency and Status

In developing countries, over 25% of the population is affected by Zn deficiency, largely due to inadequate dietary intake, whereas in industrialised nations, the prevalence is estimated at around 15% (Wessels & Rink, 2020). The groups most at risk in industrialised countries include preschool children and the elderly, as their diets often contain fewer Zn-rich animal-based foods. Zn deficiency is primarily caused by insufficient intake of bioavailable Zn – particularly in diets dominated by plant-based foods rich in phytates, which inhibit Zn absorption (Hambidge et al., 2010; Trame et al., 2018). Other contributing factors include impaired Zn absorption due to GI conditions such as Crohn's disease, celiac disease, and chronic diarrhoea, as well as increased losses through sweat, urine, and faeces in chronic illnesses (Faa et al., 2008; Wessels & Rink, 2020).

Zn deficiency can lead to significant health complications, including impaired immune function, delayed wound healing, cognitive dysfunction, and growth retardation in children (Chasapis et al., 2020; Duan et al., 2023). Severe deficiency may result in changes to skin and nails, a loss of taste and smell, and haematological abnormalities due to reduced haemoglobin synthesis, which relies on Zn-dependent enzymes (Cummings & Kovacic, 2009).

The assessment of Zn status is critical for understanding its role in health and disease. Serum Zn levels in humans are typically around 15 μM or 100 μg/dL (75–125 μg/dL), and any reduction in these levels can impair immune function, wound healing, cognitive development, and growth (O'Connor et al., 2020). Serum or plasma Zn concentration is the primary biomarker indicator recommended by the WHO, United Nations International Children's Emergency Fund (UNICEF), and the International Zinc Nutrition Consultative Group for evaluating population Zn status. Serum Zn is predominantly bound to albumin (approximately

70%) and alpha-2-macroglobulin, with a small fraction complexed with amino acids such as histidine and cysteine. This biomarker is considered reliable due to its sensitivity to dietary Zn intake and its ability to predict functional responses to Zn interventions, including supplementation and repletion studies (Gibson et al., 2008). However, its interpretation can be influenced by confounding factors such as inflammation, infection, and pregnancy, while alternative methods, including Zn measurements in hair or assessment of Zn-dependent enzymes, require further validation for routine use (Gibson et al., 2008; King et al., 2016). Addressing Zn deficiency through targeted dietary interventions, supplementation, or food fortification is crucial, particularly in vulnerable populations, to mitigate its impact on health and well-being.

1.8 Ageing and Nutritional Challenges

The WHO (2022) Health and Ageing Report reveals that the global population aged 60 years and older has increased from 382 million in 1980 to over 1 billion in 2020, representing 13.5% of the world's population of 7.8 billion, and is projected to nearly double to 2.1 billion by 2050. According to the Office for National Statistics (ONS, 2018), by 2041, approximately 26% of the UK population is projected to be aged 65 or older, with individuals aged 50 and above expected to comprise nearly half of the adult population. Ageing is a natural and multifaceted process characterised by gradual changes in physiological, cellular, and functional capacities that occur over time (Dato et al., 2016; Kirkwood, 2005). It is influenced by a combination of genetic, environmental, and lifestyle factors and is often associated with increased vulnerability to diseases, reduced adaptability to stress, and functional impairments (Dato et al., 2016).

In the United Kingdom, ageing is often examined within the context of its health and societal implications (ONS, 2019). The demographic shift associated with ageing is characterised by a growing proportion of older individuals within the population, influenced by declining fertility rates and rising life expectancy (Bloom & Luca, 2016). Chronologically, the older adult age group is commonly defined as 65 years and above, a threshold historically linked to the state retirement age (ONS, 2019). However, there are challenges in how an 'older person' is defined; while the WHO (2022) considers an older person to be over the age of 60, many countries adopt context-specific thresholds based on their demographic and social circumstances. As individuals age, their nutritional needs and physical activity requirements undergo significant changes due to physiological, metabolic, and lifestyle factors. Proper nutrition and regular physical activity are essential for maintaining health, preventing chronic diseases, and promoting independence in older adults (Faronbi et al., 2024; Marsman et al., 2018; Roberts & Rosenberg, 2006).

Older adults transitioning from independent living to residential care constitute a clinically distinct and rapidly expanding segment of the UK's ageing population. In the 2021 Census, 278,946 people aged ≥65 years were living in care homes in England and Wales (Office for National Statistics, 2023). Compared with community-dwelling peers, care-home residents typically show higher levels of functional dependency, multimorbidity and cognitive impairment. They depend on centrally planned menus, have limited autonomy over mealtimes, and are routinely prescribed multiple long-term medicines factors that may exacerbate the nutritional vulnerabilities already documented among free-living older adults.

1.8.1 Nutritional Risk in Care-Home Residents

Recent research has consistently demonstrated that dietary provision within care home settings is markedly deficient in several essential micronutrients when compared with that of community-dwelling older adults. This disparity is of particular concern given that the nutritional requirements of the elderly are often elevated due to age-related physiological changes, comorbidities, and medication use. In a systematic review of 28 cross-sectional and cohort studies (n = 2,036; 68% female; institutionalised participants), zinc intakes were below the Estimated Average Requirement (EAR) in 66% of men and 50% of women, while selenium inadequacy affected 27% of men and 44% of women (Vural et al., 2020). These shortfalls contribute to clinically significant undernutrition. The British Association for Parenteral and Enteral Nutrition (BAPEN) 2022 national screening audit indicated that 55% of UK care-home residents were at medium to high risk of malnutrition according to the Malnutrition Universal Screening Tool (MUST), a prevalence exceeding that reported in hospitals (44%) (Stratton, 2024). Pharmacotherapy may further exacerbate micronutrient deficits. A systematic review of 16 observational studies found that 72% of hypertensive care-home residents were prescribed

at least one antihypertensive medicine with diuretics most commonly prescribed (Welsh, Gladman and Gordon, 2014). Experimental evidence also indicates that three months of monotherapy with thiazide diuretics, ACE inhibitors or calcium-channel blockers can reduce serum or erythrocyte zinc concentrations and increase urinary zinc losses (Suliburska et al., 2018).

1.9 Thesis Rationale and Study Overview

Hypertension (HTN) remains a major global public health challenge, and recent UK cohort data indicate that its prevalence and pharmacological treatment have increased steadily over recent decades. By 2018, nearly one in five UK adults received at least one antihypertensive prescription, with angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers and β-blockers accounting for most prescriptions. Meanwhile, zinc (Zn) has attracted growing attention for its central roles in enzymatic, immune and cardiovascular function. Experimental and clinical evidence suggests that several antihypertensive classes particularly ACE inhibitors and thiazide diuretics can disrupt Zn homeostasis via renal and gastrointestinal mechanisms, raising the possibility that routine cardiovascular therapy may inadvertently precipitate or worsen Zn deficiency.

Despite these converging observations, the scale, consistency and clinical significance of drug–nutrient interactions involving antihypertensives and Zn have not been comprehensively synthesised, nor examined in real-world UK dietary datasets or among the nation's most vulnerable older adults.

Systematic review and meta-analysis (**Chapter 2**). This study collates and critically appraises investigations that report Zn status (serum, erythrocyte or urinary) in the context of antihypertensive use. Using random-effects models and meta-regression, it quantifies pooled effect sizes for individual drug classes and explores sources of heterogeneity, such as treatment duration, dosage and study design.

Secondary analysis of the UK National Diet and Nutrition Survey (**Chapter 3**). Leveraging 11 combined years (2008–2019) of the rolling National Diet and Nutrition Survey (NDNS), this study evaluates dietary Zn intake and plasma Zn concentrations among 11,153 adults aged ≥19 years, stratified by antihypertensive exposure, age, sex.

Cross-sectional comparison of care-home and free-living older adults (**Chapter 4**). Recognising that older adults in institutional settings may experience the greatest convergence of risk factors, this study recruits from care homes in Nottinghamshire and community-dwelling (aged 75–96 years). Detailed medication histories weighed dietary records are collected alongside functional health measures such as grip strength and Mini-Nutritional Assessment scores.

These investigations provide a coherent narrative tracing the potential Zn-depleting effects of antihypertensive therapy from controlled experimental settings through to real-world UK populations and the nation's most vulnerable older adults. This thesis outlines the research design and methodological framework adopted to address the study objectives. The research design includes the following components (see **Figure 1.4**).

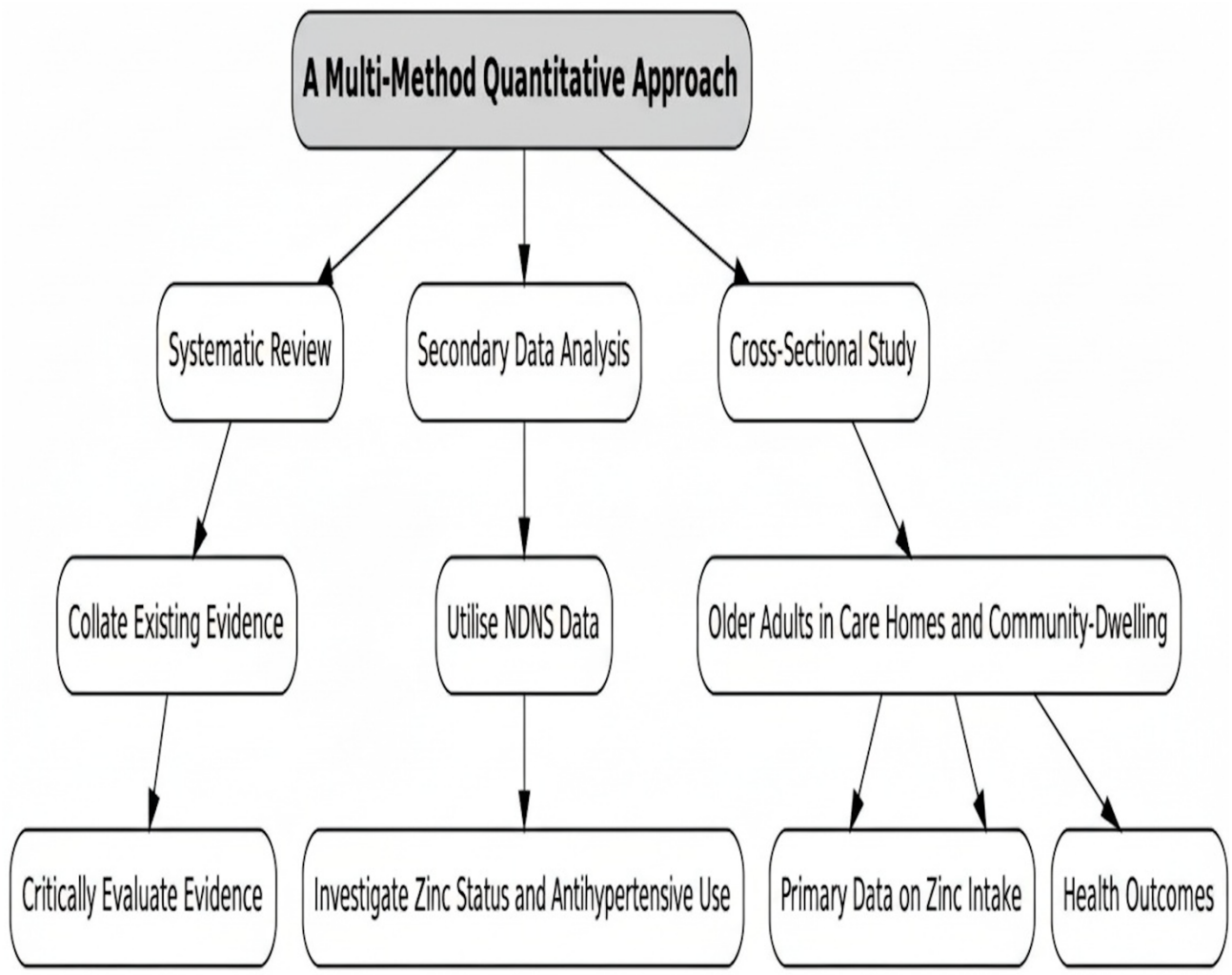


Figure 1.4 Overview of the research methodology to explore the relationship between antihypertensive medications and zinc status using a multi-method quantitative approach.

1.10 Hypotheses and Objectives

1.10.1 Hypotheses

Chronic antihypertensive medication use impacts Zn status through DNIs, with these effects becoming more pronounced in older adults due to age-related physiological changes and dietary factors. Additionally, the Zn status of older adults is influenced by living conditions and overall dietary intake, with care home residents potentially at greater risk of Zn deficiency compared to free-living individuals.

Specifically, this thesis hypothesises the following:

• Antihypertensive medications reduce Zn status, potentially leading to suboptimal Zn status.

• The impact of antihypertensive drugs on Zn status is exacerbated by advancing age, owing to age-related changes in absorption and metabolism.

1.10.2 Aim

This study aims to investigate the impact of chronic antihypertensive medication use on Zn status and evaluate the role of age, dietary patterns, and living conditions in influencing Zn status and related health outcomes in the United Kingdom.

1.10.3 Objectives

1.10.3.1 Systematic Review and Meta-analysis

• To conduct a comprehensive systematic review of the literature to evaluate the evidence regarding the relationship between antihypertensive drugs and Zn status.

• To perform a meta-analysis to quantify the effects of antihypertensive drugs on Zn status and identify key mechanisms underlying DNIs.

1.10.3.2 Secondary Data Analysis of the UK National Diet and Nutrition Survey

• To analyse data from the UK National Diet and Nutrition Survey (2008–2019) to identify trends in Zn status among adults consuming antihypertensive medications.

• To assess the impact of variables such as age, gender, dietary patterns, and medication type on Zn intake and serum Zn levels.

• To explore the relationship between Zn status and health markers.

1.10.3.3 Comparative Study of Zn Status in Older Adults

• To compare Zn status between care home residents and free-living older adults in the United Kingdom, focusing on disparities influenced by living conditions and antihypertensive drug use.

• To investigate how chronic medication use interacts with ageing and dietary intake to affect Zn status and overall health.

Chapter 2: Understanding the Impact of Antihypertensive Drugs on the Status of Zinc: A Systematic Review and Meta-analysis

Abstract

Background: Hypertension is a major global health issue, and with its increasing prevalence, effective management strategies are critical. Research has demonstrated that both hypertension and antihypertensive medications can impact the status of essential micronutrients, particularly zinc. Zinc plays a crucial role in various biological processes that support overall health and well-being.

Objective: This study aimed to assess the effects of widely used antihypertensive medications on zinc status in hypertensive patients, exploring how these drugs alter zinc levels and the potential consequences for patient health.

Methods: A systematic review and a meta-analysis were conducted in accordance with PRISMA guidelines. Relevant studies were identified using databases such as the Cochrane Library, Ovid MEDLINE, PubMed and Web of Science. The analysis focused on studies published from 2014 to 2024 that measured serum, urinary and erythrocyte zinc levels, as well as zinc intake, in hypertensive patients on antihypertensive therapy. The quality of studies was assessed using the Newcastle–Ottawa Scale. A meta-analysis involving four studies was performed using a random-effects model, and heterogeneity was assessed with I^2 statistics.

Results: Nine studies met the inclusion criteria, representing diverse populations and designs. The findings indicate that antihypertensive medications, particularly angiotensin-converting enzyme (ACE) inhibitors and diuretics, are associated with reduced serum zinc levels and increased urinary zinc excretion. These changes suggest a disruption in zinc homeostasis, potentially contributing to metabolic alterations in hypertensive patients. The meta-analysis indicated a nonsignificant reduction in serum zinc levels (pooled effect size: -0.33), while significant reductions in erythrocyte zinc levels were observed (pooled effect size: -0.64, $p <$

0.001). Increased urinary zinc excretion was also noted, especially with diuretics and ACE inhibitors, with high heterogeneity ($I^2 = 100\%$).

Discussion: The findings indicate that antihypertensive medications, particularly ACE inhibitors and diuretics, may disrupt zinc homeostasis, potentially leading to zinc deficiency in hypertensive patients. These disruptions could have clinical consequences, particularly given zinc's role in immune function and metabolism. However, variability in study designs, sample sizes and zinc measurement methodologies limits the generalisability of these results.

Conclusion: While antihypertensive therapy is essential for blood pressure control, it may negatively impact zinc status. Monitoring zinc levels in hypertensive patients, especially those on long-term medication, is advisable to prevent zinc deficiency. Further research with standardised methods and larger, more diverse populations is needed to better understand this relationship.

2.1 Introduction

Hypertension (HTN) is one of the most significant public health problems in the UK, with a rising prevalence that correlates with advancing age and varying demographics (Kulkarni et al., 2024). This is of particular concern – given that HTN is a major risk factor for cardiovascular diseases, which are among the leading causes of death and morbidity in the UK (Basta et al., 2024; Public Health England, 2020; Sinnott et al., 2017).

HTN is popularly known as high blood pressure, with systolic/diastolic pressure values ≥140/90 mmHg (Fuchs & Whelton, 2020). Previous studies have identified major contributing factors, including (1) long-term high sodium (Na) intake; (2) inadequate intake of calcium and potassium; (3) the use of alcohol and smoking; (4) increased sympathetic nervous system activity; (5) increased angiotensin-converting enzyme (ACE) activity; (6) alteration in renin secretion and increased activity of the renin-angiotensin system; (7) abnormal vessel resistance due to inflammation, elevated activity of vascular growth factors and alteration in cellular ion channels; and (8) endothelial dysfunction and vasodilators deficits, including reduced bioavailability of nitric oxide (Hall et al., 2012; Poulter et al., 2015). There is no direct clinical manifestation of the disease, and the outcomes largely appear in conditions such as heart failure, coronary artery disease, cerebrovascular accidents (stroke), atrial fibrillation, chronic renal disease and peripheral vascular disease (Drozdz & Kawecka-Jaszcz, 2013).

HTN treatment and control is essential to prevent associated life-threatening cardiovascular and kidney pathologies, and multiple antihypertensive agents are in use either as monotherapy or in combination (Gradman et al., 2010; Pereira et al., 2009). **Table 2.1** represents the major classes of anti-hypertensive drugs used to maintain normal blood pressure levels. While long-term use of antihypertensive drugs is effective in maintaining optimum blood pressure levels,

it is also associated with a range of detrimental effects, including disturbed electrolyte homeostasis and drug-induced electrolyte alterations (Liamis et al., 2008). Antihypertensive drugs are common, with an estimated 1.3 million users in the UK in 2017 (Sinnott et al., 2017). Research has indicated that HTN and antihypertensive drugs affect the body's mineral metabolism, affecting important minerals such as zinc (Zn; Bastola et al., 2020; Koren-Michowitz et al., 2005; Tubek, 2006).

Table 2.1 Commonly used antihypertensive drugs with major classes

Class	**Drugs**
Angiotensin converting enzyme inhibitor (ACE inhibitor)	Captopril, Enalapril, Perindopril, Ramipril, Fosinopril
Calcium channel blocker (Calcium antagonist)	Amlodipine, Nitrendipine, Verapamil
Alpha adrenergic receptor blocker	Doxazosin
Beta adrenergic receptor blocker	Metoprolol, Atenolol, Bisoprolol, Nebivolol
Angiotensin receptor blockers (ARBs)	Losartan, Valsartan, Telmisartan
Diuretics	Hydrochlorothiazide, Amiloride, Indapamide, Furosemide, Torsemide

Zn is essential for cell division and growth, enzyme reactions, immune function, DNA synthesis and protein production (Maret & Sandstead, 2006). Zn is an essential micronutrient, and approximately 2–3 g of Zn is found in an adult human body (Hussain et al., 2022). Replenishment of body Zn is about 0.1% daily (Maret & Sandstead, 2006). Bone and skeletal muscles contain the largest fraction of zinc (~86%), followed by the skin (4.2%) and liver (3.4%) (Maares & Haase, 2020). In healthy individuals, levels of Zn in plasma or serum range between 80 and 100 μg/dL (12–15 μmol/L), of which 99.9% remains bound to blood proteins (Wessells et al., 2010). At the cellular level, the total concentration of Zn lies in the range of 10–100 μM and is distributed in the nucleus (30%–40%), cytoplasm (50%) and cell membrane (10%) (Bafaro et al., 2017).

As a vital micronutrient, Zn plays a crucial role in numerous biological and cellular processes that are essential for proper growth and overall health in the human body (Maret, 2017). Zn^{+2}, a divalent cation, is redox neutral under physiological conditions. In biological processes, Zn acts as Lewis acid – contributing multifarious physiological actions, such as a structural component, catalytic factor and signalling mediator (Kambe et al., 2015). It is important for more than 300 enzymes, such as superoxide dismutase, alkaline phosphatase, alcohol dehydrogenase, leucine aminopeptidase, carbonic anhydrase and DNA/RNA polymerase, thereby playing a role in carbohydrate, protein, lipid and nucleic acid metabolism, as well as cell division and growth (Kruse-Jarres, 1999).

According to the British Nutrition Foundation (2021), the reference nutrient intake (RNI) for Zn varies across age groups. For children aged 0–6 years, the RNI is 6.5 mg/day, increasing to 7 mg/day for those aged 7–10 years. In both males and females aged 11–14 years, the recommended intake is 9 mg/day. For males aged 15 years and above, the RNI is 9.5 mg/day,

whereas for females in the same age group, the RNI is slightly lower at 7 mg/day. Zn can be found in various foods, and it is abundant in certain seafood, red meats and whole grains. Zn bioavailability is much lower in vegetable sources when compared to animal products (Hunt, 2003). Zn homeostasis in the human body is regulated by intestinal absorption (Kondaiah et al., 2019). Zn transporters, which are present on enterocytes' apical and basolateral membranes, and metallothioneins (MTs; Zn-binding proteins) regulate Zn homeostasis (Kambe et al., 2015). Zn absorption in the gastrointestinal tract occurs mainly at the site of proximal small intestinal enterocytes through carrier-mediated process (Kiela & Ghishan, 2016).

Zn storage occurs in the kidneys and liver, whereas there are three primary routes for Zn loss: the kidneys, gastrointestinal tract and body surface (via, for example, sweat and shed skin). Unlike iron, Zn is unable to mobilise readily from where it is stored in the body, and the human body contains only a small 'exchangeable Zn pool', which suffices Zn utilisation for a few days until the onset of homeostatic response (Braun & Rosenfeldt, 2013). Zn uptake occurs at the brush border membrane of the intestine. At this site Zn is transported from the gut lumen into the epithelium absorptive cells, called enterocytes (Maares & Haase, 2020). Zn is released into the portal blood at the basolateral side of enterocytes and bound predominantly with albumin for distribution throughout the body (Maares & Haase, 2020). Zn absorption in the intestine is predominantly mediated by ZIP4 (solute carrier; SLC39A4) and ZnT-1 (SLC30A1; Maares & Haase, 2020). ZIP4 transports divalent Zn from the gut lumen into enterocytes, while ZnT-1 exports Zn from the basolateral side of enterocytes into the portal bloodstream (Kondaiah et al., 2019; Maares & Haase, 2020). Other transporters located basolaterally, ZIP5 (SLC39A5) and ZIP14 (SLC39A14), complement ZIP4 and ZnT-1 by importing ionic Zn from the blood into enterocytes (Kambe et al., 2015). Additionally, another transport protein, ZnT-5 variant B (SLC30A5B), is located on the apical membrane of enterocytes, and it transports both luminal

and cellular Zn into enterocytes and returns the Zn into the intestinal mucosa. This finding suggests that apical secretion of mineral ions may be another mechanism that regulates Zn homeostasis (Maares & Haase, 2020; Valentine et al., 2007) (See **Figure 2.1**).

Zn homeostasis in cells is characterised by the presence of three primary Zn pools: Zn coupled to various proteins, Zn kept in vesicles and the portion unbound in the cytoplasm (Kambe et al., 2015; Kimura & Kambe, 2016). Zn transporters and metallothioneins (MTs) function as Zn mufflers and buffers, respectively (Kimura & Kambe, 2016). Four MT genes (MT-1–MT-4) in humans encode 11 functional MT isoforms (Kimura & Kambe, 2016). The human digestive system expresses predominantly two MTs: MT-1 and MT-2. MTs regulate Zn homeostasis in enterocytes by absorbing the Zn that enters the cells (Maares & Haase, 2020).

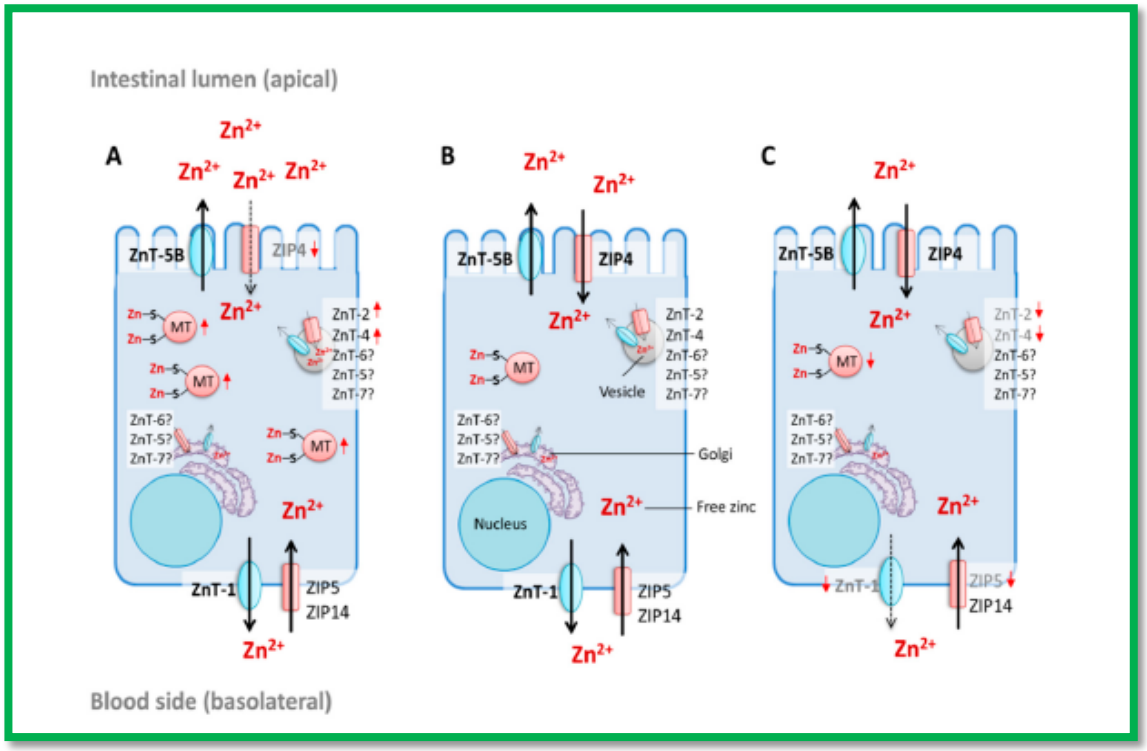


Figure 2.1 Zinc absorption into intestinal enterocytes in excess of zinc (A), adequate zinc supply (B), and zinc deficiency (C)

Obtained from (Source: Maares and Haase, 2020).

2.2 Aim and Hypothesis

Aim: The primary aim of this systematic literature review is to explore the extent to which different commonly prescribed antihypertensive medications impact zinc (Zn) status, thereby providing new insights into the varying effects these drugs may have on Zn metabolism.

Hypothesis: It is hypothesised that the use of antihypertensive medications is associated with a reduction in Zn status, with certain medications exerting a more significant impact than others. Individuals treated with these medications may be at an increased risk for developing clinical manifestations associated with zinc deficiency (ZnD).

Specific Objectives

The study is directed by the following specific objectives:

- To assess whether individuals with HTN exhibit lower Zn levels compared to those with normal blood pressure.
- To examine whether chronic administration of antihypertensive medications contributes to reductions in Zn levels.
- To evaluate the clinical outcomes associated with drug-induced ZnD, which may provide insight into the potential health implications of long-term antihypertensive treatment.

2.3 Materials and Methods

2.3.1 Search Strategy

The first phase of the study was a systematic review and meta-analysis aimed at synthesising existing literature to understand the impact of antihypertensive medications on Zn status. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Page et al., 2021) to ensure methodological rigour, transparency, and reproducibility.

Comprehensive searches were performed across multiple electronic databases, including the Cochrane Library, Ovid MEDLINE, PubMed, and Web of Science. A carefully designed search strategy was employed, using a combination of keywords and Medical Subject Headings terms tailored to identify relevant studies published between January 2014 and March 2024, chosen to update the evidence base since the last identified review on antihypertensive therapy and zinc interactions (Braun & Rosenfeldt 2013). The search terms, syntaxes, and Boolean operators utilised for database searches are outlined in **Table 2.2**, following the population, intervention, comparison, and outcome (PICO) framework (Pollock & Berge, 2018). Terms were specifically selected to cover HTN, antihypertensive drugs, and Zn, with Boolean operators used to refine the search and ensure all related studies were captured.

Table 2.2 Search strategy following the PICO framework

PICO	Search Terms and Boolean Combinations
Population	"Hypertension"[MeSH] OR hypertension* OR "high blood pressure*" OR "blood pressure*"
Intervention	"Antihypertensive Agents"[MeSH] OR "anti-hypertensive drugs*" OR "Angiotensin Receptor Antagonists"[MeSH] OR "angiotensin converting enzyme inhibitors*" OR "ACE inhibitors*" OR "angiotensin receptor antagonists*" OR "Adrenergic alpha-Antagonists"[MeSH] OR "alpha-adrenergic receptor blockers*" OR "alpha blockers*" OR "Adrenergic beta-Antagonists"[MeSH] OR "beta-adrenergic receptor blockers*" OR "beta receptor antagonists*" OR "beta blockers*" OR "Calcium Channel Blockers"[MeSH] OR "calcium channel blockers*" OR "calcium antagonists*" OR "Diuretics"[MeSH] OR "diuretics*" OR "thiazides*"
Comparison	"Healthy controls" OR "healthy individuals"
Outcome	"Zinc"[MeSH] OR zinc* OR "zinc deficiency*"

2.3.2 Study Screening and Selection

The screening and selection process of studies for this systematic review was meticulously designed, ensuring a comprehensive evaluation of relevant literature. First, predetermined inclusion and exclusion criteria were applied to the titles and abstracts of the papers found through database searches. This preliminary screening aimed to identify studies potentially relevant to the impact of antihypertensive drugs on Zn status in hypertensive individuals compared to healthy controls.

Subsequently, full texts of these potentially relevant articles were carefully examined to confirm their suitability for inclusion in the review. This stage involved a detailed assessment of the study's methodology, population, interventions, comparisons and outcomes, directly aligning with the PICO framework. The status of Zn and the primary and secondary outcomes related to the intervention's efficacy were critically appraised.

The reference lists of all included papers were systematically reviewed in addition to the database searches in order to find other studies that might have been missed in the first search. This backward-searching method aimed to capture additional literature by identifying studies cited by the articles initially deemed relevant.

2.3.3 Inclusion and Exclusion Criteria

The screening process was rigorous, following predefined inclusion and exclusion criteria:

Inclusion Criteria: Studies focusing on adult hypertensive patients (aged 18 and over), including both male and female participants. Eligible studies included randomised controlled trials (RCTs) and observational studies including retrospective cohort, case-control and cross-sectional designs that assessed Zn levels in individuals undergoing antihypertensive treatment.

Exclusion Criteria: Studies conducted on animals, research on childhood or pregnancy-induced HTN, and articles published in non-English languages or behind paywalls (refer to **Table 2.3** for detailed criteria).

Table 2.3 Criteria for study inclusion and exclusion in the review

Inclusion Criteria	Exclusion Criteria
• Adults with hypertension. • Randomised controlled trials (RCTs) and observational studies including retrospective cohort, case-control and cross-sectional designs • Full-text articles available in English. • Studies evaluating antihypertensive pharmacological interventions.	• Animal studies. • Hypertension in children or gestational-induced hypertension. • Articles behind a paywall or published in languages other than English.

2.3.4 Data Extraction and Synthesis

The data extraction and synthesis process was precisely conducted, aiming to aggregate and analyse information from studies that satisfied the predetermined inclusion criteria. Data were systematically gathered across specific categories to ensure a thorough comprehension of each included study. These categories encompassed:

Study Basics: Essential details such as publication year, study design, and duration were documented to provide a foundational understanding of the research context.

Participant Characteristics: Data pertaining to the study participants were recorded, which included health status, gender distribution, and mean age with standard deviation (SD). This information is critical for assessing the applicability and generalisability of the study findings.

Intervention Details: Specifics regarding the interventions were meticulously noted – focusing on the antihypertensive medications under investigation, including dosages. Additionally, Zn status data, such as serum and urinary Zn levels, were extracted to assess the impact of the interventions on Zn status. Where available, associated clinical outcomes linked to Zn deficiency were also recorded to better understand the potential health implications of reduced Zn levels due to antihypertensive medications.

We initially identified 132 potential articles, including 43 duplicates. After removing duplicates, the titles and abstracts were screened of the remaining 89 references. From this screening, 21 articles met our criteria for full-text review. Following this stage, 13 studies were excluded, leaving us with a final total of 9 studies (see **Figure 2.2**). Of the nine eligible studies, four were RCTs and five were observational.

2.3.5 Quality Assessment of Studies

The quality of all eligible studies was rigorously assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort or cross-sectional studies (Wells et al., 2000). This scale facilitates a comprehensive assessment by assigning scores to various criteria across three domains: selection of the study groups, comparability of the groups and determination of the outcome or exposure for case-control or cohort studies (See **Table 2.4**).

Studies were evaluated based on:

Selection (0–4 stars): Criteria within this domain assess the method of selection of the cohorts or cases, with a maximum of four stars assignable for adequately fulfilling all specified selection criteria.

Comparability (0–2 stars): This domain focuses on the comparability of cohorts or cases and controls, based on the design or analysis, allowing for up to two stars for studies that effectively address potential confounding factors.

Outcome or Exposure (0–3 stars): Assessment within this domain evaluates the ascertainment of the outcome, with a maximum of three stars for thorough outcome identification and follow-up.

Table 2.4 Overall Quality Classification Based on Newcastle–Ottawa Scale Scores

Total Score	Quality Classification
0–4 stars	Low Quality
5–7 stars	Moderate Quality
8–10 stars	High Quality

2.3.6 Statistical Analysis

Meta-analysis was conducted using the Statistical Package for the Social Sciences software (Version 29, IBM, USA) to evaluate the effect of antihypertensive drugs on Zn levels across various biological compartments, including serum, urinary excretion and erythrocytes, as well as dietary intake. A random-effects meta-analysis with effect sizes (Glass's delta) was performed to account for anticipated heterogeneity among studies, recognising that this model accommodates variations arising from differences in study design, populations and methodologies (Borenstein et al., 2021). Effect sizes and their corresponding 95% confidence intervals (CIs) were calculated for each study, culminating in an overall effect size for each Zn parameter. Heterogeneity was assessed using Tau-squared (τ^2), I-squared (I^2) and Cochran's Q test, with established thresholds to interpret the extent of variability across studies. In all forest plots, a negative mean difference (positioned to the left of zero) indicates a lower outcome measure in the antihypertensive group compared to controls, while a positive mean difference (right of zero) reflects a higher outcome in the antihypertensive group. The statistical significance of pooled effect sizes was determined through Z-tests, with p-values less than 0.05 deemed significant. This methodological framework ensured a thorough analysis, yielding a reliable synthesis of the impact of antihypertensive drugs on Zn levels.

The systematic review and meta-analysis provided a strong foundation for understanding how antihypertensive medications may influence Zn status, identifying existing knowledge gaps and informing subsequent research phases.

2.4 Results

2.4.1 Study Characteristics

A total of nine studies met the inclusion criteria, involving a diverse demographic population, were analysed to evaluate the impact of antihypertensive drugs on the status of zinc. The studies varied in their methodological approaches, including differences in population demographics, types of antihypertensive drugs studied, and the methods used to assess zinc status. Considering zinc's role in various physiological processes, including immune function and wound healing, maintaining adequate zinc levels is crucial in hypertensive patients to prevent additional health complications. Serum zinc levels and urinary zinc excretion were the most commonly used measures, with some studies also reporting erythrocyte zinc levels.

The nine eligible papers covered a wide range of sample sizes and study designs. Three population-based studies each included more than 1,500 participants – Ricaurte et al. (2020; n = 1,502), Bastola et al. (2020; n = 6,683) and Darroudi et al. (2019; n = 9,588). In contrast, two single-centre investigations enrolled far fewer subjects – Arinda-Lironika et al. (2015; n = 30) and Solanki et al. (2015; n = 100). Four of the remaining studies compared hypertensive patients with matched healthy controls: Suliburska et al. (2014; n = 45), Cipu et al. (2014; n = 90), and two datasets from Suliburska et al. (2018; n = 98 each). Serum zinc concentration was the principal outcome in almost every study, with occasional use of urinary or erythrocyte zinc. Across all the studies, a reduction in zinc status was observed among participants with hypertension, indicating that the condition is associated with diminished zinc levels.

The PRISMA flow diagram depicts the search results, with reasons for exclusion **(Figure 2.2).** All the studies were of moderate impact for quality of studies, as evaluated by the NOS score

(**Tables 2.7 - 2.9**). A few studies (n = 4) recently documented the impact of antihypertensive drugs on Zn status (**Table 2.6**). All the 9 studies followed the different study design.

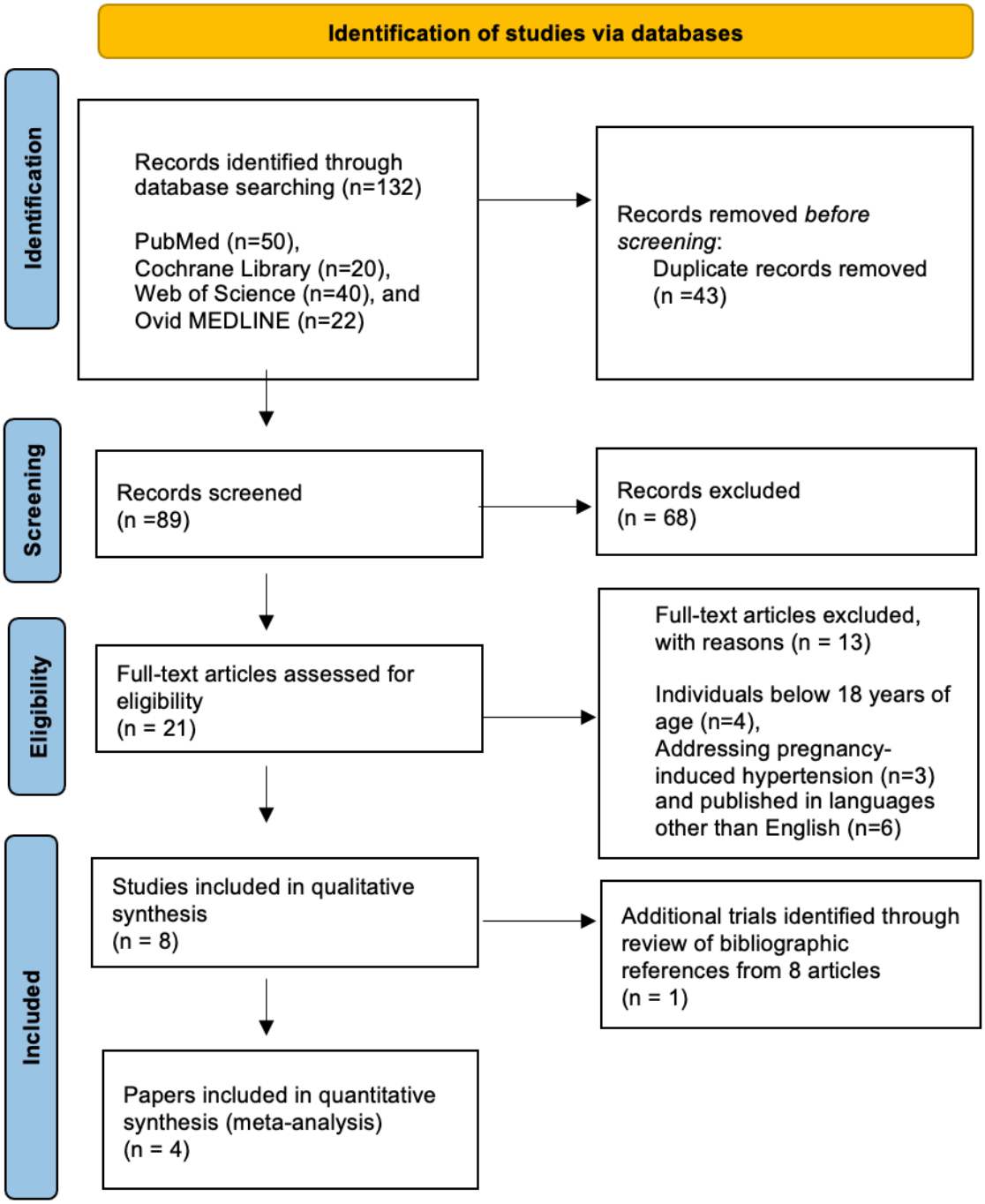


Figure 2.2 Study selection using the PRISMA flow diagram (Page et al., 2021).

2.4.2 Zn Status in Hypertensive Patients

A series of studies investigated the relationship between Zn status and HTN, revealing varied findings (See **Table 2.5**). Across the studies reviewed, hypertensive patients demonstrated varying serum Zn levels compared to controls, suggesting distinct roles for these trace elements in the pathogenesis of HTN. Arinda Lironika et al. (2015) conducted an observational study in Indonesia with 30 participants, split equally between hypertensive patients and normotensive controls. They found that the mean Zn level was slightly lower in hypertensive patients (9.96 ± 2.88 μmol/L) compared to normotensive individuals (10.9 ± 5.08 μmol/L), but the difference was not statistically significant ($p = 0.852$). Moreover, Solanki et al.'s (2015) study, which was conducted in a different geographical setting (India), found lower Zn levels in hypertensive patients compared to controls, suggesting a possible ZnD in hypertensive individuals. However, Darroudi et al. (2019) conducted a cross-sectional study in Iran involving 9,588 participants. They found no significant association between serum Zn levels and systolic blood pressure. However, lower serum Zn levels were linked to higher diastolic blood pressure ($p = 0.035$). These observations were complemented by research from Bastola et al. (2020), which analysed data from 6,683 hypertensive patients in the US. The authors found no significant association between serum Zn levels and HTN after adjusting for confounders. Finally, Ricaurte et al. (2020) conducted a cross-sectional study in Spain with 1,502 participants and observed that hypertensive patients had lower serum Zn levels and higher urinary Zn excretion compared to normotensive individuals, suggesting that HTN affects Zn distribution in the body.

