Associations of Habitual Micronutrient Intake and New-Onset Prediabetes/Diabetes after Acute Pancreatitis

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ABSTRACT

Micronutrients have many roles in human health and metabolism. However, the role of habitual dietary intake of minerals and vitamins in glucose homeostasis in individuals after acute pancreatitis (AP) is yet to be elucidated. The primary aim of this thesis was to investigate the associations of habitual micronutrient intake in individuals after AP: new-onset prediabetes/diabetes after AP (NODAP), pre-existing prediabetes/type 2 diabetes (T2DM), and normoglycaemia after AP (NAP). Associations between habitual intake of minerals and vitamins and glycaemic status were studied, as well as relationships between intake of minerals and vitamins/vitamers and markers of glucose metabolism in individuals after AP.

This thesis included two cross-sectional studies. The EPIC-Norfolk food frequency questionnaire was used to determine habitual intake of 13 dietary minerals as well as seven fat-soluble vitamins and seven water-soluble vitamins. ANCOVA as well as multiple linear regression analyses were conducted, and five statistical models were built to adjust for covariates (age, sex, daily energy intake, visceral/subcutaneous fat volume ratio, smoking status, daily alcohol intake, aetiology of AP, number of AP episodes, cholecystectomy, and use of antidiabetic medications).

A total of 106 individuals after AP were included in this thesis. In the NODAP group, habitual intake of four minerals were significantly less when compared with the NAP group: iron, nitrogen, phosphorous, and zinc. Glycated haemoglobin (HbA1c) was significantly associated with iodine intake and manganese intake in the NODAP group. Fasting plasma glucose (FPG) was significantly associated with manganese intake in the NODAP group. Habitual intake of one vitamin, vitamin B6, was significantly altered in the NODAP group compared with the NAP group. In the NODAP group, three fat-soluble vitamins/vitamers (α-carotene, β-carotene, and total carotene) were significantly associated with HOMA-β (Homeostasis Model Assessment β-cell function index). One water-soluble vitamin (vitamin B3) was also significantly associated with HOMA-β in the NODAP group. None of the studied vitamins were significantly associated with FPG or HOMA-IR (Homeostasis Model Assessment Insulin Resistance index) in the NODAP group.

In conclusion, this thesis provided the first evidence of the associations of habitual micronutrient intake in individuals after AP. Prospective longitudinal studies and randomised controlled trials are now warranted to investigate the associations between micronutrient intake and NODAP are causal and unveil the specific mechanisms underlying their involvement with NODAP.

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ABBREVIATIONS

25(OH)D	25-Hydroxyvitamin D
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AP	Acute Pancreatitis
CI	Confidence Interval
CP	Chronic Pancreatitis
DEP	Diabetes of the Exocrine Pancreas
DMT1	Divalent Metal Transporter 1
EN	Enteral Nutrition
EPD	Exocrine Pancreatic Dysfunction
FETA	FFQ EPIC tool for analysis
FFQ	Food Frequency Questionnaire
FPG	Fasting Plasma Glucose
GPR109a	Nicotinic Acid G-protein-Coupled Pathway Receptor
HbA1c	Glycated Haemoglobin
HCP1	Haem Carrier Protein 1
HOMA-IR	Homeostasis Model Assessment Insulin Resistance index
HOMA-S	Homeostasis Model Assessment Insulin Sensitivity index
HOMA-β	Homeostasis Model Assessment β-cell function index
HOMA2	Homeostasis Model Assessment Calculator
MnSOD	Manganese Superoxide Dismutase
MUIC	Median Urinary Iodine Concentration
MWIC	Median Water Iodine Concentration
NAP	Normoglycaemia after Acute Pancreatitis
NG	Nasogastric
NJ	Nasojejunal
NODAP	New-Onset Prediabetes/Diabetes after Acute Pancreatitis
SD	Standard Deviations
SFV	Subcutaneous Fat Volume
SOD	Superoxide Dismutase
T2DM	Type 2 Prediabetes/Diabetes prior to Acute Pancreatitis

T3	Triiodothyronine
T4	Thyroxine
TPN	Total Parenteral Nutrition
TSH	Thyroid Stimulating Hormone
V/S fat volume ratio	Ratio of Visceral to Subcutaneous Fat Volume
VFV	Visceral Fat Volume

CHAPTER 1. INTRODUCTION

1.1 The Pancreas

The pancreas is a retroperitoneal organ located on the posterior wall of the abdominal cavity (1). It is a complex gland containing both exocrine and endocrine tissue that plays a fundamental role in digestion, nutrient metabolism, and energy balance (Figure 1.1) (2,3). A significant proportion of pancreatic volume is comprised of exocrine cells (acinar and duct cells). Acinar cells produce digestive proenzymes responsible for food digestion once activated in the duodenum (2). Proenzymes are packaged into acidic zymogen granules to prevent activation in the pancreas, protecting against pancreatic autodigestion (3). Duct cells produce water and electrolytes (primarily bicarbonate) to produce alkaline pancreatic fluid for zymogen transport through the pancreatic duct and neutralise stomach acid in the duodenum (2). Once in the duodenum, enzymes are activated on the surface of the duodenal lumen, where trypsinogen is hydrolysed to form the active enzyme trypsin (4). Trypsin catalyses the activation pathways of remaining inactive proenzymes to form active digestive enzymes available for digestion of protein (proteases), carbohydrate (amylases), fat (lipases) and nucleic acids (nucleases) (4). Endocrine functions of the pancreas are modulated by aggregates of endocrine cells (α, β, δ, F and ε cells), known as Islets of Langerhans (2). Despite making up a mere 2% of pancreatic volume, pancreatic endocrine cells influence a range of organs throughout the body through hormone secretion (2,5). Islets of Langerhans are distributed throughout the exocrine tissue and are responsible for secreting pancreatic hormones (insulin, glucagon, amylin, somatostatin, ghrelin, and pancreatic polypeptide) for glucose homeostasis and lipid metabolism, among other functions (1,2,6).

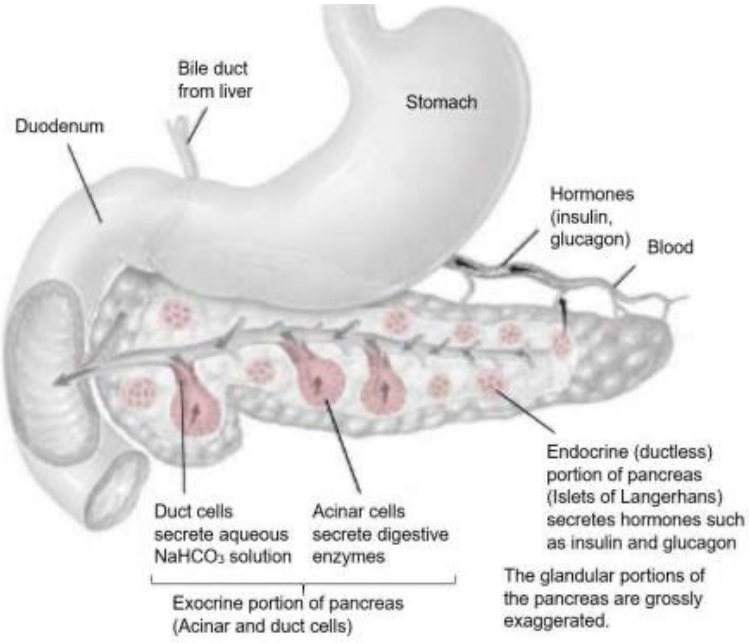

Figure 1.1 The Exocrine and Endocrine Pancreas
Figure reproduced from (7)