Table 2.5 Literature summary of zinc status in hypertensive patients

Author (Year)	Study Type (Location)	Study Population	Zinc Status	Clinical Outcomes of Zinc Deficiency	Study Limitations	NOS Scores
Arinda Lironika et al. (2015)	Observational Study (Indonesia)	N = 30 (13 males, 17 females) Normal control (n = 15). The mean age was 45.2 ± 5.54 years. Hypertensive patients (n = 15). The mean age was 55.67 ± 8.88 years.	Zinc level was generally lower in hypertensive patients (9.96 ± 2.88 µmol/L) compared to normotensive individuals (10.9 ± 5.08 µmol/L). Zinc levels did not significantly differ between the groups (p = 0.852).	Zinc deficiency was observed in both groups, with worse deficiency in hypertensive patients. Though not statistically significant (p = 0.273), zinc deficiency was linked to lower SOD levels in hypertensive patients, suggesting a potential connection to increased oxidative stress.	The small sample size limits the ability to generalise the findings to a broader population.	7[a]
Solanki et al. (2015)	Cross-Sectional Study (India)	N = 100 Normal control (n = 50). The mean age was 52.54 ± 6.63 years. Hypertensive patients (n = 50). The mean age was 56.16 ± 10.97 years.	Serum zinc levels were significantly lower in hypertensive patients compared to the control group (68.92 ± 8.94 vs. 102.12 ± 13.18 µg/dL, p < 0.05).	Lower zinc levels in hypertensive patients may lead to decreased activity of the SOD enzyme, contributing to oxidative stress and hypertension.	The cross-sectional design limits causal inference between trace element levels and hypertension. Dietary intake and lifestyle determinants were not measured, leaving residual confounding. The timeframe and specific population restrict generalisability to other groups or longer periods.	7[b]

Darroudi et al. (2019)	Cross-Sectional Study (Iran)	N = 9,588 (3,839 males, 5,749 females) Nonhypertensive (n = 5,695). The mean age was 45.85 ± 7.5 years. Hypertensive (n = 3,893). The mean age was 51.18 ± 7.67 years.	No significant association was found between serum zinc levels and systolic blood pressure. However, lower zinc levels (first quartile) were significantly associated with higher diastolic blood pressure (p = 0.035).	Lower zinc levels were associated with increased diastolic blood pressure, indicating that zinc deficiency may contribute to hypertension development.	The cross-sectional design limits causal inference. Mineral intake and zinc-dependent enzymatic activity were not assessed, potentially influencing trace element levels. Inflammatory markers and environmental determinants of blood pressure were unmeasured, limiting accuracy and generalisability of conclusions.	6[b]
Bastola et al. (2020)	Cross-Sectional Study (US)	N = 6,683 hypertensive patients (3,289 males, 3,394 females). The mean age was 39.3 ± 21.96 years.	No significant association between serum zinc levels and hypertension was found. Both low and high serum zinc levels were not significantly correlated with hypertension.	No significant association between serum zinc levels and hypertension was found, indicating that zinc deficiency did not have a direct effect on hypertension in this population.	Cross-sectional design restricts causal inference. Failure to adjust for antihypertensive use may bias blood-pressure and trace element measurements. Using a single American Heart Association threshold risk misclassifying transient elevations as hypertension, undermining accuracy and limiting generalisability.	6[b]

Ricaurte et al. (2020)	Cross-Sectional Study (Spain)	N = 1,502 (50.2% women and 49.8% men) Hypertensive patients (n = 642). The mean age was 67.56 ± 0.6 years. Nonhypertensive (n = 860). The mean age was 44.64 ± 0.6 years.	Serum zinc was lower in hypertensive than non-hypertensive patients (12.47 ± 0.10 compared to 12.83 ± 0.10 μmol/L), but not statistically significant (p = 0.058). Urinary zinc excretion was higher (2.83 ± 0.20 compared to 2.58 ± 0.10 μmol/g creatinine). These patterns suggest hypertension related alterations in zinc homeostasis, though confirmation is needed.	Increased zinc excretion may lead to zinc deficiency, which can exacerbate hypertension by affecting antioxidant enzymes (e.g. SOD) and contributing to oxidative stress. Zinc imbalance may also impair blood pressure regulation.	The cross-sectional design limits causal inference regarding the association between hypertension and alterations in zinc status. Findings may not be generalisable beyond the Valladolid population, and dietary intake was not assessed.	6[b]

Newcastle–Ottawa Scale = NOS; Number = N; Superoxide dismutase = SOD. A total score of 0–4, 5–7 or 8–10 indicated that a study was of low, moderate or high quality, respectively.

a NOS for cohort studies

b NOS for cross-sectional studies

2.4.3 Influence of Antihypertensive Agents on Zn Status

The findings suggest that antihypertensive medications typically lead to a reduction in serum Zn levels while promoting increased Zn excretion in the urine. This phenomenon was notably documented in studies from Poland by Sulibursk a et al. (2014, 2018a, 2018b) – which indicated significant decreases in serum and erythrocyte Zn concentrations following antihypertensive treatments, with partial recovery when patients were placed on a mineral-rich diet or Zn supplementation. Cipu et al.'s (2014) study in Romania further supports these findings by demonstrating that Zn supplementation could effectively elevate serum Zn levels, although the response varied significantly with the type of antihypertensive medication used. These alterations in Zn metabolism were associated with changes in lipid metabolism, oxidative stress markers and inflammatory states. The findings underscore the necessity for Zn monitoring and supplementation during antihypertensive therapy to mitigate ZnD and its metabolic consequences (See **Table 2.6**). In the four studies, the distribution of drug utilisation indicates a predominant preference for diuretics, followed by calcium antagonists. ACE inhibitors and angiotensin receptor blockers (ARBs) were also frequently prescribed, whereas beta-blockers were used less commonly in comparison. This pattern reflects the varying therapeutic approaches for managing HTN across different patient groups.

2.4.4 Different Classes of Antihypertensive Drugs Exhibiting Varying Impacts on Zn Status

2.4.4.1 ACE Inhibitors

Some of the studies demonstrated that ACE inhibitors significantly alter Zn metabolism. In Cipu et al.'s (2014) observational study, geriatric patients treated with captopril showed a significant increase in urinary Zn excretion (from 320 ± 12 mcg/24 h to 650 ± 4 mcg/24 h, $p < 0.005$) over an eight-month period. This study highlighted that captopril treatment resulted in excessive ZnD, compared to a combination therapy of amlodipine, valsartan and hydrochlorothiazide that indicated no significant interference with Zn status. This suggests that not all antihypertensive drugs affect Zn levels uniformly. Suliburska et al. (2018) also noted significant reductions in serum Zn levels with ACE inhibitors (from 10.2 ± 1.8 to 9.4 ± 1.5 μmol/L). The study concluded that three months of antihypertensive monotherapy with ACE inhibitors diminishes Zn status in patients with newly diagnosed primary arterial HTN.

2.4.4.2 Beta-Blockers

The studies reviewed did not report significant changes in Zn status specifically associated with beta-blockers. Suliburska et al. (2018) included beta-blockers in their evaluation and found no Zn metabolism alterations in patients. This indicates that beta-blockers might not substantially impact Zn levels when compared to other types of antihypertensive drugs.

2.4.4.3 Calcium Channel Blockers

The impact of calcium antagonists on Zn status was also notable. In Suliburska et al.'s (2014) study, 31% of the subjects were given calcium antagonists, which resulted in no significant differences in erythrocytes Zn levels. However, later, Suliburska et al. (2018) found that

calcium antagonists led to a decrease in erythrocyte Zn concentration (from 0.5 ± 0.1 to 0.4 ± 0.1 μmol/g Hgb).

2.4.4.4 ARBs

Cipu et al. (2014) compared the effects of combination therapy including valsartan (an ARB) and found no significant change in Zn excretion in the triple therapy group, suggesting that ARBs may have a lesser impact on Zn status compared to other antihypertensive agents. Suliburska et al. (2018) also included ARBs in their study but did not report specific effects on Zn status separate from the general findings of decreased serum and erythrocyte Zn concentrations.

2.4.4.5 Diuretics

Several studies have demonstrated that diuretics significantly affect Zn status in hypertensive patients. Suliburska et al. (2014) conducted a study in Poland involving 45 hypertensive patients (38% of subjects received diuretics). They found that serum Zn levels significantly decreased following antihypertensive treatment, which included diuretics (from 9.8 ± 1.0 to 8.2 ± 1.3 μmol/L). However, the Zn levels increased with the introduction of an optimal-mineral diet (10.9 ± 1.0 μmol/L) compared to the levels of the control group (8.5 ± 1.1 μmol/L). Additionally, there was a significant increase in Zn excretion in urine after treatment (from 5.2 ± 2.0 to 7.7 ± 2.8 μmol/24 h). Suliburska et al. (2018b) observed similar effects. They noted that diuretic administration led to decreases in serum Zn (from 10.1 ± 1.5 to 9.1 ± 1.2 μmol/L) and erythrocyte Zn concentrations (from 0.5 ± 0.1 to 0.4 ± 0.1 μmol/g Hgb), as well as increases in Zn urine concentration (from 4.8 ± 2.0 to 7.2 ± 1.8 μmol/24 h).

2.4.5 Meta-analysis of the Impact of Antihypertensive Drugs on Zn Levels

2.4.5.1 Effect on Serum Zn Levels

A meta-analysis was conducted to evaluate the impact of antihypertensive drug therapy on serum Zn levels across four studies: Suliburska et al. (2014, 2018a, 2018b) and Cipu et al. (2014). **Figure 2.3** presents the forest plot of the analysis. Each study reported standardised effect sizes, along with 95% CIs. The aggregated effect size (Glass's delta) for serum Zn levels was estimated to be -0.33 (95% CI: -1.00 to 0.34, p = 0.34), suggesting a nonsignificant effect of antihypertensive drug use on serum Zn concentrations. This outcome indicates that antihypertensive drugs did not uniformly alter serum Zn levels across the studies analysed. The heterogeneity for this analysis was moderate (τ^2 = 0.85 and I^2 = 93%) – indicating some variability in effect sizes that may be attributed to differences in study characteristics, such as drug classes or participant populations.

2.4.5.2 Effect on Zn Excretion in Urine

The meta-analysis further assessed the influence of antihypertensive drugs on urinary Zn excretion across four studies: Suliburska et al. (2014, 2018a, 2018b) and Cipu et al. (2014). The overall effect size was calculated to be 8.89 (95% CI: -7.70 to 25.47, p = 0.29), as presented in **Figure 2.4**. This wide CI reflects substantial heterogeneity among the studies (τ^2 = 636.24, I^2 =100%). Such high heterogeneity suggests considerable variability in urinary Zn excretion outcomes, likely attributable to methodological differences between studies, variations in drug classes administered or differences in the duration of antihypertensive therapy.

2.4.5.3 Effect on Erythrocyte Zn Levels

A significant reduction in erythrocyte Zn levels was observed across the three studies: Suliburska et al. (2014, 2018a, 2018b), with a pooled effect size of -0.64 (95% CI: -1.01 to -0.26, p = 0.00), as depicted in **Figure 2.5**. This result suggests that antihypertensive drug therapy may lead to a measurable decrease in erythrocyte Zn levels, highlighting erythrocytes as a potentially sensitive marker of Zn status in individuals undergoing such therapy. The heterogeneity for this analysis was moderate ($\tau^2 = 0.17$, $I^2 = 69\%$) – indicating that while studies generally report a reduction in erythrocyte Zn levels, some variability remains, possibly due to differences in specific drug types, dosages or patient populations.

2.4.5.4 Effect on Zn Intake

The final analysis investigated the potential impact of antihypertensive drugs on dietary Zn intake across Suliburska et al. (2014, 2018a) studies. The pooled effect size was -0.05 (95% CI: -0.29 to 0.18, p = 0.64), as shown in **Figure 2.6**. This nonsignificant effect indicates that antihypertensive drug use was not associated with any substantial change in Zn intake among the populations studied. Heterogeneity in this analysis was minimal (τ^2 close to 0, $I^2 = 0\%$), suggesting a consistent lack of association across the included studies.

The studies included in this meta-analysis displayed varying heterogeneity levels, as indicated by the τ^2 and I^2 statistics. For analyses with high heterogeneity (e.g. urinary Zn excretion), a random-effects model was employed to better account for interstudy variability. The significant reduction observed in erythrocyte Zn levels indicates that antihypertensive drugs may have a direct influence on intracellular Zn compartments, potentially mediated by cellular uptake mechanisms or redistribution effects linked to the pharmacodynamics of these drugs. In contrast, serum Zn levels, urinary Zn excretion and Zn intake did not show statistically

significant effects, suggesting that the impact of antihypertensive therapy on Zn status may be compartment specific. Notably, the nonsignificant results in serum and urinary Zn levels may have been due to compensatory mechanisms that maintain homeostatic Zn levels in these compartments, or these may be less sensitive indicators of Zn depletion than erythrocyte Zn levels.

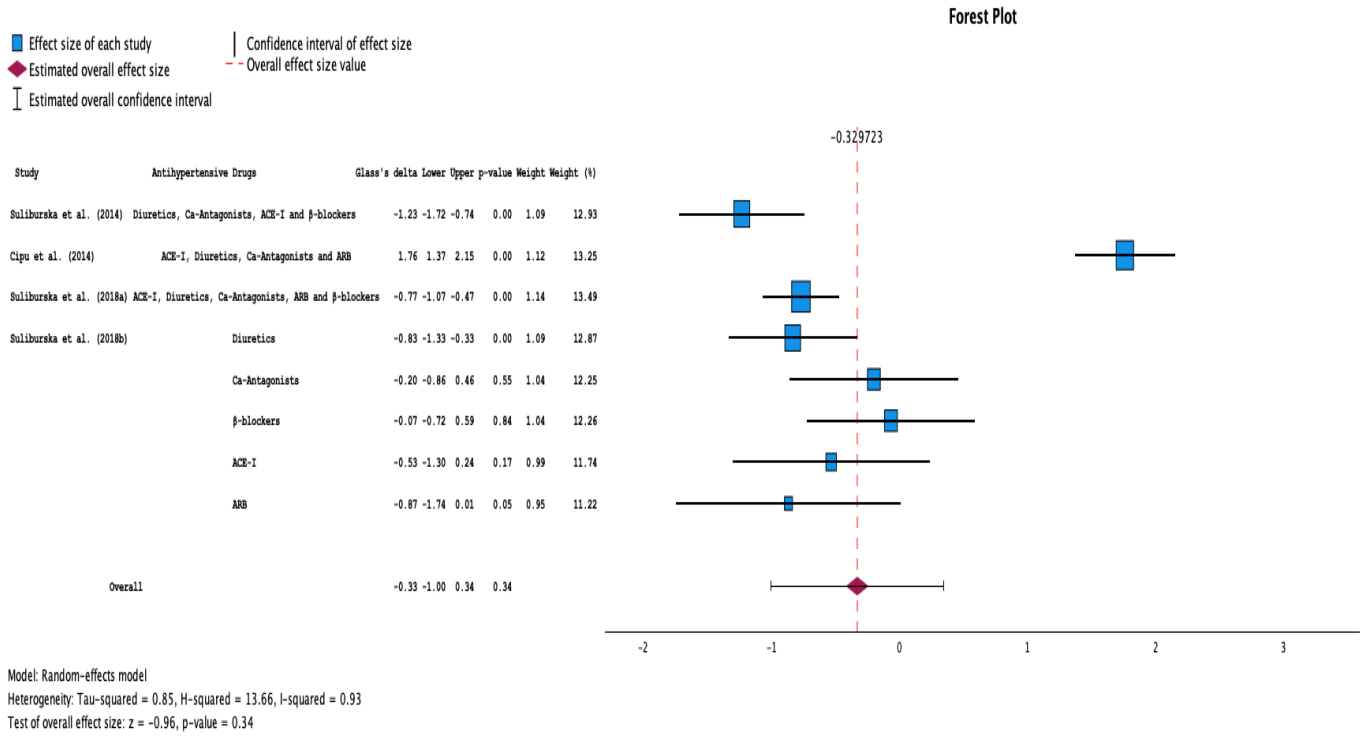


Figure 2.3 Forest plot of the effect of antihypertensive drugs on serum zinc level

This figure shows that values to the left of the vertical line at zero indicate lower serum zinc levels in individuals taking antihypertensive medications compared with controls, whereas values to the right indicate higher levels. Each blue square represents the effect size (mean difference) for an individual study, with horizontal lines showing the 95% confidence interval. The red diamond represents the pooled effect size with its confidence interval.

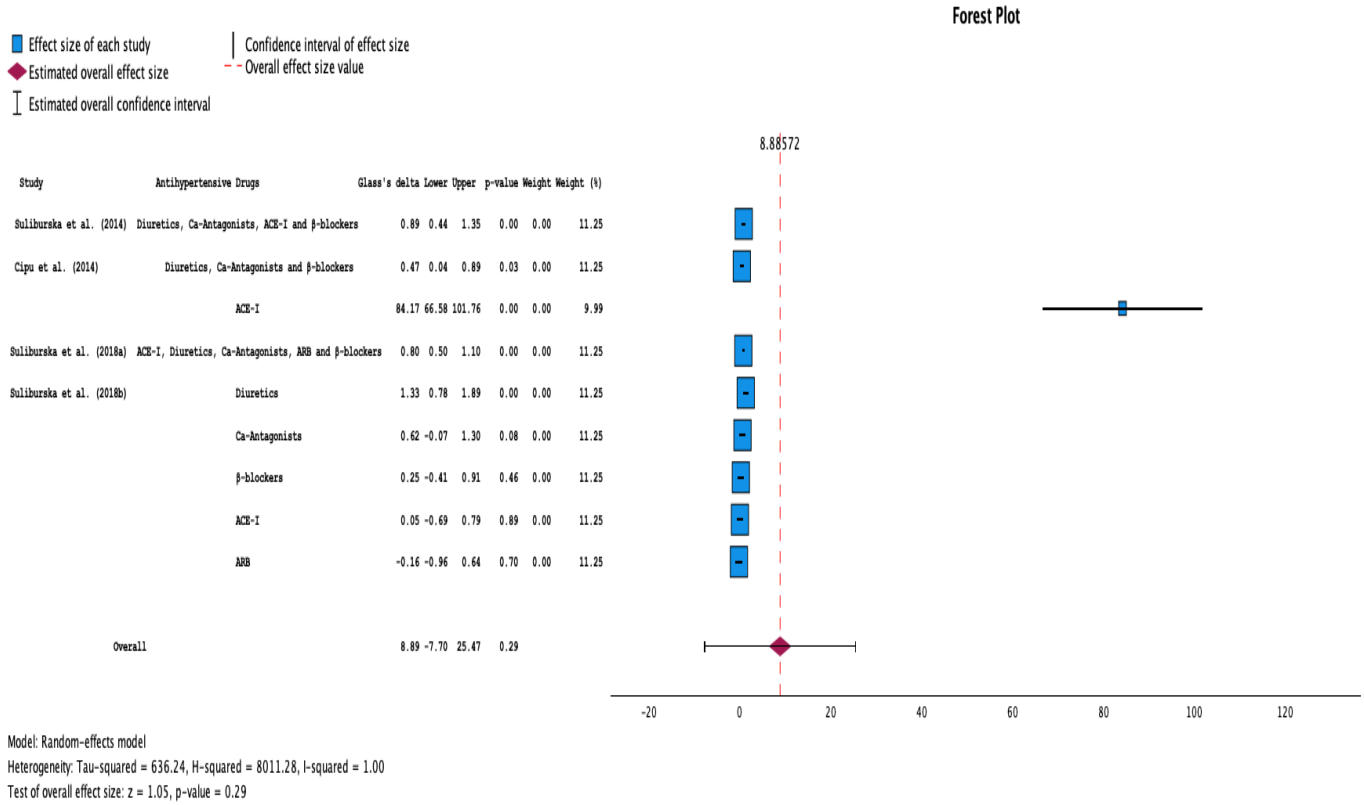


Figure 2.4 Forest plot of the effect of antihypertensive drugs on zinc excretion in urine

This figure shows that values to the left of the vertical line at zero indicate that individuals taking antihypertensive medications have lower zinc excretion compared with controls, whereas values to the right indicate higher excretion. Each blue square represents the effect size (mean difference) for an individual study, with horizontal lines showing the 95% confidence interval. The red diamond represents the pooled effect size with its confidence interval.

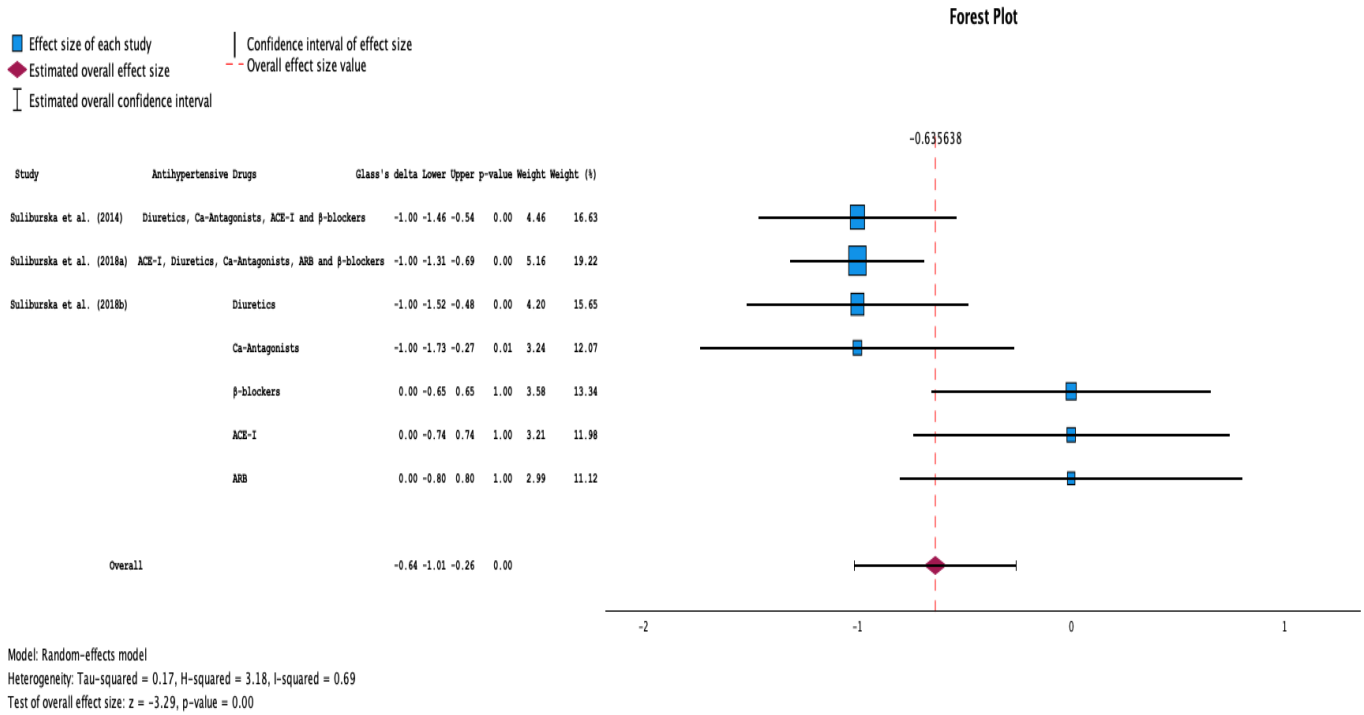


Figure 2.5 Forest plot to investigate the effect of antihypertensive drugs on erythrocytes of zinc

This figure shows that values to the left of the vertical line at zero indicate that individuals taking antihypertensive medications have lower erythrocyte zinc levels compared with controls, whereas values to the right indicate higher levels. Each blue square represents the effect size (mean difference) for an individual study, with horizontal lines showing the 95% confidence interval. The red diamond represents the pooled effect size with its confidence interval.

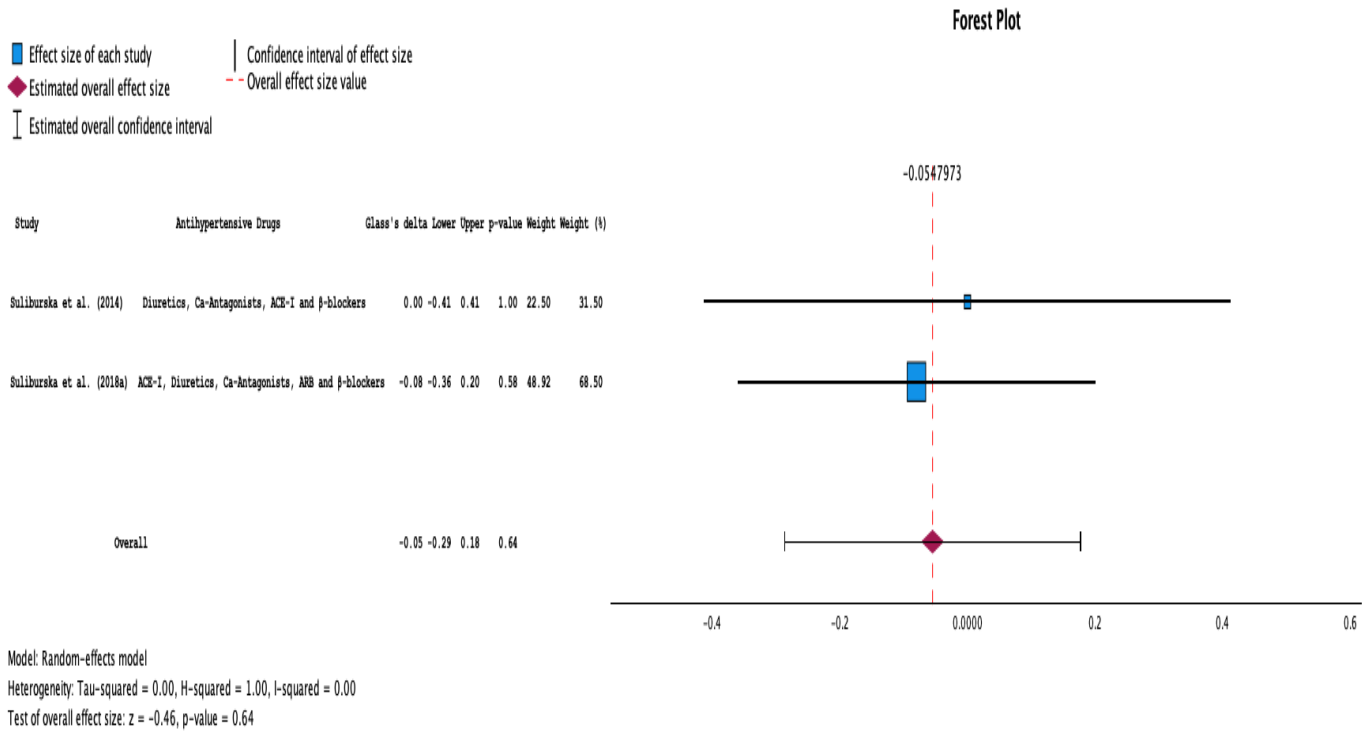


Figure 2.6 Forest plot of the effect of antihypertensive drugs on zinc intake

This figure shows that values to the left of the vertical line at zero indicate that individuals taking antihypertensive medications have lower dietary zinc intake compared with controls, whereas values to the right indicate higher intake. Each blue square represents the effect size (mean difference) for an individual study, with horizontal lines showing the 95% confidence interval. The red diamond represents the pooled effect size with its confidence interval.

Table 2.6 Literature summary of the influence of antihypertensive agents on zinc status

Author (Year)	Study Type (Location)	Study Population	Antihypertensive Drugs and Date Range	Zinc Status	Other Relevant Findings	Clinical Outcomes of Zinc Deficiency	Study Limitations	NOS Scores
Suliburska et al. (2014)	Randomised Controlled Trial (Poland)	Participants (N = 45; 19 men, 26 women; mean age 51.3 ± 14.2 years) were initially treated with antihypertensive monotherapy and then randomly assigned to either a diet group (n = 27) or a control group (n = 18).	The study spanned four months: three months of antihypertensive monotherapy followed by a one-month dietary intervention. Agents used were diuretics (38%), calcium-channel blockers (31%), ACE inhibitors (18%), and β-blockers (13%); drug doses were not reported.	Antihypertensive treatment was associated with a significant decrease in serum zinc (9.8 ± 1.0 to 8.2 ± 1.3 μmol/L). An optimal-mineral diet increased serum zinc (10.9 ± 1.0 μmol/L) compared to the controls (8.5 ± 1.1 μmol/L). Erythrocyte zinc was unchanged. Urinary zinc excretion rose significantly (5.2 ± 2.0 to 7.7 ± 2.8 μmol/24 h).	An optimal-mineral diet appeared to mitigate antihypertensive-associated reductions in serum zinc. Serum zinc was inversely correlated with glucose, suggesting a potential protective effect against dysglycaemia. Diuretics and calcium-channel blockers were most implicated in zinc perturbations. Specific drug names and doses were not reported.	Zinc deficiency can cause glucose intolerance, insulin resistance, immune dysfunction, oxidative stress and delayed healing.	Small sample size limits generalisability. The one-month dietary intervention precludes assessment of longer-term effects. Limited control of key variables particularly adherence to dietary recommendations may have introduced variability and bias into the results.	7[a]

Cipu et al. (2014)	Observational Study (Romania)	Participants (N = 90; 48 men [53%], 42 women [47%]; mean age 74.2 ± 3.4 years) were allocated equally to Group I (n = 45) and Group II (n = 45).	Duration: 8 months. Group I received captopril 50 mg twice daily. Group II received a fixed-dose single-tablet combination of amlodipine 10 mg, valsartan 320 mg, and hydrochlorothiazide 25 mg once daily. All patients took zinc sulphate 44 mg twice daily.	Zinc was measured at baseline, 4 months, and 8 months. Hypertensive elders had subnormal serum zinc (~70 µg/dL threshold): 59 ± 10 µg/dL (Group I) and 62 ± 4 µg/dL (Group II). Eight months of zinc supplementation increased serum zinc ($p < 0.005$). Baseline urinary zinc was 320 ± 12 µg/24 h (Group I) and 280 ± 8 µg/24 h. After 8 months, 24-h urinary zinc rose significantly only with captopril (650 ± 4 µg/24 h; $p < 0.005$); no significant change occurred with the amlodipine/valsartan/hydrochlorothiazide combination (285 ± 10 µg/24 h; $p > 0.005$).	Zinc status differed significantly between the two treatment groups. Specifically, urinary zinc excretion increased significantly in the captopril group but not in the group that received the combination therapy.	Zinc deficiency may lead to immune dysfunction, cognitive decline and bone health issues in elderly patients.	The small sample (n = 90) limits generalisability. The 8-month follow-up may be insufficient to capture long-term effects on zinc status. Uncontrolled variables especially dietary zinc intake could have confounded serum and urinary zinc measurements.	6[b]

Suliburska et al. (2018a)	Prospective Randomised Trial (Poland)	N=98 adults with hypertension (37 men, 61 women; mean age 53.6 ± 13.7). All began antihypertensive monotherapy, then were randomised to: mineral-rich diet (Group D), zinc supplementation (Group S), or no dietary change (Group C).	The study lasted three months. Antihypertensive therapy comprised diuretics (n=36), calcium-channel blockers (n=18), β-blockers (n=18), ACE inhibitors (n=14), and angiotensin II receptor blockers (n=12). Participants then underwent a 30-day intervention of dietary modification, zinc supplementation (15 mg/day), or no change. Drug doses were not reported.	Antihypertensive therapy significantly reduced serum zinc (10.1 ± 1.5 to 9.1 ± 1.3 μmol/L) and erythrocyte zinc (0.5 ± 0.1 to 0.4 ± 0.1 μmol/g Hb), while increasing urinary zinc excretion (5.3 ± 2.0 to 6.9 ± 2.0 μmol/24 h).	Zinc supplementation increased zinc status and reduced serum glucose. Serum zinc correlated inversely with glucose, suggesting that improving zinc status may support glycaemic control in hypertensive patients.	Zinc deficiency promotes inflammation by increasing pro-inflammatory cytokines, impairs insulin secretion, and contributes to raised blood pressure via dysfunction of blood-pressure-regulating mechanisms.	The small sample limits generalisability, and the one-month dietary intervention precludes assessment of long-term effects. Moreover, adherence to dietary recommendations was not monitored or controlled, introducing potential variability and bias into the results.	7[a]

Suliburska et al. (2018b)	Two-Stage Parallel Study conducted as a Prospective Randomised Trial (Poland)	Participants (N = 98; 37 men, 61 women) had a mean age of 53.6 ± 13.7 years.	Three-month therapy included: diuretics (n=36), CCBs (n=18), β-blockers (n=18), ACE inhibitors (n=14), or ARBs (n=12); doses unreported.	Diuretics lowered serum zinc (10.1 ± 1.5 to 9.1 ± 1.2 μmol/L) and erythrocyte zinc (0.5 ± 0.1 to 0.4 ± 0.1 μmol/g Hb) while increasing urinary zinc (4.8 ± 2.0 to 7.2 ± 1.8 μmol/24 h). Calcium-channel blockers reduced erythrocyte zinc (0.5 ± 0.1 to 0.4 ± 0.1 μmol/g Hb). ACE inhibitors significantly decreased serum zinc (10.2 ± 1.8 to 9.4 ± 1.5 μmol/L). Hair zinc was unchanged across agents.	The study also noted alterations in iron and copper status and explored how antihypertensive therapy influenced oxidative stress, inflammatory markers, and glucose and lipid metabolism. Use of ACE inhibitors, calcium-channel blockers, and thiazide diuretics was associated with reduced zinc levels in hypertensive patients.	Zinc deficiency induced by diuretics, calcium antagonists and ACE inhibitors increases urinary zinc loss, lowering serum/erythrocyte zinc, and heightens oxidative stress with impaired lipid metabolism.	The three-month duration may have been insufficient to capture long-term treatment effects. Moreover, the absence of dietary control could have confounded participants' mineral status.	7[a]

ACE: Angiotensin-Converting Enzyme inhibitors; ARB: Angiotensin II Receptor Blockers; Newcastle–Ottawa Scale = NOS; Number = N. A total score of 0–4, 5–7 or 8–10 indicated that a study was of low, moderate or high quality, respectively.

[a] NOS for case control studies

[b] NOS for cohort studies

Table 2.7 Quality assessment through Newcastle - Ottawa quality assessment scale for cohort studies

Description	**Arinda Lironika et al. (2015)** Observational study	**Cipu et al. (2014)** Observational study
SELECTION		
Representativeness of the exposed cohort	*	
Selection of the non-exposed cohort	*	*
Ascertainment of exposure	*	*
Demonstration that outcome of interest was not present at start of study	*	*
COMPARABILITY		
Comparability of cohorts on the basis of the design or analysis	**	*
OUTCOMES		
Assessment of outcome	*	*
Was follow-up long enough for outcomes to occur		*
Adequacy of follow up of cohorts		
Total Points	**7**	**6**

Table 2.8 Quality assessment through Newcastle - Ottawa quality assessment scale for case control studies

Description	**Suliburska et al. (2014)** Randomised Controlled Trial (RCT)	**Suliburska et al. (2018)** Randomised Controlled Trial (RCT)	**Suliburska et al. (2018)** Randomised Controlled Trial (RCT)
SELECTION			
Is the case definition adequate?	*	*	*
Representativeness of the cases	*	*	*
Selection of Controls			
Definition of Controls			
COMPARABILITY			
Comparability of cases and controls on the basis of the design or analysis	**	**	**
EXPOSURE			
Ascertainment of exposure	*	*	*
Same method of ascertainment for cases and controls	*	*	*
Non-Response rate	*	*	*
Total Points	**7**	**7**	**7**

Table 2.9 Quality assessment through Newcastle - Ottawa quality assessment scale for cross-sectional studies

Description	**Solanki et al. (2015)** Cross-Sectional Study	**Darroudi et al. (2019)** Cross-Sectional Study	**Bastola et al. (2020)** Cross-Sectional Study	**Ricaurte et al. (2020)** Cross-Sectional Study
SELECTION				
Representativeness of the sample	*	*	*	*
Non-respondents				
Ascertainment of the exposure	*	*	*	*
COMPARABILITY				
The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled	**	**	**	**
OUTCOMES				
Assessment of outcome	**	*	*	*
Statistical test	*	*	*	*
Total Points	**7**	**6**	**6**	**6**

2.5 Discussion

The present research investigated the evidence about Zn status in HTN and the influence of antihypertensive medications. The findings suggest that HTN and its pharmacological treatments can influence Zn metabolism. Significant class-specific effects were identified in the reviewed literature. ACE inhibitors and diuretics were indicated to notably decrease Zn concentrations (Cipu et al., 2014; Suliburska et al., 2014) – a finding corroborated by Trasobares et al. (2007), who reported similar disruptions in Zn homeostasis. Previous published clinical and experimental studies demonstrated increased gastrointestinal absorption and urinary excretion of Zn with concomitant decreased serum Zn levels in the case of primary arterial HTN (Kasai et al., 2012; Kim, 2013). Other studies have also suggested that Zn plays a role in blood pressure regulation (Tomat et al., 2007). The Williams et al. (2019) discovered that Zn had a synergistic effect on muscles, endothelium cells and sensory neurons, lowering calcium levels in muscles and causing relaxation. This leads in an increase in blood flow and a decrease in blood pressure. The association of Zn with HTN appears to be a complex process and seems to work at multiple physiological levels (Williams et al., 2019). This is evident from the facts that further disturbed Zn homeostasis increases the risk of incidence of associated pathologies, such as type 2 diabetes, obesity and cardiovascular disease (Huang et al., 2018). A recent study involving in vitro and in vivo ZnD models directly demonstrated the role of Zn^{2+} in blood pressure regulation and identified an important mechanism (NaCl cotransporter) involved in ZnD-induced Na+ retention in the kidneys, subsequently increasing blood pressure (Williams et al., 2019).

It has been documented that the Zn levels decrease in the serum, bone and lymphocytes but increase in the kidneys, erythrocytes, heart, liver, spleen and adrenal glands in the case of arterial HTN (Suliburska et al., 2018; Yu et al., 2018). However, these findings cannot be ascertained in this review, and the deviations can be attributed to the study design differences, the stringent selection criteria adopted for the review and the lack of assessment of dietary Zn status by the eligible studies. Moreover, human and animal studies have indicated that elevated blood pressure alters Zn metabolism, influencing Zn distribution among intracellular compartments (Olechnowicz et al., 2018). In addition, being an essential component of antioxidant enzymes, such as Zn/copper superoxide dismutase, disturbances in Zn level likely enhances cellular oxidative damage, including endothelial cells affected in HTN and associated pathologies (Cortese-Krott et al., 2014). It has also been reported that individuals having a low Zn diet are prone to a high prevalence of HTN, suggesting a possible inverse correlation between blood pressure and Zn level. However, this cannot be ascertained in the present review, as the eligible studies did not assess for the same (Kunutsor & Laukkanen, 2016).

Regarding the influence of antihypertensive medications on Zn levels, cumulative evidence showcases decreased Zn concentrations with the use of antihypertensive medications. However, recent evidence for the same is highly sparse. Braun and Rosenfeldt's (2013) systematic review highlighted reduced Zn levels upon the use of ACE inhibitors, ARBs and thiazide diuretics in particular based upon the eight eligible studies. Suliburska et al. (2014, 2018) confirmed similar findings. A clinical investigation revealed that the interaction is pharmacokinetic in nature and is most probably triggered by lowered Zn reabsorption in the kidneys, leading to zincuria. It is undetermined if medication types also affect Zn absorption from the gastrointestinal tract or other excretory organs, such as faeces or the skin (Braun & Rosenfeldt, 2013).

Different effects of ACE inhibitors on Zn have been demonstrated based upon chemical structure. Structurally, ACE inhibitors are classified as dicarboxyl- (namely, enalapril, lisinopril, perindopril, quinapril and moexipril), sulphydryl- (for example, captopril, fentiapril and zofenopril) and phosphonate containing (namely, fosinopril) based on binding with ACE (Sangole & Dadkar 2010). The thiol group in captopril is thought to function as a chelating agent, allowing it to bind with Zn and possibly leading to increased Zn excretion in the urine (zincuria; Trasobares et al., 2007). In contrast, other ACE inhibitors, such as enalapril, do not contain a thiol group, resulting in variations in their antioxidant properties and potential side effects (Kendall, 1987; Lee et al., 1999). This proposed theory also explains the more potent effect of captopril compared to enalapril on Zn levels in serum, urine and erythrocytes. The negative impact of ARBs, losartan and valsartan, on erythrocyte Zn level indicates the metabolic effects of angiotensin II (Koren-Michowitz et al., 2005).

The interaction between ARBs or ACE inhibitors and Zn is thought to involve a mechanism in which blocking angiotensin II reduces the activity of the renal Na/H antiporter. This reduction leads to decreased tubular Zn reabsorption, resulting in zincuria. This proposed mechanism is supported by evidence that treatment with ACE inhibitors and ARBs has been linked to zincuria and ZnD (Cohen & Golik, 2006).

Beta-blockers are essential in modulating the regulatory mechanisms that reduce myocardial contractility and cardiac output. By reducing renin secretion, beta-blockers decrease angiotensin II levels, which can contribute to zincuria (Williams, 2006). Similarly, thiazide diuretics affect Zn levels by decreasing tubular Zn reabsorption, which results in zincuria. This occurs because thiazide diuretics inhibit the NaCl cotransporter in the renal distal tubule (Raja et al., 2019).

Overall, while persistent use of antihypertensive drugs is effective in controlling blood pressure, it also incurs several detrimental effects, including ZnD. Unaddressed ZnD associated with antihypertensive drugs can enhance the risk of increased predisposition for multiple chronic pathologies, such as atherosclerosis, renal disorders and age-related degenerative diseases, through the disruption of inflammatory and oxidative homeostasis (Huang et al., 2018). Therefore, periodic assessment of Zn status among patients on antihypertensive treatment is suggested.

This systematic review, while extensive, has significant limitations that affect how its findings are interpreted. First, the studies included in this review vary significantly in their design – ranging from cross-sectional to observational, thereby resulting in inconsistencies and limiting the ability to compare them directly. Additionally, geographic and demographic differences across the studies could have influenced Zn levels independently of HTN, thereby confounding the results. Second, some of the studies have limited sample sizes, which reduces their statistical power. Additionally, the measurement of Zn status is not standardised – with various tests and biomarkers used across studies, potentially affecting the reliability of data comparisons. Third, the complicated effects of antihypertensive medications on Zn metabolism have not been completely investigated due to the limited breadth and depth of some of the included studies.

Recognising these limitations is crucial for a precise evaluation of the evidence and emphasises the importance of conducting future studies to adopt more rigorous and standardised research protocols to elucidate the precise mechanisms by which antihypertensive drugs influence Zn metabolism and to develop evidence-based strategies for mitigating these effects in clinical practice.

2.6 Conclusion

Based on current data, it appears that the relationship between Zn and HTN is complex, with antihypertensive medications having a major impact on Zn metabolism. This necessitates an integrated approach to treatment that considers both pharmacological efficacy and nutritional outcomes. The influence of the long-term use of antihypertensive agents on Zn levels, particularly decreased Zn reabsorption, seems evident, despite only a few recent studies being available.

The type of antihypertensive medication, duration of treatment, underlying health conditions, dietary Zn intake and individual patient differences are critical factors influencing Zn status. The study findings suggest that routine monitoring of Zn levels should be considered in the management of hypertensive patients to ensure optimal therapeutic outcomes and prevent ZnD-related complications. Future prospective studies with large sample sizes are needed, focusing on the documented dietary Zn and on understanding the role of HTN and hypertensive agents in Zn homeostasis.

Chapter 3: Investigating Zinc Status with Consumption of Common Antihypertensive Drugs in the UK Adult Population: A Secondary Analysis of the UK National Diet and Nutrition Survey Using Data from 2008 to 2019

Abstract

Background: Hypertension affects a significant global population, leading to an increased prescription of antihypertensive drugs. Although blood pressure management depends on essential medications, they can significantly change micronutrient levels. The most important is zinc, an essential micronutrient that is vital for numerous physiological functions. Additionally, due to the extensive consumption of antihypertensive drugs in the UK and the health benefits of zinc, it is essential to study how these drugs affect its status.

Objective: This study aims to investigate the effect of the consumption of common antihypertensive drugs on zinc status in the general UK adult population (≥19 years), using the National Diet and Nutrition Survey Rolling Programme.

Methods: The study included adults aged 19 years and older, using the National Diet and Nutrition Survey database collected between 2008 and 2019 (Years 1–11). The determination of zinc consumption from food sources and zinc status was based on measurements of plasma and serum zinc concentrations. The subjects were divided according to the use of antihypertensive drugs: angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers and diuretics. Age and gender were used as covariates when analysing the relationship between the use of antihypertensive drugs, zinc intake and zinc status.

Results: The analysis comprised 11,153 participants. An age-dependent increase in the use of antihypertensive drugs was detected, with clear-cut sex-based differences in drug choices and zinc levels. Although an overall adequacy in dietary zinc intake was found in the overall population, especially males, consumed zinc below the reference nutrient intake (64.5%). The use of antihypertensive drugs had a significant impact on deviations in zinc intake and plasma zinc levels. Nevertheless, most participants maintained normal zinc levels, which suggests that there may be compensatory mechanisms working in their bodies.

Conclusion: Antihypertensive medication use among UK adults is associated with changes in zinc status, with significant differences observed according to sex, age and medication type. Although dietary zinc intake is generally consistent with the reference nutrient intake, the impact of antihypertensive medications on zinc status requires further study to inform nutritional recommendations and ensure optimal micronutrient status in hypertensive patients.

3.1 Introduction

Hypertension (HTN) is an ever-growing health problem among males and females globally, whose incidence increases with advancing age (Jarari et al., 2015; Rapsomaniki et al., 2014). According to the World Health Organisation (2023), an estimated 1.28 billion people are affected by HTN globally. While in 1975, approximately 594 million adults were found to have HTN, this rose to 1.13 billion by 2015, with the increase mostly observed in countries with low and moderate incomes (Sinnott et al., 2017; World Health Organisation, 2023). Adults with HTN reached roughly 972 million in 2000, and this figure is predicted to grow by nearly 60% by 2025, reaching 1.56 billion (Jarari et al., 2015; Manolis et al., 2015). Worldwide, the number of antihypertensive drug prescriptions has increased, particularly in developed countries. In the context of HTN, a prevalent condition in the UK, the management often involves long-term use of antihypertensive drugs. Studies have used the UK Clinical Practice Research Datalink to examine annual prescription trends of antihypertensive drugs (Rouette et al., 2022; Sinnott et al., 2020).

The use of pharmaceutical drugs can frequently interact with the digestion, absorption, utilisation and excretion of vital nutrients. These drugs, while essential for controlling blood pressure, may have unintended impacts on the status of micronutrients, particularly zinc (Zn; Houston, 2014). These interactions can happen through effects on enzyme production, coenzyme or protein transport and hormone metabolism. Moreover, the gastrointestinal tract plays a crucial role in the absorption and status of both antihypertensive drugs and Zn. Additionally, these drugs can cause nutrient depletion through chelation in the gastrointestinal tract – where Zn binds to the drug molecules, forming complexes that inhibit its absorption and leading to decreased levels in the body and potential deficiencies over time (Braun & Rosenfeldt, 2013; Suliburska et al., 2018). Research evidence indicates a clear influence of

both the underlying disease (HTN) and antihypertensive drugs on general mineral metabolism, including that of Zn (Bastola et al., 2020; Koren-Michowitz et al., 2005; Tubek, 2006). Zn, an essential micronutrient, is vital for numerous physiological functions, including immune response, enzyme activity and DNA synthesis (Roohani et al., 2013). It is well recognised that Zn status can be influenced by various external factors, including medication intake.

Understanding the interaction between antihypertensive drugs and Zn status is of substantial importance. Zn plays a critical role in numerous health aspects, and any alteration in its status due to medication could have significant implications for dietary recommendations, drug prescriptions and overall public health strategies in the UK. Furthermore, this interaction is especially relevant for older adults, who are more likely to be affected by both HTN and potential Zn deficiencies.

The significance of this research extends to informing clinical practices in monitoring and managing Zn status in patients on long-term antihypertensive therapy. Additionally, it contributes to the broader understanding of drug-nutrient interactions, an area that is crucial yet underexplored in pharmacology and nutrition. Only a limited number of studies have explored how the consumption of antihypertensive drugs may impact Zn status. In view of the widespread use of antihypertensive drugs, the current work sought to investigate the effect of the consumption of common antihypertensive drugs on Zn status in the general UK adult population (≥19 years), using the National Diet and Nutrition Survey (NDNS) Rolling Programme (2008–2019).

3.2 Methods

3.2.1 Subjects and Study Design

The NDNS is a continuous rolling programme conducted throughout the year across the UK (England, Northern Ireland, Wales and Scotland) for assessing dietary habits, nutritional status and health-related factors in the population aged 1.5 years and above living in private households (Bates et al., 2019). The survey was designed to recruit 1,000 subjects annually (500 children [aged 1.5–18 years] and 500 adults [aged 19 years and over]). A random sample of addresses listed in the Postcode Address File was taken throughout the UK. Primary sampling units were formed from all addresses to enhance cost-effectiveness in creating small clusters of geographical areas based on postcode sectors. Participants were interviewed to collect information on demographics, lifestyle factors and dietary habits, and self-administered questionnaires were used to gather additional data on various health-related factors. To assess food consumption and nutrient intakes, the NDNS employed several methods, including a four-day food diary and food frequency questionnaires. In the former, participants recorded their food and drink intake over a consecutive four-day period. The diary captured detailed information on the type and quantity of foods consumed and the time and location of consumption. In the questionnaires, participants answered questions about the frequency of consuming specific foods and beverages (Bates et al., 2019).

The NDNS collected data on nutritional status and health-related measures, including anthropometric measurements (height, weight and body mass index were measured to assess growth and nutritional status) and biochemical analysis. For the latter, blood and urine samples were collected from a subset of participants to analyse nutrient levels, biomarkers of nutritional status and other relevant health indicators (Public Health England, 2019). Because the data used in this secondary study was anonymised, no additional ethical approval was required. The

researcher used data from the NDNS, obtained via the UK Data Service (https://www.ukdataservice.ac.uk/).

3.2.2 Inclusion Criteria

The current analysis included data from 2008 to 2019 (Years 1–11) for individuals aged ≥19 years who completed at least three out of four food diary days. Data in the UK NDNS Years 1–11 comprised 11,153 participants, of which 47.1% were males and 52.9% were females. Drugs from four antihypertensive groups were included: ACE inhibitors, beta-blockers, CCBs and diuretics. Individual (plasma profile and health parameters) and personal-level dietary data (physical food consumption intake) of the NDNS dataset from 2008 to 2019 were merged by grouping the datasets into Years 1–4, 5–6, 7–8 and 9–11. All data were weighted according to the NDNS study weights guide documentation (UK Data Archive Study, 2020). Zn biomarkers of participants who were taking antihypertensive drugs were compared to those of participants who were not taking them. Comparisons across gender and age groups were made.

3.2.3 Variables of Interest

3.2.3.1 Zn Intake from Food Sources (Milligrams per Day)

Zn intake solely from dietary sources (excluding supplements) is defined in the NDNS as 'zinc diet only'. In this study, we used the term 'dietary Zn intake' to describe this category. Dietary Zn intake was calculated from the weight of food consumed over four days. From this, we derived the average for one day, measured in milligrams (mg). This represents the daily Zn intake, excluding Zn obtained from supplements or medications. According to the British Nutrition Foundation (2021), the reference nutrient intake (RNI) refers to the quantity of a nutrient sufficient to meet the dietary needs of most (~97.5%) individuals in a population group. Using this criterion, the normal range of Zn intake for males aged 19 years and above is 9.5 mg/day, while females aged 19 years and above require ~7 mg/day.

3.2.3.2 Zn Status (Micromoles per Litre)

To evaluate Zn status, the NDNS utilised biochemical analyses, specifically measuring Zn concentrations in plasma or serum derived from blood samples. For the initial 10 years of the survey, plasma samples were analysed, while in the 11th year, serum samples were used. The age group included in this assessment was seven years and older. The technique employed for this measurement was inductively coupled plasma mass spectrometry, a highly sensitive method capable of detecting trace elements in blood. Starting from the 11th year, the analyses were conducted at University Hospital Southampton, ensuring precise and accurate assessment of Zn status across various age groups from the 11th year onwards. It is similarly referred to as either 'plasma or serum concentration', expressed in micromoles per litre (μmol/L), which is the Zn level in blood plasma or serum during fasting (or in some cases nonfasting) for the sample of individuals participating in the investigation. The recommended Zn levels in the blood differ by age and gender (South Tees Hospitals NHS Foundation Trust, 2021). For males aged 18–64, the healthy range is 10.1 to 20.2 μmol/L, whereas those 64 and older should have levels between 8 and 20 μmol/L. In females aged 18–64, the range is slightly different, from 9.6 to 20.5 μmol/L, and for those aged 64 and above, it adjusts to 9.2 to 19.2 μmol/L.

3.2.3.3 Antihypertensive Drugs

For data focussed on antihypertensive drugs, four drugs were reported in the NDNS dataset: ACE inhibitors, beta-blockers, CCBs and diuretics. Despite the inclusion of these drugs in the study, the NDNS dataset did not provide specific information about type, duration and doses.

3.2.4 Statistical Analysis

All analyses were performed using the SPSS software (version 27, IBM, USA) for the total sample. Dietary Zn intakes and plasma concentrations were analysed by gender and age group – stratified by decades. Continuous variables are presented using medians and interquartile ranges (IQRs), while categorical variables are presented as counts and percentages. IQR is the difference between the 75th percentile and 25th percentile rather than the actual values. Therefore, all the data are presented as medians (IQ) and N (%). A chi-square test of independence was used to examine whether there is a significant association between two categorical variables. To evaluate whether there is a statistically significant difference, Pearson's chi-squared test was used. When possible, nonnormally distributed variables were converted. Nonparametric tests were used to assess group differences in variables that could not be transformed into a normally distributed distribution. Kruskal–Wallis H tests was performed to determine variations for comparisons of more than two covariates. The Mann–Whitney U test was performed when significance was detected at the Kruskal–Wallis H stage. For comparing median values of Zn intake and Zn levels across age groups or between genders within age groups, the Mann–Whitney U test (for two independent samples) could be used since the data was represented as medians and IQRs, as most of the data was not normally distributed. Statistical significance was considered accepted at a level of p-value < 0.05.

3.3 Results

3.3.1 Characteristics of the Study Population

Data from the NDNS (2008–2019) for adult participants who completed at least three food diaries were analysed (N = 11,153 participants). The median ages (IQRs) for male and female participants was 48 (29) and 48 years (30), respectively. The included population comprised 47.1% of males (n = 5,248) and 52.9% of females (n = 5,905). Participants were divided into seven age groups: 19–29 years (974 males and 1,035 females, median age: 24 years), 30–39 years (917 males and 1,005 females, median age: 35 years), 40–49 years (951 males and 1,043 females, median age: 45 years), 50–59 years (895 males and 962 females, median age: 54 years), 60–69 years (769 males and 822 females, median age: 64 years), 70–79 years (526 males and 705 females, median age: 73 years) and 80+ years (215 males and 333 females, median age: 83 years). Of those included, 2,360 participants, consisting of 1,191 males (50.5%) and 1,169 females (49.5%), were using antihypertensive drugs (**Figure 3.1)**.

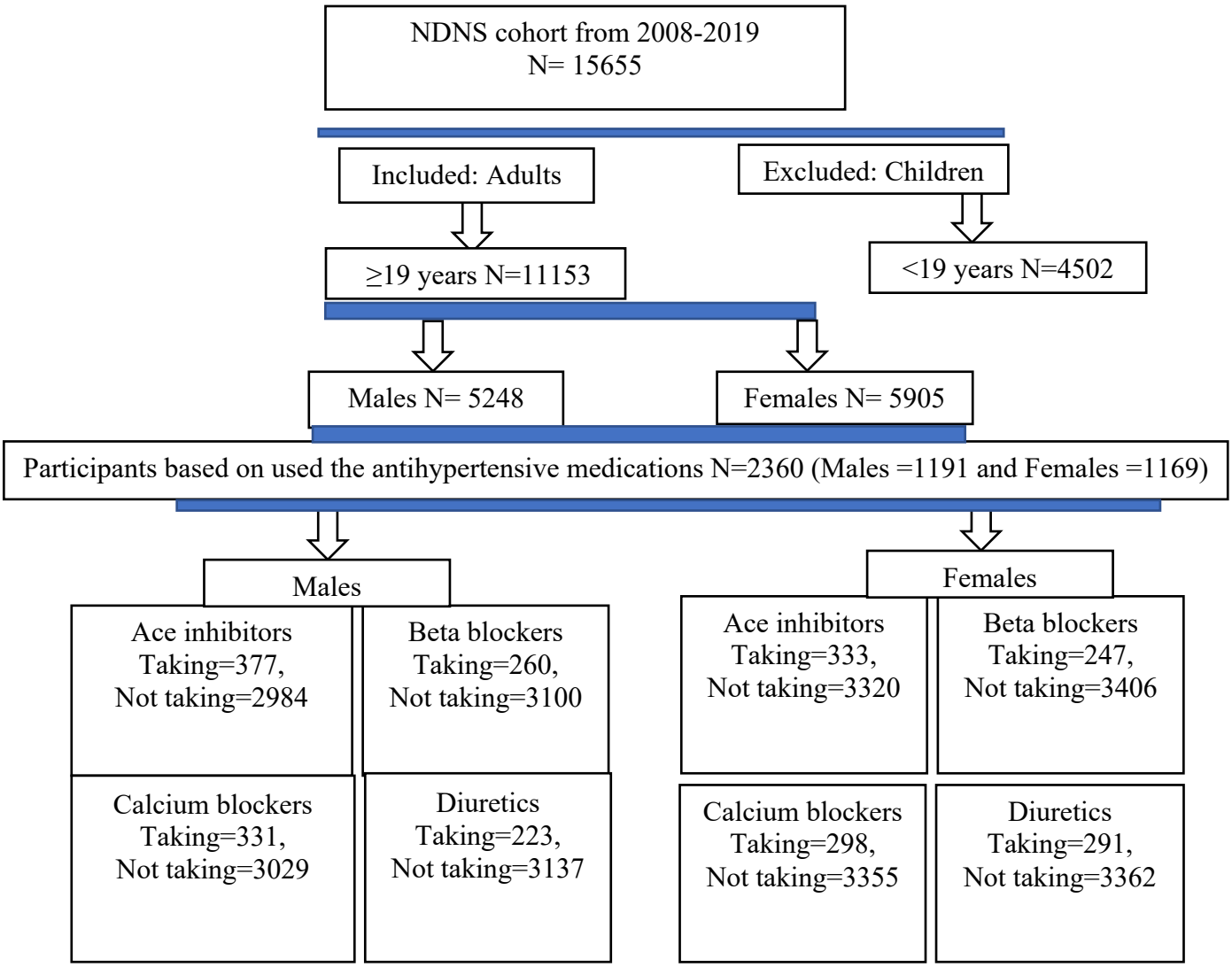


Figure 3.1 displays an overview of a flow diagram of eligible participants in the NDNS data set (years 1–11).

This figure shows that a participant who reported taking more than one drug class (e.g., an ACE inhibitor plus a diuretic) is counted in the "Taking" column for each relevant category. Consequently, the four "Taking" totals do not sum to the overall antihypertensive subgroup (N = 2,360). The "Not taking" category refers to participants who did not use that specific drug class. This discrepancy is expected and reflects routine polypharmacy in the management of hypertension.

3.3.2 Zn Intake and Status by Sex in the Adult Population

Zn intake and levels for males and females over 19 years based on the NDNS dataset are shown in **Table 3.1**. Data are presented across different age groups for males and females, including median Zn intake, percentage below the RNI, Zn levels and percentage of Zn below the reference range.

3.3.2.1 Zn Intake

The median (IQR) intake of Zn across the adult population was higher for males (8.39 mg/day [IQR: 4.03]) compared to females (7.18 mg/day [IQR: 3.21]); however, females were within the RNI, while males fell below it ($p < 0.001$). A large proportion of males over 19 years (64.5%) consumed below the RNI (see **Table 3.1**). This figure was lower in females but nonetheless substantial at 46.6% of the population. For males, intake peaked in the 50–59 age group with a median of 8.84 mg/day (IQR: 4.70), while for females, the highest median intake was reported in the 60–69 age group at 7.62 mg/day (IQR: 3.35). The dashed line in **Figure 3.2** (light blue for males and green for females) represents RNI. The differences in median intake between sexes were statistically significant ($p < 0.001$), and so was the association between sex and Zn intake below the RNI ($p = 0.023$).

Table 3.1 Compares median zinc intake and zinc levels for the participants aged over 19 years according to the National Diet and Nutrition Survey dataset (Years 1–11)

Marker	Sex	Age group (years)							Total	P-value (M vs. F)
		19–29	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**80+**		
Zn intake (mg/day) Median (IQR)	**M**	7.93 (3.97)	8.43 (4.02)	8.39 (4.28)	8.84 (4.70)	8.74 (4.14)	8.22 (3.14)	7.23 (3.36)	**8.39 (4.03)**	<0.001[a]
	F	6.95 (3.03)	7.36 (3.32)	7.13 (3.36)	7.46 (3.29)	7.62 (3.35)	7.03 (2.89)	6.73 (2.84)	**7.18 (3.21)**	
Zn below RNI N (%)	**M**	670 (12.8%)	578 (11%)	606 (11.5%)	527 (10%)	455 (8.7%)	386 (7.4%)	164 (3.1%)	**3,386 (64.5%)**	0.023[b]
	F	534 (9%)	453 (7.7%)	496 (8.4%)	399 (6.8%)	341 (5.8%)	342 (5.8%)	188 (3.2%)	**2,753 (46.6%)**	

Zn levels (µmol/L) Median (IQR)	**M**	13.79 (2.55)	13.65 (2.85)	13.68 (2.47)	13.64 (2.62)	13.16 (2.64)	13.20 (3.06)	12.54 (3.13)	**13.54 (2.63)**	<0.001[a]
	F	12.70 (2.87)	12.91 (2.82)	12.80 (2.57)	13.09 (2.55)	13.20 (2.51)	12.75 (2.15)	12.33 (2.48)	**12.90 (2.69)**	
Zn levels below reference range N (%)	**M**	4 (0.2%)	3 (0.1%)	15 (0.6%)	11 (0.4%)	25 (0.9%)	2 (0.1%)	0	**59 (2.2%)**	<0.001[b]
	F	10 (0.3%)	15 (0.5%)	14 (0.5%)	7 (0.2%)	3 (0.1%)	13 (0.4%)	4 (0.1%)	**66 (2.2%)**	

Milligrams = mg; Micromoles per litre = µmol/L; Number = N; Percentage = %; Interquartile range = IQR; Reference nutrient intake = RNI; Zinc = Zn; Male = M; Female = F. Continuous variables are presented as medians (IQRs), and categorical variables as N (%).

[a] Mann–Whitney U test was used for comparisons involving more than two groups (sex & Zn intake and level).

[b] Differences in the frequency of individuals represented in Zn intake below the RNI and Zn level below reference ranges for sex and age group were tested with Pearson's chi-squared test.

Values with different superscript letters (a and b) indicate significant differences between groups at $p < 0.05$ level.

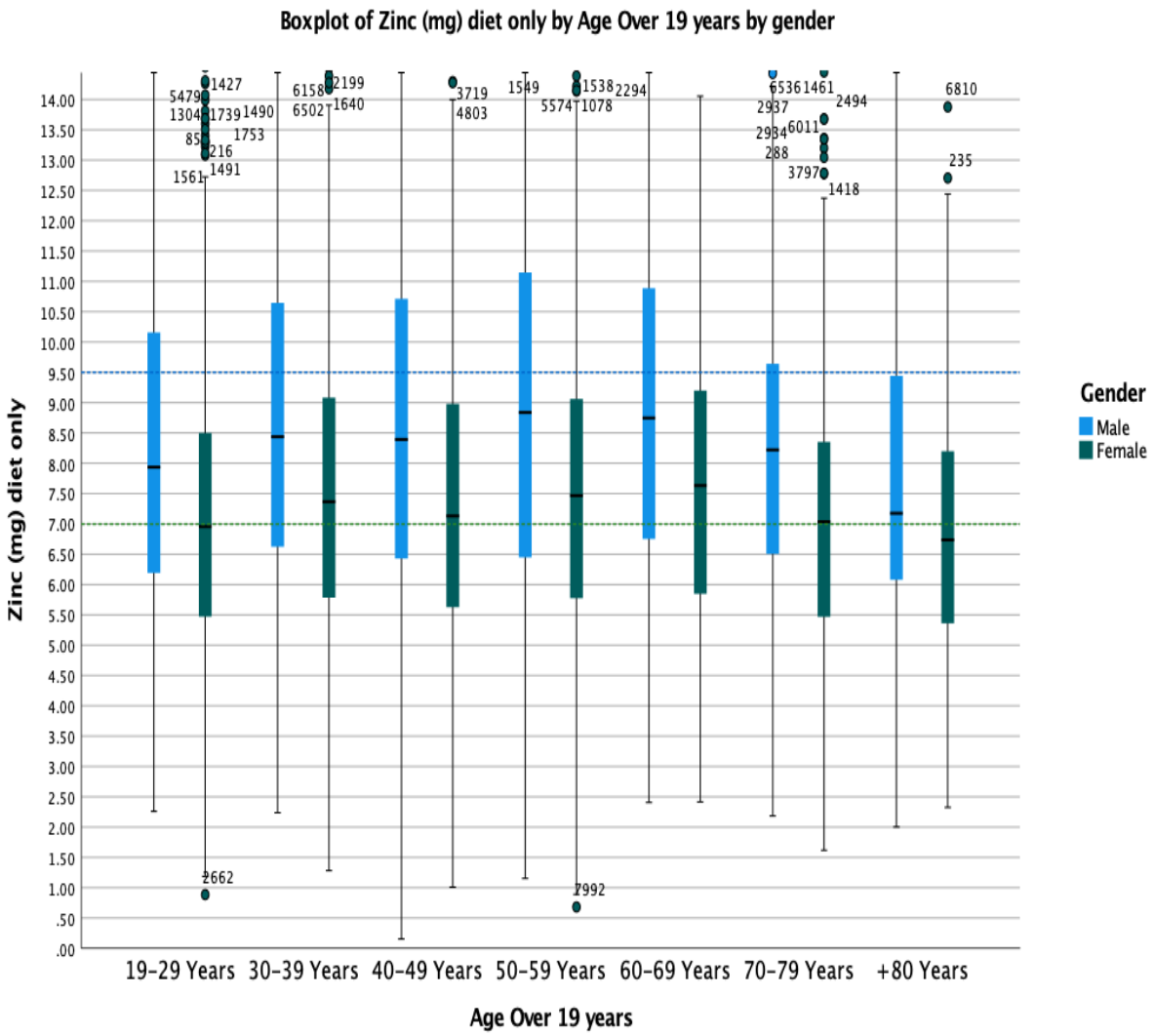


Figure 3.2 Zinc intake for adult participants in the National Diet and Nutrition Survey dataset (Years 1–11).

3.3.2.2 Zn Status

Zn levels remained relatively stable across different age groups, with only minor fluctuations. The median (IQR) concentrations of Zn status across the adult population were 13.54 μmol/L 2.63) for males and 12.90 μmol/L (2.69) for females, with the differences being statistically significant ($p < 0.001$). Regarding Zn levels, males had higher median levels than females in all age groups. The median Zn level for males was highest in the 19–29 age group at 13.79 μmol/L (IQR: 2.55) and lowest in the above 80 age group at 12.54 μmol/L (IQR: 3.13). Females showed the highest median level in the 60–69 age group with 13.20 μmol/L (IQR: 2.51) and the lowest in the above 80 group at 12.33 μmol/L (IQR: 2.48).

While Zn intake varied across age groups, the proportion of individuals with Zn levels below the reference ranges remained consistently low for both genders. This indicates that Zn intake does not necessarily correlate with Zn levels, suggesting that the body may have compensatory mechanisms or that other factors influence Zn status. Zn levels were below the reference ranges for women compared to men. In terms of Zn status, only 4.4% of males and females had plasma Zn levels below the reference range, which was statistically significant ($p < 0.001$; **see Table 3.1**).

3.3.2.3 Age-related differences in zinc intake and status

Analysis of NDNS data (2008–2019) revealed significant differences in dietary zinc intake and serum zinc concentrations across age groups ($p < 0.001$). Among men, median zinc intake decreased from 8.84 mg/day in those aged 50–59 years to 7.23 mg/day in those aged 80+ years, while women showed a similar decline from 7.46 mg/day to 6.73 mg/day. The proportion of participants with intake below the UK RNI increased markedly with age, particularly in men (from 8.7% at 60–69 years to 64.5% at ≥80 years) and women (from 5.8% at 60–69 years to 46.6% at ≥80 years) ($p = 0.023$). Serum zinc concentrations also declined with age, from 13.64 μmol/L in men aged 50–59 years to 12.54 μmol/L at ≥80 years, and from 13.09 μmol/L to 12.33 μmol/L in women. The prevalence of serum zinc levels below the reference range, although low overall, was highest in the oldest age groups (2.2% in both sexes).

3.3.2.4 Correlation Between Zn Intake and Zn Status

The results of correlation coefficient between dietary Zn and Zn status are presented in **Table 3.2**. There were positive correlations between dietary Zn intakes and Zn status that were statistically significant ($p < 0.001$). A Spearman's rank-order correlation was conducted to assess the relationship between dietary Zn intake (mg) and serum Zn concentration (μmol/L). There was a weak but statistically significant positive correlation between the two variables ($rs = 0.078$, $p < 0.001$), indicating that as dietary Zn intake increases, serum Zn levels tend to increase slightly. The analysis included 10,785 observations for dietary Zn and 5,467 paired observations for serum Zn levels. This correlation, although weak, suggests a potential relationship between dietary intake and serum Zn levels.

Table 3.2 Correlation between dietary zinc intake and zinc levels

Nutrients	**Blood measurements**	**Spearman correlation (r)**	**Significance (p)**
Dietary zinc	Zinc levels	0.078	$p < 0.001$

3.3.3 Antihypertensive Medication Patterns Among UK Adults

We next assessed the relationship between Zn intake, Zn status and usage of different classes of antihypertensive drugs among participants aged 19 years and over in the NDNS dataset spanning Years 1–11. In the current study, medication consumption patterns revealed that most participants who consumed antihypertensive medications predominantly consumed ACE inhibitors, followed by CCBs ($p < 0.05$; **Table 3.4**). The results indicated that more males (n = 377) took ACE inhibitors than females (n = 333). Conversely, more females (n = 291) took diuretics than males (n = 223). It was noted that participants' drug consumption doubled when comparing the 40–49 age group to the 50–59 age group and continued to increase in the older age groups.

Furthermore, it was observed that the consumption of antihypertensive drugs was associated with significant lower Zn intakes in both genders. A larger proportion of male participants taking antihypertensive drugs had Zn intakes below the RNI compared to female participants. Contrary to the trend observed in males, a higher proportion of females taking blood pressure medications were able to achieve the RNI for Zn. Regarding Zn status, most participants had Zn levels within the reference range, However, more males taking ACE inhibitors had Zn levels below the reference range compared to females ($p = 0.029$; see **Table 3.3**).

A chi-square analysis was conducted to compare males and females in different age groups for various drugs. However, the analysis was limited to individuals aged 50 and above because including younger age groups resulted in an insufficient sample size, making the analysis inappropriate. Therefore, younger age groups were excluded from this analysis.

In **Tables 3.5 and 3.6**, percentages are used to represent the proportion of individuals according to their Zn intake or Zn levels, categorised by whether they were taking antihypertensive drugs or not and further by sex and age group. Each percentage represents the proportion of individuals within a specific subgroup, making it easier to interpret patterns and compare the nutritional status of different demographic groups. The percentages were calculated by dividing the number of individuals in a specific category (e.g. 'Achieve RNI' or 'Below RNI') by the total number of individuals in the same category for a given sex, age group and drug status and then multiplying by 100.

3.3.3.1 ACE Inhibitors

We observed a significant difference in ACE inhibitor consumption and Zn intake across different groups, while Zn status did not show a significant variation. There was a notable increase in ACE inhibitor usage with age, with the highest use observed in those over 50 years. The overall distribution indicated a statistically significant difference ($p = 0.002$) in the association of sex with ACE inhibitor treatment, with more males taking them compared to females (**Table 3.4**). Among those taking ACE inhibitors, females generally had a higher percentage of achieving the RNI for Zn compared to males, particularly in the older age groups, suggesting a positive association between the medication and Zn intake. A significantly higher proportion of males had Zn intake below the RNI compared to females for taking ACE inhibitors (63.6% vs 36.4%, $p = 0.002$; **Table 3.3**). Male subjects taking ACE inhibitors or not indicated a statistically significant in Zn intake but not in Zn status ($p = 0.001$ and 0.143, respectively). However, in female subjects, no significant difference was observed ($p = 0.860$ and 0.641; **Table 3.5 and 3.6**). The plasma Zn status appeared to be positively influenced by ACE inhibitor usage, as participants taking the medication were more likely to have Zn levels within the reference range compared to those not taking the medication. For those taking ACE inhibitors, 53.9% of males had Zn levels within the reference range, compared to 46.1% of

females. However, the difference was not statistically significant for either sex (p = 0.143 for males and p = 0.641 for females).

3.3.3.2 Beta-blockers

Beta-blocker usage increased with age, peaking in the 70–79 years group for both genders. Among those, 51.3% were males and 48.7% females (p = 0.007). Across all age groups, females generally demonstrated superior Zn intake relative to the RNI, especially among non-beta-blocker users. Regarding Zn intake, 35.7% of males and 64.3% of females on beta-blockers achieved the RNI. The 70–79 age group exhibited the most significant disparities – with females overtaking males in achieving Zn RNI, particularly among those not consuming beta-blockers (see **Table 3.3**). The difference in Zn levels with beta-blockers was not statistically significant for males (p = 0.340) or females (p = 0.192). We observed a consistent pattern indicating that females maintained higher adherence to Zn status reference ranges compared to males, regardless of beta-blocker usage (see **Tables 3.5 and 3.6**).

3.3.3.3 CCBs

A significant increase in CCB usage was observed with advancing age, reaching a peak in males aged 60–69 years and females aged 70–79 years. Across all demographic groups, females consistently achieved a higher percentage of the RNI for Zn compared to males, especially among those not taking CCBs (see **Table 3.5 and 3.6**). There was no significant difference in Zn intake or serum Zn levels between participants taking CCBs and those not taking them. For example, in the male cohort, 54.4% of those taking CCBs had serum Zn levels within the reference range, compared to 45.6% of females. The p-value for males was 0.676 and for females was 0.521. This lack of difference suggests that CCBs may not influence Zn intake or serum levels in this cohort. This contrasts with other drug groups, where significant differences in Zn intake were observed. One possible explanation is that the pharmacological mechanism of CCBs might have a limited impact on Zn metabolism compared to other

antihypertensive drugs. Understanding these unique characteristics could provide insights into the relationship between CCB usage and nutrient intake.

3.3.3.4 Diuretics

Diuretic use was distinctly higher in females across most age groups, with the greatest discrepancy appearing in the 70–79 age bracket (females at 16.3% vs. males at 14.0%). A notable number of diuretic users, especially among older females, achieved the RNI (females at 70.3% vs. males at 29.7%). When analysing Zn intake in relation to the RNI, females generally had higher levels of Zn intake than males, especially in the 70–79 age group. Among participants taking diuretics, a larger proportion – 54.8% of males and 45.2% of females – had intakes below the RNI. Among those using diuretics, 42.2% of males and 57.8% of females had serum Zn levels within the reference range. A significantly higher proportion of males (78.8%) had levels below the reference range ($p = 0.034$), compared to 21.2% of females ($p = 0.240$), indicating that diuretic usage may not have the same impact on Zn levels in females as it does in males (see **Tables 3.5 and 3.6**). This trend is further reflected in adherence to Zn status reference ranges, with females demonstrating better overall adherence than males.

Table 3.3 Zinc intake and levels with antihypertensive drugs for males and females aged ≥50 years according to the National Diet and Nutrition Survey dataset (Years 1–11)

Marker	Sex	Antihypertensive drugs (N [%])											
		ACE inhibitors		P-value	Beta-blockers		P-value	Calcium channel blockers		P-value	Diuretics		P-value
		Taking	Not taking		Taking	Not taking		Taking	Not taking		Taking	Not taking	
Zn intake Achieve RNI	M	99 (2.8%)	510 (14.6%)		75 (2.1%)	534 (15.3%)		109 (3.1%)	500 (14.3%)		60 (1.7%)	549 (15.7%)	
	F	170 (4.9%)	843 (24.1%)	0.783	128 (3.7%)	885 (25.4%)	0.850	153 (4.4%)	860 (24.6%)	0.139	139 (4.0%)	874 (25.0%)	0.021*
Zn intake Below RNI	M	244 (7.0%)	801 (22.9%)		146 (4.2%)	899 (25.8%)		184 (5.3%)	861 (24.7%)		142 (4.1%)	903 (25.9%)	
	F	141 (4.0%)	684 (19.6%)	0.001*	88 (2.5%)	737 (21.1%)	0.032*	106 (3.0%)	718 (20.6%)	0.005*	111 (3.2%)	713 (20.4%)	0.941

Zn levels In reference range	**M**	223 (9.0%)	897 (36.1%)	0.004*	112 (4.5%)	1,007 (40.6%)	0.439	180 (7.2%)	940 (37.9%)	0.007*	115 (4.6%)	1,005 (40.5%)	0.315
	F	200 (8.0%)	1,099 (44.3%)		118 (4.8%)	1,181 (47.6%)		159 (6.4%)	1,140 (46.0%)		150 (6.0%)	1,149 (46.3%)	
Zn levels Below reference range	**M**	11 (0.4%)	26 (1.1%)	0.101	0 (0.0%)	37 (1.5%)	N/A	5 (0.2%)	32 (1.3%)	0.501	8 (0.3%)	30 (1.2%)	0.058
	F	3 (0.1%)	22 (0.9%)		0 (0.0%)	25 (1.0%)		2 (0.1%)	23 (0.9%)		1 (0.1%)	24 (0.9%)	

Number = N; Percentage = %; Reference nutrient intake = RNI; Zinc = Zn; Male = M; Female = F. Categorical variables are presented as N (%). A chi-square test of independence was used to examine whether there is a significant association between two categorical variables. Differences in the frequency of individuals represented in Zn intake and status for sex and antihypertensive drugs were tested with Pearson's chi-squared test (* significant at the $p < 0.05$ level). N/A indicates test not performed due to zero cell count.

Table 3.4 Participants aged over 19 years taking antihypertensive drugs according to the National Diet and Nutrition Survey dataset

Taking antihypertensive drugs, N (%)	Sex	Age group (years)							Total	P-value
		19–29	30–39	40–49	50–59	60–69	70–79	80+		
ACE inhibitors	M	0 (0.0%)	9 (1.2%)	25 (3.6%)	104 (14.6%)	103 (14.6%)	98 (13.8%)	38 (5.3%)	**377 (53.1%)**	0.002*
	F	3 (0.5%)	3 (0.5%)	15 (2.2%)	55 (7.8%)	104 (14.6%)	102 (14.3%)	50 (7.0%)	**333 (46.9%)**	
Beta-blockers	M	7 (1.4%)	11 (2.1%)	22 (4.4%)	52 (10.3%)	63 (12.4%)	80 (15.7%)	26 (5.1%)	**260 (51.3%)**	0.007*
	F	7 (1.5%)	10 (1.9%)	14 (2.7%)	38 (7.5%)	49 (9.7%)	78 (15.4%)	51 (10.0%)	**247 (48.7%)**	
Calcium channel blockers	M	3 (0.5%)	11 (1.7%)	25 (4.0%)	72 (11.4%)	92 (14.6%)	89 (14.2%)	40 (6.4%)	**331 (52.6%)**	<0.001*
	F	6 (1.0%)	10 (1.6%)	23 (3.6%)	49 (7.8%)	57 (9.0%)	84 (13.4%)	69 (11.0%)	**298 (47.4%)**	
Diuretics	M	5 (0.9%)	6 (1.1%)	11 (2.1%)	48 (9.3%)	62 (12.1%)	72 (14.0%)	20 (3.9%)	**223 (43.4%)**	<0.001*
	F	7 (1.3%)	17 (3.3%)	17 (3.2%)	34 (6.7%)	67 (13.0%)	84 (16.3%)	66 (12.8%)	**291 (56.6%)**	

ACE: Angiotensin-Converting Enzyme inhibitors; Number = N; Percentage = %; Male = M; Female = F. Categorical variables are presented as N (%). A chi-square test of independence was used to examine whether there is a significant association between two categorical variables (analysis was limited to individuals aged 50 and above because including younger age groups resulted in an insufficient sample size).

* Significant at the $p < 0.05$ level.

Table 3.5 Zinc intake with consuming antihypertensive drugs for males and females aged over 19 years in the National Diet and Nutrition Survey dataset

Antihypertensive drugs, N (%)		Zn intake	Sex	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
ACE inhibitors	Taking	Achieve RNI	M	0 (0.0%)	5 (0.1%)	6 (0.1%)	30 (0.4%)	30 (0.4%)	32 (0.5%)	7 (0.1%)	110 (1.6%)	0.001*
		Below RNI		0 (0.0%)	4 (0.1%)	20 (0.3%)	74 (1.1%)	73 (1.0%)	66 (0.9%)	31 (0.4%)	267 (3.8%)	
	Not taking	Achieve RNI		157 (2.2%)	189 (2.7%)	208 (3.0%)	216 (3.1%)	200 (2.8%)	67 (1.0%)	28 (0.4%)	1,064 (15.2%)	
		Below RNI		390 (5.6%)	352 (5.0%)	376(5.4%)	301 (4.3%)	247 (3.5%)	190 (2.7%)	63 (0.9%)	1,919 (27.4%)	
	Taking	Achieve RNI	F	3 (0.0%)	1 (0.0%)	6 (0.1%)	42 (0.6%)	59 (0.8%)	55 (0.8%)	14 (0.2%)	180 (2.5%)	0.860
		Below RNI		0 (0.0%)	3 (0.0%)	9 (0.1%)	14 (0.2%)	45 (0.6%)	46 (0.7%)	36 (0.5%)	153 (2.1%)	
	Not taking	Achieve RNI		285 (4.1%)	315 (4.5%)	350 (5.0%)	325 (4.6%)	262 (3.7%)	184 (2.6%)	71 (1.0%)	1,793 (25.5%)	
		Below RNI		283 (4.0%)	253 (3.6%)	307(4.4%)	250 (3.6%)	192 (2.7%)	152 (2.2%)	90 (1.3%)	1,527 (21.8%)	

Beta blockers	Taking	Achieve RNI	M	2 (0.0%)	2 (0.0%)	5 (0.1%)	27 (0.4%)	16 (0.2%)	23 (0.3%)	9 (0.1%)	83 (1.1%)	
		Below RNI		5 (0.1%)	9 (0.1%)	18 (0.2%)	25 (0.4%)	46 (0.7%)	57 (0.8%)	17 (0.2%)	177 (2.5%)	
	Not taking	Achieve RNI		156 (2.2%)	192 (2.7%)	209 (3.0%)	219 (3.1%)	213 (3.0%)	76 (1.1%)	26 (0.4%)	1,091 (15.5%)	0.340
		Below RNI		385 (5.5%)	347 (4.9%)	378 (5.4%)	350 (5.0%)	274 (3.9%)	199 (2.8%)	77 (1.1%)	2,009 (28.6%)	
	Taking	Achieve RNI	F	5 (0.1%)	7 (0.1%)	11 (0.2%)	25 (0.4%)	27 (0.4%)	49 (0.7%)	28 (0.4%)	150 (2.3%)	
		Below RNI		3 (0.0%)	3 (0.0%)	3 (0.0%)	13 (0.2%)	22 (0.3%)	29 (0.4%)	23 (0.3%)	97 (1.2%)	
	Not taking	Achieve RNI		284 (4.0%)	309 (4.4%)	346 (4.9%)	342 (4.9%)	294 (4.2%)	191 (2.7%)	58 (0.8%)	1,824 (25.9%)	0.192
		Below RNI		280 (4.0%)	253 (3.6%)	313 (4.5%)	251 (3.6%)	214 (3.1%)	169 (2.4%)	102 (1.5%)	1,582 (22.7%)	
Calcium channel blockers	Taking	Achieve RNI	M	1 (0.0%)	0 (0.0%)	3 (0.0%)	35 (0.5%)	42 (0.6%)	20 (0.3%)	12 (0.2%)	113 (1.6%)	
		Below RNI		2 (0.0%)	11 (0.1%)	22 (0.3%)	36 (0.5%)	50 (0.7%)	70 (1.0%)	28 (0.4%)	218 (3.0%)	0.881
	Not taking	Achieve RNI		157 (2.2%)	194 (2.8%)	210 (3.0%)	210 (3.0%)	188 (2.7%)	79 (1.1%)	23 (0.3%)	1,061 (15.1%)	

		Below RNI		388 (5.5%)	345 (4.9%)	374 (5.3%)	339 (4.8%)	271 (3.9%)	186 (2.6%)	66 (0.9%)	1,968 (27.9%)	
	Taking	Achieve RNI	F	2 (0.0%)	9 (0.1%)	10 (0.1%)	39 (0.6%)	30 (0.4%)	49 (0.7%)	34 (0.5%)	173 (2.4%)	0.170
		Below RNI		5 (0.1%)	1 (0.0%)	13 (0.2%)	10 (0.1%)	27 (0.4%)	35 (0.5%)	35 (0.5%)	125 (1.8%)	
	Not taking	Achieve RNI		287 (4.1%)	307 (4.4%)	347 (4.9%)	328 (4.7%)	291 (4.2%)	190 (2.7%)	51 (0.7%)	1,801 (25.7%)	
		Below RNI		278 (4.0%)	255 (3.6%)	303 (4.3%)	254 (3.6%)	210 (3.0%)	164 (2.3%)	90 (1.3%)	1,554 (22.1%)	
Diuretics	Taking	Achieve RNI	M	2 (0.0%)	3 (0.0%)	4 (0.1%)	19 (0.3%)	22 (0.3%)	15 (0.2%)	4 (0.1%)	69 (1.0%)	0.025
		Below RNI		3 (0.0%)	3 (0.0%)	6 (0.1%)	29 (0.4%)	40 (0.6%)	57 (0.8%)	16 (0.2%)	154 (2.1%)	
	Not taking	Achieve RNI		156 (2.2%)	191 (2.7%)	210 (3.0%)	226 (3.2%)	208 (3.0%)	84 (1.2%)	31 (0.4%)	1,105 (15.7%)	
		Below RNI		387 (5.5%)	353 (5.0%)	389 (5.5%)	346 (4.9%)	280 (4.0%)	198 (2.8%)	78 (1.1%)	2,033 (28.8%)	
	Taking	Achieve RNI	F	3 (0.0%)	12 (0.2%)	10 (0.1%)	26 (0.4%)	36 (0.5%)	52 (0.7%)	25 (0.4%)	164 (2.3%)	0.876
		Below RNI		3 (0.0%)	5 (0.1%)	7 (0.1%)	8 (0.1%)	31 (0.4%)	32 (0.4%)	41 (0.6%)	127 (1.7%)	

	Not taking	Achieve RNI		285 (4.1%)	305 (4.3%)	346 (4.9%)	341 (4.9%)	285 (4.1%)	187 (2.7%)	61 (0.9%)	1,810 (25.9%)	
		Below RNI		280 (4.0%)	250 (3.6%)	309 (4.4%)	256 (3.6%)	206 (2.9%)	167 (2.4%)	84 (1.2%)	1,552 (22.1%)	

Number = N; Percentage = %; Reference nutrient intake = RNI; Zinc = Zn; Male = M; Female = F.