1.2 Acute Pancreatitis

1.2.1 Definition, Epidemiology, and Aetiology of Acute Pancreatitis

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, marked by oxidative stress and acinar cell dysfunction. AP severity ranges from mild to critical local (pancreatic oedema and inflammation to infected pancreatic and peripancreatic necrosis) and systemic determinants (mild hypoxemia to multiple organ failure) (8). It is one of the most common diseases of the pancreas and a leading cause of gastrointestinal-related hospital admissions worldwide (9). The global incidence of AP is 33.7 per 100,000 population per year, whereas the incidence of chronic pancreatitis (CP) is 9.6 per 100,000 population per year (10); However, the incidence of AP in New Zealand is much higher at 58.4 per 100,000 population per year (11). AP is also associated with a significant burden on patients, healthcare providers, and the economy (9,10,12). This epidemiological burden is projected to increase over the coming decades, estimating the incidence in New Zealand to reach 115.3 per 100,000 population per year in 2050 and is estimated to result in 16,500 years of life lost (13). The projected increase of AP is attributed to increasing rates of obesity, alcohol consumption, and aging populations, which are risk factors of AP (14,15).

The leading causes of AP are gallstones and alcohol consumption, causing up to 80% of AP cases. Migrating gallstones can cause transient obstruction of the pancreatic ducts leading to

acinar damage, increased ductal pressure, interstitial oedema, and accumulation of pancreatic fluid (16). Prolonged alcohol consumption is also a common cause of AP; However, the pathogenesis is unclear. Alcoholic AP is likely related to toxic effects on acinar cells and immunologic mechanisms (17). Less common causes of AP include hypertriglyceridemia (18), hypercalcemia (19), familial pancreatitis, use of some drugs/medications (20), and viral infections (mumps, Coxsackie B virus, Epstein-Barr virus, measles, and more) (21). In some cases, the cause of AP cannot be determined, thus classified as idiopathic AP (16).

1.2.2 Diagnosis and Classification of Acute Pancreatitis

The diagnosis of AP requires two of the three following criteria to be fulfilled, in line with international guidelines (22,23):

1. Abdominal pain consistent with AP (acute onset of severe, persistent, epigastric pain, often radiating to the back).
2. Serum lipase and/or amylase levels are at least three times greater than the upper limit of normal.
3. Characteristics of AP observed on contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography.

Accompanying symptoms often include nausea, vomiting, low to moderate-grade fever, abdominal distension, and decreased bowel sounds (19).

There are two main systems for classifying the severity of AP, the revised Atlanta Classification system and the more recent Determinant-Based Classification system. The revised Atlanta classification system categorises AP into three categories: mild, moderate, or severe AP (24). However, this classification system is suboptimal as the defined categories are based on factors associated with predicted severity rather than factors causally associated with severity (22). The more recent Determinant-based Classification system bases severity of AP on the presence of infected and/or peripancreatic necrosis and persistent organ failure, which are causally associated with AP severity (8,23). Thus this system has improved discriminative ability to categorise AP patients into one of four categories of severity: mild, moderate, severe, or critical AP as shown in Figure 1.2 (8,22).

	Mild AP	Moderate AP	Severe AP	Critical AP
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	AND	*AND/OR*	*OR*	*AND*
Organ failure	No	Transient	Persistent	Persistent

Figure 1.2. Determinant-Based Classification System for Severity of Acute Pancreatitis
Reproduced from (22).

1.3 Sequalae of Acute Pancreatitis

1.3.1 New-Onset Prediabetes/Diabetes after Acute Pancreatitis

New-onset prediabetes/diabetes after AP (NODAP) is the most common diabetes of the exocrine pancreas (DEP), followed by pancreatic cancer related diabetes and cystic fibrosis related diabetes as shown in Figure 1.3 (25). NODAP is characterised by impaired glycaemic control and dysfunction of pancreatic endocrine cells following an attack of AP (13,26). Hyperglycaemia is a common feature of AP and is generally considered transient, as a result, glucose homeostasis is not routinely measured after hospital admission. The LACERTA study conducted by the COSMOS group investigated changes in glycaemic regulation in individuals after AP (26). It was observed that derangement of glucose metabolism and subsequent NODAP occur progressively (3.3% at 6 months, 7.2% at 12 months, 9.2% at 18 months, and 11.2% at 24 months follow-up) highlighting the need for AP patients to be followed up after hospital discharge (26). In New Zealand, the incidence of NODAP was 1.8 per 100,000 general population in 2010, with a predicted average growth of 2.8% per annum (13). Historically, the pathogenesis of NODAP was attributed to loss of pancreatic β-cells related to CP or pancreatic necrosis. Recent evidence indicates this is not the case; A meta-analysis by the COSMOS group observed that NODAP developed in nearly 40% of individuals after AP, with little effect of disease severity (27). These results suggest that mechanisms other than mechanical destruction of the pancreas contribute to the development of NODAP (27). Chronic low-grade inflammation, intra-pancreatic fat deposition, increased lipolysis, and dysfunction of the

pancreas-gut-brain axis have also been associated with development of NODAP (28–32). Risk factors for NODAP include age, sex, body composition, recurrent AP, and exocrine pancreatic dysfunction (EPD) (33,34). NODAP has significantly worse clinical outcomes compared with type 2 diabetes, including increased risk of renal disease, gastrointestinal disease, infectious disease, cancer (non-pancreatic and pancreatic), and higher all-cause mortality (33,35,36).

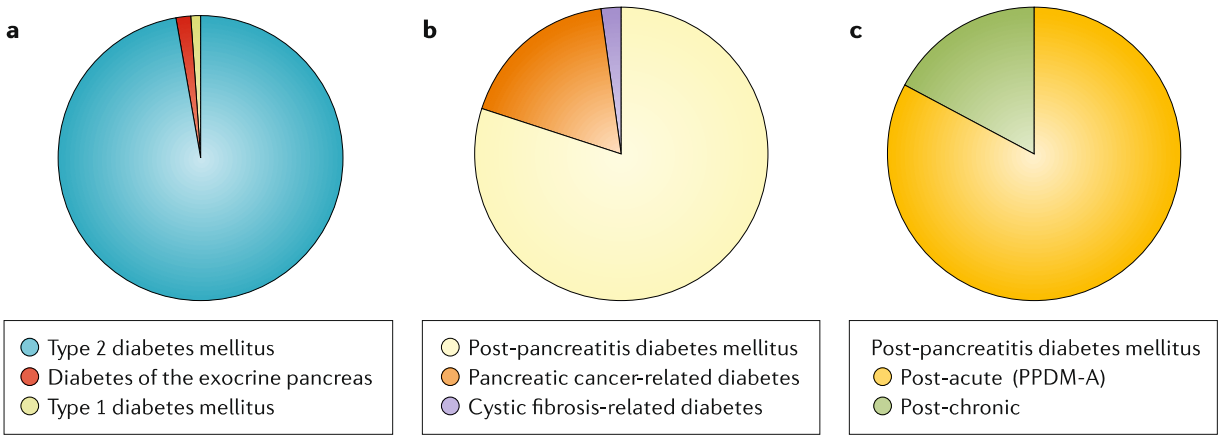

Figure 1.3 Epidemiology of Diabetes of the Exocrine Pancreas. **(a)** frequency of the exocrine pancreas in adults**. (b)** frequency of subtypes of diabetes of the exocrine pancreas**. (c)** frequency of subtypes of post-pancreatitis diabetes mellitus/new-onset diabetes after acute pancreatitis.
Figure reproduced from (25).

1.3.2 Exocrine Pancreatic Dysfunction

EPD is a condition characterised by dysfunction of pancreatic enzyme secretion. Lack of pancreatic enzymes may result in maldigestion and malabsorption of food and nutrients, leading to subsequent nutrient deficiencies (particularly of fat-soluble vitamins) and malnutrition (37). EPD can develop secondary to many conditions, including cystic fibrosis and pancreatic cancer; however, the most common cause of EPD is pancreatitis (38). Although previously considered a consequence of CP, EPD has been observed in up to 29% of individuals after AP (34,39). Alcoholic aetiology and severe and necrotising AP are associated with higher risk of EPD, however, EPD also occurs in 19.4% of individuals with mild AP (39).

Recent evidence suggests that EPD may also be associated with development of NODAP. Das et al. found that 40% of individuals with NODAP also had concomitant EPD (34). A study by the COSMOS group investigated the associations between EPD and NODAP, observing individuals after AP with EPD were 4.9 times more likely to develop NODAP than those without EPD (40). Furthermore, aetiology and severity of AP did not influence the significant associations between EPD and NODAP and there was no significant difference in risk of

between those with AP and CP (40). Individuals with EPD often require pancreatic enzyme replacement therapy to improve nutrient digestion and absorption, reduce gastrointestinal symptoms, and improve quality of life (41,42). It is not clear if pancreatic enzyme replacement therapy with have an impact of risk of NODAP; Therefore, future prospective studies are now justified to investigate these associations further.

1.4 Hospital Management of Acute Pancreatitis

1.4.1 Medical Treatment of Acute Pancreatitis

Hospital management of AP is well established and is dependent on the predicted severity of AP. Patients with mild AP typically receive pain management and are kept under observation until their pain resolves (43). Acute abdominal pain is the primary symptom of AP; thus, symptom management with sufficient analgesia is a priority. There are no current guidelines for pain management specific for an attack of AP, and it is recommended to adhere to acute pain management guidelines in the perioperative setting (44).

Patients with non-mild AP require more extensive management. Fluid resuscitation is the primary supportive treatment of AP. Moderate to critical AP is associated with hypovolemia and increased fluid sequestration; thus patients have increased fluid requirements (45). The premise of fluid resuscitation is to restore circulating blood volume and support macro and microcirculatory systems to prevent/limit the development of pancreatic necrosis (43). Evidence suggests that intravenous fluids should be administered within 24-48 hours of hospital admission for AP to improve prognosis and decrease mortality (46,47). It is also suggested that aggressive fluid resuscitation above 10-15 $mlkg^{-1}h^{-1}$ should be avoided as it may increase the rate of infectious complications and mortality (44,48). Ringer's lactate solution is the preferred fluid due to its possible anti-inflammatory effects (49,50). Clinical markers of hemodynamic function (heart rate, blood pressure, respiratory rate, O_2 saturation, urine output) and laboratory markers of volemia and tissue perfusion (haematocrit, blood urea nitrogen, creatinine, and lactate) should be monitored regularly during an attack of AP, and fluid requirements should be reassessed every 6 hours within the first 24-48 hours (44,51). Depending on the severity of AP, pancreatic necrosis and necrotic infection can be present and prophylactic antibiotics may be administered (52).

1.4.2 Nutrition Management of Acute Pancreatitis

1.4.2.1 Oral Feeding

Mild AP is typically self-limiting, with patient's recovering less than a week from the onset of an AP attack. Tolerance of oral intake is a typical indicator for hospital discharge, along with the resolution of pain (44). During hospital admission, oral intake is typically reintroduced in a stepwise fashion, starting with a clear oral fluid diet, transitioning to a light (low fat or soft texture), then a regular diet (solid texture, normal calorie and fat content) as tolerated by the patient (53). However, numerous studies have observed that early oral feeding with a light or regular diet is generally well-tolerated in those with mild to moderate AP (54). Early oral feeding has not been associated with increased feeding intolerance, exacerbated abdominal pain or gastrointestinal symptoms, and has also been associated with reduced length of hospital admission (54–57). Therefore, light and regular diets can be considered first-line nutrition therapy for mild to moderate AP, as per patient preference and tolerance.

1.4.2.2 Enteral and Parenteral Nutrition

Individuals with non-mild AP are at high risk of malnutrition due to their altered metabolism and protein catabolism. These patients can also be accompanied by diminished nutrient status and nutrient deficiencies (particularly with alcohol-related AP) (58). Therefore, adequate nutrition support is imperative for improved outcomes (59). Historically, total parenteral nutrition (TPN) was considered the gold standard for nutrition management of AP due to the concept of 'pancreatic rest'. The rationale behind 'pancreatic rest' is based on reducing oral intake to avoid stimulus of the pancreas, preventing further inflammation and damage to pancreatic tissues. As TPN delivers nutrition intravenously, a patients nutrition requirement can be met without stimulating the pancreas. However, 'pancreatic rest' is now an outdated concept. There is a wealth of evidence that enteral nutrition (EN) significantly reduces infectious complications, the need for surgical intervention, and mortality when compared with TPN (59,60). TPN is also associated with other complications, including electrolyte and metabolic disturbances, villous atrophy, and gut barrier failure and is more expensive to administer (61–63). Therefore, administration of EN within the first 24-48 hours of hospital admission now is preferred for those with non-mild AP. TPN is indicated for AP patients who cannot tolerate EN, targeted EN requirements, or have contraindications of EN (bowel obstruction, abdominal compartment syndrome, prolonged paralytic ileus, or mesenteric ischemia) (64,65).

EN feed (semi-elemental, elemental, or polymeric formulae) can be administered via nasogastric (NG) or nasojejunal (NJ) tubes (44,64). In the past, NJ feeding has been preferred over NG feeding; A strategy also influenced by the concept of 'pancreatic rest' as the feed bypasses the duodenum and is delivered into the jejunum. NG feeding has previously been associated with aspiration pneumonitis, pancreatic secretion, and ineffective restoration of gut permeability (66,67). However, recent randomised control trials and meta-analyses have demonstrated no evidence of increased complications with NG feeding compared with NJ feeding, thus NG feeding is considered safe for those with non-mild AP (68–72). NG feeding is now the favourable route of EN due to the simplicity of NG tube insertion, in contrast with NJ tube insertion which requires fluoroscopic or endoscopic guidance and can delay feeding (44,64,71). NJ feeding can be considered instead of NG feeding in cases of digestive intolerance.

1.5 Thesis Premise

Nutrition management of AP is well established in an acute inpatient setting, and there are evidence-based guidelines for the use of oral intake, EN, and TPN during hospital admission. Upon discharge, AP patients are encouraged to resume their regular diets and often receive no or very little nutrition advice. As a sequalae of AP, NODAP is, in theory, preventable and treatable. Yet there are currently no screening tools or evidence-based guidelines for individuals at risk or with NODAP. The increasing incidence and epidemiological burden of NODAP precipitates the need to investigate prevention strategies and appropriate management guidelines for individuals after AP and at risk of NODAP. It is well known that nutrition management is a cornerstone of prevention and management of type 2 diabetes and is often implemented by a dietitian. There is also emerging evidence to suggest a role of micronutrients in onset of type 2 diabetes and glucose metabolism in individuals with type 2 diabetes. Therefore, it is possible that nutrition management and dietetic input may be beneficial for individuals after AP and potentially reducing the risk of developing NODAP. However, there is a scarcity of clinical studies investigating dietary factors and nutrition guidelines for individuals after AP and at risk of NODAP. Specifically, associations of habitual micronutrient intake and glucose metabolism in individuals after AP has not yet been investigated.