A chi-square test of independence was used to examine whether there is a significant association between two categorical variables (analysis was limited to individuals aged 50 and above because including younger age groups resulted in an insufficient sample size).

* Significant at the $p < 0.05$ level.

Table 3.6 Zinc levels with consuming antihypertensive drugs for males and females aged over 19 years in the National Diet and Nutrition Survey dataset

Antihypertensive drugs, N (%)		**Zn levels**	**Sex**	**Age group (years)**								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
ACE inhibitors	Taking	In reference range	M	0 (0.0%)	7 (0.1%)	22 (0.5%)	85 (1.7%)	55 (1.1%)	58 (1.2%)	25 (0.5%)	252 (5.1%)	0.143
		Below reference range		0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.1%)	7 (0.1%)	0 (0.0%)	0 (0.0%)	11 (0.2%)	
	Not taking	In reference range		337 (6.8%)	391 (7.9%)	418 (8.5%)	378 (7.7%)	304 (6.2%)	160 (3.2%)	55 (1.1%)	2,043 (41.4%)	
		Below reference range		4 (0.1%)	2 (0.0%)	15 (0.3%)	6 (0.1%)	18 (0.4%)	2 (0.0%)	0 (0.0%)	46 (0.9%)	
	Taking	In reference range	F	3 (0.1%)	1 (0.0%)	12 (0.2%)	40 (0.8%)	72 (1.5%)	61 (1.2%)	26 (0.5%)	216 (4.3%)	0.641
		Below reference range		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	3 (0.1%)	0 (0.0%)	3 (0.1%)	

	Not taking	In reference range		352 (7.1%)	387 (7.8%)	476 (9.6%)	431 (8.7%)	323 (6.6%)	239 (4.8%)	105 (2.1%)	2,315 (46.7%)	
		Below reference range		10 (0.2%)	8 (0.2%)	12 (0.2%)	7 (0.1%)	1 (0.0%)	10 (0.2%)	3 (0.1%)	51 (1.0%)	
Beta-blockers	Taking	In reference range	M	7 (0.1%)	11 (0.2%)	12 (0.2%)	37 (0.8%)	34 (0.7%)	28 (0.6%)	13 (0.3%)	142 (2.9%)	0.043*
		Below reference range		0 (0.0%)	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	
	Not taking	In reference range		330 (6.7%)	387 (7.8%)	428 (8.7%)	426 (8.6%)	326 (6.6%)	189 (3.8%)	67 (1.4%)	2,153 (43.6%)	
		Below reference range		4 (0.1%)	2 (0.0%)	11 (0.2%)	11 (0.2%)	25 (0.5%)	2 (0.0%)	0 (0.0%)	54 (1.0%)	
	Taking	In reference range	F	7 (0.1%)	7 (0.1%)	7 (0.1%)	26 (0.5%)	25 (0.5%)	38 (0.8%)	29 (0.6%)	138 (2.7%)	0.114
		Below reference range		1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	

	Not taking	In reference range		349 (7.1%)	381 (7.7%)	481 (9.8%)	445 (9.0%)	371 (7.5%)	262 (5.3%)	103 (2.1%)	2,392 (48.5%)	
		Below reference range		9 (0.2%)	8 (0.2%)	12 (0.2%)	7 (0.1%)	2 (0.0%)	13 (0.3%)	3 (0.1%)	54 (1.1%)	
Calcium channel blockers	Taking	In reference range	M	3 (0.1%)	10 (0.2%)	18 (0.4%)	52 (1.1%)	49 (1.0%)	55 (1.1%)	24 (0.5%)	210 (4.4%)	0.676
		Below reference range		0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.1%)	
	Not taking	In reference range		334 (6.8%)	388 (7.9%)	422 (8.6%)	410 (8.3%)	311 (6.3%)	162 (3.3%)	56 (1.1%)	2,084 (42.3%)	
		Below reference range		4 (0.1%)	2 (0.0%)	15 (0.3%)	8 (0.2%)	23 (0.5%)	2 (0.0%)	0 (0.0%)	52 (1.1%)	
	Taking	In reference range	F	4 (0.1%)	3 (0.1%)	11 (0.2%)	37 (0.7%)	34 (0.7%)	53 (1.1%)	35 (0.7%)	176 (3.6%)	0.521
		Below reference range		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.0%)	3 (0.0%)	

	Not taking	In reference range		351 (7.1%)	385 (7.8%)	477 (9.7%)	434 (8.8%)	362 (7.3%)	248 (5.0%)	96 (2.0%)	2,354 (47.7%)	
		Below reference range		10 (0.2%)	8 (0.2%)	12 (0.2%)	7 (0.1%)	1 (0.0%)	13 (0.3%)	2 (0.0%)	52 (1.0%)	
Diuretics	Taking	In reference range	M	5 (0.1%)	3 (0.1%)	5 (0.1%)	34 (0.7%)	35 (0.7%)	33 (0.7%)	12 (0.3%)	127 (2.7%)	0.034*
		Below reference range		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.2%)	0 (0.0%)	0 (0.0%)	8 (0.2%)	
	Not taking	In reference range		332 (6.7%)	395 (8.0%)	435 (8.8%)	429 (8.7%)	324 (6.6%)	185 (3.7%)	67 (1.4%)	2,168 (43.9%)	
		Below reference range		4 (0.1%)	2 (0.0%)	15 (0.3%)	11 (0.2%)	17 (0.3%)	2 (0.0%)	0 (0.0%)	50 (0.9%)	
	Taking	In reference range	F	5 (0.1%)	11 (0.2%)	8 (0.2%)	21 (0.4%)	38 (0.8%)	60 (1.2%)	31 (0.6%)	174 (3.5%)	0.240
		Below reference range		1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	2 (0.0%)	

	Not taking	In reference range		350 (7.1%)	377 (7.6%)	480 (9.7%)	450 (9.1%)	358 (7.2%)	240 (4.9%)	101 (2.0%)	2,356 (47.6%)	
		Below reference range		9 (0.2%)	8 (0.2%)	12 (0.2%)	7 (0.1%)	2 (0.0%)	13 (0.3%)	2 (0.0%)	52 (1.0%)	

Number = N; Percentage = %; Reference nutrient intake = RNI; Zinc = Zn; Male = M; Female = F.

A chi-square test of independence was used to examine whether there is a significant association between two categorical variables (analysis was limited to individuals aged 50 and above because including younger age groups resulted in an insufficient sample size).

* Significant at the $p < 0.05$ level.

3.3.4 Measurements of Haematological Markers

Assessing Zn's Contribution to Blood Analyte Levels in Patients Taking Antihypertensive drugs

Circulating biomarkers of health were compared across different age groups for males and females taking various antihypertensive drugs. The blood analytes considered were white blood cell (WBC) count, red blood cell (RBC) count, C-reactive protein (CRP), haemoglobin, haematocrit and mean cell volume (MCV). These blood analytes were evaluated to determine their association with the health outcomes observed in the study population.

3.3.4.1 WBC Count

The WBC reference range is 3.6–11.0 × 10^9/L, which serves as an indicator of immune status and reflects potential infections or inflammatory conditions (NHS Foundation Trust, 2024). The median WBC counts showed minor variations across age groups for both males and females. Overall, the median WBC count was higher for participants taking antihypertensive drugs who achieved the RNI for Zn compared to those with intakes below the RNI, for both genders. A trend analysis revealed no consistent pattern between Zn intake and WBC counts, as variations depended on the type of antihypertensive drug and the sex of the participants. Most differences in WBC counts were not statistically significant; however, there were two notable exceptions. Males taking beta-blockers had a significantly higher median WBC count compared to males not taking beta-blockers ($p = 0.041$), indicating that beta-blocker usage is associated with increased WBC counts. Similarly, males taking diuretics also had significantly higher WBC counts compared to nonusers ($p = 0.029$). These findings suggest that antihypertensive drugs, particularly beta-blockers and diuretics, may be linked to elevated WBC counts in males. The impact of these drugs on WBC counts appears to be influenced by

Zn intake, as the differences were more pronounced in males who did not meet the RNI for Zn. When dietary Zn intake met or exceeded the RNI, the effect of these drugs on WBC counts seemed to diminish. This suggests that achieving adequate Zn intake may potentially mitigate the impact of certain antihypertensive drugs on WBC counts (see **Table 3.7**).

Table 3.7 Effect of zinc intake with antihypertensive drugs on white blood cell count for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
White Blood Cell Count (10^9/L)	M	ACE inhibitors	Achieve RNI	N/A	7.8 (0.1; 5)	5.7 (2.4; 6)	6.1 (3.1; 30)	8.1 (4.0; 30)	4.9 (1.4; 32)	6.0 (1.2; 7)	6.0 (2.7; 110)	0.277
			Below RNI	N/A	11.6 (0.0; 4)	7.1 (1.0; 20)	6.0 (2.7; 74)	6.2 (2.4; 73)	5.9 (2.6; 66)	6.4 (1.7; 31)	6.3 (2.4; 267)	
		Beta-blockers	Achieve RNI	5.5 (0.0; 2)	10.9 (0.0; 2)	6.1 (0.0; 5)	5.9 (3.5; 27)	5.7 (0.2; 16)	4.9 (1.1; 23)	6.0 (1.6; 9)	5.8 (1.8; 83)	0.041*
			Below RNI	6.3 (0.2; 5)	7.9 (4.5; 9)	6.5 (1.8; 18)	5.5 (0.5; 25)	6.4 (2.1; 46)	7.2 (2.1; 57)	6.3 (1.3; 17)	6.3 (1.7; 177)	
		Calcium channel blockers	Achieve RNI	10.2 (0.0; 1)	. (0)	5.8 (2.3; 3)	8.2 (1.6; 35)	6.8 (2.3; 42)	4.8 (0.7; 20)	6.0 (0.0; 12)	6.0 (2.6; 113)	0.916
			Below RNI	4.9 (0.0; 2)	7.9 (3.7; 11)	6.3 (1.3; 22)	6.4 (2.0; 36)	6.4 (2.5; 50)	6.3 (2.3; 70)	6.3 (0.6; 28)	6.4 (2.0; 218)	

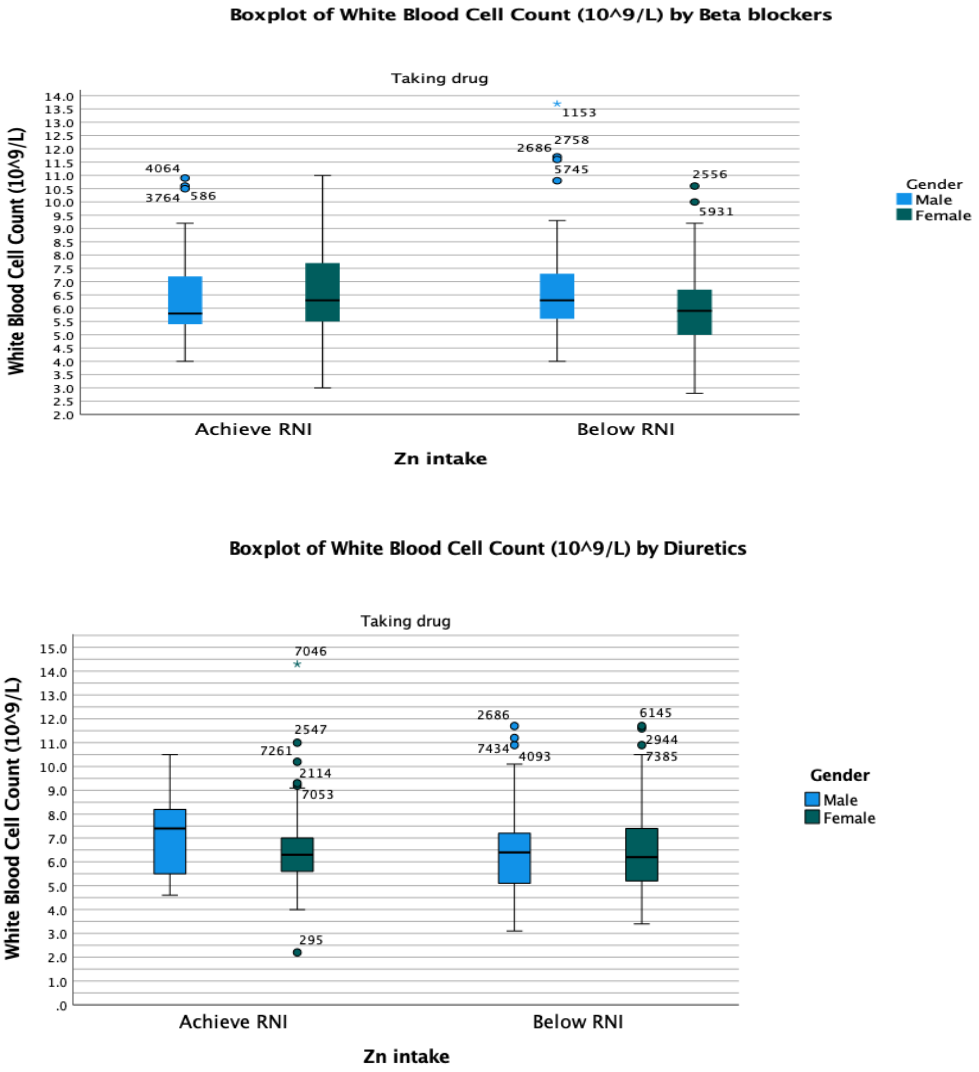
		Diuretics	Achieve RNI	5.5 (0.0; 2)	10.5 (0.0; 3)	5.8 (2.3; 4)	8.2 (2.3; 19)	5.6 (2.8; 22)	5.5 (2.6; 15)	6.8 (5.0; 4)	7.4 (2.7; 69)	0.029*
			Below RNI	6.1 (0.0; 3)	4.8 (1.0; 3)	6.9 (0.0; 6)	6.4 (2.2; 29)	6.4 (3.2; 40)	6.3 (1.2; 57)	7.9 (3.7; 16)	6.4 (2.1; 154)	
	F	ACE inhibitors	Achieve RNI	8.4 (0.0; 3)	4.6 (0.0; 1)	8.6 (1.9; 6)	5.8 (2.0; 42)	6.2 (1.9; 59)	6.3 (1.3; 55)	6.1 (2.9; 14)	6.2 (2.1; 180)	0.443
			Below RNI	N/A	13.8 (0.0; 3)	7.0 (1.0; 9)	7.0 (0.0; 14)	5.7 (1.6; 45)	6.2 (1.6; 46)	5.6 (0.6; 36)	5.8 (1.9; 153)	
		Beta-blockers	Achieve RNI	7.7 (0.0; 5)	6.3 (2.5; 7)	7.6 (1.0; 11)	6.6 (1.9; 25)	6.6 (2.8; 27)	6.1 (1.0; 49)	6.1 (1.9; 28)	6.3 (2.2; 150)	0.082
			Below RNI	7.9 (0.0; 3)	6.6 (3.5; 3)	5.7 (0.0; 3)	5.4 (1.7; 13)	5.7 (0.5; 22)	5.0 (2.9; 29)	6.1 (3.0; 23)	5.9 (1.7; 97)	
		Calcium channel blockers	Achieve RNI	5.0 (0.0; 2)	6.9 (0.0; 9)	6.7 (2.6; 10)	6.6 (1.9; 39)	5.8 (1.5; 30)	5.8 (1.6; 49)	5.6 (1.9; 34)	6.1 (2.1; 173)	0.093
			Below RNI	4.5 (0.0; 5)	13.8 (0.0; 1)	7.7 (4.2; 13)	5.0 (1.0; 10)	6.1 (2.3; 27)	5.8 (1.5; 35)	5.6 (0.3; 35)	5.7 (1.9; 125)	

		Diuretics	Achieve RNI	7.8 (3.0; 3)	5.6 (0.7; 12)	7.3 (1.8; 10)	6.5 (1.2; 26)	6.5 (1.0; 36)	6.7 (2.1; 52)	5.6 (1.1; 25)	6.3 (1.4; 164)	0.446
			Below RNI	6.9 (0.0; 3)	6.0 (1.5; 5)	5.3 (0.0; 7)	4.8 (3.2; 8)	5.7 (1.5; 31)	6.7 (1.4; 32)	5.5 (0.7; 41)	6.2 (2.2; 127)	

ACE: Angiotensin-Converting Enzyme inhibitors; Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.



Figures 3.3 Boxplot of White Blood Cell Count by Beta Blocker and Diuretic Use, Zinc Intake, and Gender in the NDNS Data Set

3.3.4.2 RBC Count

RBC counts typically vary based on gender, with a range of 4.50 to 6.50 x 10^12/L for men and 3.8 to 5.8 x 10^12/L for women, deviations suggesting conditions such as anaemia or polycythaemia (NHS Foundation Trust, 2024). The data indicated notable differences in RBC count across various antihypertensive medication classes in relation to RNI adherence for both males and females (see **Table 3.8**). Males and females on antihypertensive drugs displayed some variation in median RBC counts based on whether they achieved or were below the RNI. For example, diuretics in both males and females produced a reduced RBC count for those below the RNI compared to those achieving the RNI. In males using diuretics, the median RBC count was 4.92 × 10^12/L for those achieving the RNI (n = 69), compared to 4.60 × 10^12/L for those below the RNI (n = 154). Similarly, in females using diuretics, the median RBC count was 4.44 × 10^12/L for RNI achievers (n = 164), compared to 4.40 × 10^12/L for those below the RNI (n = 127). These results suggest a potential interaction between nutrient deficiency and medication response. Although these variations suggest a potential trend, the p-values indicate that Zn intake is not a significant determinant of RBC count in this cohort of antihypertensive drug users.

Table 3.8 Effect of zinc intake with antihypertensive drugs on red blood cell count for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
Red Blood Cell Count (10^12/L)	M	ACE inhibitors	Achieve RNI	N/A	4.70 (0.0; 5)	5.33 (0.04; 6)	4.75 (0.8; 30)	4.97 (0.57; 30)	4.70 (0.17; 32)	4.50 (0.09; 7)	4.75 (0.69; 110)	0.224
			Below RNI	N/A	4.94 (0.0; 4)	5.00 (0.38; 20)	4.90 (0.5; 74)	4.60 (1.0; 73)	4.70 (0.63; 66)	4.40 (0.64; 31)	4.80 (0.64; 267)	
		Beta-blockers	Achieve RNI	4.00 (0.0; 2)	4.49 (0.0; 2)	4.90 (0.0; 5)	4.66 (0.57; 27)	4.70 (0.21; 16)	4.70 (0.22; 23)	4.41 (1.5; 9)	4.66 (0.49; 83)	0.464
			Below RNI	5.26 (0.64; 5)	4.47 (0.76; 9)	4.46 (0.25; 18)	5.00 (0.4; 25)	4.81 (0.3; 46)	4.59 (0.61; 57)	4.00 (0.47; 17)	4.62 (0.60; 177)	
		Calcium channel blockers	Achieve RNI	3.92 (0.0; 1)	0	4.84 (0.0; 3)	4.75 (0.92; 35)	4.96 (0.88; 42)	4.66 (0.12; 20)	4.50 (0.87; 12)	4.80 (0.87; 113)	0.500
			Below RNI	4.71 (0.0; 2)	4.94 (0.8; 11)	5.10 (0.4; 22)	4.94 (0.2; 36)	5.20 (0.5; 50)	4.70 (0.73; 70)	4.10 (1.29; 28)	4.94 (0.59; 218)	

		Diuretics	Achieve RNI	4.00 (0.0; 2)	4.41 (0.0; 3)	4.84 (0.45; 4)	5.06 (0.57; 19)	4.92 (1.3; 22)	4.21 (1.89; 15)	5.00 (0.75; 4)	4.92 (1.24; 69)	0.093
			Below RNI	4.62 (0.0; 3)	4.41 (0.21; 3)	5.65 (0.0; 6)	4.50 (0.64; 29)	4.90 (0.7; 40)	4.60 (0.57; 57)	4.09 (0.47; 16)	4.60 (0.71; 154)	
	F	ACE inhibitors	Achieve RNI	4.65 (0.0; 3)	4.22 (0.0; 1)	4.10 (0.0; 6)	4.35 (0.43; 42)	4.40 (0.41; 59)	4.49 (0.56; 55)	4.20 (0.39; 14)	4.40 (0.46; 180)	0.779
			Below RNI	N/A	4.60 (0.0; 3)	4.60 (0.8; 9)	4.50 (1.02; 14)	4.40 (0.6; 45)	4.40 (0.3; 46)	4.40 (0.58; 36)	4.40 (0.67; 153)	
		Beta-blockers	Achieve RNI	4.90 (0.0; 5)	4.23 (0.43; 7)	4.10 (0.11; 11)	4.50 (0.81; 25)	4.50 (0.41; 27)	4.39 (0.40; 49)	4.20 (1.10; 28)	4.39 (0.48; 150)	0.056
			Below RNI	4.82 (0.0; 3)	4.56 (0.04; 3)	4.50 (0.0; 3)	4.44 (0.16; 13)	4.60 (0.52; 22)	4.50 (0.3; 29)	4.40 (0.65; 23)	4.50 (0.30; 97)	
		Calcium channel blockers	Achieve RNI	4.17 (0.0; 2)	3.89 (0.0; 9)	4.33 (0.0; 10)	4.35 (0.51; 39)	4.50 (0.62; 30)	4.49 (0.33; 49)	4.39 (0.49; 34)	4.40 (0.38; 173)	0.508

			Below RNI	4.66 (0.0; 5)	4.60 (0.0; 1)	4.40 (0.50; 13)	4.20 (0.31; 10)	4.42 (0.48; 27)	4.40 (0.39; 35)	4.40 (0.60; 35)	4.40 (0.40; 125)	
		Diuretics	Achieve RNI	4.43 (0.0; 3)	4.64 (0.08; 12)	3.68 (1.78; 10)	4.71 (1.20; 26)	4.44 (0.34; 36)	4.44 (0.81; 52)	4.30 (0.93; 25)	4.44 (0.61; 164)	0.987
			Below RNI	4.92 (0.0; 3)	4.30 (0.75; 5)	4.40 (0.0; 7)	4.40 (0.55; 8)	4.44 (0.42; 31)	4.40 (0.37; 32)	4.26 (0.76; 41)	4.40 (0.40; 127)	

Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.

3.3.4.3 CRP

CRP is a marker of systemic inflammation, with normal levels generally below 5 mg/L (NHS Foundation Trust, 2022). Elevated CRP levels are associated with acute or chronic inflammatory states and may indicate an ongoing infection or other inflammatory processes. With respect to their Zn intake, we observed varying median CRP levels among participants taking antihypertensive drugs (see **Table 3.9**). In males using beta-blockers, those who achieved the RNI had lower CRP levels across most age groups compared to those below the RNI; however, this difference was not statistically significant ($p = 0.095$). Conversely, for males on diuretics, those achieving the RNI exhibited significantly higher CRP levels, particularly in the 70–79 age group, compared to males on diuretics who did not meet the RNI ($p = 0.004$). This suggests a potential interaction between adequate Zn intake and elevated inflammation markers in this subgroup of diuretic users. For females, there was a nonsignificant trend of higher CRP levels in those below the RNI on diuretics. Overall, females displayed consistently higher CRP values than males across most age groups, indicating potential sex-related differences in inflammatory response in the context of Zn intake and antihypertensive drug use.

Table 3.9 Effect of zinc intake with antihypertensive drugs on C-reactive protein for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
C-Reactive Protein (mg/L)	M	ACE inhibitors	Achieve RNI	N/A	3.52 (0.0; 5)	1.37 (0.59; 6)	5.28 (6.93; 30)	2.36 (4.28; 30)	2.18 (12.12; 32)	3.01 (1.81; 7)	2.64 (5.03; 110)	0.092
			Below RNI	N/A	2.69 (0.0; 4)	1.74 (2.79; 20)	2.13 (2.54; 74)	1.72 (3.15; 73)	1.66 (1.94; 66)	2.30 (1.93; 31)	1.90 (2.36; 267)	
		Beta blockers	Achieve RNI	1.33 (0.0; 2)	5.88 (0.0; 2)	4.89 (0.0; 5)	2.27 (1.45; 27)	2.00 (1.06; 16)	2.23 (1.51; 23)	1.39 (0.19; 9)	2.00 (1.31; 83)	0.095
			Below RNI	4.32 (2.39; 5)	2.69 (2.58; 9)	0.78 (2.48; 18)	1.58 (1.60; 25)	1.60 (0.62; 46)	4.10 (3.80; 57)	3.47 (0.56; 17)	2.20 (2.90; 177)	
		Calcium channel blockers	Achieve RNI	1.43 (0.0; 1)	N/A	10.82 (8.13; 3)	2.90 (7.25; 35)	2.36 (2.90; 42)	2.23 (2.90; 20)	2.19 (1.62; 12)	2.36 (2.77; 113)	0.495
			Below RNI	1.15 (0.0; 2)	3.29 (5.04; 11)	3.57 (3.56; 22)	1.70 (1.45; 36)	1.98 (3.67; 50)	2.70 (2.94; 70)	3.47 (10.50; 28)	2.55 (3.51; 218)	

		Diuretics	Achieve RNI	1.33 (0.0; 2)	11.89 (0.0; 3)	10.82 (8.13; 4)	2.90 (3.09; 19)	2.53 (3.74; 22)	16.83 (17.02; 15)	2.99 (2.40; 4)	2.99 (4.31; 69)	0.004*
			Below RNI	1.93 (0.84; 3)	4.13 (0.0; 3)	7.09 (0.0; 6)	1.60 (0.33; 29)	1.96 (1.17; 40)	2.31 (4.36; 57)	4.50 (3.23; 16)	1.96 (2.45; 154)	
	F	ACE inhibitors	Achieve RNI	17.68 (0.0; 3)	0.78 (0.0; 1)	11.40 (9.63; 6)	2.11 (2.41; 42)	2.90 (4.04; 59)	2.69 (8.05; 55)	3.49 (3.76; 14)	2.71 (4.21; 180)	0.457
			Below RNI	N/A	7.70 (0.0; 3)	6.49 (6.09; 9)	10.80 (17.94; 14)	3.09 (3.57; 45)	2.37 (10.22; 46)	3.10 (3.53; 36)	3.10 (5.72; 153)	
		Beta blockers	Achieve RNI	10.20 (0.0; 5)	2.16 (6.93; 7)	11.40 (14.89; 11)	2.11 (9.45; 25)	1.82 (1.51; 27)	2.69 (3.11; 49)	3.49 (6.83; 28)	2.29 (6.89; 150)	0.446
			Below RNI	6.89 (0.0; 3)	1.83 (0.95; 3)	3.20 (0.0; 3)	1.48 (7.91; 13)	2.97 (2.37; 22)	2.10 (3.02; 29)	2.87 (0.23; 23)	2.87 (2.48; 97)	
		Calcium channel blockers	Achieve RNI	0.71 (0.0; 2)	2.61 (0.0; 9)	10.72 (13.28; 10)	2.00 (9.72; 39)	2.80 (4.58; 30)	2.04 (1.19; 49)	2.37 (2.20; 34)	2.33 (3.10; 173)	0.202

			Below RNI	1.47 (0.0; 5)	7.70 (0.0; 1)	6.49 (2.70; 13)	3.02 (7.78; 10)	3.44 (3.17; 27)	1.78 (8.45; 35)	3.60 (4.30; 35)	3.12 (4.64; 125)	
		Diuretics	Achieve RNI	1.74 (1.03; 3)	2.16 (0.99; 12)	5.25 (1.71; 10)	4.10 (9.45; 26)	2.80 (1.52; 36)	3.84 (10.32; 52)	3.49 (2.91; 25)	3.02 (7.06; 164)	0.817
			Below RNI	2.71 (0.0; 3)	5.61 (7.01; 5)	6.68 (0.67; 7)	0.78 (1.24; 8)	2.99 (3.17; 31)	4.39 (7.97; 32)	3.10 (2.50; 41)	3.10 (6.21; 127)	

Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn; Milligrams per litre = mg/L.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.

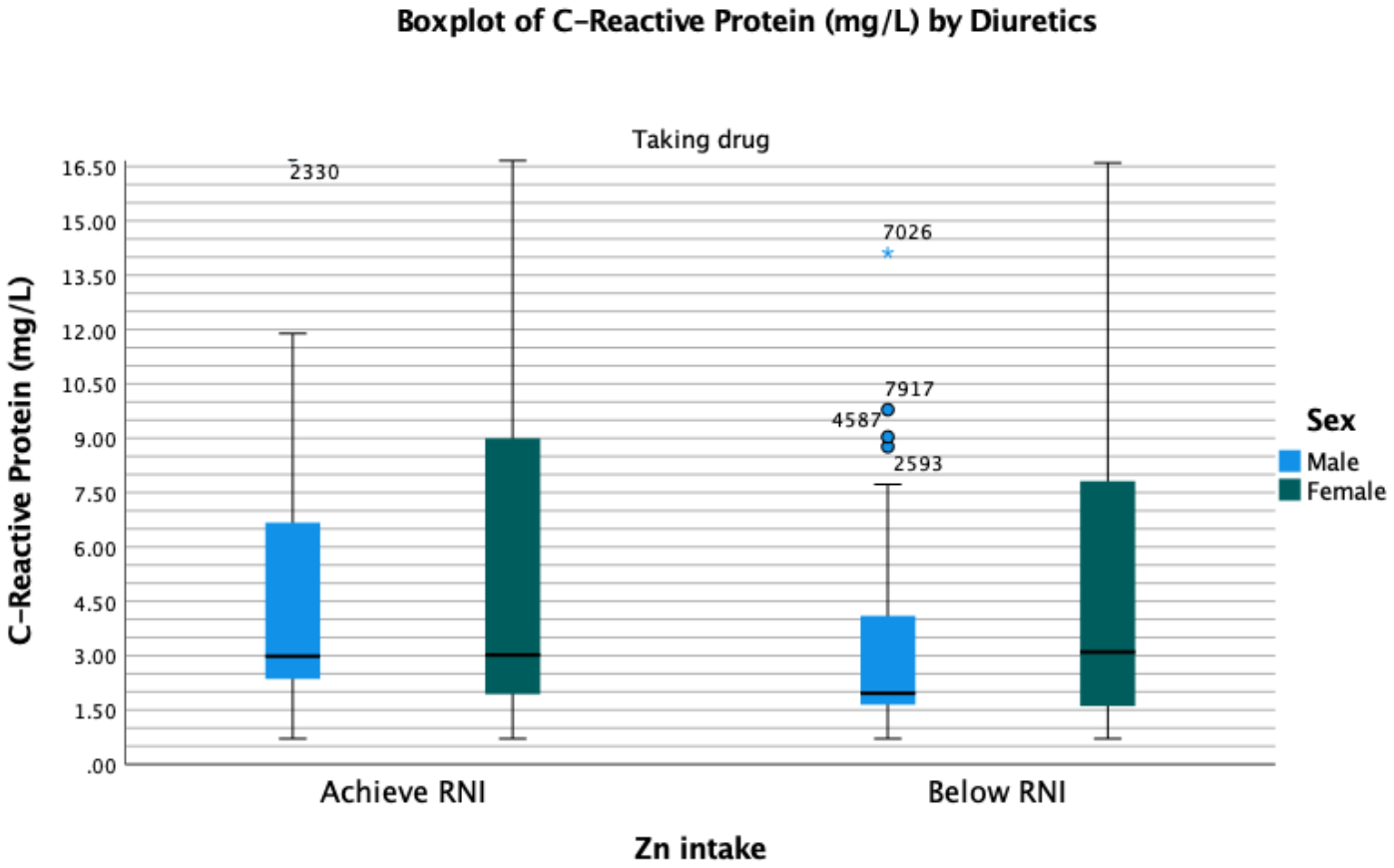


Figure 3.4 Boxplot of C-Reactive Protein by Diuretic Use, Zinc Intake, and Gender in the NDNS Data Set

3.3.4.4 Haemoglobin

Haemoglobin, which measures the oxygen-carrying capacity of the blood, has a typical range of 130–180 g/L in men and 115–165 g/L in women, and abnormal values may suggest anaemia or other haematological disorders (NHS Foundation Trust, 2024). Males exhibited higher haemoglobin levels than females across all age groups, with a slight decreasing trend observed for both genders as age increased (see **Table 3.10**). In males, a statistically significant increase in median haemoglobin levels was observed in those achieving the RNI for Zn while taking ACE inhibitors ($p = 0.024$), CCBs ($p = 0.021$) and diuretics ($p = 0.016$). In contrast, females showed no significant difference in haemoglobin levels based on their Zn intake across all types of antihypertensive drugs, except for a marginal nonsignificant trend noted for beta-blockers ($p = 0.056$). These results imply that adequate Zn intake may have a more pronounced impact on haemoglobin levels in males using specific types of antihypertensive drugs, while this effect appears to be minimal or absent in females.

Table 3.10 Effect of zinc intake with antihypertensive drugs on haemoglobin for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
Haemoglobin (g/dL)	M	ACE inhibitors	Achieve RNI	N/A	14.1 (0.0; 5)	15.9 (0.0; 6)	14.7 (0.4; 30)	15.7 (0.9; 30)	14.8 (0.8; 32)	13.1 (0.5; 7)	14.8 (1.6; 110)	0.024*
			Below RNI	N/A	16.0 (0.0; 4)	15.1 (1.0; 20)	14.7 (1.2; 74)	14.3 (2.1; 73)	14.1 (2.2; 66)	12.9 (1.5; 31)	14.6 (1.8; 267)	
		Beta-blockers	Achieve RNI	13.9 (0.0; 2)	11.6 (0.0; 2)	15.9 (0.0; 5)	15.0 (1.3; 27)	14.9 (0.2; 16)	15.0 (1.1; 23)	13.6 (1.2; 9)	14.9 (1.2; 83)	0.352
			Below RNI	15.1 (0.4; 5)	13.6 (3.5; 9)	14.3 (0.9; 18)	15.0 (1.2; 25)	15.1 (1.4; 46)	13.9 (2.5; 57)	12.6 (1.0; 17)	14.4 (2.2; 177)	
		Calcium channel blockers	Achieve RNI	12.9 (0.0; 1)	N/A	14.6 (2.2; 3)	14.6 (1.8; 35)	14.7 (2.5; 42)	14.3 (0.5; 20)	13.1 (1.0; 12)	14.3 (1.8; 113)	0.021*
			Below RNI	14.8 (0.0; 2)	13.1 (3.5; 11)	15.3 (0.0; 22)	15.1 (1.2; 36)	15.0 (2.0; 50)	13.9 (2.3; 70)	12.6 (3.0; 28)	14.9 (1.9; 218)	

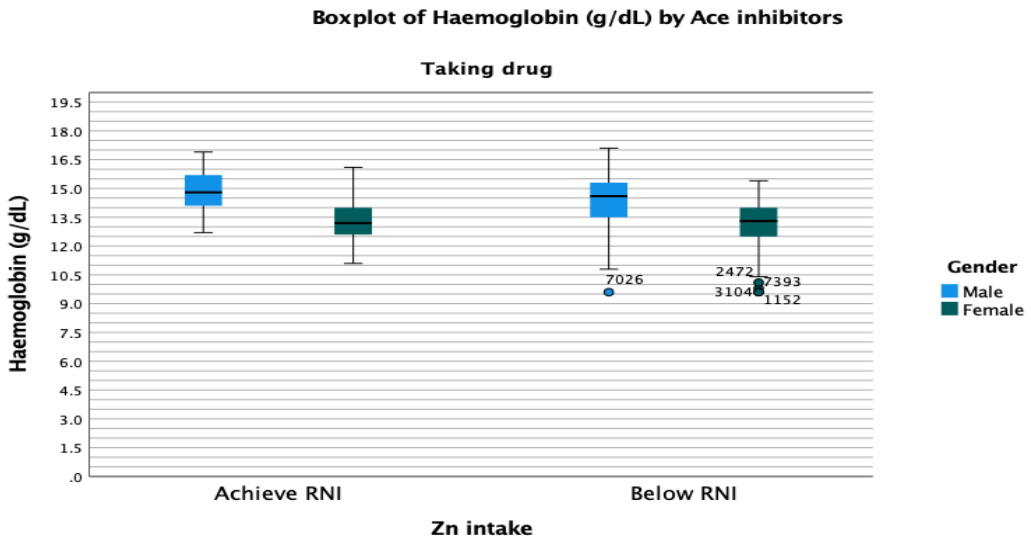
		Diuretics	Achieve RNI	13.9 (0.0; 2)	14.0 (0.0; 3)	14.6 (2.2; 4)	14.9 (2.2; 19)	15.0 (3.2; 22)	12.6 (6.4; 15)	15.3 (0.0; 4)	15.0 (2.1; 69)	0.016*
			Below RNI	14.7 (0.0; 3)	13.7 (0.9; 3)	17.6 (0.0; 6)	14.1 (3.0; 29)	14.7 (3.0; 40)	14.2 (1.8; 57)	12.8 (2.5; 16)	14.2 (2.6; 154)	
	F	ACE inhibitors	Achieve RNI	11.1 (0.0; 3)	12.9 (0.0; 1)	12.4 (0.4; 6)	13.4 (1.0; 42)	13.5 (1.1; 59)	13.1 (1.3; 55)	12.0 (2.2; 14)	13.2 (1.4; 180)	0.566
			Below RNI	N/A	14.4 (0.0; 3)	13.4 (1.3; 9)	13.6 (1.7; 14)	13.2 (1.5; 45)	13.3 (1.5; 46)	13.0 (1.5; 36)	13.3 (1.5; 153)	
		Beta-blockers	Achieve RNI	15.4 (0.0; 5)	14.1 (2.0; 7)	12.3 (0.4; 11)	13.2 (2.4; 25)	13.1 (1.4; 27)	12.7 (1.8; 49)	12.9 (3.8; 28)	13.1 (2.0; 150)	0.056
			Below RNI	14.0 (0.0; 3)	13.9 (1.8; 3)	14.3 (0.0; 3)	13.4 (0.5; 13)	14.1 (0.9; 22)	13.5 (0.4; 29)	14.0 (0.9; 23)	13.7 (0.8; 97)	
		Calcium channel blockers	Achieve RNI	12.4 (0.0; 2)	12.4 (0.0; 9)	13.0 (0.7; 10)	13.4 (1.3; 39)	13.1 (1.3; 30)	13.6 (1.1; 49)	13.2 (1.1; 34)	13.3 (1.0; 173)	0.924
			Below RNI	13.9 (0.0; 5)	14.4 (0.0; 1)	12.7 (2.4; 13)	12.1 (1.6; 10)	13.9 (2.4; 27)	13.7 (1.6; 35)	13.6 (1.5; 35)	13.6 (1.5; 125)	

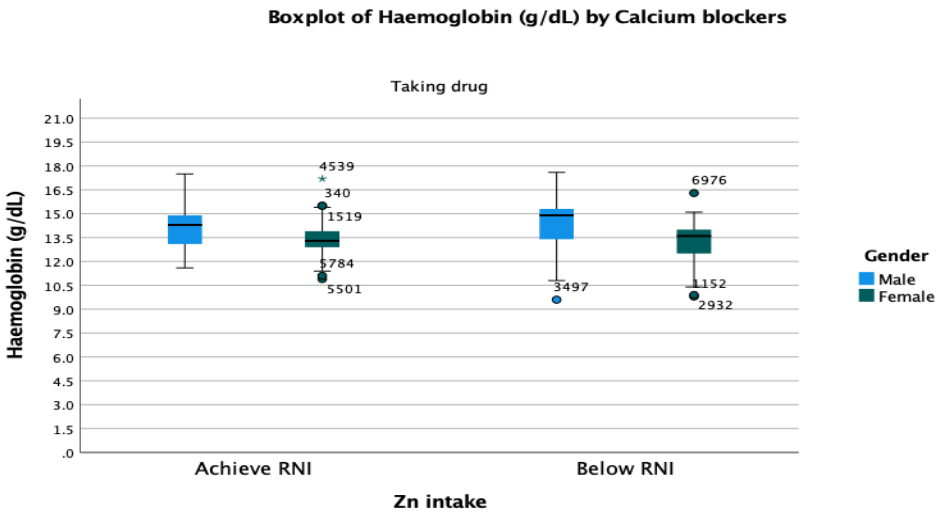
		Diuretics	Achieve RNI	14.2 (1.7; 3)	14.4 (0.7; 12)	11.9 (3.0; 10)	13.9 (3.6; 26)	13.3 (1.3; 36)	13.3 (1.9; 52)	13.7 (2.0; 25)	13.5 (1.9; 164)	0.201
			Below RNI	14.7 (0.0; 3)	13.1 (2.3; 5)	13.8 (1.1; 7)	12.7 (1.5; 8)	13.2 (1.6; 31)	13.2 (1.5; 32)	13.0 (1.2; 41)	13.2 (1.5; 127)	

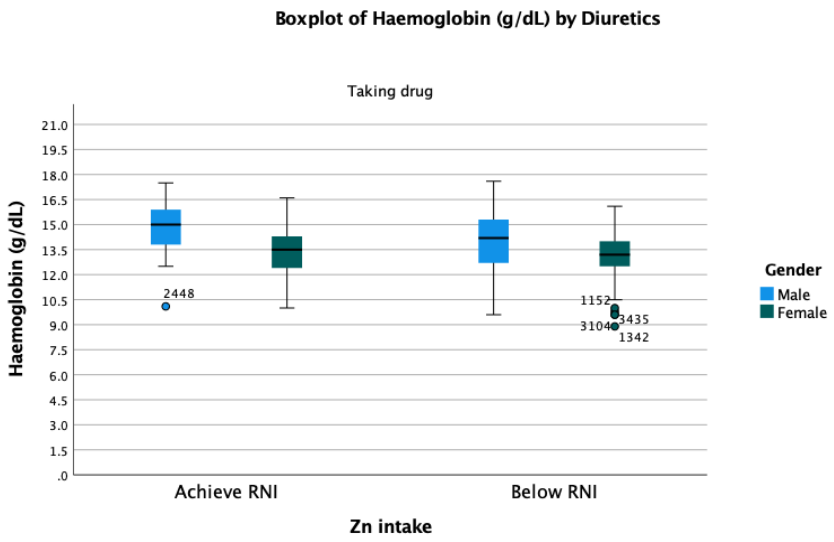
Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn; Grams per decilitre = g/dL.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.