1.6 Thesis Aims

1.6.1 Primary Aim of Thesis

To investigate the associations of habitual micronutrient intake and NODAP, as summarised in Figure 1.4.

1.6.2 Secondary and Tertiary Aims of Thesis

1. Investigate the associations of habitual mineral intake in individuals after AP.
    1.1. Investigate associations between habitual mineral intake and glycaemic status after AP.
    1.2. Assess associations between dietary intake of minerals and markers of glucose metabolism in individuals after AP.
    1.3. Assess associations between dietary intake of minerals and insulin traits in individuals after AP.
2. Investigate the associations of habitual vitamin intake in individuals after AP.
    2.1. Investigate associations between habitual vitamin intake and glycaemic status after AP.
    2.2. Investigate the associations between habitual fat-soluble vitamin intake and glucose metabolism in individuals after AP.
    2.3. Investigate the associations between habitual water-soluble vitamin intake and glucose metabolism in individuals after AP.

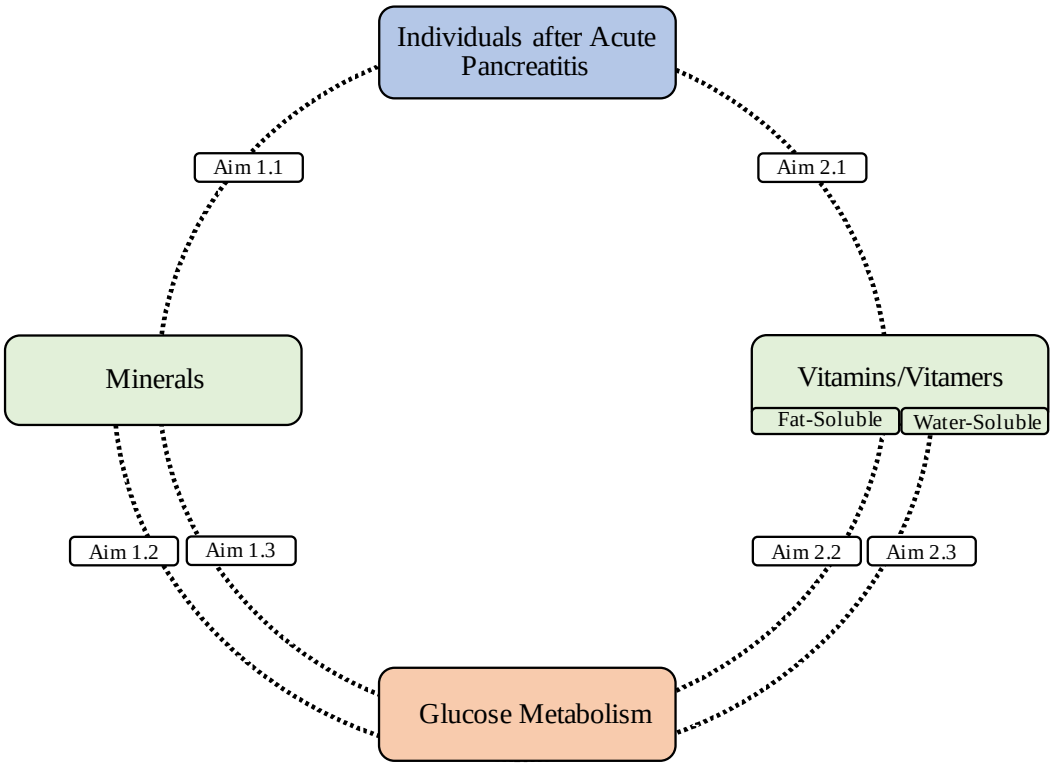

Figure 1.4 Summary of Thesis Aims
Key: Blue box = individuals after acute pancreatitis. dotted line = indicates associations investigated in this thesis. green box = habitual micronutrient intake. orange box = indicators of glucose metabolism and insulin traits.

CHAPTER 2. GENERAL METHODS

2.1 Study Design

This thesis included two cross-sectional studies embedded in an ongoing prospective observational study investigating individuals after an attack of AP. The studies were conducted as part of the ANDROMEDA (Assessment of Nutrition and DietaRy factOrs in Metabolic Disorders after pAncreatitis) project by the COSMOS group. The protocol for this research was granted by the Health and Disability Ethics committee (13/STH/182).

2.2 Study Population

2.2.1 Inclusion Criteria

Individuals were eligible to participate if they fulfilled the following criteria:

1. Had a primary diagnosis of AP (defined by international guidelines as described in Chapter 1, section 1.1.2).
2. Were 18 years of age or older.
3. Lived in Auckland (New Zealand) throughout the study.
4. Provided informed consent for participation.

2.2.2 Exclusion Criteria

If any of the following criteria was fulfilled, individuals were not eligible to participate in the study:

1. Previous or current diagnosis of CP.
2. Intra-operative diagnosis of AP.
3. Post-endoscopic retrograde cholangiopancreatography pancreatitis.
4. History of type 1 or gestational diabetes prior to an individual's first hospital admission for AP.
5. Pregnancy at the time of or following AP diagnosis.
6. History of steroid use.
7. Malignancy.
8. Coeliac disease.
9. Cystic fibrosis.

2.3 Study groups

The following study groups were developed for analysis in Chapters 3 and 4. According to the 'DEP criteria', study participants were categorised into three non-overlapping groups based on HbA1c and FPG levels as described in Table 2.1 (73).

Table 2.1 Study Group Criteria

Study Group	During attack of AP		At the time of the study
Normoglycaemia after AP (NAP)	HbA1c <5.7% (39mmol/mol) and/or FPG <100mg/dL	and	HbA1c <5.7% (39mmol/mol) and/or FPG <100mg/dL
Type 2 diabetes or prediabetes (T2DM)	HbA1c ≥ 5.7% (39 mmol/mol) and/or FPG≥ 100 mg/dL (5.6 mmol/L)	and	HbA1c ≥ 5.7% (39 mmol/mol) and/or FPG≥ 100 mg/dL (5.6 mmol/L)
New-onset diabetes or prediabetes after AP (NODAP)	HbA1c ≥ 5.7% (39 mmol/mol) and/or FPG≥ 100 mg/dL (5.6 mmol/L)	and	HbA1c ≥ 5.7% (39 mmol/mol) and/or FPG≥ 100 mg/dL (5.6 mmol/L)

Abbreviations: AP = Acute Pancreatitis. FPG = fasting plasma glucose. HbA1c = glycated haemoglobin. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes/prediabetes after acute pancreatitis.
Footnotes: Study group criteria is based off 'DEP criteria' (73).

Participants who had FPG>100 mg/dL (5.6 mmol/L) but HbA1c < 5.7% (39 mmol/mol) during their qualifying AP attack were not considered in this study to account for effects of transient stress hyperglycaemia (27).