Boxplot of Haemoglobin (g/dL) by Ace inhibitors
Taking drug
Haemoglobin (g/dL)
19.5
18.0
16.5
15.0
13.5
12.0
10.5
9.0
7.5
6.0
4.5
3.0
1.5
.0
7026
2472
3104
7393
1152
Achieve RNI
Below RNI
Zn intake
Gender
Male
Female


Boxplot of Haemoglobin (g/dL) by Calcium blockers
Taking drug
Haemoglobin (g/dL)
21.0
19.5
18.0
16.5
15.0
13.5
12.0
10.5
9.0
7.5
6.0
4.5
3.0
1.5
.0
4539
340
1519
5784
5501
3497
6976
1152
2932
Achieve RNI
Below RNI
Zn intake
Gender
Male
Female



Figures 3.5 Boxplot of Haemoglobin by ACE inhibitors, and Calcium blockers Diuretic Use, Zinc Intake, and Gender in the NDNS Data Set

3.3.4.5 Haematocrit

The HCT indicates the proportion of RBCs in the blood, with a reference range of 0.40–0.54 L/L for men and 0.37 to 0.47 L/L for women (NHS Foundation Trust, 2024). This parameter helps assess the blood's capacity to carry oxygen and can reflect states such as dehydration or fluid overload. The median HCT values were consistently higher in males compared to females across all age brackets. In male participants, achieving the RNI for Zn was associated with significantly lower haematocrit levels among those taking CCBs ($p = 0.010$). Similarly, in females, a statistically significant difference was observed in haematocrit levels for those below the RNI when using beta-blockers ($p = 0.001$). These findings suggest that Zn sufficiency may influence haematocrit values, depending on the type of antihypertensive medication used, and that this effect may vary between sexes. However, for other antihypertensive drug categories, such as ACE inhibitors in both sexes and diuretics in males, the differences were not statistically significant, indicating a more selective influence of Zn intake on haematocrit levels within this cohort (see **Table 3.11**).

Table 3.11 Effect of zinc intake with antihypertensive drugs on haematocrit for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
Haematocrit (L/L)	M	ACE inhibitors	Achieve RNI	N/A	0.424 (0.0; 5)	0.484 (2.5; 6)	0.485 (7.5; 30)	0.476 (5.8; 30)	0.446 (6.3; 32)	0.414 (0.5; 7)	0.455 (0.078; 110)	0.168
			Below RNI	N/A	0.489 (0.0; 4)	0.459 (4.5; 20)	0.459 (5.1; 74)	0.452 (7.6; 73)	0.440 (7.8; 66)	0.418 (7.7; 31)	0.451 (0.070; 267)	
		Beta-blockers	Achieve RNI	0.449 (0.0; 2)	0.357 (0.0; 2)	0.505 (0.0; 5)	0.448 (6.9; 27)	0.462 (2.8; 16)	0.470 (5.2; 23)	0.415 (5.4; 9)	0.449 (0.052; 83)	0.170
			Below RNI	0.462 (2.9; 5)	0.418 (10.0; 9)	0.447 (6.0; 18)	0.502 (7.5; 25)	0.472 (6.2; 46)	0.408 (6.8; 57)	0.386 (5.5; 17)	0.447 (0.087; 177)	
		Calcium channel blockers	Achieve RNI	0.378 (0.0; 1)	N/A	0.427 (8.2; 3)	0.433 (7.7; 35)	0.431 (3.4; 42)	0.420 (0.6; 20)	0.415 (2.6; 12)	0.431 (0.040; 113)	0.010*
			Below RNI	0.454 (0.0; 2)	0.411 (10.0; 11)	0.459 (3.5; 22)	0.468 (4.7; 36)	0.472 (4.0; 50)	0.431 (8.8; 70)	0.409 (10.4; 28)	0.454 (0.068; 218)	

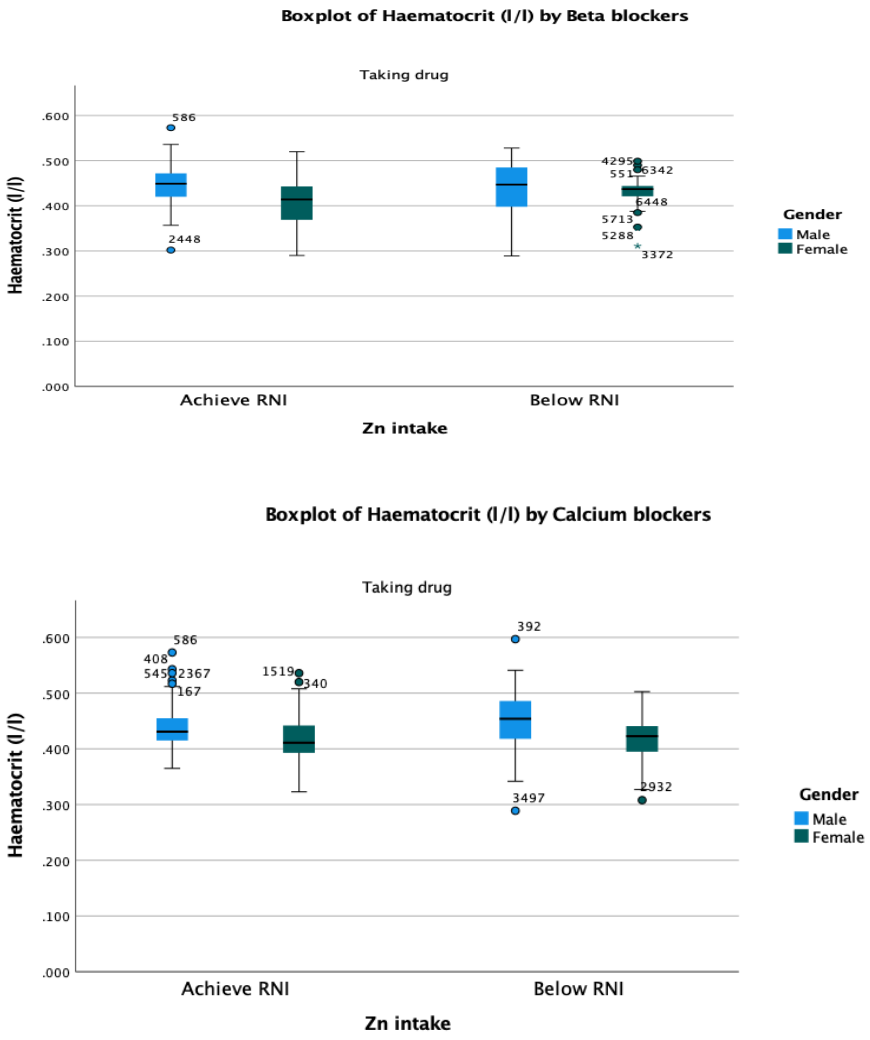
		Diuretics	Achieve RNI	0.449 (0.0; 2)	0.422 (0.0; 3)	0.427 (8.2; 4)	0.485 (5.5; 19)	0.448 (9.3; 22)	0.376 (19.2; 15)	0.511 (6.7; 4)	0.463 (0.092; 69)	0.058
			Below RNI	0.433 (0.0; 3)	0.407 (3.0; 3)	0.541 (0.0; 6)	0.459 (8.5; 29)	0.451 (9.4; 40)	0.430 (7.4; 57)	0.378 (9.7; 16)	0.439 (0.071; 154)	
	F	ACE inhibitors	Achieve RNI	0.354 (0.0; 3)	0.382 (0.0; 1)	0.389 (2.6; 6)	0.415 (4.8; 42)	0.419 (4.8; 59)	0.421 (6.2; 55)	0.411 (2.3; 14)	0.414 (0.055; 180)	0.292
			Below RNI	N/A	0.503 (0.0; 3)	0.402 (4.7; 9)	0.429 (12.1; 14)	0.416 (4.7; 45)	0.429 (5.4; 46)	0.429 (2.6; 36)	0.425 (0.050; 153)	
		Beta-blockers	Achieve RNI	0.500 (0.0; 5)	0.414 (4.5; 7)	0.376 (3.3; 11)	0.394 (7.6; 25)	0.425 (2.2; 27)	0.398 (7.0; 49)	0.411 (16.5; 28)	0.414 (0.074; 150)	0.001*
			Below RNI	0.423 (0.0; 3)	0.434 (9.2; 3)	0.490 (0.0; 3)	0.409 (3.0; 13)	0.438 (1.2; 22)	0.437 (2.6; 29)	0.438 (0.0; 23)	0.437 (0.023; 97)	
		Calcium channel blockers	Achieve RNI	0.373 (0.0; 2)	0.371 (0.0; 9)	0.385 (1.1; 10)	0.415 (4.9; 39)	0.397 (4.0; 30)	0.429 (6.6; 49)	0.406 (3.3; 34)	0.411 (0.049; 173)	0.493
			Below RNI	0.412 (0.0; 5)	0.503 (0.0; 1)	0.427 (4.1; 13)	0.395 (6.3; 10)	0.416 (5.0; 27)	0.441 (4.5; 35)	0.418 (2.7; 35)	0.423 (0.046; 125)	

		Diuretics	Achieve RNI	0.419 (5.6; 3)	0.429 (4.0; 12)	0.351 (12.5; 10)	0.456 (8.4; 26)	0.425 (2.6; 36)	0.404 (5.3; 52)	0.405 (6.3; 25)	0.420 (0.054; 164)	0.595
			Below RNI	0.444 (0.0; 3)	0.397 (6.9; 5)	0.444 (4.8; 7)	0.412 (0.0; 8)	0.422 (4.0; 31)	0.412 (4.3; 32)	0.418 (4.5; 41)	0.418 (0.042; 127)	

Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn; Litres per litre = L/L.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.



Figures 3.6 Boxplot of Haematocrit by Beta-blockers and Calcium blockers Use, Zinc Intake, and Gender in the NDNS Data Set

3.3.4.6 MCV

Lastly, the MCV, which describes the average size of RBCs, typically ranges from 80 to 100 fL and can be used to differentiate between types of anaemia, such as microcytic, normocytic or macrocytic (NHS Foundation Trust, 2024). The MCV demonstrated a gradual increase with age among males, whereas in females, MCV levels remained relatively stable across age groups (see **Table 3.12**). Among males taking CCBs, a marginally significant decrease in MCV was observed in those achieving the RNI for Zn compared to those below the RNI ($p = 0.050$). Conversely, females on beta-blockers exhibited a statistically significant reduction in MCV when achieving the RNI ($p = 0.033$). No significant differences were noted in other antihypertensive drug categories for either sex, suggesting a variable relationship between Zn intake and MCV that may be modulated by the specific type of antihypertensive medication used.

Table 3.12 Effect of zinc intake with antihypertensive drugs on mean cell volume for the participants in the National Diet and Nutrition Survey dataset

Haematological marker, median (IQR; n)	Sex	Taking Antihypertensive drugs	Zn intake	Age group (years)								
				19–29	30–39	40–49	50–59	60–69	70–79	80+	Total	P-value
Mean Cell Volume (fL)	M	ACE inhibitors	Achieve RNI	N/A	90.4 (0.0; 5)	90.8 (5.3; 6)	95.5 (11.4; 30)	96.1 (4.7; 30)	94.1 (9.4; 32)	92.0 (0.7; 7)	94.8 (7.1; 110)	0.655
			Below RNI	N/A	99.0 (0.0; 4)	89.3 (3.7; 20)	94.8 (7.5; 74)	97.1 (10.1; 73)	97.3 (7.9; 66)	100.0 (5.9; 31)	96.4 (9.1; 267)	
		Beta-blockers	Achieve RNI	112.0 (0.0; 2)	79.3 (0.0; 2)	102.7 (0.0; 5)	99.8 (11.9; 27)	96.1 (5.5; 16)	96.7 (10.2; 23)	92.7 (38.8; 9)	97.7 (11.5; 83)	0.610
			Below RNI	87.9 (5.9; 5)	93.4 (5.8; 9)	94.7 (5.8; 18)	99.3 (9.3; 25)	99.5 (9.9; 46)	96.8 (14.4; 57)	102.3 (11.4; 17)	96.8 (9.2; 177)	
		Calcium channel blockers	Achieve RNI	96.3 (0.0; 1)	N/A	88.3 (7.8; 3)	95.5 (6.5; 35)	94.0 (9.3; 42)	90.5 (3.6; 20)	92.0 (10.1; 12)	92.0 (7.8; 113)	0.050*

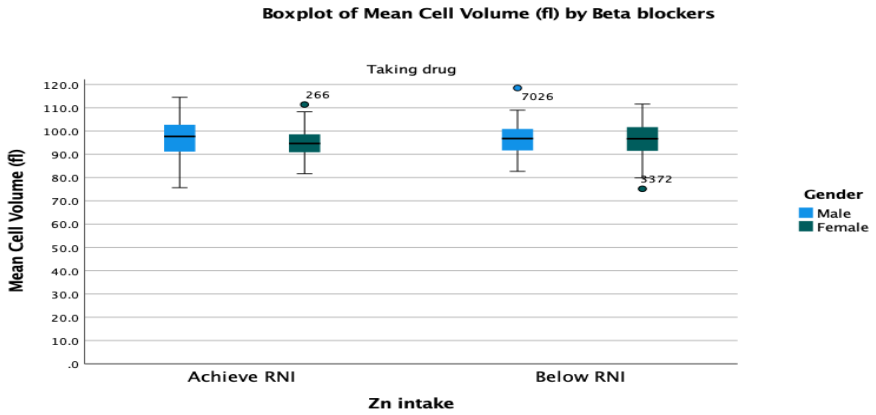
			Below RNI	96.3 (0.0; 2)	93.2 (16.6; 11)	88.9 (4.5; 22)	94.8 (9.3; 36)	92.3 (9.5; 50)	96.5 (6.9; 70)	97.9 (8.0; 28)	94.3 (9.0; 218)	
		Diuretics	Achieve RNI	112.0 (0.0; 2)	95.9 (0.0; 3)	88.3 (7.8; 4)	92.2 (6.7; 19)	96.1 (6.5; 22)	89.3 (5.2; 15)	101.1 (7.2; 4)	95.9 (6.7; 69)	0.974
			Below RNI	93.8 (0.4; 3)	92.3 (2.2; 3)	95.6 (0.0; 6)	94.8 (6.7; 29)	94.6 (5.6; 40)	97.3 (14.1; 57)	96.0 (10.8; 16)	94.8 (7.6; 154)	
	F	ACE inhibitors	Achieve RNI	76.1 (0.0; 3)	90.5 (0.0; 1)	94.4 (6.1; 6)	91.9 (10.5; 42)	92.9 (10.7; 59)	90.7 (5.5; 55)	96.6 (1.9; 14)	92.9 (9.5; 180)	0.134
			Below RNI	N/A	108.4 (0.0; 3)	95.0 (7.9; 9)	96.5 (5.9; 14)	95.9 (8.2; 45)	95.1 (10.1; 46)	100.9 (15.9; 36)	95.7 (9.0; 153)	
		Beta-blockers	Achieve RNI	102.8 (0.0; 5)	94.1 (4.8; 7)	92.4 (6.1; 11)	91.9 (9.5; 25)	92.8 (6.2; 27)	96.9 (12.2; 49)	96.6 (4.5; 28)	94.7 (7.7; 150)	0.033*
			Below RNI	87.7 (0.0; 3)	94.5 (21.2; 3)	109.2 (0.0; 3)	94.5 (4.2; 13)	95.9 (9.6; 22)	100.1 (5.0; 29)	96.9 (15.3; 23)	96.7 (10.2; 97)	

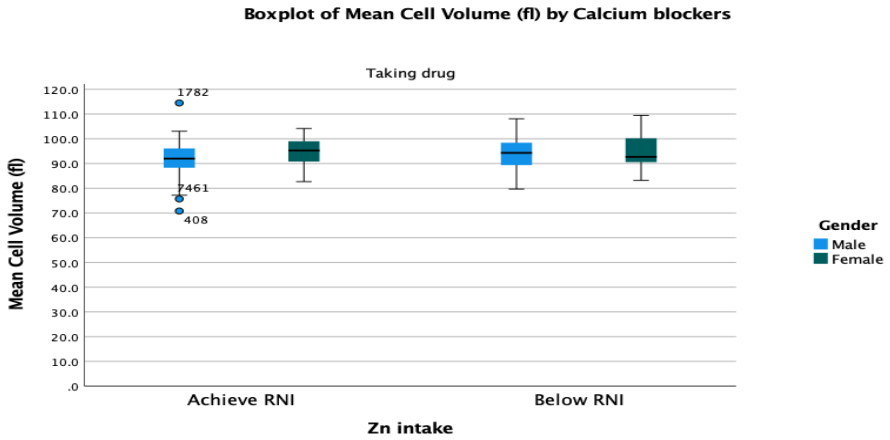
		Calcium channel blockers	Achieve RNI	89.4 (0.0; 2)	95.3 (0.0; 9)	90.9 (1.5; 10)	95.2 (7.1; 39)	92.9 (6.9; 30)	96.9 (7.6; 49)	96.4 (5.4; 34)	95.3 (8.2; 173)	0.487
			Below RNI	88.5 (0.0; 5)	108.4 (0.0; 1)	92.1 (11.1; 13)	92.1 (9.6; 10)	94.1 (8.9; 27)	92.8 (10.1; 35)	97.3 (9.6; 35)	92.7 (9.6; 125)	
		Diuretics	Achieve RNI	94.6 (2.3; 3)	94.1 (2.5; 12)	96.1 (16.7; 10)	92.1 (9.5; 26)	92.8 (5.6; 36)	90.8 (7.4; 52)	94.4 (10.4; 25)	92.8 (6.7; 164)	0.773
			Below RNI	90.3 (0.0; 3)	96.9 (5.6; 5)	98.8 (2.9; 7)	93.8 (3.0; 8)	91.5 (12.0; 31)	92.8 (4.3; 32)	91.3 (22.4; 41)	92.8 (7.2; 127)	

Number = N; Male = M; Female = F; Not applicable = N/A; Reference nutrient intake = RNI; Zinc = Zn; Femtolitre = fL.

Mann–Whitney U test was used for comparisons involving more than two groups (haematological marker and Zn intake level).

* Significant at the $p < 0.05$ level.





Figures 3.7 Boxplot of Mean Cell Volume by Beta-blockers and Calcium blockers Use, Zinc Intake, and Gender in the NDNS Data Set

3.4 Discussion

Based on the NDNS, the present study examined dietary Zn intake, Zn status and the usage of antihypertensive medications across diverse age groups and genders among free-living adults aged 19 and over within the general population of the UK. Moreover, it examined blood biomarkers in participants receiving antihypertensive medications and consuming Zn. Evidence from a broad range of research, including observational studies and experimental research, indicates that inadequate Zn intake and low serum Zn concentrations are associated with several negative health outcomes in humans, such as impaired immune response, delayed wound healing and increased susceptibility to chronic diseases (Hara et al., 2023; Li et al., 2022).

Adequate intracellular zinc ions (Zn^{2+}) act as second messengers that inhibit IκB kinase, thereby regulating the nuclear translocation of nuclear factor-κB (NF-κB). This pathway suppresses transcription of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α) and interleukins 1, 6 and 8 (IL-1, IL-6 and IL-8 (Bonaventura et al. 2015; Wessels and Rink 2020; Wong and Ho 2012). A systematic review and meta-analysis of 21 randomised controlled trials ($n \approx 1{,}321$) found that zinc supplementation reduced circulating C-reactive protein by 0.92 milligrams per litre (mg L) and TNF-α by 0.49 picograms per millilitre (pg mL), while simultaneously lowering malondialdehyde, a marker of oxidative stress (Hosseini et al. 2021).

In this study, the zinc intake of most participants was below the RNI, indicating that their dietary consumption was insufficient to meet established nutritional requirements for zinc. The data indicated a decrease in dietary Zn with age: the highest intake was in middle age, with a decline in older people. This deficiency was primarily evident in males, and this finding is in

agreement with the larger literature on micronutrient intake (Maret & Sandstead, 2006). This raises questions about the dietary habits of this population and whether external factors, such as lifestyle or medication, affect the deficiency. This trend aligns with research that has suggested that dietary patterns evolve over the lifetime, often as a result of factors such as metabolic changes, hunger, oral health and social concerns (Andriollo-Sanchez et al., 2005; Kaur et al., 2019; King et al., 2015). It should be noted that the analysis did not adjust for zinc intake from dietary supplements, which may have led to an overestimation of intake for participants who used them, or conversely, an underestimation of deficiency prevalence in those who did not. Although NDNS data do capture supplement use, the majority of zinc intake values in this analysis were derived from food sources only.

Additionally, plasma Zn concentration was relatively consistent across age groups, despite the lower amount of Zn consumed. However, 4.4% of the total population had Zn concentrations below the reference range, indicating zinc deficiency (ZnD). This decoupling of Zn intake and plasma levels could imply efficient Zn absorption or mobilisation from stores, or perhaps the biomarkers of Zn status are maintained even when intake is below the RNI, until a more severe deficiency state arises (King et al., 2015). These observations align with the hypothesis proposed by Maywald and Rink (2022) that the human body might harbour compensatory mechanisms to maintain homeostasis, even when experiencing deficient dietary intake. This might suggest a homeostatic mechanism that the body employs to maintain Zn status or indicate that plasma Zn is not the most sensitive marker for Zn status (King, 2011).

The body's capacity to regulate the level of Zn in the plasma could also explain why, despite decreased Zn intake, a significant portion of the participants had a plasma Zn levels within the normal range. This is in agreement with other studies that have suggested that the body has

mechanisms for maintaining a stable concentration of Zn in the plasma (Roohani et al., 2013). This suggests that the body's internal processes can still function despite changes in dietary Zn intake. The significant discrepancies in Zn levels between men and women during adolescence and adulthood are likely caused by factors such as menstruation, pregnancy and lactation in women, which can influence Zn metabolism (Nasiadek et al., 2020). Dietary Zn intake and Zn levels tend to decline with age and lifestyle factors such as medication use.

An age-dependent increase in antihypertensive drug intake was notable, particularly among older people. Prior research has similarly documented an age-related rise in antihypertensive drug consumption, which aligns with the observation that the prevalence of HTN rises with age (Burnier et al., 2020; Lim et al., 2015). A significant observation was the variation in antihypertensive drug consumption between genders.

Most male participants consumed ACE inhibitors, whereas female participants leaned towards diuretics. This differentiation could be due to potential gender-based differences in drug response or possible side effects that might be more prevalent in one gender (Zhao et al., 2020). Furthermore, the association between antihypertensive drug consumption and decreased Zn intake suggests that these medications influence nutrient absorption or metabolism. The observed differences in Zn intake between genders on antihypertensive drugs might be attributed to factors such as diet, lifestyle or biological differences in Zn homeostasis (Suliburska et al., 2018). However, while there was an observable decrease in Zn intake, particularly in males on antihypertensive drugs, the chi-square test results indicated a significant statistical association between antihypertensive drug consumption and Zn intake/status. This finding prompts further inquiry into potential external factors that may be influencing these outcomes. External factors such as diet, absorption rates and other

medications could play a role (D'Alessandro et al., 2022). Previous studies have demonstrated that Zn plays a role in regulating blood pressure through its involvement in pathways such as the modulation of vascular tone, Na-potassium balance and nitric oxide synthesis (Kim, 2013). Interestingly, while Zn intake and status showed significant associations with ACE inhibitor usage, no association was evident for other antihypertensive drugs (Cohen & Golik, 2006). The exact mechanism, however, remains to be fully elucidated. Given that the associations with other antihypertensive drugs were not statistically significant, further investigation might be needed to pinpoint the exact relationship between Zn and ACE inhibitors.

The findings of the present study highlight the complex interactions between Zn status and haematological biomarkers in adults taking antihypertensive drugs, with variations observed based on sex, age and drug class. Zn is pivotal for several physiological processes, including immune function, protein synthesis, wound healing, DNA synthesis and cell division (Chasapis et al., 2020). Zn is integral for immune function, and reduced levels could influence the WBC response, a trend identified by Someya et al. (2009). Our results suggest that adequate Zn intake may help mitigate adverse changes in biomarkers such as WBC count and haemoglobin, particularly in males, while its impact in females is less pronounced. Similarly, parameters such as haemoglobin and haematocrit levels might be influenced by Zn levels since Zn plays a role in haemoglobin synthesis (Fukushima et al., 2009). Abnormalities in these blood parameters could indicate disrupted Zn homeostasis. For instance, ZnD has been linked to WBC count change, signifying a weakened immune response (Someya et al., 2009). Inflammation is influenced by numerous factors, including age, dietary patterns and underlying health conditions, and it could be exacerbated by deficiencies of micronutrients, including Zn (Furman et al., 2019). Given these findings, optimising Zn intake in hypertensive patients should be considered part of a personalised nutritional strategy to support haematological

health, particularly in the context of long-term medication use. Evidence from various studies supports that addressing ZnD and targeting populations at risk can significantly reduce health-related comorbidities (Gibson, 2012; Maywald & Rink, 2022).

3.4.1 Limitations

This study has several limitations that should be noted. First, the lack of detailed information on the dosages of the antihypertensive drugs and duration of use, as well as the timing between food diary entries and blood sample collection, restricts the accuracy of the findings. Without this information, it is difficult to establish clear relationships between nutrient intake, medication use and Zn status.

Additionally, underreporting is a common issue in dietary assessments, especially in individuals with a higher body mass index (>25 kg/m²). This could lead to an underestimation of nutrient intake and misinterpretation of Zn status. Another limitation is the cross-sectional design of the study, which prevents inferring causality. While associations were observed, it is unclear whether the use of antihypertensive drugs directly impacts Zn levels or other factors are involved.

Finally, it should be noted that self-reported data have the potential for recall bias. Participants may not have accurately recorded their dietary intake, and short-term food diaries may not reflect long-term habits. This could have affected the reliability of the reported Zn intake and its association with drug use.

3.4.2 Future Directions

Further research is needed to address these limitations. Future studies should consider using a longitudinal design to capture the long-term impact of antihypertensive drug use on Zn status. This would help clarify causal relationships and provide stronger evidence. Additionally, studies that explore the direct effects of Zn supplementation on the need for antihypertensive drugs are recommended. This could reveal whether improving Zn status reduces medication use or alters blood pressure outcomes.

Research should also focus on individuals with moderate, rather than acute, ZnD. Understanding the impact of small nutrient variations on drug-nutrient interactions could offer new insights. Finally, it is important to monitor the effects of changing dietary trends, food fortification and public health policies on Zn status in the UK population. Tracking these trends could inform future dietary guidelines and health strategies.

3.5 Conclusion

This research comprehensively studied the effect of commonly used antihypertensive drugs on Zn intake, Zn status and blood biomarkers in different age groups and sexes. While specific associations were observed, particularly regarding the consumption of Zn and drugs for the treatment of high blood pressure, more research is necessary to comprehend the underlying principles and possible health effects. Additionally, public health initiatives can be focused on dietary recommendations and supplements, especially for patients that have a significant portion that is below the RNI or are at risk of potential health implications of ZnD. This is particularly important for patient taking antihypertensive medications to ensure overall health and well-being.

Chapter 4: A Comparative Analysis of Zinc Status and Overall Health in Care Home Residents and Free-Living Older Adults in the United Kingdom

4.1 Introduction

The proportion of older individuals is increasing rapidly worldwide (World Health Organisation, 2024). In 2022, the population of individuals aged 65 and over in the United Kingdom was approximately 12.7 million, accounting for 19% of the total population. This figure is projected to increase significantly by 2072, reaching an estimated 22.1 million individuals (27% of the population), reflecting the ongoing demographic shift towards an ageing society (UK Parliament Commons Library, 2024).

Over the past decade, the rising proportion of individuals aged 65 and older has become a considerable challenge to healthcare systems, as over 50% of this population are affected by at least two chronic conditions (Kingston et al., 2018). Moreover, the nutritional status of older adults in the United Kingdom is a significant public health concern, as it plays a vital role in maintaining individual health and reducing the progression of chronic diseases. Both care home residents and free-living individuals encounter challenges that adversely affect their dietary intake and nutrient status. As many as 14% of older adults who live independently and 21% of those in care institutions are regarded as being at risk of undernutrition, highlighting a significant concern for both community-dwelling and institutionalised older populations (Margetts et al., 2003). The elderly are at a heightened risk of zinc (Zn) deficiency, with estimates suggesting that approximately 31% of individuals over 60 years old may be affected (Yasuda & Tsutsui, 2016). This deficiency is exacerbated by dietary habits that often include high-phytate foods, which inhibit Zn absorption, and by the common use of medications that can further impair Zn status (Djou et al., 2022; Nakagawa, 2023). According to the Office for National Statistics (2023), the percentage of individuals aged 65 and over residing in care homes in England and Wales decreased from 3.2% in 2011 to 2.5% in 2021. Among those aged 85 and over, this proportion declined from 13.7% to 10.8% over the same period.

The UK National Diet and Nutrition Survey data indicates that a substantial proportion of older adults fail to meet recommended intakes for key nutrients, including Zn (Derbyshire, 2018). These deficiencies are compounded by age-related dietary challenges, such as reduced nutrient absorption, changes in taste and appetite, and the presence of chronic diseases. Zn, a critical micronutrient for immune function, wound healing, and overall metabolic health, is of particular concern for older adults, whose vulnerability to deficiency is heightened by these age-related physiological changes.

Previous chapters in this thesis have explored Zn intake and nutritional status among older adults taking different antihypertensive drugs. The findings revealed that the type and combination of medications can influence dietary patterns and Zn status. Antihypertensive drugs, which are frequently prescribed to older adults, may interact with dietary components and impact Zn metabolism through mechanisms such as altered gastrointestinal absorption and increased urinary excretion. The issue is further exacerbated by polypharmacy – a common phenomenon among older adults with hypertension, which may significantly influence dietary intake and Zn status.

Studies have demonstrated that institutionalised older adults are at a heightened risk of malnutrition, which is closely linked to inadequate Zn intake. For instance, a systematic review highlighted that older adults in care settings frequently do not meet their nutritional needs – including essential minerals such as Zn, which can exacerbate health issues such as infections and cognitive decline (Omar et al., 2011; Vural et al., 2020). The prevalence of Zn deficiency in institutionalised populations can be attributed to factors such as limited dietary variety and the challenges associated with food preparation and consumption in care homes (Asl et al.,

2021). In contrast, free-living older adults may have greater access to diverse diets, potentially mitigating the risk of Zn deficiency (Afzali et al., 2022).

The interplay between nutrition and medication in older adults is a critical area of study, particularly given the numerous health challenges faced by this demographic. Addressing these issues necessitates comprehensive strategies to optimise nutrition and well-being among both care home residents and free-living older adults in the United Kingdom.

4.2 Aim and Objectives

4.2.1 Aim

The aim of this study was to investigate the impact of antihypertensive medication use and living environment on dietary zinc intake, and selected health outcomes in older adults in Nottinghamshire, UK, and to explore related differences in dietary patterns, nutrient adequacy, and biochemical markers of health.

Furthermore, urinary iodine concentration (UIC) and urinary creatinine were measured to determine whether disturbances in Zn status extend to thyroid and muscle metabolism in older individuals. Zn is an indispensable co-factor for type I and II de-iodinase enzymes that convert thyroxine (T_4) to the biologically active triiodothyronine (T_3); inadequate Zn can therefore impair iodine utilisation even when iodine intake is sufficient (Rohner et al., 2014). Roughly half of total body Zn is sequestered in skeletal muscle where it supports ribosomal protein synthesis; chronic deficiency may reduce muscle mass and, consequently, endogenous creatinine generation (Maret & Sandstead 2006; Mares & Haase 2020). Assessing iodine thus provided a mechanistic adjunct to the primary Zn outcomes.

4.2.2 Research Objectives

- Assess and compare the Zn status between elderly care home residents and free-living older adults using FANSS data.
- Evaluate the impact of different classes of antihypertensive drugs (ACE inhibitors, beta blockers, CCBs, and diuretics) on Zn status and other minerals in elderly care home residents.
- Examine the association between zinc intake and selected health outcomes, including immune function, cognitive health, and physical well-being, in both care home residents and free-living older adults.
- Compare dietary patterns and the adequacy of zinc and other essential nutrient intakes between elderly care home residents and free-living older adults.
- Explore urinary iodine concentration (UIC) and urinary creatinine as mechanistic indicators related to zinc status, thyroid function, and muscle metabolism.

4.2.3 Research Question

How do living environment and antihypertensive medication use influence zinc status, and related health outcomes, in older adults in Nottinghamshire, UK?

4.2.4 Hypothesis

The use of antihypertensive medications, particularly diuretics and ACE inhibitors, is associated with reduced Zn status and poorer health outcomes in elderly care home residents compared to free-living older adults.

4.3 Methodology

4.3.1 Care Home Residents and Free-Living Older Adults

The third study is a cross-sectional analysis comparing Zn status and overall health between elderly care home residents and free-living older adults in Nottinghamshire, England, United Kingdom. A multi-method quantitative approach was employed, combining dietary assessments with health evaluations to provide a comprehensive understanding of dietary Zn intake and associated health outcomes.

4.3.2 Ethical Considerations

4.3.2.1 Care Home Group

The procedures followed were in accordance with the guidelines of the Research Ethics Committee of the Health Research Authority, United Kingdom, and officially granted on 12 March 2024 (reference no.: 24/IEC 08/0005). All procedures were in accordance with the poster advertisement and participant information sheet (refer to **Appendices 1 and 2**). The purpose of the study was described to participants individually, after which written informed consent was taken from all participants prior to data collection (refer to **Appendix 3**).

4.3.2.2 Free-Living Group (Food and Nutrition Security Survey)

This research received ethical approval from the University of Nottingham's Faculty of Medicine and Health Sciences Research Ethics Committee (reference no.: FMHS 208-0223 FANSS). Comprehensive information for participants, including details of the study and the procedures involved, was provided in the participant information sheet, which can be found in **Appendix 4**.

4.3.3 Recruitment Procedure

4.3.3.1 Care Home Study

Initial contact with care homes was established via email, whereby detailed information regarding the study objectives and methodology was provided and an invitation to participate was extended. Four care homes indicated preliminary interest; however, following subsequent discussions aimed at elucidating the study methodology, only one care home provided formal consent to participate. Prospective participants were evaluated based on defined eligibility criteria. Inclusion required that individuals be aged 65 years or older, irrespective of an upper age limit; encompass both genders from varied sociodemographic backgrounds; and be current residents of the care home. Furthermore, participants had to possess the capacity to provide informed consent and demonstrate sufficient English proficiency to engage effectively with the study tasks. Residents who were not feeding orally (e.g. those receiving enteral or parenteral nutrition) were excluded to maintain consistency in the dietary intake assessment.

Within the care home, the recruitment process was coordinated by the care home manager. The study was first introduced to residents through the care home's newsletter, after which those who expressed interest were given additional details. The manager, in consultation with residents' relatives, assessed eligibility based on the residents' capacity to provide informed consent in accordance with the criteria outlined in the English Mental Capacity Act (2005). Direct approach by the researchers was avoided; instead, an introduction to the researchers were facilitated if a resident expressed willingness to participate. At this stage, participants were informed that their participation was entirely voluntary and that they could withdraw from the study at any point without consequence. Subsequently, eligible participants attended an anthropometric assessment session – conducted in a convenient location within the care home – during which researchers recorded body weight, height, and hand-grip strength and collected health, demographic, and other study-related data using standardised forms supplemented by

information from care home staff. At this session, participants also provided spot urine samples using designated collection vessels. Finally, over four consecutive days, food intake data was meticulously collected through the weighing of residents' trays before and after each meal to determine their mineral intake from food sources. Recruitment was conducted between 17 and 21 June 2024. Of the residents approached, eight indicated a willingness to participate, although written consent was ultimately received from five participants (see **Figure 4.1**).

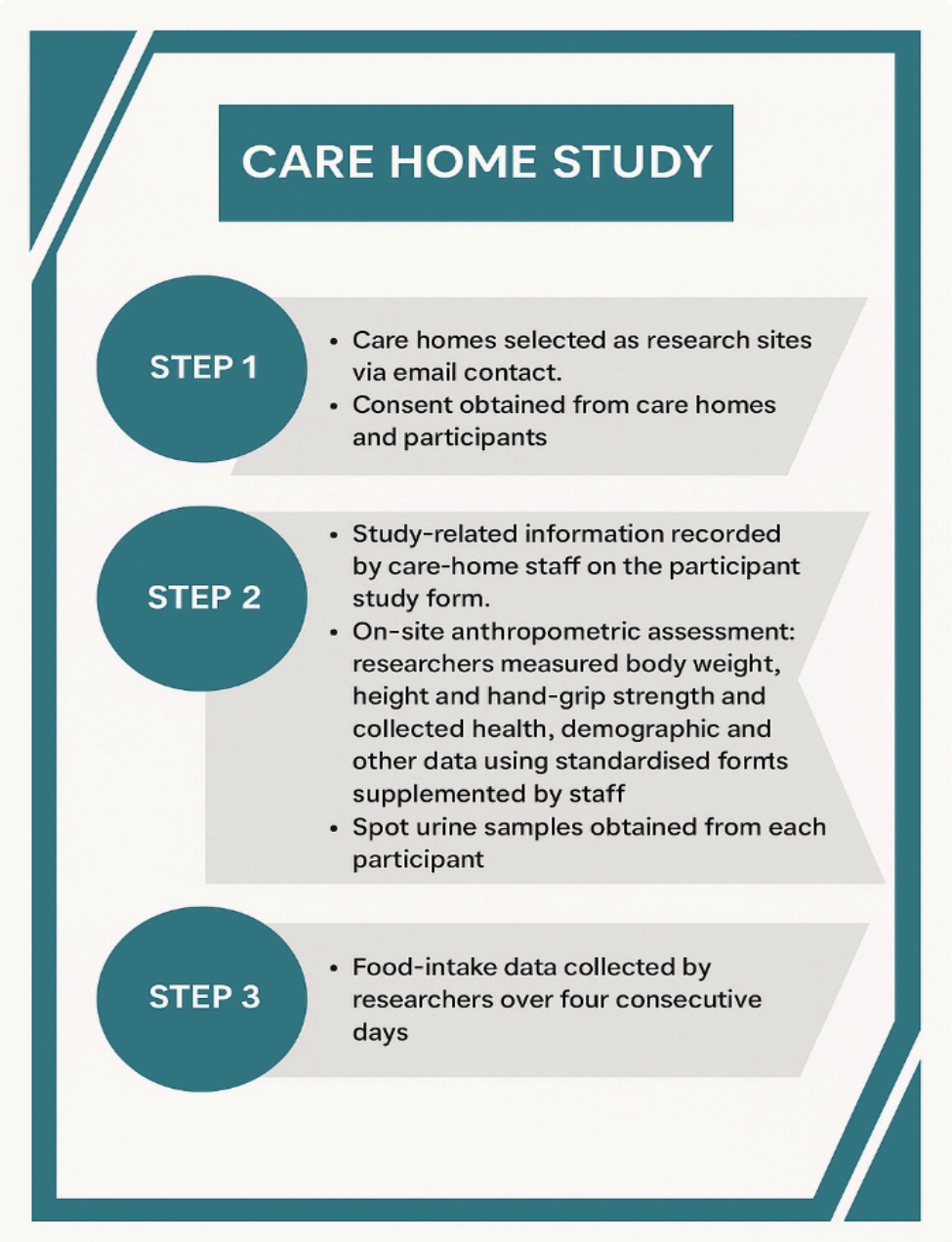


Figure 4.1 Basic summary of the study steps for care home residents

4.3.3.2 Free-Living Older Adults Study

This study targeted free-living individuals aged ≥ 75 years residing in Nottinghamshire. This age band represents the majority of UK care-home residents and corresponds to the "middle-old" segment in gerontology, a period characterised by sharp increases in frailty and multimorbidity. Focusing on this cohort yields a demographically representative and clinically homogeneous sample, thereby enhancing the internal validity and comparability of our findings. The study was advertised via social media (Facebook and X) associated with Reach PLC and in local Nottingham newspapers, with prospective participants directed to an online survey hosted on the Joint Information Systems Committee platform. The survey collected demographic details, health information, and data on food security, shopping habits, and usual dietary intake through a food frequency questionnaire encompassing the previous 12 months. Participants are also invited to engage in a further study component – which involved completing four computerised 24-hour dietary recalls via Intake24 and, optionally, providing a spot urine sample. The free-living study was conducted over a nine-month period, start on 1 February 2023 and concluding on 30 September 2023 (see **Figure 4.2**).

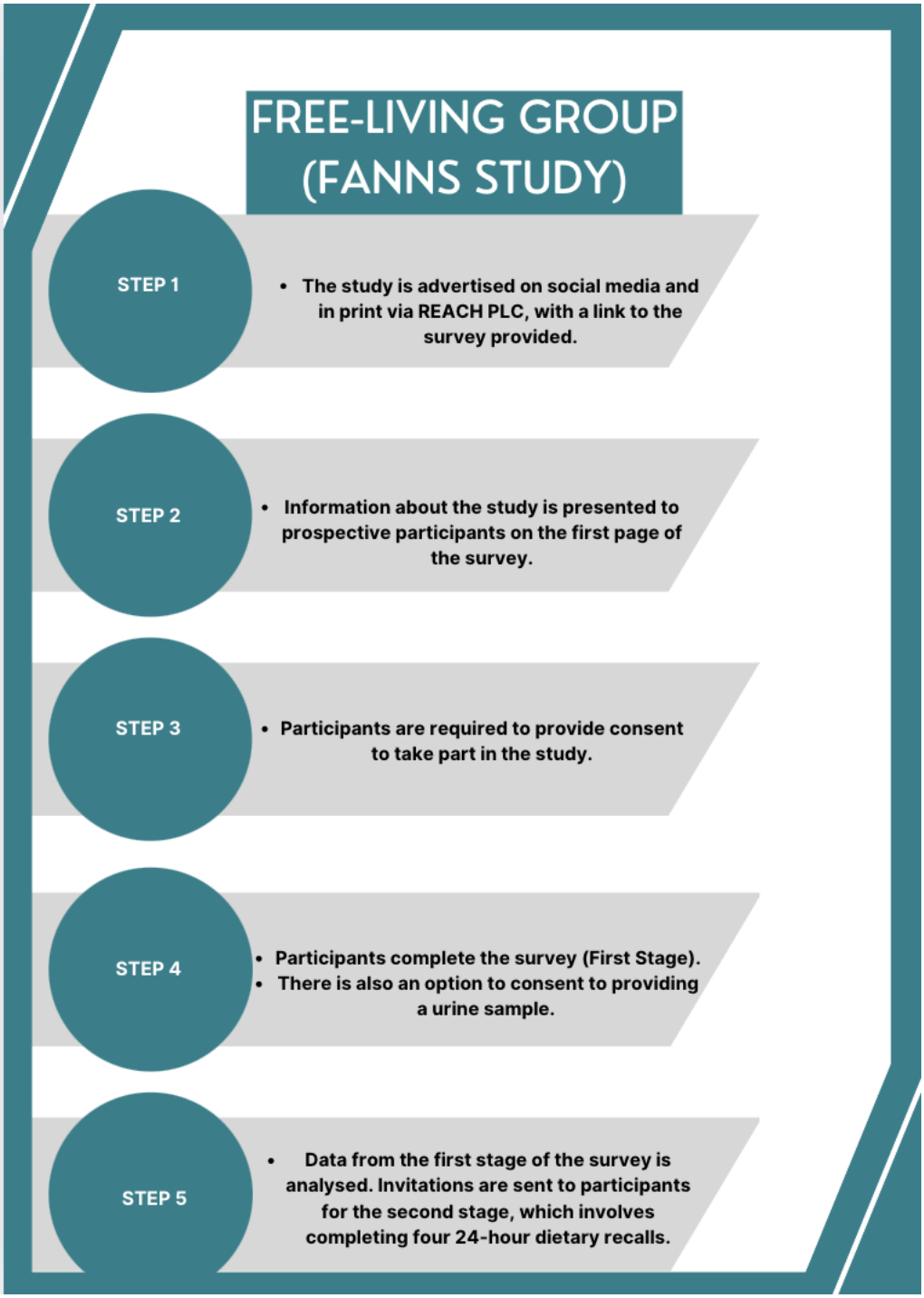


Figure 4.2 Flowchart illustrating the process for selecting subjects process for the FANNS study

4.3.4 Data Collection

After evaluating the sample with the inclusion and exclusion criteria, eligible participants were given a unique participant study number for including their data in an electronic database to ensure anonymity and facilitate data security.

4.3.4.1 Demographic and Medical Information Collection

For the care home residents, a structured questionnaire (**Appendix 5**) was designed to capture a wide range of demographic and medical information, including age, sex, weight, height, and body mass index. Body mass index was calculated as weight (kg) divided by height (m) squared and categorised according to World Health Organisation standards (i.e. underweight [<18.5], normal weight [18.5–24.9], overweight [25.0–29.9], and obese [≥30.0]). In parallel, detailed medical histories documenting health conditions with potential impacts on nutrition and physical well-being, as well as comprehensive records of prescribed medications (including type, dosage, and frequency) and dietary supplements, were obtained. Socioeconomic factors, such as educational attainment, occupation, and annual income, were also self-reported, thereby providing an additional context to the nutritional outcomes. Additionally, information regarding dietary habits – such as meal consumption patterns, dietary restrictions, and supplement use – was collected to facilitate subsequent statistical analysis of their relationship with mineral deficiencies. For participants in the free-living group, data were gathered via an online survey hosted on the Joint Information Systems Committee platform (**Appendix 6**). This survey incorporated questions pertaining to demographic characteristics, self-reported health status, food security, and shopping habits.

4.3.4.2 Nutritional Assessment of Elderly Participants

In this thesis, dietary intake was assessed using a combination of methods tailored to meet the specific needs of the populations and settings under investigation. The dietary intakes of care home residents were assessed using the plate waste method. In this method, residents' trays were weighed before and after each meal (breakfast, lunch, dinner, and snacks), including total solid and fluid intake during the four consecutive days, and recorded by researchers. Additionally, standardised serving portions were established using a specially calibrated spoon, which was considered a portion unit for items that were difficult to measure by weight alone, such as sauces and pureed foods. This calibrated spoon provided a consistent benchmark across meals, ensuring that every resident received an accurately measured portion. The use of this serving utensil, which was incorporated during staff training, improved the accuracy and consistency of dietary assessment. Detailed serving portions for food items provided to residents on a regular texture diet are detailed in **Table 4.1**. The dietary data were subsequently analysed using the Nutritics software (https://www.nutritics.com/) – which incorporates the McCance and Widdowson (2014) food composition database, alongside additional international datasets. This software's capability to process complex recipes and mixed dishes made it particularly suitable for care home settings, providing accurate nutrient profiling of meals prepared on-site and reflecting actual consumption patterns.

Conversely, the free-living group's (Food and Nutrition Security Survey) dietary intake was evaluated using a combination of a food frequency questionnaire (FFQ) and four 24-hour dietary recalls administered via the Intake24 platform. The FFQ, adapted from the European Perspective Investigation into Cancer and Nutrition, captured habitual dietary intake over the preceding 12 months by assessing consumption frequency and portion sizes across various food items (**Appendix 6**). In addition to the FFQ, participants were invited to complete four computerised 24-hour dietary recalls using the Intake24 platform. Intake24 is an online dietary

recall tool designed to collect detailed information about dietary intake using the multiple-pass 24-hour recall method. Participants enter all food and beverage items consumed during the previous 24-hour period (midnight to midnight) using free-text entry. These entries are then matched against a comprehensive database of food items. Portion sizes are estimated with over 3,000 food photographs, enhancing the accuracy of reported intakes. Intake24 has been utilised in various research studies to assess dietary intake across diverse population groups in the United Kingdom and is a key component of the NDNS. Further details about the system, including a demonstration version, are available online (https://app.intake24.org/demo). Nutrient analyses for both the FFQ and 24-hour recalls were supported by the McCance and Widdowson (2014) food composition database, ensuring consistency and accuracy across the different dietary assessment methods.

The FANSS dataset was used to obtain dietary intake data, including zinc and other nutrient intakes, for free-living older adults. Reported values reflect nutrient intake from food sources only; information on dietary supplement use was not available in the dataset and therefore was not included in the analysis. As a result, zinc adequacy may be underestimated in participants who consume supplements and overestimated in those who do not.

Table 4.1 Food items (serving size) served in care home for residents consuming regular texture diet:

Breakfast (Same breakfast options are served every day)	Serving/portion size in gram
-Wheat Bisks (Cereal/Biscuits) Fortified with Niacin (B3), Iron, Riboflavin (B2), Thiamine (B1) and Floc Acid (B9) (Asda)	42 grams
-Pancake	33 grams
-Corn Flakes	32 grams
-Drop Scones (Scotch pancake)	60 grams
-Multi Seed Loaf Bread (Morrisons)	42 grams
-Rice Krispies	40 grams
-Porridge	75 grams
-Mix Crumbled/grinded Cereals	35 grams
-Muesli	69 grams
-Custard Cream Biscuits	59 grams
-Spreadable Cheese Made with Cheddar (Seriously Vintage)	12 grams
-Fried Egg	62 grams
-Strawberry Jam No Sugar Added (STUTE)	54 grams
-Fine Cut Orange Marmalade No Sugar Added (STUTE)	55 grams
- Lakeland Dairies Salted Butter	6 grams
-Whole Milk (Fresh ways)	85 grams (for cereals) 36 grams (for tea and coffee)
-Tea	136 grams
-Coffee	131 grams
-Baileys Irish Cream	19 grams

LUNCH	
-Hunters Chicken in Barbecue Sauce	123 grams
-Butternut Squash Risotto	172 grams
-Homemade Coleslaw	61 grams
-Fresh Mixed Vegetable Salad (Lettuce, tomato, pepper, cucumber, radish)	25 grams
-New Potato	76 grams
-Strawberry Eton Mess	84 grams
-Peach Compote	78 grams
-Cream	36 grams
-Chicken Kiev	96 grams
-Venison Pork Meatballs with Mushroom Gravy	99 grams
-Mashed Potato	71 grams
-Boiled Vegetables (Broccoli &Cauliflower)	74 grams
-Coconut Sponge Cake	49 grams
-Cream	36 grams
-Braised Steak with Gravy	104 grams
-Mushroom and Leek in a Cream Sauce	48 grams
-Boiled Cabbage	43 grams
-Mashed Potato	71 grams
-New Potatoes	76 grams
-Cherry Sponge Cake	34 grams
-Cream	36 grams
-Sausage Casserole with Gravy	61 grams (without gravy)

-Gravy	48 grams
-Yorkshire Pudding	56 grams
-Mashed Potato	71 grams
--Boiled Vegetables (Broccoli &Cauliflower)	74 grams
-Strawberry Yoghurt	125 grams
-Dairy Ice-Cream Vanilla with Fructose	35 grams
DINNER (TEATIME)	
-Cheese Coleslaw Sandwich	46 grams
-Bacon Vegetable Sandwich	54 grams
-Pork Pie	16 grams
-Sausage Roll	35 grams
-Lemon Cake	60 grams
-Strawberry Yoghurt	125 grams
-Dairy Ice-Cream Vanilla with Fructose	36 grams
-Banana	30 grams
-Cream	36 grams
-Broccoli Stilton Soup	96 grams
-Cheese Omelette	66 grams
-Tinned Tomato	30 grams
-Bakewell Tart	40 grams
-Cream	36 grams
-Mini chicken & steak pie	29 grams
-Steak and Guinness Pie	90 grams
-Fried Chips with Sea Salt	54 grams

-Mandarin Oranges in Tinned	76 grams
-Dairy Ice-Cream Vanilla with Fructose	36 grams
-Vegetable Soup (Tomato, carrot, peppers, orange peppers)	92 grams
-Roast filling with corn beef and tomato	72 grams
-Roast filling with egg and cross mayo	79 grams
-Walkers Ready Salted Crisps	8 grams
-Spotted Dick Cake	52 grams
-Custard	38 grams
-Peach and Pear in Fruit Juice	113 grams

4.3.4.3 Nutritional Status for the Care Home Study

According to Rubenstein et al. (2001), the Mini Nutritional Assessment was used to assess nutritional status, with the following classifications: normal nutritional status (scores between 12 and 14), at risk of malnutrition (scores between 8 and 11), and malnourished (scores less than 7; see **Table 4.2**).

Table 4.2 Mini-Nutritional Assessment Short-Form (MNA-SF): components and scoring guide

A- Has food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing difficulties? 0=Severe decrease in food intake 1=Moderate decrease in food intake 2=No decrease in food intake
B- Weight loss during the last three months 0=Weight loss greater than 3 kg (6.6 Ibs) 1=Does not know 2=Weight loss between 1 and 3 kg (2.2 and 6.6 Ibs) 3=No weight loss
C- Mobility 0=Bed or chair bound 1=Able to get out of bed/chair but does not go out 2=Goes out
D- Has suffered psychological stress or acute disease in the past three months? 0=Yes 2=No

E- Neuropsychological problems 0=Severe dementia 1=Mild dementia 2=No psychological problems
F- Body Mass Index (BMI) (weight in kg) / (height in m2) 0=BMI less than 19 1=BMI 19 to less than 21 2=BMI 21 to less than 23 3=BMI 23 or greater
SCREENING SCORE (Max. 14 points) 12-14 points= Normal Nutritional Status 8-11 points= At the risk of Malnutrition 0-7 points= Malnourished

4.3.4.4 Urinary Iodine and Creatinine Analysis

Urine samples were processed and analysed to assess iodine status and account for hydration levels within the study population. Samples were centrifuged at 2,000 rpm at 20°C for 5 minutes using a GT4R centrifuge (Thermo Fisher Scientific) to separate the supernatant. The resulting supernatants were carefully transferred into clean tubes for further analysis.

For the determination of urinary iodine concentration (UIC), 1 mL of the supernatant was diluted with 9 mL of a 1% tetramethylammonium hydroxide solution, achieving a 1:10 dilution ratio. For creatinine analysis, urine samples were diluted at a 1:10 ratio with Milli-Q grade water. Both diluted samples were mixed thoroughly, stored at room temperature, and analysed within two weeks of preparation to ensure sample stability and accuracy.

4.3.4.4.1 Iodine Analysis

UIC was measured using inductively coupled plasma mass spectrometry (Thermo Fisher Scientific) at the Gateway Building Laboratories, University of Nottingham. This method was selected due to its high sensitivity and specificity for detecting trace levels of iodine in biological samples. Calibration was performed using certified iodine standards, with internal controls included in each batch to ensure analytical accuracy and minimise the risk of drift during measurements. Quality assurance protocols encompassed measures such as blanks, and duplicate analyses. These measures were implemented to validate the reliability and reproducibility of the results, ensuring robust and precise quantification of UIC for assessing iodine status in the study population.

4.3.4.4.2 Creatinine Analysis

Urinary creatinine concentrations were determined using the Jaffe reaction, a well-established colorimetric assay. Each diluted urine sample was analysed in triplicate to ensure precision and accuracy. In this method, creatinine reacts with alkaline picrate to form a yellow-orange complex, which was quantified by measuring absorbance at 550 nm using a Bio-Rad microplate reader (Model 680 XR). Calibration standards and quality control samples were incorporated into each assay to validate the results and maintain analytical integrity. Both the iodine and creatinine analyses were performed following stringent quality control protocols – providing reliable and reproducible data for evaluating iodine status, adjusted for hydration levels, in the adult population of Nottinghamshire.

4.3.5 Data Analysis

All data were extracted to Microsoft Excel (Version 16.88) for the purpose of saving, comparing, and validating. Nutritics (Version 5.96) was used conducted to determine Zn intake and quantitatively analyse dietary ingredients in the Division of Food, Nutrition and Dietetics, School of Biosciences, University of Nottingham. The estimated energy requirements were calculated using the average age, weight, and height of the participants, along with the physical activity coefficient for sedentary individuals. All analyses were completed with the SPSS software (Version 27, IBM, USA). Descriptive statistics were utilised to provide a comprehensive summary of the population and their associated outcomes. Quantitative data were presented as means and SDs. Demographic data underwent descriptive and frequency analysis to summarise the prevalence of deficiencies and Zn intake.

4.4 Results

4.4.1 Demographic and Health Characteristics

The results are presented to investigate the impact of antihypertensive medication on Zn status and overall health in elderly care home residents and compare these findings with data from free-living older adults, using the FANSS, in Nottinghamshire to provide a broader understanding of nutritional and health outcomes across different elderly populations. Among the study population of 11 elderly individuals, 5 participants were residents of care homes, while 6 lived independently. The age range of participants was 75–94 years. The mean age of care home residents was 90.8 ± 2.17, higher than the mean age of 79.33 ± 4.76 observed among the free-living group. Regarding gender distribution, the free-living group consisted of two males (33.3%) and four females (66.7%), whereas all care home residents were female (100%). Marital status analysis revealed that four free-living participants (66.7%) were divorced, whereas most care home residents (80%) were widowed.

Health status indicators revealed a higher prevalence of cardiovascular disease (CVD) among care home residents, with 100% of participants compared to only one male (16.7%) in the free-living group reporting a similar condition. The mean weight and height for males living in their own homes were 76.88 ± 8.65 kg and 1.83 ± 0.04 m, respectively. For females living in their own homes, the mean weight and height were 63.62 ± 5.72 kg and 1.63 ± 0.02 m, respectively. Among individuals living in care homes, the mean weight and height were 58.20 ± 12.08 kg and 1.58 ± 0.06 m, respectively.

Using the standard World Health Organisation (WHO) adult body mass index (BMI) categories—under-weight < 18.5 kg m^{-2}, normal weight 18.5–24.9 kg m^{-2}, over-weight 25.0–29.9 kg m^{-2} and obesity ≥ 30 kg m^{-2} (Kıskaç et al., 2022). The anthropometric data for both groups indicated a mean BMI within the normal range (see **Table 4.3**). Among care-home residents, 20 % were under-weight, 40 % normal-weight and 40 % over-weight, with no participants meeting the obesity threshold. In the free-living cohort no individual was under-weight; 16.7 % of males were normal-weight and a further 16.7 % over-weight, while 50 % of females were normal-weight and 16.7 % over-weight. However, it is important to note that for older adults (typically ≥65 years), research suggests the optimal BMI range associated with lowest mortality risk may be higher (often ~23–30 kg/m^2) than the standard WHO 'normal' range. Interpretation of BMI categories, especially 'underweight' and 'overweight,' in the care home resident group (likely comprising older adults) should therefore consider these adjusted ranges.

All five participants (100%) in the care home study were prescribed antihypertensive medications, with varied use across the four drug classes. Two participants reported using two types of drugs, while one participant reported using three types. Additionally, two participants indicated the use of only one type of hypertension drug. ACE inhibitors were the most frequently used, with three participants (60%) taking them – followed by CCBs, which were also used by three participants (60%). Diuretics were prescribed to two participants (40%), while beta blockers were the least commonly used, with only one participant (20%). Notably, two participants (40%) were taking more than one class of antihypertensive medication: the combination of ACE inhibitors and CCBs, as well as diuretics and beta blockers.

The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values varied across the different medication classes. Participants using ACE inhibitors had a mean SBP of 146.67 ± 33.47 mmHg and a DBP of 69 ± 20.07 mmHg. Beta blocker users exhibited slightly higher SBP values (154 mmHg) with a comparable DBP of 70 mmHg. CCB users demonstrated an SBP of 146.33 ± 16.86 mmHg and a DBP of 78.67 ± 11.72 mmHg. Diuretic users had the highest SBP of 163.50 ± 13.44 mmHg and a DBP of 62.50 ± 10.61 mmHg. Additionally, nutritional risk assessment data, based on the Mini Nutritional Assessment (MNA) indicated that three (60%) care home residents were at risk of malnutrition, underscoring a critical need for proactive nutritional support within the care facility (see **Table 4.4**).

Table 4.3 Demographic and Health Characteristics of Participants by Living Environment and Gender Classification

Participant Demographic and Health Profile	**Total**	**Care Home Residents (All female)**	**Free-Living**	
			Male	**Female**
Participant number (N (%))	11(100%)	5 (100%)	2 (33.3%)	4 (66.7%)
Age (Years) (mean ± SD)	85±7	90.8±2.17	76±1	81±5
Marital status (N (%))				
Married	2 (18.2%)	0	1 (16.7%)	1 (16.7%)
Divorced	5 (45.5%)	1 (20%)	1 (16.7%)	3 (50%)
Widowed	4 (36.4%)	4 (80%)	0	0

Diagnosed with Cardiovascular Disease (N (%))				
Yes	6 (54.6%)	5 (100%)	1 (16.7%)	0
No	5 (45.5%)	0	1 (16.7%)	4 (66.7%)
Weight (Kg) (mean ± SD)	63.57±11.2	58.20±12.08	76.88 ±8.65	63.62±5.72
Height (M) (mean ± SD)	1.64±0.10	1.58±0.06	1.83 ±.04	1.63±0.2
Body Mass Index (BMI) (kg/m$^{2)}$ (mean ± SD)	23.62±3.82	23.47±5.51	23.10 ±3.56	24.06±1.87

BMI classification (N (%))				
Underweight (<18.5 kg/m2)	1 (9.1%)	1 (20%)	0	0
Normal (18.5 to 24.9 kg/m^2)	6 (54.6%)	2 (40%)	1 (16.7%)	3 (50%)
Overweight (25 to 29.9 kg/m^2)	4 (36.4%)	2 (40%)	1 (16.7%)	1 (16.7%)

N = Number; % = Percentage; SD = Standard Deviation; Kg = Kilograms; M = Meters; BMI = Body Mass Index

Table 4.4 Demographic and Health Comparisons Between Antihypertensive Users and Non-Users Among Elderly Care Home Residents

Participant number (N (%))	**Total**	**ACE Inhibitor**		**Beta Blocker**		**Calcium Channel Blocker**		**Diuretics**	
		Users	**Nonusers**	**Users**	**Nonusers**	**Users**	**Nonusers**	**Users**	**Nonusers**
	5 (100%)	3 (60%)	2 (40%)	1 (20%)	4 (80%)	3 (60%)	2 (40%)	2 (40%)	3 (60%)
Age- (Years) (mean ± SD)	**90.8±2.17**	90.67±3.06	91±.00	91±.00	90.75±2.50	90 ±1.73	92±2.83	92.50±2.12	89.67±1.53
Sex (N (%))									
Male	**0**	0	0	0	0	0	0	0	0
Female	**5 (100%)**	3 (60%)	2 (40%)	1 (20%)	4 (80%)	3 (60%)	2 (40%)	2 (40%)	3 (60%)
Marital status (N (%))									
Divorced	**1 (20%)**	0	1 (100%)	1 (100%)	0	1 (100%)	0	1 (100%)	0
Widowed	**4 (80%)**	3 (75%)	1 (25%)	0	4 (100%)	2 (50%)	2 (50%)	1 (25%)	3 (75%)

Systolic Blood Pressure (mmHg) (mean ± SD)	**144.20±25.74**	146.67±33.47	140.50±19.09	154±0	141.75±29.04	146.33±16.86	141±45.25	163.5±13.44	131.33±24.79
Diastolic Blood Pressure (mmHg) (mean ± SD)	**70.20±14.36**	69±20.07	72±2.83	70±0	70.25±16.58	78.67±11.72	57.5±3.54	62.5±10.61	75.33±16.04
Weight (Kg) (mean ± SD)	**58.20±12.08**	53.37±13.41	65.45±7	70.40±0	55.15±11.51	66.57±5.31	45.65±1.48	57.50±18.24	58.67±11.16
Height (M) (mean ± SD)	**1.58±.06**	1.59±.08	1.57±0	1.57±.0	1.58±.07	1.56±.01	1.61±.11	1.55±.03	1.60±.07
Body Mass Index (BMI) (kg/m$^{2)}$ (mean ± SD)	**23.47±5.51**	21.41±6.38	26.55±2.84	28.56±0	22.20±5.44	27.25±2.34	17.80±1.77	23.81±6.72	23.24±6.15
BMI classification (N (%))									
Underweight (<18.5 kg/m^2)	**1 (20%)**	1 (100%)	0	0	1 (100%)	0	1 (100%)	0	1 (100%)
Normal (18.5 to 24.9 kg/m^2)	**2 (40%)**	1 (50%)	1 (50%)	0	2 (100%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Overweight (25 to 29.9 kg/m^2)	**2 (40%)**	1 (50%)	1 (50%)	1 (50%)	1 (50%)	2 (100%)	0	1 (50%)	1 (50%)

Mini-Nutritional Assessment (MNA) (N (%))	**5 (100%)**								
Normal Nutritional Status (12-14 points)	**2 (40%)**	0	2 (100%)	1 (50%)	1 (50%)	2 (100%)	0	1 (50%)	1 (50%)
At the risk of Malnutrition (8-11 points)	**3 (60%)**	3 (100%)	0	0	3 (100%)	1 (33.3%)	2 (66.7%)	1 (33.3%)	2 (66.7%)
Malnourished (0-7 points)	**0**	0	0	0	0	0	0	0	0

N = Number; % = Percentage; SD = Standard Deviation; mmHg = Millimetres of Mercury; Kg = Kilograms; M = Meters; BMI = Body Mass Index; MNA = Mini-Nutritional Assessment

4.4.2 Dietary Intake and Recommendations

The dietary analysis of elderly care home residents and free-living older adults revealed significant nutritional deficiencies across both groups, as summarised in **Tables 4.5 and 4.6**. Both groups exhibited inadequate intake levels for a range of macronutrients and micronutrients, with care home residents consistently below recommended levels and free-living adults showing marginally higher but still insufficient intakes.

Care-home residents consumed significantly less calories, with an average intake of 1,241 ± 137 kcal day—representing 67.5 % of the UK Estimated Average Requirement (EAR) for women aged ≥ 75 years (1,840 kcal day). In contrast, free-living participants met 66.7 % of the age-adjusted male EAR (2,294 kcal day) and 72.8 % of the female EAR. These reference values are taken from the Scientific Advisory Committee on Nutrition (SACN) tables for adults aged ≥ 75 years, thus already reflect the lower energy needs of older adults (British Nutrition Foundation, 2023).

Carbohydrate intake was below recommended levels (203–325 g/day) for care home residents, whereas free-living adults reported slightly higher intake, with males consuming more than females. Protein intake was particularly low among care home residents, indicating a risk of protein-energy malnutrition, while free-living adults had slightly higher but still inadequate intake. Both groups' fat intake was within the recommended range, with free-living adults slightly exceeding care home residents in this context.

Micronutrient analysis revealed significant deviations from recommended levels, with both groups demonstrating suboptimal intake of essential nutrients. Among care home residents, Zn intake averaged 4.67 ± 0.66 mg/day, equating to 66.7% of the recommended intake (7 mg/day).

Variations in Zn intake were observed across different medication groups within the care home cohort, with the highest intake recorded among ACE inhibitor users (4.97 ± 0.73 mg/day) and the lowest among beta blocker users (4.28 ± 0 mg/day). Diuretic users (4.39 ± 0.16 mg/day) and CCB users (4.35 ± 0.22 mg/day) displayed intermediate levels of intake. In comparison, females in the free-living cohort achieved 89.3% of the recommended Zn intake (6.25 ± 1.39 mg/day), while males achieved 70.2% (6.67 ± 0.36 mg/day). However, neither group met the reference nutrient intake (RNI) of 7 mg/day for females and 9.5 mg/day for males, highlighting a pervasive inadequacy in Zn intake across both genders.

Vitamin C intake was highest in free-living females at 80.7 ± 29.11 mg/day (201.7% of the recommendation) and lowest among care home residents on beta blockers and diuretics – who consumed 25.2 ± 4.40 and 24.80 ± 0.63 mg/day, respectively, compared to the recommended 40 mg/day. Similarly, Vitamin A intake was deficient in care home residents – particularly beta blocker users, who consumed 243.13 ± 0 µg/day – while free-living females reached 85.5% of the recommendation. However, this intake was still below the recommended levels of 600 µg/day for women and 700 µg/day for men. Selenium intake was critically low across all groups, with care home residents consuming an average of 10.36 ± 1.43 µg/day (17.3% of the recommendation). Free-living males and females achieved 65.4% and 56.2% of the recommendation, respectively – which are still below the RNI of 60 µg/day for women and 75 µg/day for men, highlighting a consistent shortfall in selenium consumption across all groups.

For iron, free-living males achieved the highest intake at 8.42 ± 0.33 mg/day (96.8%), while care home residents on beta blockers consumed the lowest amount at 2.60 mg/day (29.9%), compared to the recommended 8.7 mg/day. Vitamin D intake was critically low in both groups, with free-living males achieving only 15.1% of the recommendation and care home diuretic

users consuming 2.62 ± 0.07 µg/day (26.2%). By contrast, free-living females demonstrated unexpectedly high intakes, averaging 21.63 ± 25.68 µg/day (216.3% of the recommendation), likely due to supplementation. Copper intake was inadequate across all groups, with free-living females achieving the highest intake at 1.12 ± 0.47 mg/day (93.5%) – compared to beta blocker users in care homes, who consumed just 0.49 mg/day (40.8%) against the recommendation of 1.2 mg/day. Magnesium intake was similarly below recommended levels, with care home residents consuming 105.10 mg/day. Free-living males achieved 288.37 ± 15.7 mg/day, approaching but not fully meeting the recommendation of 300 mg/day, while free-living females met the recommendation at 287.61 ± 125.66 mg/day (106.5% of the recommendation for women, 270 mg/day). Vitamin B6 intake was suboptimal in care home residents, who consumed less than the recommended 1.2 mg/day (women) and 1.4 mg/day (men), while free-living adults demonstrated better intake levels. Folate (vitamin B9) intake was also suboptimal in care home residents but exceeded recommendations in free-living females, who consumed 234.06 ± 37.45 µg/day (117% of the recommendation of 200 µg/day). Finally, vitamin B12 intake was sufficient across all groups, with free-living participants exceeding 300% of the recommendation, while care home beta blocker users achieved 3.52 µg/day compared to the recommended 1.5 µg/day.

These findings underscore significant nutritional disparities between care home residents and free-living older adults – with particular deficiencies noted in care home residents. Addressing these disparities is crucial for improving the overall health and nutritional well-being of these populations.

Table 4.5 Comparison of Nutritional Intake Across Care Home Residents and Free-Living Participants Against Dietary Recommendations

List of Nutritional Variables (mean ± SD)	**Target Intake**	**Care Home Residents**		**Free-Living**			
		Female	**Percent of Dietary Recommendations**	**Male**	**Percent of Dietary Recommendations**	**Female**	**Percent of Dietary Recommendations**
Energy (kcal)	**1840 (women), 2294 (men) kcal/day**	**1241.24 ± 137.31**	67.5%	1531.17 ± 385.46	66.7%	1339.22 ± 383.58	72.8%
Carbohydrate (g)	**245 (women), 306 (men) g/day**	**141.78 ± 21.39**	57.9%	202.13 ± 28.17	66.1%	140.04 ± 52.13	57.2%
Protein (g)	**46.5 (women), 53.3 (men) g/day**	**44.65 ± 5.71**	96.1%	63.93 ± 3.51	119.9%	58.27 ± 7.11	125.3%
Fat (g)	**72 (women), 89 (men) g/day**	**53.77 ± 6.41**	74.7%	53.55 ± 34.16	60.2%	64.84 ± 28.15	90%

Zinc (mg)	**7 (women),** **9.5 (men) mg/day**	**4.67±.66**	66.7%	6.67 ± 0.36	70.2%	6.25 ± 1.39	89.3%
Vitamin C (mg)	**40 mg/day**	**49.9±44.13**	124.7%	46.35 ± 11.96	115.9%	80.7 ± 29.11	201.7%
Vitamin A (ug)	**600 (women),** **700 (men) ug /day**	**290.45±47.08**	48.4%	388.12 ± 276.22	55.4%	513.05 ± 119.43	85.5%
Selenium (ug)	**60 (women),** **75 (men) ug/day**	**10.36±1.43**	17.3%	49.06 ± 2.96	65.4%	33.72 ± 3.0	56.2%
Iron (mg)	**8.7 mg/day**	**3.93 ± 1.28**	45.1%	8.42 ± 0.33	96.8%	6.9 ± 1.83	79.3%
Vitamin D (ug)	**10 ug/day**	**3.19 ± 0.65**	31.9%	1.51 ± 0.54	15.1%	21.63 ± 25.68	216.3%
Copper (mg)	**1.2 mg/day**	**0.73 ± 0.31**	61%	1.01 ± 0.03	84.2%	1.12 ± 0.47	93.5%

Magnesium (mg)	**270 (women),** **300 (men) mg/day**	**105.10 ± 16.53**	38.9%	288.37 ± 15.7	96.1%	287.61 ± 125.66	106.5%
Vitamin B6 (mg)	**1.2 (women),** **1.4 (men) mg/day**	**0.59 ± 0.13**	49.5%	1.48 ± 0.11	105.4%	1.19 ± 0.21	98.8%
Vitamin B9 **(Folate)** (ug)	**200 ug/day**	**115.36 ± 25.60**	57.7%	201.04 ± 53.02	100.5%	234.06 ± 37.45	117%
Vitamin B12 (ug)	**1.5 ug/day**	**2.35 ± 0.84**	156.7%	4.56 ± 2.55	304%	4.59 ± 0.9	306%

N/A = Not Available; SD = Standard Deviation; g = Grams; mg = Milligrams; ug = Micrograms; kcal = Kilocalories

Table 4.6 Nutritional Intake and Target Recommendations for Care Home Residents by Medication Use

List of Nutritional Variables (mean ± SD)	**Target Intake**	**ACE Inhibitor**		**Beta Blocker**		**Calcium Channel Blocker**		**Diuretics**	
		Users	**Nonusers**	**Users**	**Nonusers**	**Users**	**Nonusers**	**Users**	**Nonusers**
Energy (kcal)	1840 kcal/day	1164.92 ± 109.72	1355.71 ± 87.50	1293.84 ± N/A	1228.09 ± 154.87	1267.06 ± 165.55	1202.52 ± 124.89	1204.02 ± 127.02	1266.05± 165.32
Carbohydrate (g)	245 g/day	131.09 ± 11.97	157.82 ± 26.20	139.29 ± N/A	142.41 ± 24.64	144.73 ± 29.28	137.37 ± 7.08	135.83 ± 4.90	145.75±29. 05
Protein (g)	46.5 g/day	41.09 ± 3.65	49.98 ± 2.96	52.07 ± N/A	42.79 ± 4.52	46.59 ± 6.23	41.73 ± 4.93	45.16 ± 9.77	44.31±4.11
Fat (g)	72 g/day	51.62 ± 8.03	57.00 ± 0.61	57.44 ± N/A	52.86 ± 7.01	54.91 ± 3.66	52.07 ± 11.31	50.76 ± 9.45	55.79±4.73
Zinc (mg)	7 mg	4.97±.73	4.23±.08	4.28±0	4.77±.72	4.35±.22	5.16±.93	4.39±.16	4.86±.85

Vitamin C (mg)	40 mg	58.06±59.06	37.47±17.27	25.24±0	56.06±48.41	67.10±52.77	24.10±.35	24.80±.63	66.63±53.33
Vitamin A (ug)	600 ug	319.68±34.89	246.60±4.92	243.13±0	302.28±44.97	281.18±59.99	304.35±32	262.42±27.29	309.13±52.46
Selenium (ug)	60 ug	10.81±1.46	9.69±1.55	10.78±0	10.26±1.63	10.61±1.94	9.98±.41	10.24±.77	10.44±1.94
Iron (mg)	8.7 mg	4.54 ± 1.31	3.00 ± 0.57	2.60 ± N/A	4.26 ± 1.21	3.26 ± 0.60	4.92 ± 1.59	3.20 ± 0.85	4.41 ± 1.43
Vitamin D (ug)	10 ug	3.14 ± 0.68	3.27 ± 0.85	2.66 ± N/A	3.32 ± 0.66	3.17 ± 0.63	3.23 ± 0.94	2.62 ± 0.07	3.58 ± 0.53
Copper (mg)	1.2 mg	0.80 ± 0.16	0.63 ± 0.55	0.24 ± N/A	0.86 ± 0.17	0.65 ± 0.39	0.86 ± 0.17	0.49 ± 0.35	0.89 ± 0.19
Magnesium (mg)	270 mg	106.61 ± 15.87	102.85 ± 23.92	85.94 ± N/A	109.90 ± 14.53	99.12 ± 18.11	114.08 ± 12.97	95.43 ± 13.41	111.56 ± 17.33

Vitamin B6 (mg)	1.2 mg	0.55 ± 0.08	0.65 ± 0.22	0.50 ± N/A	0.62 ± 0.14	0.60 ± 0.18	0.59 ± 0.07	0.57 ± 0.10	0.61 ± 0.17
Vitamin B9 (Folate) (ug)	200 ug	128.31 ± 23.45	95.93 ± 16.25	84.44 ± N/A	123.09 ± 21.81	112.56 ± 31.00	119.57 ± 25.31	93.06 ± 12.18	130.23 ± 20.19
Vitamin B12 (ug)	1.5 ug	2.24 ± 0.62	2.52 ± 1.41	3.52 ± N/A	2.06 ± 0.62	2.66 ± 1.03	1.89 ± 0.16	2.65 ± 1.23	2.16 ± 0.72

N/A = Not Available; SD = Standard Deviation; g = Grams; mg = Milligrams; ug = Micrograms; kcal = Kilocalories

4.4.3 Zn Intake Among Elderly Care Home Residents and Free-Living Older Adults

Zn intake was assessed among elderly care home residents and free-living older adults using both the RNI and the lower reference nutrient intake (LRNI). The Zn intake analysis (**Tables 4.7 and 4.8**) revealed no significant disparities between the groups, as 100% of participants in both settings exceeded the LRNI, and overall intake patterns were similar across all categories.

In care home residents, Zn intake was 66.8% of the RNI, with no participants exceeding the RNI threshold. However, all participants met the LRNI, achieving 116.9% of this value. In comparison, free-living males consumed 70.2% of the RNI, with none exceeding the RNI threshold, but all met the LRNI, achieving 121.2% of the value. Free-living females exhibited higher Zn intake levels – achieving 89.3% of the RNI, with one participant surpassing the RNI threshold – and all met the LRNI.

Zn intake among care home residents on antihypertensive medications varied by drug class. Participants using ACE inhibitors achieved 71% of the RNI and 124.3% of the LRNI, with none meeting the RNI. Those using beta blockers exhibited the lowest Zn intake, achieving 61.2% of the RNI, but this was similar to the intake of those on CCBs (62.2% of the RNI) and diuretics (62.8% of the RNI).

Zn intake was consistently below the RNI across both care home residents and free-living older adults, demonstrating a widespread inadequacy. This shortfall was particularly pronounced in care home residents. These findings underscore the necessity for targeted dietary interventions to improve Zn intake and status among elderly populations.

Table 4.7 Zinc Intake Adequacy Based on RNI and LRNI Among Care Home Residents and Free-Living Groups

Assessment of Zinc Intake Based on RNI and LRNI		**Care Home Residents** (n=5)	**Free-Living**	
			Male (n=2)	**Female** (n=4)
Percent Zn according to RNI (%)		66.8	70.2	89.3
Percent Zn according to LRNI (%)		116.9	121.2	156.2
Above RNI Zinc (N (%))	**Yes**	0 (0.0%)	0 (0.0%)	1 (16.67%)
	No	5 (100%)	2 (33.33%)	3 (50%)
Above LRNI Zinc (N (%))	**Yes**	5 (100%)	2 (33.33%)	4 (66.67%)
	No	0 (0.0%)	0 (0.0%)	0 (0.0%)

RNI = Reference Nutrient Intake; LRNI = Lower Reference Nutrient Intake; SD = Standard Deviation; Zn = Zinc

This table presents the percentage of zinc intake relative to the LRNI ("Percent Zn according to LRNI (%)"). Values may exceed 100% because the LRNI represents the minimum daily zinc intake required for nearly all healthy individuals (5.5 mg for males and 4 mg for females). Values greater than 100% therefore indicate that the group's mean zinc intake exceeded this minimum requirement.

Table 4.8 Zinc Intake Adequacy Based on RNI and LRNI Among Care Home Residents Using Antihypertensive Medications

Assessment of Zinc Intake Based on RNI and LRNI		**Antihypertensive drugs**			
		Taking ACE Inhibitor	**Taking Beta Blocker**	**Taking Calcium Channel Blocker**	**Taking Diuretics**
Percent Zn according to RNI (%)		71	61.2	62.2	62.8
Percent Zn according to LRNI (%)		124.3	107.1	108.8	109.9
Above RNI Zinc (N (%))	**Yes**	0	0	0	0
	No	3 (33.33%)	1 (11.11%)	3 (33.33%)	2 (22.23%)
Above LRNI Zinc (N (%))	**Yes**	3 (33.33%)	1 (11.11%)	3 (33.33%)	2 (22.23%)
	No	0	0	0	0

RNI = Reference Nutrient Intake; LRNI = Lower Reference Nutrient Intake; SD = Standard Deviation; Zn = Zinc

This table presents the percentage of zinc intake relative to the LRNI ("Percent Zn according to LRNI (%)"). Values may exceed 100% because the LRNI represents the minimum daily zinc intake required for nearly all healthy individuals (5.5 mg for males and 4 mg for females). Values greater than 100% therefore indicate that the group's mean zinc intake exceeded this minimum requirement.

4.4.4 Food Group Contributions to Zn Intake

4.4.4.1 Zn Intake in Care Home Residents

In the dietary patterns of care home residents, meat and meat products emerged as the predominant sources of Zn intake, contributing an average of 9.63 ± 1.44 mg per individual. This substantial contribution is largely attributable to the frequent consumption of high-Zn foods – such as braised steak and sausages, with a single serving of 172 g of beef providing approximately 8.8 mg of Zn. Additionally, miscellaneous foods accounted for a notable average intake of 5.34 ± 1.12 mg, encompassing processed foods, ready meals, and sauces fortified with Zn or containing Zn-rich ingredients.

Cereals and cereal products contributed a moderate average of 1.82 ± 1.17 mg of Zn, primarily through fortified breakfast cereals and wholegrain breads, while dairy products provided a smaller average of 1.52 ± 0.60 mg, mainly sourced from milk and cheese. Vegetables were the least significant contributors, supplying an average of 0.38 ± 0.06 mg of Zn, consistent with their inherently low Zn content.