2.4 Covariates

The COSMOS team previously collected anthropometric and demographic data from participants during standardised face-to-face health examinations. Abdominal visceral fat volume (VFV) and subcutaneous fat volume (SFV) of participants were measured by magnetic resonance imaging at the Centre for Advanced Magnetic Resonance Imaging (University of Auckland, Auckland, New Zealand) using a 3T MAGNETOM Skyra scanner (Siemens, Erlangen, Germany). Participants were required to lie supine and hold breath at maximum expiration. Axial T1-weighted volumetric interpolated breath-hold examination Dixon sequence was applied as reported elsewhere (28). To obtain VFV and SFV data for the present studies, ImageJ software (National Institutes of Health, Bethesda, MD, USA) was used to quantify abdominal fat phase images between the second lumbar vertebral level (L2) and the fifth lumbar vertebral level (L5) (74). The threshold function of ImageJ was used to convert

grayscale pixels into binary images using the global histogram-derived method (28). The non-adipose tissue was excluded from the measurement of visceral fat. Finally, the total number of pixels from the slices series was calculated and multiplied by the pixel area and slice thickness to obtain the VFV and SFV (75). Subsequently, the ratio of visceral to subcutaneous fat volume (V/S fat volume ratio) was calculated. Average daily energy intake (kcal) and alcohol intake (g/day) was obtained using the EPIC Norfolk food frequency questionnaire (FFQ) and determined by the FFQ EPIC tool for analysis (FETA) software (76). Tobacco smoking status was recorded using a standardised questionnaire (77). Antidiabetic medications and cholecystectomy data were derived from participants' health records. Information on the aetiology of AP was also acquired from health records and was categorised into biliary, alcohol-related, and other.

2.5 Laboratory Assays

All participants were required to fast 8 hours before blood collection. HbA1c (mmol/mol), FPG (mmol/L), and fasting insulin (mU/L) were measured by Lab Plus (International Accreditation New Zealand accredited medical laboratory at Auckland City Hospital). FPG was measured using an enzymatic colourimetric assay (©2015 F. Hoffmann-La Roche Ltd., Basel, Switzerland). HbA1c was analysed using the boronate affinity chromatography assay (©2015 Roche Products (New Zealand) Ltd., Auckland, New Zealand and Roche Diagnostics NZ Ltd., Auckland, New Zealand). Insulin was measured using chemiluminescence sandwich immunoassay (Roche Diagnostics, Auckland, New Zealand). A Homeostasis Model Assessment calculator (HOMA2), developed by Oxford University, was used to estimate homeostasis model assessment insulin sensitivity index (HOMA-S), homeostasis model assessment insulin resistance index (HOMA-IR) and homeostasis model assessment β-cell function index (HOMA-β) indices (version 2.2.4 Diabetes Trials Unit, University of Oxford, Oxford, UK).

CHAPTER 3. ASSOCIATIONS OF HABITUAL MINERAL INTAKE WITH NEW-ONSET PREDIABETES/DIABETES AFTER ACUTE PANCREATITIS

3.1 Background

Diabetes mellitus is the most frequent non-communicable disease worldwide. Classifications of diabetes include both the widely recognised type 1 and type 2 and less appreciated types of secondary diabetes, such as DEP (10,33). NODAP is the most frequent DEP, characterised by dysfunction of endocrine cells in the pancreas secondary to an attack of AP (13,78,79). The risk of new-onset diabetes is at least 2 times higher in individuals after an attack of AP compared with the general population (11,80). Also, a prospective longitudinal cohort study by the COSMOS group observed glucose metabolism derangement occurred progressively after an attack of AP, with 11% of individuals (who did not have diabetes at the time of hospitalisation) developing NODAP up to 24 months post AP attack (26). Further studies have found the incidence of AP and NODAP rising over the years; consequently, the burden of these diseases is also increasing and is expected to keep rising over the next three decades (10,13). NODAP is commonly unrecognised and misdiagnosed as type 2 diabetes; however, there are marked differences between them. People with NODAP have poorer glycaemic control, increased risk of developing cancer (in particular, pancreatic cancer), have a younger average age at death, and increased risk of mortality (33,79,81). Men (80,82), young to middle-aged adults (83), and lean or overweight individuals (79) are also at higher risk of NODAP compared with type 2 diabetes. Due to these established differences between the types of diabetes, treating NODAP as type 2 diabetes is detrimental to optimal management (33,79,84).

Current first-line prevention and non-pharmaceutical management of type 2 diabetes is nutrition therapy—an integral component of a diabetes treatment plan (85,86). Nutrition therapy improves glycaemic control, insulin resistance, and also aids weight loss, resulting in decreased mortality and morbidity associated with type 2 diabetes (85,87–89). Individualised nutrition therapy includes modifying patients' dietary intake, moving towards a healthful diet prioritising whole foods while reducing intake of processed, less nutritious, and energy-dense foods (85). Current nutritional research for treatment of type 2 diabetes predominantly focuses on altered dietary intake, dietary patterns, and macronutrient intake, with less focus on micronutrient intake (88). At the same time, there are no current disease specific nutrition

interventions for those at risk of, or with NODAP, with these people receiving generalised nutrition advice. Minerals are essential for glucose metabolism by serving as co-factors, activating insulin receptor sites, and affecting insulin sensitivity (90,91). Previous studies investigating the role of minerals in type 2 diabetes observed that dietary intake of calcium (90,92), magnesium (92–94), and manganese (95–97) may have protective effects on type 2 diabetes, while increased dietary iron (98–103) and selenium (104–106) intake may increase risk of this type of diabetes. To the best of our knowledge, similar research has yet to be conducted on associations of habitual mineral intake with NODAP. We hypothesised that habitual mineral intake plays a role in the dysregulation of glucose metabolism after AP.

This chapter primarily aimed to investigate the associations between habitual intake of minerals and glycaemic status of individuals after AP (aim 1.1). Secondary aims were to assess associations between the dietary intake of minerals and markers of glucose metabolism (FPG and HbA1c) (aim 1.2) and insulin traits (fasting insulin, HOMA-S, and HOMA-β) after AP (aim 1.3).

3.2 Methods

3.2.1 General Methods

General methods specific to this chapter (study design, study population, covariates, and laboratory assays) are described in Chapter 2.

3.2.2 Ascertainment of Habitual Mineral Intake

Participants' habitual diet over the year before recruitment was assessed using the EPIC-Norfolk FFQ developed by the University of Cambridge (76). The FFQ is a self-administered, validated, and semi-quantitative instrument that consists of two parts. Part one assesses the intake of 130 commonly and less commonly consumed foods. Part two consists of additional questions, gathering information on types and brands of foods such as breakfast cereal, milk, meat, and cooking fats. Ascertainment of habitual intake included minerals from food sources only; therefore, intake of supplements was not considered in the present study. The FFQ data were analysed using FETA software to calculate daily intake of 13 minerals: calcium (mg), chloride (mg), copper (mg), iodine (μg), iron (mg), magnesium (mg), manganese (mg), nitrogen (g), phosphorous (mg), potassium (mg), selenium (μg), sodium (mg), and zinc (mg). FFQ data were analysed and FFQs were excluded from the study if ten or more questions were

left unanswered as this level of missing data would lead to significant underestimation of intake (76). In addition, FFQ data were excluded if the ratio of total energy intake (estimated from the FFQ data) and estimated basal metabolic rate (determined by the Harris-Benedict equation) were more than two standard deviations (SD) outside the mean ratio (i.e., <0.28 and >1.82) (76).

3.2.3 Statistical Analyses

All statistical analyses were performed using SPSS 27.0. (IBM Corporation, Armonk, NY, USA). The differences in baseline characteristics between the study groups (NODAP, T2DM, and NAP) were investigated using one-way analysis of variance (ANOVA). Data were presented as mean (SD) or frequency (percentage). First, analysis of covariance (ANCOVA) between the NODAP, T2DM, and NAP groups (reference group) was undertaken to assess variance in mean mineral intakes between the groups while adjusting for the effect of covariates. All investigated minerals were log-transformed to account for non-normal distribution (based on the Shapiro-Wilk test). Five models were built for ANCOVA analysis. Model 1 was unadjusted; model 2 was adjusted for age, sex, and daily energy intake; model 3 was adjusted for age, sex, daily energy intake, and V/S fat volume ratio; model 4 was adjusted for age, sex, daily energy intake, V/S fat volume ratio, smoking status, and daily alcohol intake; model 5 was adjusted for age, sex, daily energy intake, V/S fat volume ratio, smoking status, daily alcohol intake, aetiology of AP, number of AP episodes, cholecystectomy, and use of antidiabetic medications. These covariates were selected as they may influence glucose homeostasis, thus statistical analyses were adjusted to minimise risk of confounding. Data were presented as a β coefficient, *p* value, and 95% confidence interval. Last, to investigate the associations between the investigated minerals and markers of glucose metabolism as well as insulin traits, multiple linear regression analyses were conducted for each study group. Each marker of glucose metabolism and insulin trait was treated as a dependent variable. Multiple linear regression analyses were conducted using the same five statistical models as the ANCOVA analysis. Data were presented as R^2, unstandardised B, *p* value, and 95% confidence interval. *P* values less than 0.05 were considered statistically significant in all analyses, and data were not corrected for multiple tests.

3.3 Results

3.3.1 Characteristics of Study Cohort

A total of 106 eligible individuals diagnosed with AP were included in the present study. The mean and SD time since the last AP attack was 26 ± 20 months, and the number of participants with recurrent attacks of AP did not differ significantly between the groups ($p = 0.125$). The NODAP group consisted of 37 participants, the T2DM group consisted of 37 participants, and the NAP group consisted of 32 participants. Table 3.1 shows the characteristics of the study cohort. There were statistically significant differences in means between the three groups for the following characteristics: V/S fat volume ratio ($p = 0.035$), use of antidiabetic medications ($p < 0.001$), HbA1c (mmol/mol) ($p < 0.001$), and FPG (mmol/L) ($p < 0.001$).

Table 3.1 Characteristics of Study Cohort

Characteristic	Total (*n* = 106)	NODAP (*n* = 37)	T2DM (*n* = 37)	NAP (*n* = 32)	*p* *
Age	56.1 (14.5)	58.9 (14.4)	57.2(15.0)	51.6(13.3)	0.094
Sex					
Men	69 (65.1)	26 (70.3)	28 (75.7)	15 (46.9)	**0.031**
Women	37 (34.9)	11 (29.7)	9 (24.3)	17 (53.1)	
Daily energy intake (kcal)	1686 (609)	1776 (692)	1728 (534)	1534 (574)	0.226
V/S fat volume ratio	0.77 (0.43)	0.81 (0.40)	0.87 (0.46)	0.61 (0.40)	**0.035**
Alcohol intake (g/day)	11.1 (17.9)	13.4 (21.9)	8.7 (13.1)	11.1 (17.7)	0.527
Smoking status					
Never	47 (44)	11 30)	21 (57)	15 (47)	
Former	35 (33)	16 (4)	11 (30)	8 (25)	0.052
Light (<20 [a]/d)	8 (8)	3 (8)	2 (5)	3 (9)	
Moderate (20–39 [a]/d)	15 (14)	7 (19)	2 (5)	6 (19)	
Heavy (>39 [a]/d)	0 (0)	0 (0)	0 (0)	0 (0)	
Aetiology of AP					
Biliary	40 (38)	14 (38)	14 (38)	12 (38)	0.563
Alcohol-related	21 (20)	12 (32)	5 (14)	4 (13)	
Other	45 (43)	11 (30)	18 (49)	16 (50)	
Number of AP episodes	1.9 (2.8)	2.3 (3.8)	1.4 (1.0)	1.8 (2.8)	0.434
Cholecystectomy					
No	66 (62)	24 (65)	25 (68)	17 (53)	0.538
Yes	39 (37)	13 (35)	12 (32)	14 (44)	
Anti-diabetic medication usage					
None	92 (87)	37 (100)	23 (62)	32 (100)	**<0.001**
Oral medication	8 (8)	0 (0)	8 (22)	0 (0)	
Insulin	6 (6)	0 (0)	6 (16)	0 (0)	
HbA1c (mmol/mol)	40.61 (10.82)	39.05 (4.80)	47.19 (15.23)	34.61 (2.55)	**<0.001**
Fasting plasma glucose (mmol/L)	5.86 (1.74)	5.86 (0.92)	6.61 (2.55)	4.96 (0.34)	**<0.001**
Fasting insulin (mU/L)	16.68 (36.01)	12.98 (9.96)	24.62 (59.95)	12.15 (10.27)	0.277
HOMA-S (%)	0.88 (0.74)	1.02 (1.06)	0.72 (0.44)	0.90 (0.49)	0.228
HOMA-β (%)	106.97 (56.87)	95.74 (45.63)	103.24 (57.12)	125.07 (65.87)	0.098

Abbreviations: AP = acute pancreatitis. HbA1c = glycated haemoglobin. HOMA-S = homeostasis model assessment of insulin sensitivity. HOMA-β = homeostasis model assessment of β-cell dysfunction. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. V/S fat volume ratio = visceral to subcutaneous fat volume ratio.

Footnotes: Data are presented as mean (standard deviation) or frequency(percentage). [a] cigarettes per day. * *p* values were calculated from one way ANOVA. Significance was set at $p < 0.05$. Significant values are shown in bold.

3.3.2 Associations between Habitual Mineral Intake and Diabetes Types

In the NODAP group, four minerals (iron, nitrogen, phosphorous, zinc) were significantly different when compared with the NAP group (Table 3.2). The mean iron intake was significantly different in all adjusted models ($p = 0.029$ in model 2, $p = 0.030$ in model 3, $p = 0.036$ in model 4, and $p = 0.013$ in model 5). The mean nitrogen intake was significantly different in all adjusted models ($p = 0.003$ in model 2, $p = 0.003$ in model 3, $p = 0.002$ in model 4, and $p = 0.003$ in model 5). The mean phosphorous intake was significantly different in all adjusted models ($p = 0.005$ in model 2, $p = 0.005$ in model 3, $p = 0.005$ in model 4, and $p = 0.006$ in model 5). The mean zinc intake was significantly different in all adjusted models ($p = 0.002$ in model 2, $p = 0.003$ in model 3, $p = 0.003$ in model 4, and $p = 0.001$ in model 5). Intake of other investigated minerals in the NODAP group did not differ significantly from the reference group.

In the T2DM group, one mineral was significantly different when compared with the NAP group (Table 3.2). The mean copper intake was significantly different in the unadjusted model ($p = 0.012$) and adjusted models 2–4 ($p = 0.039$ in model 2, $p = 0.026$ in model 3, and $p = 0.049$ in model 4). However, the difference in mean intake became insignificant in the most adjusted model ($p = 0.147$). Intake of other investigated minerals in the T2DM group did not differ significantly from the reference group.