Lunch provided the most substantial contribution to daily Zn intake (53.12 mg), followed by dinner (20.46 mg). Although snacks contributed the least to Zn intake due to their relatively low Zn content, their frequent consumption highlights their role in the overall diet (see **Table 4.9**).

Table 4.9 Contribution of Different Meals and Food Categories to Total Dietary Zinc Intake in Elderly Care Home Residents

Meal	Total (mg)	Meat and Meat Products	Dairy Products	Cereal and Cereal Products	Miscellaneous	Vegetables
Breakfast	12.74	0.0	0.95	3.2	9.54	0.0
Lunch	53.12	40.76	2.29	3.88	4.67	1.52
Dinner	20.46	7.41	4.34	0.8	6.78	0.18
Snacks	7.09	0.0	0.0	1.2	5.72	0.18
Total	93.42	48.17	7.58	9.08	26.7	1.88

mg = Milligrams

4.4.4.2 Food Group Consumption in Free-Living Adults

In free-living older adults, milk and milk products demonstrated the highest mean consumption, with males consuming 570.94 ± 260.92 g/day and females consuming 347.6 ± 321.55 g/day. Vegetables and potatoes were the second most consumed food group, with males consuming 464.85 ± 218.97 g/day and females consuming 395.84 ± 229.6 g/day. Cereal and cereal products contributed 221.93 ± 42.87 g/day for males and 175.45 ± 95.96 g/day for females. Meat and meat products indicated lower consumption levels compared to other food groups, with males consuming 49.11 ± 4.7 g/day and females consuming 70.82 ± 47.41 g/day (see **Table 4.10**).

Table 4.10 Food group consumption (g) in free-living adults

Food group (mean ± SD)	**Total**	**Free-Living**	
		Male	**Female**
Milk and milk products	422.05±298.25	570. 94±260.92	347.6±321.55
Vegetable and potatoes	418.84±206.13	464.85±218.97	395.84±229.6
Cereal and cereal products	190.94±80.43	221.93±42.87	175.45±95.96
Meat and meat products	63.58±38.45	49.11±4.7	70.82±47.41

SD = Standard Deviation; mg = Milligrams

4.4.4.3 Comparison Between Care Home Residents and Free-Living Adults

Care home residents obtained a substantial portion of their Zn intake from meat and meat products, particularly during lunch, while free-living adults demonstrated higher overall consumption of milk and milk products and vegetables. This contrast in dietary patterns suggests potential nutritional vulnerabilities among care home residents due to their reliance on fewer food groups, primarily meat and dairy products, for Zn intake. Free-living adults, on the other hand, exhibited a broader dietary pattern that included higher intakes of vegetables and cereals. These differences emphasise the need for tailored dietary interventions to promote diverse Zn-rich food sources in care home residents, particularly for individuals with limited meat or dairy intake.

4.4.5 Urinary Iodine Status in Care Home Residents and Free-Living Participants

Urinary iodine concentration (UIC) is a sensitive indicator and serves as a reliable marker of iodine sufficiency, reflecting recent dietary iodine intake over the span of a few days (Abduazimovna, 2024). Severe iodine deficiency is classified by UIC below 20 µg/L, moderate deficiency by a UIC of 20–49 µg/L, and mild deficiency by a UIC of 50–99 µg/L. Adequate iodine intake falls between 100 and 199 µg/L, levels of 200–299 µg/L indicate more than adequate intake, and ≥300 µg/L suggests excessive intake, which may harm thyroid health (Hussain et al., 2019). In older adults, UIC adjusted for creatinine levels provides a more accurate measure by accounting for hydration and urine volume. Zn and meat consumption also influence thyroid health – with Zn essential for thyroid hormone synthesis and meat contributing to creatinine levels, affecting the interpretation of UIC adjusted for creatinine levels (Rohner et al., 2014).

4.4.5.1 UICs Across Groups

The mean UIC was compared between care home residents (n = 5) and free-living participants (n = 6) without correcting for creatinine values (**Table 4.11**). Care home residents had a lower mean iodine concentration (78.38 ± 35.77 µg/L) compared to free-living participants (109.99±54.97 µg/L). These results suggest that iodine intake may differ between the two groups, potentially reflecting variations in dietary iodine sources or access to iodine-rich foods.

4.4.5.2 Creatinine Concentrations and Dietary Insights

Urinary creatinine concentrations were also analysed independently to explore potential dietary and physiological factors. The mean creatinine concentration was slightly lower in care home residents (0.58 ± 0.69 g/L) compared to free-living participants (0.67±0.39 g/L). This may reflect differences in dietary protein intake, as higher creatinine levels are often associated with increased meat consumption. However, care should be taken when interpreting these values – as low creatinine levels can also indicate compromised renal function, which may affect the validity of iodine-to-creatinine ratios in this population.

4.4.5.3 Iodine-to-Creatinine Ratios

The iodine-to-creatinine ratio was calculated to account for variations in hydration status and provide an additional measure of iodine excretion. Care home residents exhibited a higher mean iodine-to-creatinine ratio (257.94 ± 226.27 µg/gCr) compared to free-living participants (197.77±93.94 µg/gCr). While these findings may offer some insights, the limitations of using creatinine as a correction factor, particularly in populations with potential renal function variability, must be acknowledged (see **Table 4.11**).

Table 4.11 Urinary analysis to test iodine concentration

Urinary analysis (mean ± SD)	**Care Home Residents (n=5)**	**Free-Living (n=6)**
Iodine Concentration (µg/ L)	78.38±35.77	109.99±54.97
Creatinine Concentration (g /L)	0.58±0.69	0.67±0.39
Iodine-to-Creatinine Ratio (µg /gCr)	257.94±226.27	197.77±93.94

µg/L = micrograms per litre; g/L = grams per litre; µg/gCr = micrograms per gram of creatinine

4.5 Discussion

To our knowledge, this is the first study to investigate the impact of antihypertensive medication on Zn status and health outcomes in residents of care homes for the elderly in Nottinghamshire. The study further aimed to compare these findings with those of free-living older adults in Nottinghamshire, using the FANSS. Additionally, urinary analysis was used to investigate iodine content to help validate dietary iodine intake against iodine concentration in older adults. Health problems are quite common among older adults. Older adults living in both community and institutional settings face a significant risk of inadequate food intake and malnutrition (Roberts et al., 2019). This often leads to deficiencies in essential minerals vital for various functions, including muscle function, thyroid metabolism, bone health, and immune and cognitive functions (Vural et al., 2020). Adequate nutritional intake plays a role in preventing adverse health outcomes and reducing the risk of further deterioration of existing poor health in older adults. This is particularly relevant in the United Kingdom – where the population is ageing rapidly, leading to a substantial increase in the proportion of individuals in older age groups.

The findings of this study demonstrate that care home residents were older (mean age: 90.8 years) than free-living participants (mean age: 79.3 years). This aligns with existing literature suggesting that individuals with higher health needs are more likely to reside in care homes. The age disparity observed reflects a broader trend – with institutionalised elderly populations typically being older and more dependent, often due to chronic health conditions such as CVD. The study's findings that care home residents had a higher incidence of CVD and were on multiple antihypertensive medications underscore the complex interplay between chronic disease management and nutritional status in this population. Tsiachristas et al. (2023) emphasised that individuals with higher care needs, including those with dementia or mental

health conditions, are more likely to live in care homes, as they require substantial community care services. Similarly, Cook et al. (2017) observed that care home populations frequently exhibit high levels of dependency and multimorbidity, further supporting the conclusion that older adults with complex health profiles are more likely to reside in such settings.

Regarding BMI, both groups generally fell within normal weight ranges. However, BMI values below 18.5, indicative of being underweight, were observed in 20% of care home residents, compared to none among the free-living participants. This finding aligns with the results of Margetts et al. (2003), who similarly reported a higher prevalence of underweight individuals among care home residents compared to the free-living older population. Furthermore, nutritional analysis revealed significant deficiencies across both groups – particularly among care home residents, with 60% at risk of malnutrition as measured by the MNA. According to the European Society for Clinical Nutrition and Metabolism, the MNA has been widely validated as a reliable tool for assessing nutritional status in elderly populations and is frequently used in geriatric evaluations to identify malnutrition risk (Besora-Moreno et al., 2020). Malnutrition in elderly populations contributes to a range of adverse outcomes, including impaired immune function, increased susceptibility to illness, frailty, and a diminished quality of life.

Polypharmacy is even more prevalent among institutionalised elderly individuals compared to those living in the community (Ramage-Morin, 2009). Antihypertensive drug use among care home residents was associated with significant variations in dietary intake, particularly Zn. This inadequacy is concerning since all participants in care homes were on antihypertensive medications – which have been demonstrated to impair Zn absorption or increase urinary excretion, particularly diuretics and CCBs (Baykal et al., 2003; Braun & Rosenfeldt, 2013;

Suliburska et al., 2018). In this study, care home residents on beta blockers exhibited lower Zn intake (4.28 mg), which may reflect both dietary inadequacies and medication-induced Zn losses. Similarly, the use of ACE inhibitors, CCBs, and diuretics, which were prevalent among the study participants, may interact with Zn metabolism. Although this study did not measure serum Zn levels, the dietary inadequacies observed point to a potential risk of Zn deficiency, particularly in those on medications that affect nutrient absorption. However, all participants exceeded the LRNI for Zn, similar to other studies that report Zn inadequacies without complete deficiencies in older populations (Vural et al., 2020). In the current study, the prevalence of Zn intake below the UK LRNI was estimated using two cut-off values of 4 mg/day (females) and 5.5 mg/day (males). The LRNI is considered sufficient for only 2.5% of the population (British Nutrition Foundation, 2021).

The presented study has demonstrated that for many elderly individuals, dietary energy intake is insufficient, which raises concerns regarding the potential for nutrient deficiencies. Care home residents demonstrated significantly lower intakes of calories, protein, and essential micronutrients, including Zn, vitamin C, and vitamin D, compared to their free-living counterparts. These findings support prior research indicating that institutionalised elderly individuals are more vulnerable to malnutrition. This vulnerability is often attributed to factors such as reduced functional independence, diminished self-esteem, social isolation, and loneliness, all of which are more prevalent in care home settings than among community-dwelling older adults (Pavlovic et al., 2019). Zn intake was particularly inadequate in both groups, but care home residents were notably at greater risk of deficiency, achieving only 66.8% of the recommended intake. This finding aligns with research indicating that care home residents are particularly vulnerable to Zn deficiency, which is often compounded by factors such as dietary restrictions and limited food variety (Şimşek & Uçar, 2021). The observed Zn

deficiency is of particular concern – given its vital role in immune function and wound healing, which are critical for elderly individuals (Patil et al., 2023). The present study also indicates a high prevalence of low Zn intake among older adults, consistent with the existing literature. This deficiency can be attributed to several factors – including reduced consumption of Zn-rich foods, often linked to a decline in taste acuity, poor dentition, and inadequate mastication. Additionally, the intake of foods that reduce Zn status and the presence of noncommunicable diseases further exacerbate the risk of inadequate Zn status in this population (Abeywickrama et al., 2024).

Dietary sources of Zn in care home residents were primarily meat and meat products (9.63 mg/day), a pattern consistent with studies highlighting that institutionalised populations often rely heavily on a limited variety of foods. These findings align with those of Kwun and Kwon (2000), who identified meat, poultry, and related products as the primary sources of Zn intake among South Koreans. In contrast, free-living individuals had more diverse diets, with higher intakes of dairy, cereals, and vegetables. Cereals have been reported as the major food group contributors to Zn intake in Japanese and American populations (Sarukura et al., 2011; Sharma et al., 2013).

The biochemical rationale for including UIC and creatinine strengthens the interpretation of the Zn findings. Zn is required for the activity of de-iodinases and other thyroidal enzymes; experimental Zn depletion reduces the conversion of T_4 to T_3, thereby diminishing the functional value of absorbed iodine (Rohner et al., 2014). The lower UIC observed in care-home residents, despite broadly similar estimated iodine intakes, may therefore reflect impaired utilisation secondary to sub-optimal Zn status rather than simple dietary insufficiency. Likewise, creatinine is produced at a near-constant rate in proportion to skeletal-muscle mass.

Because Zn supports myofibrillar protein synthesis and almost 50 % of total body Zn is located in muscle tissue (Maret & Sandstead 2006; Mares & Haase 2020), the reduced creatinine levels seen in Zn-deficient residents could indicate Zn-related sarcopenia rather than differences in hydration alone. Together, these mechanistic links suggest that inadequate Zn may propagate wider disturbances in thyroid and muscle function—findings that warrant consideration in nutritional care plans for very old adults. The findings suggest a lower UIC of 78.38 ± 35.77 µg/L in care home residents compared with 127.31 ± 67.95 µg/L in free-living participants, likely reflecting differences in dietary iodine intake and access to iodine-rich foods. Similarly, Miller et al. (2016) reported that elderly residents in long-term care facilities in New Zealand demonstrate a high prevalence of low iodine status, which is further exacerbated by the high incidence of chronic diseases and medication use that can affect nutrient metabolism and requirements. Understanding the nutritional status of older adults in care homes and addressing mineral deficiencies could support healthier ageing, enhance well-being, and potentially decrease the likelihood of requiring institutional care.

4.5.1 Strength of the Study

A key strength of this study is its comparative design, which includes both care home and free-living elderly individuals. This approach provides valuable insights into the influence of living environments on nutritional outcomes. The inclusion of these two groups allows for a more comprehensive understanding of the nutritional challenges that older adults face.

4.5.2 Limitations and Challenges

This study has several limitations that should be acknowledged. First, the sample size was relatively small due to the constraints imposed by the COVID-19 pandemic and time limitations, which significantly restricted participation. This impacts the generalisability of the findings and highlights the need for larger, more diverse samples in future research. Second, the participant pool was not fully representative of care home residents in Nottinghamshire, as it predominantly consisted of white female individuals. This lack of diversity limits the applicability of the findings to broader populations, particularly those with different ethnic and gender compositions. Third, the study's cross-sectional design, while practical within the given time frame, restricted the ability to establish causal relationships. While associations between nutritional status and other variables were identified, the findings remain exploratory and require longitudinal studies for more definitive conclusions. Fourth, dietary intake data for free-living older adults were self-reported using Intake24, which is prone to recall bias, inaccuracies, and misreporting. These issues are particularly relevant in older populations – where memory and cognitive function may be compromised, potentially affecting the accuracy of the reported nutrient intake. Fifth, variability in adherence to antihypertensive medications among participants may have influenced the observed nutritional outcomes. This inconsistency complicates interpretation and underscores the importance of accounting for medication adherence in future research. Finally, the study did not include biochemical measures, such as

serum Zn levels, to validate dietary intake data or identify subclinical deficiencies. The absence of these markers limits the depth of analysis and the ability to draw definitive conclusions about micronutrient status – particularly for Zn, which is essential for immune function and overall health.

Interpretation of FANSS data should be considered with caution, as the dataset did not include details on supplement use. Consequently, this study may not capture the full contribution of supplements to zinc and other nutrient intakes in free-living older adults. This limitation could influence the comparison with care home residents, particularly if supplement use patterns differ between groups.

4.6 Conclusion

This study provides a comparative analysis of Zn status and overall health outcomes in elderly care home residents and free-living older adults in Nottinghamshire, England, United Kingdom. Maintaining good nutritional status in older adults is crucial, benefiting both individuals and society. It leads to improve health outcomes, reduced dependence, and more efficient use of healthcare resources. The study findings highlighted the impact of antihypertensive medications, particularly diuretics and ACE inhibitors, on Zn levels – essential for immune function, cognitive health, and physical well-being. Care home residents, as a particularly vulnerable group, were found to have poorer Zn intake and greater nutritional inadequacies compared to community-dwelling older adults. Nutritional intake among care home residents were inadequate, while community-dwelling older adults showed relatively better, though still suboptimal, intakes of certain key nutrients. Dietary patterns differed between the two populations, with meat, poultry, dairy products, and cereals identified as the main sources of dietary Zn. Despite this, many individuals, especially in care homes, failed to meet the recommended levels for Zn and other essential nutrients.

Improving Zn intake and overall nutrition in older adults, whether in care homes or the community, could lead to substantial improvements in health and quality of life. Strategies such as Zn supplementation, personalised dietary advice, and regular nutritional monitoring should be prioritised. Routine screening for malnutrition, along with counselling on healthy eating and lifestyle choices, should also become standard practice in the care of older adults. These measures would help address nutritional deficiencies and promote healthier ageing. Future research should focus on the interaction between antihypertensive medications and nutritional status to develop more tailored interventions. Efforts to address these challenges are essential to improving the health and well-being of the ageing population.

Chapter 5: General Discussion and Conclusion

The World Health Organisation (2022) reports that the global population aged 60 and older has increased significantly in recent decades, rising from 382 million in 1980 to over 1 billion in 2020. By 2050, this figure is projected to nearly double, reaching 2.1 billion. In parallel with this demographic shift, the global prevalence of hypertension (HTN) is expected to exceed 1.5 billion by 2030 (Jafar et al., 2016). HTN management typically begins with the prescription of first-line antihypertensive medications, either as monotherapy or combination therapy (Garjon et al., 2020). In the United Kingdom, a study spanning 1988 to 2018 reported a substantial increase in the proportion of patients prescribed antihypertensive medications, rising from 7.8% to 21.9% over the 30-year period (Rouette et al., 2022). A key area of interest in this context is the impact of drug-nutrient interactions (DNIs) on zinc (Zn) metabolism. Zn plays an essential role in cardiovascular health, enzymatic function, and immune system activity (Chasapis et al., 2020). Zn deficiency remains a significant global concern, affecting over 25% of people in developing countries and approximately 15% in industrialised nations (Wessels & Rink, 2020).

The primary aim of this thesis was to investigate the relationship between antihypertensive medications and Zn status, prompted by the rising prevalence of HTN and the critical role of Zn in human health. Understanding how antihypertensive drugs influence Zn metabolism is vital for improving health outcomes and informing clinical practice. This research comprised three key components: **Chapter 2** established the foundational evidence through a systematic review and meta-analysis – identifying patterns of Zn disruption associated with specific classes of antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and diuretics. **Chapter 3** extended this investigation by presenting a secondary analysis of UK dietary survey data, revealing age- and sex-dependent effects of these medications on Zn status.

Chapter 4 examined Zn status among care home residents and free-living older adults, highlighting the compounded vulnerabilities faced by institutionalised individuals.

Building on the detailed discussions presented in each chapter of this thesis, the current chapter aims to synthesise the main findings, explore the factors influencing the results, and provide a critical analysis of the overall strengths and limitations of the research. The implications of the findings will also be discussed.

5.1 Understanding the Impact of Antihypertensive Drugs on Zn Status

This research synthesised evidence from nine studies to evaluate the impact of antihypertensive medications on Zn status in hypertensive patients. The data from the systematic review in **Chapter 2** indicated that while numerous studies have examined the effects of antihypertensive medications on Zn status, the findings remain inconsistent due to variations in study design and methodology. For example, several studies have reported significant reductions in serum Zn levels and increased urinary Zn excretion in hypertensive patients receiving ACE inhibitors and diuretics, thereby supporting the hypothesis that drug-induced disruptions in Zn homeostasis may involve the suppression of Zn reabsorption in the renal distal tubules (Samaras et al., 2013; Sulibursk a, 2014; Sulibursk a et al., 2018). These findings align with those of studies that have explored Zn's role in blood pressure regulation through mechanisms such as vascular relaxation and renal sodium transport modulation (Tubek, 2007; Williams et al., 2019). Previous research on Zn deficiency and its physiological consequences has primarily focused on its implications for immune dysfunction, oxidative stress, and chronic diseases such as diabetes and cardiovascular disorders (Chasapis et al., 2020; Knez & Glibetic, 2021).

The meta-analysis revealed that specific classes of antihypertensive drugs, particularly ACE inhibitors and diuretics, are associated with altered Zn homeostasis. This aligns with existing literature highlighting DNIs as a critical mechanism underlying micronutrient deficiencies in individuals with chronic disease management regimens (Braun & Rosenfeldt, 2013; Sulibursk a et al., 2018). A significant finding of **chapter 3** was the role of specific antihypertensive drug classes in altering Zn levels. ACE inhibitors, particularly those containing thiol groups (e.g. captopril), demonstrated the most pronounced effects, leading to increased zincuria and decreased serum Zn levels (Golik et al., 1998). The presence of thiol groups (-SH) in these medications facilitates the chelation of Zn ions, which impairs Zn reabsorption in the renal

distal tubules. This chelation-mediated inhibition of Zn reabsorption leads to enhanced urinary excretion of Zn and consequently lowers serum Zn concentrations (Samaras et al., 2013). This class-specific variability underscores the importance of considering pharmacological differences when prescribing medications to hypertensive patients. These findings support the first hypothesis that antihypertensive medications reduce Zn status.

5.2 Investigating Zn Status with Consumption of Common Antihypertensive Drugs in the UK Adult Population

Chapter 3 expanded the investigation by presenting a secondary analysis of the UK National Diet and Nutrition Survey (NDNS) data from 2008 to 2019. This analysis included 11,153 UK adults aged 19 and over, assessing Zn intake from dietary sources and plasma Zn concentrations in relation to antihypertensive drug use. The findings of this study revealed significant associations between antihypertensive drug use and Zn status, highlighting variations influenced by age, sex, and medication type. While dietary Zn intake was generally adequate across the population, a notable proportion, particularly males, consumed Zn below the recommended levels, with older adults and those on ACE inhibitors or diuretics showing lower Zn levels. The analysis revealed a clear pattern of lower serum Zn levels in individuals taking antihypertensive medications, particularly diuretics and ACE inhibitors. These results align with evidence that antihypertensive medications, particularly ACE inhibitors, may disrupt Zn homeostasis through increased urinary excretion (Samaras et al., 2013). Importantly, this relationship was more pronounced in older adults, supporting the hypothesis that age exacerbates the effects of these medications on Zn status.

The NDNS data highlighted dietary inadequacies as a contributing factor, with a significant proportion of older adults failing to meet the recommended dietary intake for Zn. This was particularly evident in individuals aged 65 and older, where declining serum Zn levels coincided with lower dietary Zn intake and age-related changes in nutrient absorption. For example, the decline in dietary Zn intake with age observed in this study aligns with broader trends in dietary behaviour and metabolic changes in older adults (Mocchegiani et al., 2013). These findings demonstrate that Zn deficiency in older adults is multifactorial, involving both physiological changes and medication effects.

While the discussion considers some factors influencing dietary zinc intake, additional determinants warrant consideration. Cognitive decline, particularly in older adults, can impair meal planning, grocery shopping, and food preparation, potentially reducing dietary zinc intake. Similarly, living alone has been associated with lower diet quality and decreased intake of micronutrient-rich foods, possibly due to reduced motivation to prepare balanced meals or limited social eating opportunities. Food insecurity may also restrict access to zinc-rich foods, especially in individuals on fixed incomes, while mobility issues can limit both shopping frequency and the ability to prepare diverse meals.

In **Chapter 4,** differences between care home residents and free-living participants may reflect some of these influences. Although institutional catering may partially compensate for these challenges by providing regular meals, this benefit might be reduced in advanced age if factors such as poor appetite, swallowing difficulties, or specific dietary restrictions limit consumption. For free-living older adults, the combined effects of social isolation, financial constraints, and physical limitations could compound the risk of zinc inadequacy. These broader social and functional factors should be considered in nutritional interventions aimed at improving zinc status in ageing populations.

5.3 A Comparative Analysis of Zn Status and Overall Health of Care Home Residents and Free-Living Older Adults in the United Kingdom

Chapter 4 detailed a cross-sectional study that focused on comparing Zn status and overall health between elderly care home residents and free-living older adults in Nottinghamshire. This study indicated the significant influence of antihypertensive medications on Zn status and overall health outcomes in elderly care home residents compared to free-living older adults in the United Kingdom. The findings revealed that care home residents – who are typically older and on multiple medications, including antihypertensive medications – exhibit higher risks of nutritional inadequacies, including Zn deficiency (Keser et al., 2018). To evaluate Zn status and assess the risk of Zn deficiency among older adults in the United Kingdom, this study measured dietary intake (De Benoist et al., 2007). The findings revealed that free-living older adults consumed significantly higher levels of Zn and protein than those residing in care homes. These observations are consistent with findings from other studies that have similarly reported lower dietary intake of essential nutrients among institutionalised elderly individuals compared to their free-living counterparts (Pavlovic et al., 2019; Şimşek & Uçar, 2021; Vural et al., 2020). The cross-sectional study found that care home residents had significantly lower dietary Zn intake than free-living older adults, with care home residents consuming only 66.8% of the reference nutrient intake for Zn. Furthermore, care home residents demonstrated higher rates of malnutrition, with 60% classified as being at risk of malnutrition based on the Mini Nutritional Assessment. These findings demonstrate the compounded vulnerability of care home residents, who experience the dual impact of poor dietary intake and chronic medication use on Zn status. Notably, participants using multiple classes of antihypertensive drugs exhibited the lowest Zn intake, underscoring the role of polypharmacy in exacerbating nutritional deficiencies.

Despite dietary Zn intake often exceeding the UK's lower reference nutrient intake, the reduced diversity of diets and reliance on Zn-limiting foods in care homes result in inadequate Zn status, with implications for immune function, wound healing, and overall well-being (Patil et al., 2023; Vural et al., 2020). Furthermore, the observed discrepancies in dietary patterns and nutrient intake between care home residents and free-living individuals emphasise the critical role of personalised nutritional interventions in supporting healthier ageing and minimizing the adverse effects of polypharmacy (Pavlovic et al., 2019; Şimşek & Uçar, 2021).

The systematic review demonstrated the mechanistic basis for drug-induced Zn deficiencies, while the NDNS analysis quantified these effects at the population level, identifying older adults as a particularly vulnerable group. The comparative study further illustrated how living conditions influence Zn status, with care home residents facing greater nutritional challenges than their free-living counterparts. These findings underscore the interplay between medication use, ageing, and environmental factors in determining Zn status and highlight the need for targeted interventions to address these issues.

5.4 Implications of Findings

The findings presented across the thesis have significant implications for clinical practice, nutritional policy, and patient care, particularly for individuals on long-term antihypertensive treatment. While these drugs are essential for managing HTN, their impact on Zn status warrants greater attention. The observed reductions in Zn levels due to medications such as ACE inhibitors and diuretics suggest potential risks of micronutrient deficiencies that can exacerbate other health conditions, such as impaired immune function and increased oxidative stress.

The findings of this thesis have significant clinical implications for the management of hypertensive patients. The consistent association between antihypertensive drug use and Zn depletion demonstrates the need for regular monitoring of Zn levels, particularly in patients on long-term therapy. Routine assessment of Zn status, using reliable biomarkers (such as erythrocyte or urinary Zn levels), could help identify at-risk individuals and prevent the onset of Zn-related deficiencies.

Nutritional interventions, including dietary counselling and Zn supplementation, should be considered part of comprehensive HTN management strategies. For example, patients prescribed diuretics or ACE inhibitors could benefit from tailored meal plans that incorporate Zn-rich foods, such as seafood, nuts, and legumes. Supplementation may be particularly beneficial for older adults or those with dietary restrictions, though further research is needed to determine optimal dosing regimens. Policies aimed at fortifying staple foods with Zn, similar to existing practices for iodine and vitamin D, could help address population-level deficiencies.

Healthcare providers should be made aware of the potential nutritional side effects of antihypertensive medications and incorporate nutritional screening and counselling into routine care for older adults. These strategies could mitigate the effects of Zn deficiency, improving health outcomes and quality of life in this population.

5.5 Strengths and Limitations of the Study

Although the strengths and limitations of each component of this research have been discussed in each chapter, this section provides a comprehensive summary of the strengths and limitations of the thesis. This thesis presents several important strengths across its chapters, highlighting its contribution to understanding the relationship between antihypertensive medications and Zn status. One significant strength lies in the comprehensive methodology employed – including a systematic review and meta-analysis conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, thereby ensuring a rigorous synthesis of evidence from diverse studies. The use of high-quality databases, such as the Cochrane Library, PubMed, Ovid MEDLINE, and Web of Science, underscores the breadth of the literature search, ensuring robust and representative findings. Another strength is the inclusion of multiple Zn biomarkers, such as serum, urinary, and erythrocyte Zn levels, alongside dietary intake data, providing a multidimensional perspective on Zn status. This study is the first to utilise national data from the NDNS to analyse the association between antihypertensive drugs and Zn status in the UK adult population. The study generated a high-quality dataset and included a large sample size. The findings from this thesis contribute valuable evidence to the research area of the relationship between antihypertensive medications and Zn status.

Furthermore, the comparative analysis of care home residents and free-living older adults offers a unique exploration of Zn status and nutritional health within distinct yet vulnerable populations, contributing valuable evidence to the field of geriatric nutrition. By integrating age, sex, and medication type as key variables, the study demonstrates nuanced differences in Zn status, offering actionable insights for public health and clinical practice. Lastly, the thesis emphasises the broader implications of its findings for HTN management, advocating for nutritional monitoring and interventions to improve patient outcomes. These strengths collectively underscore the study's robust design, relevance, and potential to inform future research and clinical practice.

When interpreting the findings of this thesis, it is essential to consider several limitations. First, the diversity in study designs among the included research, which ranged from cross-sectional to observational studies, made direct comparisons and meta-analytic synthesis challenging and may have introduced inconsistencies in the findings, limiting their overall interpretability and generalisability.

Another limitation is the small sample sizes of several studies, which made the findings less robust. Additionally, Zn status was measured using various methods – such as serum, plasma, and erythrocyte Zn levels – that were not standardised across studies. This variability complicates comparisons and raises concerns about the consistency and reliability of the data.

The complex effects of antihypertensive drugs on Zn metabolism are still not fully understood. This is partly because some studies provided limited information and lacked crucial pharmacological details, such as dosage, duration, and adherence to medication regimens. These details are essential for a clearer understanding of how these drugs influence Zn status.

The cross-sectional design of many included studies is another limitation, as it prevents conclusions about causation. While associations between antihypertensive drug use and Zn status were observed, it remains unclear whether the medications directly impact Zn levels or other factors are at play. Longitudinal research is needed to explore these relationships in greater depth.

Finally, some analyses relied heavily on self-reported dietary intake data, which is prone to recall bias and inaccuracies. This is particularly problematic in populations with higher Body Mass Index (BMI) or cognitive impairments, where underreporting or misreporting of nutrient intake is more common. Furthermore, many datasets lacked biochemical validation, such as serum or urinary Zn measurements, which limits the ability to confirm trends and detect subclinical deficiencies.

5.6 Potential Future Works

To improve knowledge in this area, several future studies should be considered to further investigate the relationship between antihypertensive medications and zinc (Zn) status:

5.6.1 Diverse and Global Populations

Future studies should include larger, more diverse populations, particularly from low- and middle-income countries. This approach would provide a more comprehensive understanding of global trends in Zn status and its interactions with antihypertensive medication use, addressing gaps in the current literature that predominantly focuses on high-income countries.

5.6.2 Longitudinal Study Designs

Longitudinal research is needed to better understand the causal pathways linking antihypertensive medication use, ageing, and changes in Zn status. These studies should adopt standardised Zn measurement protocols, such as the consistent use of serum or urinary Zn biomarkers, to improve the reliability and comparability of findings across different studies.

5.6.3 Randomised Controlled Trials

Randomised controlled trials evaluating the efficacy of Zn supplementation in older adults on antihypertensive medications are crucial. Such trials would provide high-quality evidence to inform clinical guidelines and help determine whether Zn supplementation could mitigate the micronutrient depletion associated with long-term medication use.

5.6.4 Broader Exploration of DNIs

Future research should broaden its scope to examine the impact of other commonly prescribed medications on Zn and other micronutrient statuses. This would help develop a more comprehensive understanding of DNIs in older adults, a population often managing multiple comorbidities and polypharmacy. By addressing these gaps, future studies can contribute to more effective and nutritionally informed strategies for managing HTN, ultimately enhancing the ability of healthcare professionals and researchers to optimise the health and well-being of patients worldwide—particularly vulnerable populations, in whom the interplay of medications and nutrition is most critical.

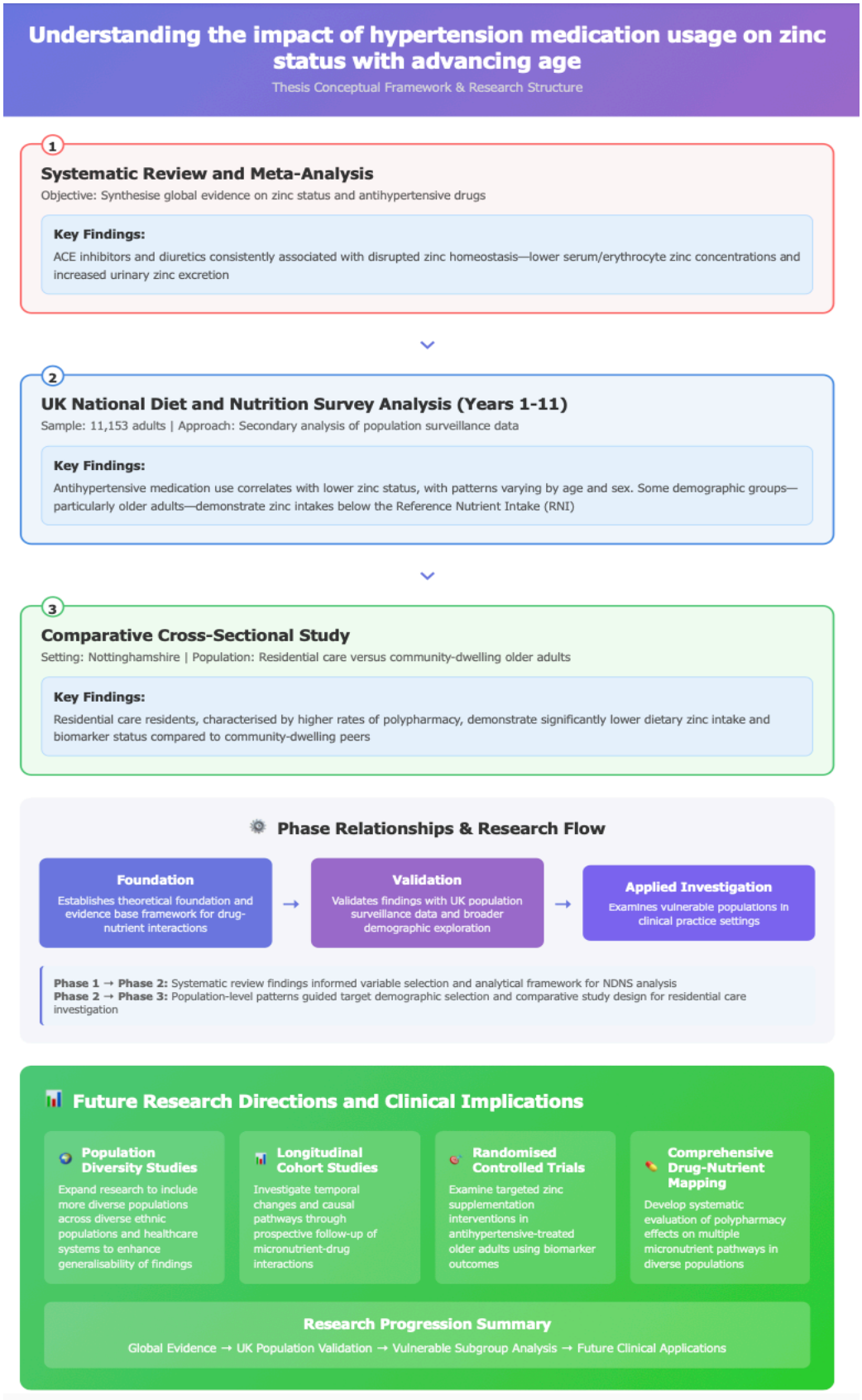


Figure 5.1 Conceptual Framework Summarising Thesis Structure, Inter-Phase Relationships, and Future Research Directions

5.7 Conclusion

This thesis has demonstrated that antihypertensive medications, particularly ACE inhibitors and diuretics, can significantly impact Zn status, leading to disruptions in Zn homeostasis. The systematic review and meta-analysis revealed a clear disruption of Zn homeostasis associated with antihypertensive drug use – particularly ACE inhibitors and diuretics, which contribute to increased urinary Zn excretion and reduced Zn levels. These disruptions underscore the need to monitor Zn status in hypertensive patients to mitigate potential deficiencies and related health risks.

The secondary analysis of the NDNS highlighted significant variations in Zn status among UK adults based on sex, age, and antihypertensive drug use. While dietary Zn intake appeared adequate for most participants, subsets of the population – especially older males – fell below recommended levels, emphasising the importance of targeted nutritional interventions for vulnerable groups. These findings not only suggest potential compensatory mechanisms in some individuals but also call for further exploration of the long-term effects of antihypertensive medications on Zn metabolism.

The comparative analysis of care home residents and free-living older adults illuminated the heightened nutritional vulnerabilities of care home populations, who demonstrated poorer dietary Zn intake and greater overall nutritional inadequacies. The role of antihypertensive medications in exacerbating these deficiencies was evident, particularly for diuretics and ACE inhibitors, reinforcing the need for routine nutritional assessments and tailored dietary strategies in these settings.

The findings highlight the complex relationship between antihypertensive therapy and Zn metabolism, influenced by factors such as the type of medication, duration of use, and individual patient characteristics. Ensuring adequate Zn status represents a critical step towards optimising the health and well-being of hypertensive patients.

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Chapter 7: Appendices

Appendix 1

TO DETERMINE THE PREVALENCE OF MINERAL DEFICIENCY IN OLDER ADULTS: CARE HOME STUDY

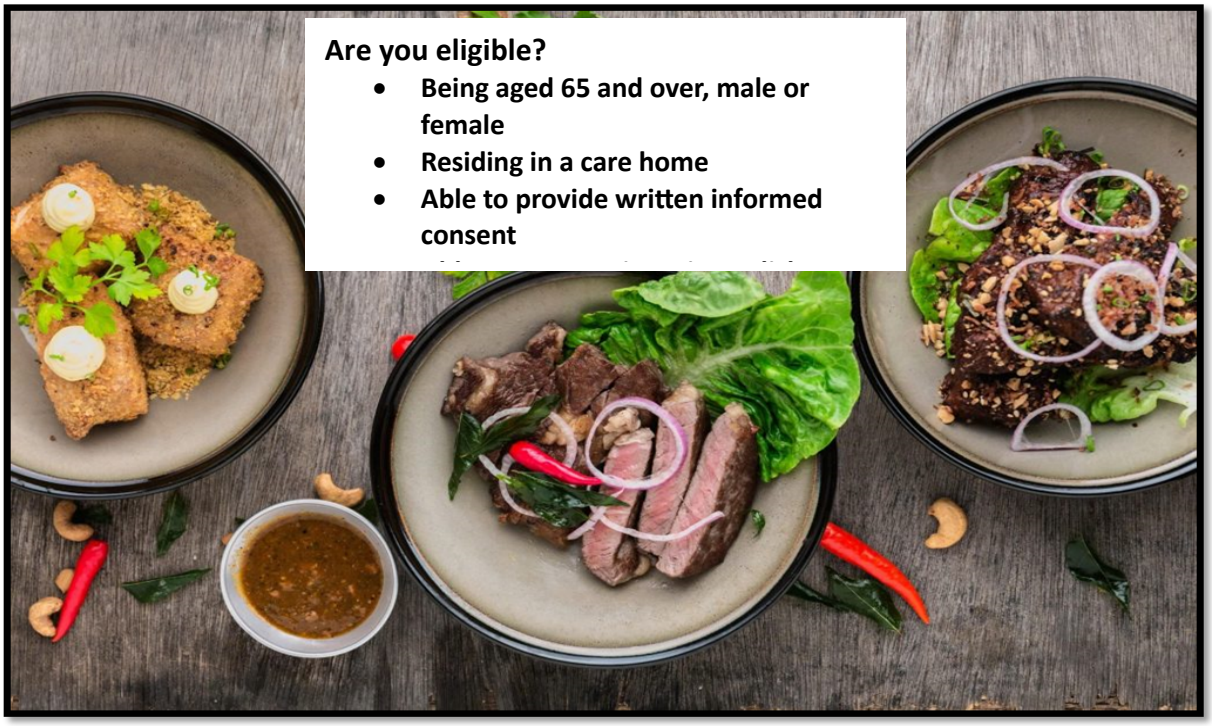
IRAS PROJECT ID: 335876 REC NUMBER: 24/IEC08/0005 Final Version 1.0 05.03.2024

A Nutrition Study for Care home residents

This study is looking at whether older adults living in care homes may have any nutritional deficiencies. We are especially interested in minerals. Mineral deficiency is associated with several health problems such as fatigue, frailty and a weakened immune system. This is why identifying and understanding this problem could be so helpful for the well-being of older adults.

What will be required in the study?

- **Attending a screening session (Measurement of body weight, height, and hand grip strength)**
- **Providing a spot urine sample**
- **Providing a saliva sample**



Are you eligible?

- **Being aged 65 and over, male or female**
- **Residing in a care home**
- **Able to provide written informed consent**

If you would like to learn more about the study, please contact us:
Researchers: Zeynep Vural & Sultan Almutairi
Email: zeynep.vural@nottingham.ac.uk stxsa47@nottingham.ac.uk
OR, you can express your interest in this study through the home manager and staff, and we will meet with you to provide more information about the study.

***This study is being carried out as part of an educational project**

Appendix 2

PARTICIPANT INFORMATION SHEET for CARE HOME RESIDENTS

Final Version 2.0 Date 05.03.2024

IRAS Project ID: 335876

Title of Study: To Determine the Prevalence of Mineral Deficiency in Older Adults- CARE HOME STUDY

Name of Chief Investigator: Simon Welham

Local Researchers: Zeynep Vural & Sultan Almutairi

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

The importance of nutrition is undeniable in ensuring people are able to maintain an active life and age healthily. Minerals are crucial for the human body, serving essential roles in muscle and nerve function, cardiovascular health, bone and dental maintenance, immune system support, cognitive abilities, and antioxidant activities. That is why the determination of mineral inadequacies due to their significant roles is vital in the elderly.

This study aims to investigate whether mineral deficiencies pose a health concern in older adults and to determine the prevalence of such deficiencies. Determining the deficiency will help us improve the health and well-being of older adults, develop future policies, and take necessary measures.

Why have I been invited?

You have been invited to participate in this research because your care home is volunteering for the study, and you are a person aged 65 or older, from any sociodemographic background, currently residing in this care home.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you choose to take part, you are still free to withdraw at any time and without giving a reason. This will not affect your legal rights.

What will happen to me if I take part?