Table 3.2 Associations between Habitual Mineral Intake and the Study Groups.

Mineral	Model	T2DM				NODAP			
		β	*p*	95% CI		β	*p*	95% CI	
				Lower	Upper			Lower	Upper
Calcium (mg)	1	0.009	0.821	−0.070	0.089	−0.023	0.565	−0.102	0.056
	2	−0.020	0.537	−0.082	0.043	−0.059	0.063	−0.120	0.003
	3	−0.018	0.581	−0.080	0.045	−0.058	0.064	−0.120	0.003
	4	−0.022	0.506	−0.089	0.044	−0.057	0.073	−0.120	0.005
	5	−0.010	0.797	−0.087	0.067	−0.056	0.091	−0.121	0.009
Chloride (mg)	1	0.047	0.326	−0.047	0.141	0.040	0.396	−0.053	0.133
	2	0.000	0.996	−0.057	0.057	−0.020	0.471	−0.077	0.036
	3	0.003	0.926	−0.054	0.060	−0.020	0.471	−0.077	0.036
	4	0.002	0.939	−0.057	0.061	−0.023	0.417	−0.079	0.033
	5	0.024	0.492	−0.045	0.093	−0.025	0.394	−0.084	0.033
Copper (mg)	1	0.123	**0.012**	0.027	0.219	0.090	0.064	−0.005	0.185
	2	0.073	**0.039**	0.004	0.141	0.026	0.445	−0.042	0.094
	3	0.078	**0.026**	0.010	0.146	0.026	0.436	−0.041	0.093
	4	0.072	**0.049**	0.000	0.144	0.026	0.458	−0.043	0.094
	5	0.061	0.147	−0.022	0.145	0.019	0.592	−0.052	0.090
Iodine (μg)	1	0.046	0.259	−0.034	0.126	0.017	0.675	−0.063	0.097
	2	0.030	0.402	−0.040	0.099	−0.007	0.846	−0.076	0.062
	3	0.037	0.269	−0.029	0.104	−0.007	0.843	−0.073	0.059
	4	0.015	0.666	−0.054	0.084	−0.009	0.787	−0.074	0.056
	5	0.010	0.811	−0.071	0.091	0.000	0.990	−0.069	0.068
Iron (mg)	1	0.012	0.785	−0.076	0.101	−0.002	0.963	−0.090	0.086
	2	−0.037	0.205	−0.096	0.021	−0.064	**0.029**	−0.122	−0.007
	3	−0.036	0.220	−0.095	0.022	−0.064	**0.030**	−0.122	−0.006
	4	−0.034	0.272	−0.094	0.027	−0.061	**0.036**	−0.119	−0.004
	5	−0.034	0.342	−0.104	0.036	−0.076	**0.013**	−0.135	−0.016
Magnesium (mg)	1	0.025	0.513	−0.051	0.100	0.034	0.371	−0.041	0.109
	2	−0.013	0.582	−0.062	0.035	−0.013	0.581	−0.061	0.035
	3	−0.011	0.665	−0.059	0.038	−0.013	0.579	−0.061	0.034
	4	−0.015	0.559	−0.066	0.036	−0.013	0.600	−0.061	0.035
	5	−0.016	0.589	−0.076	0.043	−0.017	0.516	−0.067	0.034
Manganese (mg)	1	0.022	0.687	−0.085	0.128	0.028	0.600	−0.078	0.134
	2	−0.006	0.878	−0.089	0.076	−0.017	0.687	−0.098	0.065
	3	−0.003	0.942	−0.085	0.079	−0.017	0.688	−0.098	0.065
	4	−0.021	0.633	−0.107	0.065	−0.020	0.634	−0.101	0.062
	5	−0.049	0.343	−0.150	0.053	−0.035	0.418	−0.121	0.051
Nitrogen (g)	1	0.010	0.784	−0.060	0.079	−0.025	0.474	−0.094	0.044
	2	−0.023	0.299	−0.066	0.021	−0.066	**0.003**	−0.109	−0.023
	3	−0.021	0.346	−0.064	0.023	−0.066	**0.003**	−0.109	−0.023
	4	−0.042	0.055	−0.086	0.001	−0.065	**0.002**	−0.106	−0.024
	5	−0.033	0.205	−0.084	0.018	−0.066	**0.003**	−0.110	−0.023
Phosphorous (mg)	1	0.017	0.610	−0.048	0.081	−0.005	0.880	−0.069	0.059
	2	−0.017	0.291	−0.050	0.015	−0.046	**0.005**	−0.078	−0.014
	3	−0.015	0.351	−0.047	0.017	−0.046	**0.005**	−0.078	−0.015
	4	−0.026	0.124	−0.059	0.007	−0.045	**0.005**	−0.077	−0.014
	5	−0.023	0.241	−0.061	0.015	−0.046	**0.006**	−0.078	−0.014
Potassium (mg)	1	0.017	0.642	−0.055	0.088	0.020	0.578	−0.051	0.091
	2	−0.019	0.449	−0.069	0.031	−0.025	0.318	−0.074	0.024
	3	−0.015	0.543	−0.064	0.034	−0.025	0.310	−0.073	0.023
	4	−0.018	0.492	−0.069	0.034	−0.024	0.324	−0.073	0.024
	5	−0.020	0.510	−0.080	0.040	−0.026	0.322	−0.076	0.025
Selenium (μg)	1	0.058	0.202	−0.032	0.147	0.035	0.439	−0.054	0.123
	2	0.024	0.445	−0.038	0.085	−0.011	0.716	−0.072	0.049
	3	−0.011	0.713	−0.071	0.049	−0.011	0.713	−0.071	0.049
	4	0.009	0.780	−0.053	0.071	−0.014	0.637	−0.073	0.045
	5	−0.008	0.828	−0.081	0.065	−0.011	0.722	−0.072	0.050

Table 3.2 *Cont.*

Mineral	Model	T2DM				NODAP			
		β	*p*	95% CI		β	*p*	95% CI	
				Lower	Upper			Lower	Upper
Sodium (mg)	1	0.042	0.380	−0.053	0.137	0.030	0.536	−0.065	0.124
	2	−0.004	0.895	−0.062	0.054	−0.031	0.281	−0.089	0.026
	3	−0.002	0.953	−0.060	0.056	−0.031	0.281	−0.088	0.026
	4	−0.005	0.875	−0.065	0.055	0.009	0.780	−0.053	0.071
	5	0.022	0.537	−0.048	0.092	−0.034	0.256	−0.094	0.025
Zinc (mg)	1	0.025	0.489	−0.046	0.096	−0.024	0.510	−0.094	0.047
	2	−0.017	0.459	−0.063	0.029	−0.071	**0.002**	−0.116	−0.026
	3	−0.017	0.467	−0.063	0.029	−0.071	**0.003**	−0.117	−0.026
	4	−0.029	0.232	−0.077	0.019	−0.070	**0.003**	−0.116	−0.025
	5	−0.017	0.527	−0.071	0.037	−0.078	**0.001**	−0.124	−0.033

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as β coefficients, 95% CI, and *p* values (from ANCOVA analysis). NAP group was used as the reference group. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

3.3.3 Associations between Habitual Mineral Intake and Markers of Glucose Metabolism in the Study Groups

HbA1c levels were associated with two minerals in the NODAP group. Iodine intake was significantly directly associated with HbA1c levels in adjusted models 3 and 5 ($p = 0.037$ and $p = 0.032$, respectively) (Table 3.3, Figure 3.1). Manganese intake was significantly inversely associated with HbA1c in the NODAP group in all adjusted models ($p = 0.003$ in model 2, $p = 0.003$ in model 3, $p = 0.002$ in model 4, and $p = 0.003$ in model 5) (Figure 3.1). Associations between intake of other investigated minerals and HbA1c in the NODAP group were not statistically significant.