If you decide to participate in this study, you first need to sign a consent form. After taking your consent, we will organise a measurement session. Study measurements (weight, height and hand-grip strength) will be taken in a private area in care home. Then, we will request from you to give small amount of urine sample (approximately 10-20 mL) and small amount of saliva sample (5-10 mL) to determine mineral deficiency. To do this, small urine and saliva vessels will be provided to you. Staff members will be available, if needed, to assist with collection of urine samples. The part where you physically participate in the study ends here.

After that, we will request the care team to provide responses and complete information regarding your health and demographic details relevant to the study by reviewing the records of the care home. Finally, we will record your food intake during four consecutive days. To do this, we will record your food intake before and after each meal, weighing each portion served and the remaining amount on the plates. Your trays before and after each meal (breakfast, lunch, dinner and snacks) will be weighed by researchers for four consecutive days.

Expense and Payment

We will not make any payment for participation in the study.

What are the possible disadvantages and risks of taking part?

There is no risk of taking part in the study. Collecting urine and saliva samples is safe and non-invasive. Therefore, there is no expected harm or adverse event from giving urine and saliva samples and no adverse event is expected due to MINDEF study.

What are the possible benefits of taking part?

We cannot promise the study will help you directly, but the information we gather from the study may contribute to future precautions and research.

The research team will share summary of the study findings with care home managers, care home dietitian and participants (if participants wish). If the researchers detect mineral deficiency, this notification can enable the care homes to conduct their own assessment to confirm the findings of our study. Based on the confirmed deficiency, the healthcare team can develop a plan tailored to the resident's needs in care homes.

What if there is a problem?

If you have any problem or concern about the study, you can ask the researchers in the first instance, trying to do their best. Their contact details are given at the end of this information sheet. If you are still not satisfied and would like to make a formal complaint,

you should then contact Louise Sabir, who is the Faculty of Medicine and Health Sciences Research Ethics Committee Administrator.
E-mail: fmhs-researchethics@nottingham.ac.uk

How will we use information about you?

The University of Nottingham are the sponsor of this study. This means we are responsible for looking after your information and using it properly.
We will need to use information from you and from your care home records for this research project. This information will include your name and initials.
People will use this information to do the research or to check your records to make sure that the research is being done properly.
People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.
We will keep all information about you safe and secure.
Once we have finished the study, we will keep some of the data so we can check the results.
We will write our reports in a way that no-one can work out that you took part in the study.

You will be able to obtain a copy of the final results after the study has ended from the research team but individual study results will not be available. We may share our research data with researchers in other universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data shared in this way will be anonymised.

Normal safeguarding procedures will be followed in the event that the study team identify information that may suggest there is a risk of harm to the participant, or others and that this may involve informing relevant parties about participants' involvement in the study. This means that although what you say to us confidential; should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

You can find out more about how we use your information

- reading our privacy statement https://www.nottingham.ac.uk/utilities/privacy/privacy-information-for-research-participants.aspx
- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to simon.welham@nottingham.ac.uk , or
- by ringing us on 01159516122.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you would like to withdraw, contact local researchers and they can organise this for you. If you withdraw, or are withdrawn from the study for any reason, we will no longer collect any information about you or from you but we will keep the information about you that we have already obtained.

What will happen to any samples I give?

Urine and saliva samples will be used to measure urinary and saliva mineral extraction to determine whether you suffer from mineral deficiency. Samples will be stored securely at the UoN under the University's Human Tissue Research Licence (No: 12265). We would also like to seek your consent for any remaining samples to be stored and used in possible future research. Some of these future studies may be carried out by researchers other than current team of MINDEF study, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you don't agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

What will happen to the results of the research study?

The study is a student project and researchers will be hoping to gain a PhD at the end of it. This research is being carried out as part of an educational project and will contribute to University of Nottingham PhD thesis. Findings will also be published in academic journals and will be presented in conferences. All such data will be presented anonymously so that none of the participants can be identified.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Who has reviewed the study?

All research involving vulnerable people is looked at by an independent group of people, called Research Ethics Committee (REC), to protect your interests. This study has been reviewed and given favourable opinion by NHS Social Care Research Ethics Committee (REC). The REC Reference Number is 24/IEC08/0005.

Further information and contact details

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Amanda Avery E-mail: amanda.avery@nottingham.ac.uk

Neil Fraser (Clinical Care Home Lead/GP Trainer) E-mail: neil.fraser7@nhs.net
neilandrewfraser@gmail.com

Appendix 3

University of Nottingham
UK | CHINA | MALAYSIA

CARE HOME RESIDENT CONSENT FORM
(Final version 2.0 Date: 05.03.2024)

Title of Study: To Determine the Prevalence of Mineral Deficiency in Older Adults- CARE HOME STUDY

IRAS Project ID: 335876

Name of Researcher: Zeynep Vural & Sultan Almutairi

Name of Participant: **Please initial box**

1. I confirm that I have read and understood the information sheet version number 2.0 dated 05.03.2024 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care and legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand and agree that I will give saliva sample to be used for the analysis of Saliva Mineral Concentration. ☐

5. I understand and agree that I will give mid-stream spot urine sample to be used for the analysis of Urinary Mineral Concentration. ☐

6. Consent for storage and use in possible future research (Optional)

I agree that the samples I have given and the information gathered about me can be stored by the University of Nottingham at the Division of Nutritional Science, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway.

Ye ☐ N ☐

Ye ☐ No ☐

7. I agree to members of the research team storing my details for the purpose of contacting me with a summary of the study findings (Optional)

8. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the care home records

Appendix 4

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences
School of Bioscience
B34 Room 2nd Floor, North laboratory Building
Sutton Bonington Campus
Sutton Bonington
LE12 5RD

Dr Simon Welham, Assistant Professor in Nutritional Science, simon.welham@nottingham.ac.uk
Michelle Thomas, michelle.thomas1@nottingham.ac.uk, Research Assistant
Study email address: fanss@nottingham.ac.uk

Study Title:

Establishing the extent, severity and drivers of nutritional insecurity in Nottinghamshire to identify the most effective policies for its alleviation.

PARTICIPANT INFORMATION SHEET

Research Ethics Reference: **FMHS 208-0223 FANSS**
Version 2.0 Date: 24/03/2023

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to go through the information sheet and email us to answer any questions you have (fanss@nottingham.ac.uk). Please take time to read this carefully and discuss it with others if you wish. Ask us anything that is not clear.

What is the purpose of the research?

The purpose of the study is to understand the food and nutritional security of adults aged 18 years and over living in Nottinghamshire. In collaboration with Nottinghamshire County Council the results from the study will used to identify polices to alleviate food and nutritional insecurity in Nottinghamshire.

Food insecurity in the United Kingdom was increasing before the COVID-19 pandemic and continues to increase as the cost-of-living increases. Some population groups are more likely to experience food insecurity than others. Food security is concerned with all members of a household having access to enough food for an active and healthy life.

The experience of food insecurity can alter the type of foods included in the diet impacting on nutritional security. Nutritional security is defined as regular and fair access to food which is healthy, affordable, and safe to eat which promotes optimal health and wellbeing. Nutritional security is concerned with the foods we eat and the nutrients within them and how they influence our health.

The aims of the study are:

1. Map the number of adults in Nottinghamshire experiencing food insecurity.
2. Estimate energy and nutrient intakes to understand if any nutrients are consumed more than or below the government dietary recommendations and how this might impact health. (Nutrients include carbohydrates, fats, protein vitamins and minerals)
3. Identify polices to alleviate food and nutritional insecurity in Nottinghamshire.

Why have I been invited to take part?

You have been invited to take part in this research because you are aged 18 years and over and live in Nottinghamshire.

We will be recruiting up to 1000 participants in this study.

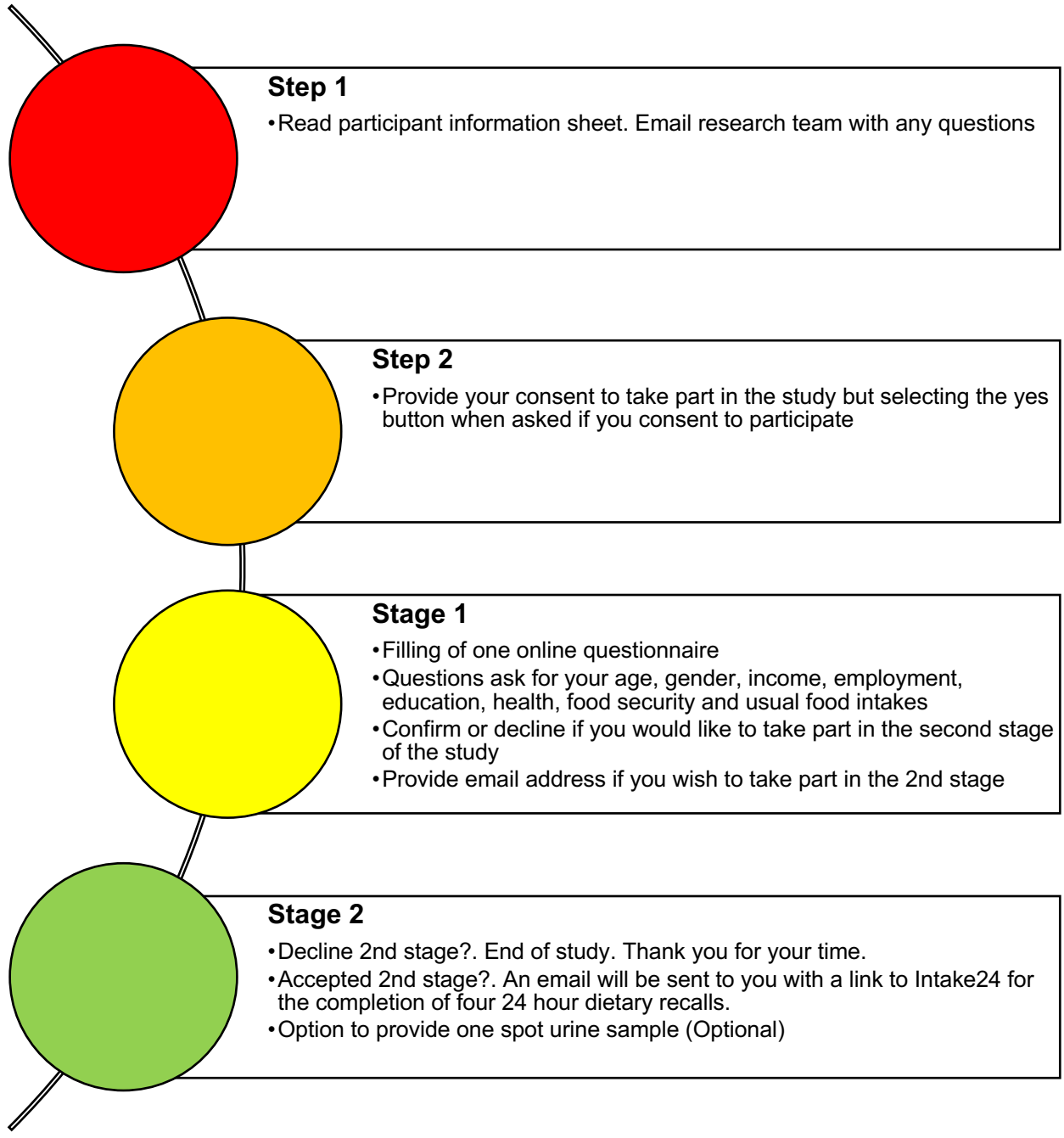
Do I have to take part?

It is up to you to decide if you want to take part in this research. If you agree to participate, we will ask you to select “yes” when asked on the first page of the survey presented after clicking the link. However, you would still be free to withdraw from the study at any time, without giving a reason, simply let the research team know.

1. What will happen to me if I take part?

If you agree to take part in the first stage of the study, you will be asked to complete one online survey with the option to participate in the second stage of the study if you wish. There is also the option to provide a urine sample.

Please see diagram below for the stages of the study and what is involved



2. *W*hat is Food Security Questionnaire?

In this study we use the United States Adult Security Questionnaire which asks 10 questions related to food eaten in your household in the previous 30 days. The questions are designed to understand if a household has experienced anxiety of worry about running out of food due to not having enough money, if they have had to make changes to the type and quality of food eaten or if they have had to skip meals or go without food in a whole day because of lack of money.

2.1. *What is a Food frequency questionnaire?*

In this study we use the EPIC Food Frequency Questionnaire (FFQ). A FFQ is a dietary assessment tool that captures an individual's usual food consumption using a predefined list of food and in the study, we ask for the frequency at which foods were consumed in the previous 12 month. FFQs are a common method for measuring dietary patterns in large population-based studies.

2.2. *What is Intake24?*

Intake24 is self-completed computerised dietary recall based on multiple pass 24-hour recall. The multiple pass method will promote you for any foods and beverages they may have been missed. Intake24 has been used in previous studies looking into dietary intake amongst UK population groups and is used in the UK Government National Diet and Nutrition Survey (NDNS).

3. Are there any disadvantages in taking part?

There are no known risk risks to participating in this study, however, the topic of food security may be upsetting. Throughout the study we have provided links to external organisations who may be able to provide help and advice.
Collection of Urine is a non-invasive procedure (optional).
We appreciate you giving up your valuable free time to help with this project.

4. Are there any benefits in taking part?

There will be no direct benefit to you from taking part in this research but your contribution may help in the understanding of the causes of food and nutritional insecurity and identification of polices to alleviate both in Nottinghamshire.
If you would like the results from your dietary assessment and BMI, we can provide you with these details. As a token of our appreciation the first 200 participants who complete stage 1 and stage 2 of the study in full will receive a £50 gift voucher for Sainsbury's (maximum 200 people).

5. Will my time/travel costs be reimbursed?

Participants will not receive an inconvenience allowance to participate in the study. Participation is entirely voluntary. We are unable to provide reimbursement for cost associated with travel to drop of the urine samples.

6. What will happen to any samples I give?

We will use your urine sample to test for urine iodine concentration (UIC) and adjust for hydration levels with appropriate method e.g., creatinine or osmolality. The results will be used to understand iodine status of adults living in Nottinghamshire.

The urine sample will be made a cellular that is any cells in the urine will be removed as disposed of in line with university protocol. Samples will be stored in a locked freezer at -20oC in the North Laboratory, Sutton Bonington Campus before testing.
We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Nottingham under the University's Human Tissue Research Licence (no 12265).

Some of these future studies may be carried out by researchers other than current team of Food and Nutrition Security, who ran the first study, including researchers working outside the University. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

Will any genetic tests be done? No genetic test will be conducted.

7. What happens to the data provided?

All research data will be anonymised, and the original screening data will be stored securely in a locked archive, accessible only to staff members of the research team.
None of the research data will be personally identifiable since personal details including contact details (address, email address, telephone number) will be removed and entered into another system, which will be password-protected and only the chief and principal investigators will be able to access it.
The data will be analysed by the principal researchers and research assistants and, here again, the data will be password-protected, and the password itself will be changed when individuals connected to the project leave the university.
This study has been designed in line with ethical and legal standards and guidelines, and any information which is collected will be treated as confidential.
Participants' data will be examined by authorised individuals from the University of Nottingham, who oversee managing the research, and authorised people whose role is to oversee that the study is being undertaken correctly. Research investigators are aware of the duty of confidentiality across the research participant, and they will follow strict guidelines and try to their best.
The information which is gathered about you during this study will remain confidential and will be stored on a password-protected computer database and in a locked, secure office. Any information which is used externally will not contain your name or

address so that you will remain anonymous and protected from being identified using a unique study identification number (for example P01 for participant number). Your name and any information about you will not be disclosed outside the study centre. If applicable: We would like your permission to use fully anonymised direct quotes in research publications.

All research data and records will be stored for a minimum of [7] years after publication or public release of the work of the research.

We would like your permission to use anonymised data in future studies, and to share our research data (e.g., in online databases) with other researchers in other Universities and organisations both inside and outside the European Union. This would be used for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. All personal information that could identify you will be removed or changed before information is shared with other researchers or results are made public.

Data sharing in this way is usually anonymised (so that you could not be identified)

8. What will happen if I don't want to carry on with the study?

Even after you have signed the consent form, you are free to withdraw from the study at any time without giving any reason. Any personal data will be destroyed. If you leave the study, it will not be possible to obliterate any information you have provided up to that point, and it could still be used in the analysis of the study findings. If you withdraw, we will no longer collect any information about you or from you, but we will keep the anonymous research data that has already been collected and stored. This information may have already been used in some analyses and may still be used in the final study analyses.

9. Who will know that I am taking part in this research?

Data will be used for research purposes only and in accordance with the General Data Protection Regulations. Electronic storage devices will be encrypted while transferring and saving all sensitive data generated in the course of the research. All such data are kept on password-protected databases sitting on a restricted access computer system and any paper information (such as your consent form, contact details and any research questionnaires) would be stored safely in lockable cabinets in a swipe-card secured building and would only be accessed by the research team.

Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data).

You can find out more about how we use your personal information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx/

Designated individuals of the University of Nottingham may be given access to data for monitoring and/or audit of the study to ensure we are complying with guidelines.

With your consent, we will keep your personal information on a secure database in order to contact you for future studies.

10. What will happen to the results of the research?

The research will be published in a relevant scientific journal as an article. Also, your research data is always presented as anonymous, so you are not identified and identifiable in any publications or reports.

11. Who has reviewed this study?

All research involving people is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests.

12. Who is organising and funding the research?

The Principal Investigator of the study is Dr Simon Welham and this research is being supported by the University of Nottingham.

13. What if there is a problem?

If you have a concern about any aspect of this project, please speak to the researcher [Michelle Thomas] or the Principal Investigator [Dr Simon Welham] who will do their best to answer your query. The researcher should acknowledge your concern and give you an indication of how he/she intends to deal with it. If you remain unhappy and wish to complain formally, you can do this by contacting the FMHS Research Ethics Committee Administrator, Faculty Hub, Medicine and Health Sciences, E41, E Floor, Medical School, Queen's Medical Centre Campus, Nottingham University Hospitals, Nottingham, NG7 2UH or via E-mail: FMHS-ResearchEthics@nottingham.ac.uk.
Please quote ref no: FMHS xx-xxx

14. Contact Details

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Michelle Thomas
School of Biosciences, Division of Food Science Nutrition and Dietetics
Room B34, North Laboratory, Sutton Bonington Campus
Email: FANSS@nottingham.ac.uk

Appendix 5

PARTICIPANT STUDY FORM for CARE HOME RESIDENTS

Final Version 1.0: Date: 11.01.2024

Title of Study: To Determine the Prevalence of Mineral Deficiency in Older Adults- CARE HOME STUDY

Short Title: *MINeral DEFiciency in the Elderly (MINDEF)*

IRAS PROJECT ID: 335876

Name of Researcher: Zeynep Vural & Sultan Almutairi

Date:

Participant Unique Study Number:

DEMOGRAPHICS

Age:	
Sex:	
-Female -Male	
Marital status:	
-Single -Married -Divorced -Widowed -Civil Partner -Not known	
Ethnicity:	
-White -Mixed Ethnic Group -Asian or Asian British -Black or Black British -Any other Ethnic Groups	

The highest level of education completed:	
-Degree or Graduate Education (BSc, BA) -Post Graduate Education (PhD, MSc, MA) -Vocational Education (NVQ, HNC, HND) -No qualification	
Yearly income:	
-Lowest Tertile (0-20,500 pounds) -Middle Tertile (20,500-35,700 pounds) -Highest Tertile (≥35,700 pounds)	
Admission Date in Care Home	

HEALTH and LIFESTYLE QUESTIONS

Involved in Any Social Activities	
-Yes -No	
Smoking	
-Yes (Cigarette, pipe, cigar, other) -No -Former Smoker	
If yes, how often do you smoke? -Daily (number per day) -At least weekly (number per week)	
Alcohol	
-Yes (Beer, wine, champagne, cider, whisky, vodka, gin, spirits, alcopop, other) -No	
Diagnosed with the Following Diseases:	
-Diabetes Mellitus -Ischemic Heart Disease (Coronary Heart Disease) -Heart Failure -High Blood Pressure (Hypertension)	

-Chronic Kidney Disease -High Cholesterol -Liver Disease -Chronic Obstructive Pulmonary Disease -Arthritis -Osteoporosis -Cancer -Gout -Coeliac Disease -Crohn's Disease -Irritable Bowel Syndrome -Ulcerative Disease -Asthma -Alzheimer -Dementia -Depression -Other (specify here)	
Whether Taking Prescribed Medication -Yes -No	
The List of Medications Taken (Start Date, Dose, Frequency and Time)	
Physiological Monitoring Data/Medical-Health Examination Findings of Residents (If available) **-**Blood Pressure -HemoglobinA1c -Blood Glucose Level	
Dietary Supplement Usage and Oral Nutritional Supplement Intake	
-Yes (If yes, please specify type, amount and frequency) -No	
Diet Texture/Levels	
-Regular Diet -Regular Easy Chew -Soft and Bite-sized -Minced and Moist -Pureed -Liquidized -Transitional Foods	
Diet Prescription/Any Restricted Diet	
-Diabetic	

-Ketogenic -Gluten-free -Lactose-free -High Fibre -Vegan -Vegetarian -Low fat -Low salt -Please specify any specific/restricted diet (e.g. low fat, low carbohydrate, low salt etc.)	
The Number of Full Meals Eaten Daily	
Mode of Feeding	
-Unable to eat without assistance -Self-fed with some difficulty -Self-fed without any problem	
Last Full Revision of the Menu • Less than six months • 6-12 months • 13-18 months • More than 18 months	
Menu Cycle Length	

WEIGHT:

HEIGHT:

BODY MASS INDEX:

HAND-GRIP STRENGTH:

RIGHT HAND:

1. **ATTEMPT:** 2. **ATTEMPT:** 3. **ATTEMPT:**

LEFT HAND:

1. **ATTEMPT:** 2. **ATTEMPT:** 3. **ATTEMPT:**

MINI-NUTRITIONAL ASSESSMENT SHORT-FORM (MNA-SF)

MNA-SF SCREENING
A Has food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing difficulties? 0=Severe decrease in food intake 1=Moderate decrease in food intake 2=No decrease in food intake
B Weight loss during the last three months 0=Weight loss greater than 3 kg (6.6 lbs) 1=Does not know 2=Weight loss between 1 and 3 kg (2.2 and 6.6 lbs) 3=No weight loss
C Mobility 0=Bed or chair bound 1=Able to get out of bed/chair but does not go out 2=Goes out
D Has suffered psychological stress or acute disease in the past three months? 0=Yes 2=No
E Neuropsychological problems 0=Severe dementia 1=Mild dementia 2=No psychological problems
F Body Mass Index (BMI) (weight in kg) / (height in m2) 0=BMI less than 19 1=BMI 19 to less than 21 2=BMI 21 to less than 23 3=BMI 23 or greater
SCREENING SCORE **(Max. 14 points)** 12-14 points= Normal Nutritional Status 8-11 points= At the risk of Malnutrition 0-7points= Malnourished

BARTHEL INDEX ACTIVITIES OF DAILY LIVING

Bowels Resident's Score: 0=Incontinent (or needs to be given enemata) 1=Occasional accident (once/week) 2=Continent
Bladder Resident's Score: 0=Incontinent, or catheterized and unable to manage 1=Occasional Accident (Max. once per 24 hours) 2=Continent (for over seven days)
Grooming Resident's Score: 0=Needs help with personal care 1=Independent face/hair/teeth/shaving (implements provided)
Toilet Use Resident's Score: 0=Dependent 1=Needs some help but can do something alone 2=independent (on and off, dressing, wiping)
Feeding Resident's Score: 0=Unable 1=Needs help to cut, spread butter, etc. 2=Independent (food provided within reach)
Transfer Resident's Score: 0=Unable-no sitting balance 1=Major help (one or two people, physical), can sit 2=Minor help (verbal or physical) 3=Independent
Mobility Resident's Score: 0=Immobile 1=Wheelchair independent, including corners, etc. 2=walks with the help of one person (verbal or physical) 3= Independent (but may use any aid, e.g., stick)
Dressing Resident's Score: 0=Dependent 1=Needs help, but can do about half unaided 2=Independent (including buttons, zips, laces, etc.)
Stairs Resident's Score: 0=Unable 1=Needs help (verbal, physical, carrying aid) 2=Independent up and down
Bathing Resident's Score 0=Dependent 1=Independent (or in the shower)
The resident's final score isx5 to get a number on a 100-point score. Barthel scores of 0-20 indicate 'total' dependency, 21-60 indicate 'severe' dependency, 61-90 indicate 'moderate' dependency and 91-99 show 'slight' dependency.

THE FRAILTY INSTRUMENT OF THE SURVEY OF HEALTH, AGEING AND RETIREMENT IN EUROPE (SHARE FRAILTY INSTRUMENT / SHARE-FI)

EXHAUSTION In the last month, have you had too little energy to do the things you wanted to do? -Yes -No
LOSS OF APPETITE What has your appetite been like? -Diminution in desire for food and/or eating less than usual -No change in desire for food and/or eating the same as usual -Increase in desire for food and/or eating more than usual
WEAKNESS Maximum hand-grip strength in kilograms: **Right Hand:** Attempt 1: Attempt 2: **Left Hand:** Attempt 1: Attempt 2:
WALKING DIFFICULTIES Because of a health or physical problem, do you have any difficulty doing any of the following everyday activities? **Walking 100 metres:** -Yes -No **Climbing one flight of stairs without resting:** -Yes -No
LOW PHYSICAL ACTIVITY How often do you engage in activities requiring low or moderate energy, such as gardening, cleaning the car, or walking? -Hardly ever, or never -One to three times a month -Once a week -More than once a week
FRAILTY SCORE: **-**Non-frail -Pre-frail -Frail

THE QUALITY OF MEALS and MEAL SERVICE SET OF INDICATORS APPLIED TO THE RESIDENTIAL HOMES

	YES	NO
STRUCTURAL INDICATORS (1-6)		
INDICATOR 1: A procedure for screening and caring for malnourished residents is established		
Criteria 1a: Is a standardized weighing policy available?		
Criteria 1b: Is a validated screening instrument available?		
Criteria 1c: Is an action plan for malnourished residents available?		
Criteria 1d: Is a staff member referred to as responsible for the screening and treatment policy?		
INDICATOR 2: A policy for tailoring meals to the preferences and needs of the residents is established		
Criteria 2a: Is a structural consultation established with kitchen staff and staff of at least two different care disciplines?		
Criteria 2b: Is a procedure established to involve residents in compiling the menu?		
Criteria 2c: Is a procedure established for systematically inquiring the residents about food, food service and choice?		
Criteria 2d: Is it possible for residents to individually adjust the taste of their meals (e.g., the presence of sauces, flavours, etc.)?		
INDICATOR 3: Recipes are tailored to the needs of the residents		
Criteria 3a: Are written recipes available for the staff preparing the meals?		
Criteria 3b: Are specific recipes available for residents with chewing and swallowing difficulties?		
Criteria 3c: Are the recipes systematically reviewed?		
INDICATOR 4: Staff involved in meal care has the right competences		
Criteria 4a: Has the chef an appropriate diploma to execute their function in the kitchen?		
Criteria 4b: Did the chef de cuisine follow a supplementary education in tailoring meals to the elderly?		
Criteria 4c: Is training in meal care provided for each feeding assistant?		
INDICATOR 5: A vision of meal care is established		
Criteria 5a: Is a vision of meal care written?		
Criteria 5b: Has the vision of meal care been communicated to the staff involved in meal care?		
Criteria 5c: Has the vision of meal care been communicated to the residents?		
INDICATOR 6: The food being served is varied		
Criteria 6: Is a system that guarantees variation in food used?		
PROCESS INDICATORS (7-10)	**%**	**%**
INDICATOR 7: The proportion of residents whose weight change was documented (between last month and the month before)		

• Numerator: number of residents with a documented weight difference between last month and the month before • Denominator: number of residents living in residence for at least three months		
INDICATOR 8: The proportion of residents with documented results of a malnutrition screening (during the last three months) • Numerator: Number of residents with documented results of a malnutrition screening during the last three months • Denominator: Number of residents living in residence for at least four months		
INDICATOR 9: The proportion of residents whose eating habits were documented (at least twice during the last year • Numerator: Number of residents whose habits according to food, service and choice have been registered at least twice during the year • Denominator: Number of residents living in the residents for at least 12 months		
INDICATOR 10: The number of residents per meal assistant who needs help with the principal meal • Numerator: Number of residents needing help with the principal meal • Denominator: Number of meal assistants in residence during the main meal		
OUTCOME INDICATORS (11-13)		
INDICATOR 11: The prevalence of residents with a risk of malnutrition • Numerator: Number of residents with a risk of malnutrition according to the last screening from the last three months • Denominator: number of residents being screened with a validated malnutrition screening instrument during the last three months		
INDICATOR 12: The prevalence of malnourished residents • Numerator: Number of residents with malnutrition according to the last screening from the last three months • Denominator: Number of residents being screened with a validated malnutrition screening instrument during the last three months		
INDICATOR 13: The prevalence of residents expressing mealtime satisfaction • Numerator: Number of residents reporting being (very) satisfied with mealtime quality according to the last question from the last six months • Denominator: Number of residents who responded to the question about mealtime satisfaction at the last questioning from the last six months		

RESIDENTS' FOOD RECORDS DURING FOUR CONSECUTIVE DAYS

DAY1		
BREAKFAST		
Name of Dishes	**Amount on the plate**	**Any Leftovers on the Plate**
LUNCH		
Name of dishes	**Amount on the plate**	**Any leftovers on the plate**
DINNER		
Name of Dishes	**Amount on the Plate**	**Any leftovers on the plate**
The amount of Snacks and Liquids Consumed during the Day		

DAY2		
BREAKFAST		
Name of Dishes	**Amount on the plate**	**Any Leftovers on the Plate**
LUNCH		
Name of dishes	**Amount on the plate**	**Any leftovers on the plate**
DINNER		
Name of Dishes	**Amount on the Plate**	**Any leftovers on the plate**
The Amount of Snacks and Liquids consumed during the day		

DAY3		
BREAKFAST		
Name of Dishes	**Amount on the plate**	**Any Leftovers on the Plate**
LUNCH		
Name of dishes	**Amount on the plate**	**Any Leftovers on the plate**
DINNER		
Name of Dishes	**Amount on the Plate**	**Any Leftovers on the plate**
The Amount of Snacks and Liquids Consumed during the day		

DAY4		
BREAKFAST		
Name of Dishes	**Amount on the plate**	**Any Leftovers on the Plate**
LUNCH		
Name of dishes	**Amount on the plate**	**Any Leftovers on the plate**
DINNER		
Name of Dishes	**Amount on the Plate**	**Any Leftovers on the plate**
The Amount of Snacks and Liquids Consumed:		

URINE AND SALIVA COLLECTION INSTRUCTION SHEET

The Mineral Study Team would like you to provide urine and saliva samples for mineral analysis. Therefore, you will collect a small (spot) urine and saliva samples and follow the appropriate guidance below.

COLLECTION OF SPOT URINE AND SALIVA SAMPLEs

What is a spot urine sample?

A spot urine sample is a small sample of urine, i.e. you do not need to collect all of the urine passed. Instead, we ask that you collect a mid-stream sample into the sterile tube labelled with your unique study number provided within the study. This means you do not collect the first or last part of the urine, just the urine you pass when emptying your bladder. This reduces the risk of the sample being contaminated with bacteria from your hands or the skin.

- ✓ Open the urine collection vessel carefully.
- ✓ Position yourself over the toilet and start urinating.
- ✓ After the initial stream, collect a mid-stream urine sample by allowing the urine to the flow directly into the urine vessel until it reaches the marked line (approximately 10-20 mL).

Saliva Sample Collection Instruction

- ✓ Collect saliva sample at least one hour after eating, drinking, or brushing your teeth.
- ✓ Open the saliva collection vessel carefully.
- ✓ Do not spit forcefully; allow saliva to pool in your mouth naturally.
- ✓ Tilt your head forward slightly to avoid excess drool.
- ✓ Spit gently into the saliva collection vessel until it reaches the marked line (approximately 5-10 mL).

What should I do after the collection of the urine and saliva samples?

If possible, the urine and saliva tubes should be delivered to the researchers as soon as your earliest convenience. The researchers will be in a care home to collect your urine and saliva samples.

Appendix 6

Food and Nutrition Security Survey (FANSS)

Participant Information and Consent

Welcome to the Food and Nutrition Security Survey (FANSS).

Thank you for your interest in our study.

This research is concerned with understanding the extent, severity and causes of food and nutritional insecurity in Nottinghamshire to identify the most effective policies for its alleviation.

Previous research has suggested that food insecurity in the UK is increasing and that some people are more likely to experience food insecurity than others. The experience of food insecurity can alter the quantity and quality of foods in the diet, changing the nutritional profile of the diet.

We're also recruiting 200 people to take part in a further study looking into the types of foods in the diet and influence on diet quality and micronutrient intakes, this is optional. If you would like to find out more, there is an option to enter your email address and we will contact you with the details.

As a token of our appreciation for completing this survey as well as taking part in the follow up study for the first 200 people there is a £50 gift voucher for Sainsbury's.

You are invited to take part because you are aged 18 years and over. We ask you to complete one online survey (with the option to take part in a further study), this will take no more than 25 minutes to complete.

Please read through the participant information sheet https://static.onlinesurveys.ac.uk/media/account/171/survey/1000627/question/FANSS_Participant_Information__daa41jm.docx before agreeing to participate. You can ask any questions before deciding by contacting the researchers (details below). Taking part is entirely voluntary.

This research has been approved by the University of Nottingham Faculty of Medicine & Health Sciences Research Ethics Ref: FMHS 208-0223 FANSS.

Research Team: Dr Simon Welham, Professor Sally Hibbert, Dr John Harvey, Michelle Thomas, School of Biosciences. Division of Food science, Dietetics and Nutrition. University of Nottingham.

Study email: fanss@nottingham.ac.uk

Consent.

The following questions confirm that you consent to taking part in this online survey.

Data will be stored in accordance with the General Data Protection Regulation (GDPR). Cookies, personal data stored by your Web browser, are not used in this survey. However, as an online participant in this research, there is always the minimal risk of intrusion by outside agents and therefore the possibility of being identified.

- I confirm that I have read the participant information sheet and I understand all information.
- I am 18 years old and/or older
- I understand that my participation is voluntary and I can end the study at any time and withdraw my data by clicking the EXIT button.

- I understand that my answers are anonymous.
- I understand the overall anonymized data from this study may be used in the future for research (with research ethics approval) and teaching purposes.

Consent

1. I CONSENT to take part in the online survey and for my answers to be used * *Required*

- Yes
- No

If you're struggling to afford the essentials or need advice and support, Nottinghamshire County Council dedicated Cost of living support website has information on help available to households https://www.nottinghamshire.gov.uk/business-community/cost-of-living-support

The Trussell Trust also provide free advice and you can search for your local Food Bank via their website here: https://www.trusselltrust.org/get-help/find-a-foodbank/

Please tell us about yourself

2. What was your age on your last birthday? (in years) ✱ *Required*

3. What best describes your gender? ✱ *Required*

- ○ Male
- ○ Female
- ○ Prefer to self-describe in another way
- ○ Prefer not to answer

3.a. If you selected Prefer to self-describe in another way: Please write here :

4. What is your marital status? ✱ *Required*

5. Which of the following best describes your ethnic origin? ✱ *Required*

Height and weight

6. Which measurement would you like to use to provide details of your height?

- Feet and inches (ft In)
- Meters (m)
- Centimetres (cm's)

6.a. Height in feet

6.a.i. Inches

6.b. Meters

6.c. Centimetres

7. Which measurement would you like to use to provide details of your weight?

- kilograms (kg)
- Stones and pounds (St, lbs)
- Pounds (lbs)

7.a. Weight in stone

7.a.i. pounds (lbs)

7.b. kilograms (kg)

7.c. Pounds (lbs)

8. Which of the following best describes your current physical activity level?

You and your household

9. What is your postcode? (This is required for mapping nutritional outcomes only, we will not be able to identify you from your postcode).

10. In which ways do you occupy your accommodation?

10.a. If you selected Other, please specify:

11. How much do you pay on your mortgage or rent each month?

12. How many adults aged over 18 years including yourself live in your household? ✱ *Required*

13. Do you have children (0-18 years of age) living with you in your household? ✱ *Required*

- Yes
- No
- Prefer not to say

13.a. How many children (aged 0-18 years) live with you in your household?

13.a.i. What is the age of your first child?

13.a.ii. What is the age of your first child?

13.a.ii.a. What is the age of your second child?

13.a.iii. What is the age of your first child?

13.a.iii.a. What is the age of your second child?

13.a.iii.b. What is the age of your third child?

13.a.iv. What is the age of your first child?

13.a.iv.a. What is the age of your second child?

13.a.iv.a.i. What is the age of your third child?

13.a.iv.a.ii. What is the age of your fourth child?

13.a.v. What is the age of your first child?

13.a.v.a. What is the age of your second child?

13.a.v.a.i. What is the age of your third child?

13.a.v.a.ii. What is the age of your fourth child?

13.a.v.a.ii.a. What is the age of your fifth child?

14. Are you pregnant or breast feeding?

15. Is/are your child/ren entitled to Free School Meals

16. Are you in receipt of Healthy Start? You can check find information on Healthy Start, check your eligibility and apply here: https://www.healthystart.nhs.uk/frequently-asked-questions/applying-for-healthy-start-faqs/

17. Do you pay for your NHS prescriptions? You can find information and check if you are eligible for free prescriptions here: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/

We would now like to ask you some questions about education and work related training.

18. Which of the qualifications listed do you have?, please look at the list and tell me the first one you come to that you have passed.

18.a. If you selected Other, please specify:

What is your employment status?

19. What is your employement status?

- Full-time (paid employment) (37.5hrs per week or more)
- Part-time (paid employment) (under 37.5hrs per week)
- Volunteer (not paid)
- Not working at present
- Retired
- Other

19.a. If you selected Other, please specify:

What is your total household income and food spend?

All information collected in this survey is completely anonymous and you are not identifiable. Your responses to this survey do not impact on any benefit payments you receive.

Total household income is income from all persons living in the household who make a financial contribution to the household cost/bills.

For example, a lone adult, earning a monthly income of £722.45 from employment and is entitled to Universal Credit receive an estimated £437.56 per month. Their total monthly household income is £1160.01 (£13920.12 per year) based on earnings from employment plus Universal Credit (not based on real values).

Another example is a 2 adult, 1 child household, their total household monthly income is the combined income of both adults, plus any benefit payments including child benefit. For example, Income from employment for both adults = £1444.90 per month, income from Universal Credit = £2376.88 per month, child benefit = £104 per month. Total monthly estimated household income is £3924.90 (£47098.80 per year) (not based on real values).

20. What is your **household's GROSS** income in the last 12 months, **Before** any deductions for tax etc. Please include income from earnings, self-employment, benefits, pensions, and interest from savings. **(Figures in brackets are monthly income).** ✱ *Required*

The next questions asks for your NET household income. Net income is after any taxes and national insurance contribution have been paid and any deductions such as child maintenance payments, pension contributions, sanctions on benefit payments.

21. What is your **household's NET** income in the last 12 months, **AFTER** any deductions for tax etc. Please include income from earnings, self-employment, benefits, pensions, and interest from savings. Figures in brackets are monthly income. ✱ *Required*

22. Could you tell me how much you (your household) usually spends on food and drink **each week?** Please include main shopping, top-up shopping, school dinners and money given to children for food purchases as well as money spent on food bought from cafes and restaurants. **Please do not include alcoholic drinks or other items such as**
cleaning materials, cigarettes, pet food, newspapers or magazines ✱ *Required*

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23. Please could you tell me which kinds of income you (and your husband, wife partner) receive? (please tick all that apply). ✱ *Required*

- ☐ Earnings from employment or self-employment
- ☐ State retirement pension
- ☐ Pension from former employer
- ☐ Personal Pensions
- ☐ Job-Seekers Allowance
- ☐ Employment and Support Allowance
- ☐ Income Support
- ☐ Pension Credit
- ☐ Working Tax Credit
- ☐ Child Tax Credit
- ☐ Housing Benefit
- ☐ Universal Credit
- ☐ Personal Independence Payment (PIP)
- ☐ Other

23.a. If you selected Other, please specify:

Household Food Security

Please read the set of statements that people have made about their food situation.

For these statements, please tell me whether the statement was often true, sometimes true, or never true for (you/your household) in the last 30 days—that is, since the time of completeing this survey.

24. The first statement is "I worried whether my food would run out before I got money to buy more." Was that often true, sometimes true, or never true for you in the last 30 days? ✱ *Required*

25. "The food that I bought just didn't last, and I didn't have money to get more." Was that often, sometimes, or never true for you in the last 30 days? ✱ *Required*

26. "I couldn't afford to eat balanced meals." Was that often, sometimes, or never true for you in the last 30 days? ✱ *Required*

27. In the last 30 days, prior to completing this survey, did you ever cut the size of your meals or skip meals because there wasn't enough money for food? ✱ *Required*

- Yes
- No
- Don't know

27.a. If Yes, In the last 30 days, how many days did this happen?

28. In the last 30 days, did you ever eat less than you felt you should because there wasn't enough money for

food? ✱ *Required*

- Yes
- No
- Don't know

29. In the last 30 days were you ever hungry but didn't eat because there wasn't enough money for food? ✱ *Required*

- Yes
- No
- Don't Know

30. In the last 30 days, did you lose weight because there wasn't enough money for food? ✱ *Required*

- Yes
- No
- Don't know

31. In the last 30 days, did you ever not eat for a whole day because there wasn't enough money for food? ✱ *Required*

- Yes
- No
- Don't know

31.a. If Yes, In the last 30 days, how many days did this happen?

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The Trussell Trust also provide free advice and you can search for your local Food Bank via their website here: https://www.trusselltrust.org/get-help/find-a-foodbank/

Ways of coping with not having enough food

32. Prior to completing this survey, if there have been times when you did not have enough food or money to buy food please click yes, otherwise click no.

- Yes
- No

Ways of coping with not having enough food

33. During the past 30 days, did you receive any meals delivered to the home from community programs, “Meals on Wheels,” or any other programs?

- Yes
- No

34. **During the past 30 days, did you go to a community program or senior centre to eat prepared meals?**

- Yes
- No

35. **In the last 12 months, did you ever get emergency food from a church, a food pantry, or food bank?**

- Yes
- No

35.a. **How often did this happen-almost every month, some months but not every month, or in only 1 or 2 months?**

- Almost every month
- Some months but not every month
- Only 1 or 2 months

35.a.i. **Did this happen in the last 30 days?**

- Yes
- No

36. **Is there a church, food pantry or food bank in your community where you could get emergency food if you needed it?**

- Yes
- No