In the T2DM group and the NAP group, there were no statistically significant associations between any investigated minerals and HbA1c levels in all models.

FPG levels were associated with one mineral in the NODAP group (Table 3.4, Figure 3.1). Manganese was significantly inversely associated with FPG in all adjusted models ($p = 0.029$ in model 2, $p = 0.031$ in model 3, $p = 0.020$ in model 4, and $p = 0.027$ in model 5) (Figure 3.1).

In the T2DM group, associations between the investigated minerals and FPG were not statistically significant (Table 3.4).

In the NAP group, FPG levels were associated with three minerals (copper, magnesium, and potassium) (Table 3.4). Copper intake was significantly inversely associated with FPG levels in adjusted models 2 and 5 ($p = 0.044$ in model 2 and $p = 0.023$ in model 5). Magnesium intake was significantly inversely associated with FPG levels in all adjusted models ($p = 0.008$ in model 2, $p = 0.023$ in model 3, $p = 0.027$ in model 4, and $p = 0.030$ in model 5). Potassium intake was significantly inversely associated with FPG levels in all adjusted models ($p = 0.011$ in model 2, $p = 0.029$ in model 3, $p = 0.031$ in model 4, and $p = 0.036$ in model 5).

Table 3.3 Associations between Habitual Mineral Intake and HbA1c in the Study Groups

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Calcium (mg)	1	0.003	0.695	0.772	−4.164	5.554	0.028	−15.434	0.368	−49.861	18.994	0.055	8.423	0.164	−3.610	20.456
	2	0.278	0.404	0.886	−5.315	6.123	0.039	−16.023	0.528	−67.269	35.222	0.170	12.012	0.172	−5.491	29.515
	3	0.280	0.452	0.875	−5.397	6.301	0.081	−15.410	0.541	−66.347	35.528	0.190	14.180	0.124	−4.111	32.470
	4	0.347	1.608	0.595	−4.558	7.774	0.173	−22.037	0.380	−72.650	28.576	0.247	13.916	0.131	−4.383	32.216
	5	0.382	1.344	0.683	−5.415	8.103	0.493	−14.339	0.568	−65.521	36.844	0.275	12.586	0.199	−7.032	32.204
Chloride (mg)	1	0.085	4.268	0.112	−1.059	9.596	0.044	−15.515	0.227	−41.158	10.127	0.051	5.530	0.179	−2.658	13.718
	2	0.323	5.032	0.198	−2.798	12.863	0.063	−24.427	0.325	−74.324	25.471	0.126	4.013	0.603	−11.565	19.590
	3	0.341	6.349	0.139	−2.201	14.900	0.109	−24.191	0.326	−73.745	25.364	0.133	4.323	0.582	−11.515	20.160
	4	0.382	5.548	0.217	−3.484	14.580	0.222	−32.960	0.184	−82.570	16.650	0.191	3.785	0.633	−12.267	19.837
	5	0.424	5.932	0.215	−3.720	15.585	0.484	−11.699	0.619	−59.769	36.371	0.233	3.655	0.657	−13.081	20.391
Copper (mg)	1	0.042	2.683	0.268	−2.177	7.544	0.022	−13.209	0.390	−44.091	17.672	0.004	1.427	0.706	−6.181	9.035
	2	0.298	3.412	0.386	−4.547	11.371	0.037	−8.386	0.677	−49.121	32.349	0.151	−6.212	0.283	−17.795	5.370
	3	0.303	3.655	0.368	−4.553	11.863	0.079	−1.616	0.938	−43.979	40.746	0.153	−5.948	0.317	−17.864	5.968
	4	0.343	1.698	0.701	−7.325	10.722	0.170	−3.533	0.864	−45.511	38.445	0.208	−5.829	0.356	−18.551	6.893
	5	0.379	1.663	0.785	−10.893	14.218	0.478	0.148	0.994	−37.444	37.740	0.242	−4.840	0.472	−18.487	8.807
Iodine (µg)	1	0.050	3.050	0.226	−1.998	8.098	0.040	−21.520	0.247	−58.669	15.629	0.065	7.667	0.129	−2.340	17.674
	2	0.298	2.446	0.394	−3.351	8.244	0.052	−18.384	0.425	−64.815	28.047	0.185	9.758	0.116	−2.534	22.049
	3	0.301	2.571	0.382	−3.382	8.524	0.084	−10.465	0.667	−59.635	38.706	0.241	14.951	**0.037**	0.997	28.905
	4	0.359	2.552	0.401	−3.613	8.717	0.181	−14.979	0.533	−63.706	33.747	0.276	14.135	0.065	−0.929	29.200
	5	0.390	2.185	0.520	−4.771	9.140	0.498	−19.879	0.350	−62.977	23.219	0.354	17.763	**0.032**	1.601	33.926
Iron (mg)	1	0.017	1.807	0.490	−3.479	7.093	0.065	−22.774	0.140	−53.395	7.848	0.004	1.644	0.697	−6.852	10.139
	2	0.278	−0.183	0.959	−7.449	7.082	0.099	−41.281	0.146	−97.747	15.184	0.153	−7.510	0.264	−20.979	5.958
	3	0.279	−0.041	0.991	−7.555	7.473	0.139	−39.418	0.163	−95.710	16.874	0.159	−7.557	0.268	−21.211	6.098
	4	0.348	2.304	0.562	−5.805	10.412	0.202	−30.213	0.294	−88.098	27.672	0.205	−6.118	0.392	−20.529	8.294
	5	0.392	3.614	0.477	−6.799	14.027	0.478	−3.564	0.893	−57.916	50.788	0.242	−5.279	0.478	−20.352	9.794
Magnesium (mg)	1	0.015	2.080	0.517	−4.410	8.570	0.029	−16.583	0.329	−50.606	17.439	0.000	−0.035	0.995	−10.529	10.459
	2	0.278	0.748	0.872	−8.730	10.226	0.045	−17.348	0.523	−72.103	37.408	0.198	−15.774	0.084	−33.813	2.264
	3	0.281	1.328	0.794	−9.013	11.668	0.090	−16.465	0.541	−70.912	37.982	0.199	−15.595	0.101	−34.382	3.193
	4	0.342	1.603	0.752	−8.779	11.985	0.182	−17.570	0.509	−71.398	36.259	0.241	−14.792	0.152	−35.363	5.779
	5	0.377	0.706	0.900	−10.879	12.292	0.481	−9.455	0.698	−59.159	40.248	0.291	−15.995	0.138	−37.481	5.492
Manganese (mg)	1	0.035	2.419	0.311	−2.381	7.220	0.003	3.558	0.751	−19.041	26.157	0.041	−4.493	0.230	−11.951	2.965
	2	0.322	4.217	0.201	−2.395	10.829	0.070	16.181	0.274	−13.505	45.866	0.338	−15.097	**0.003**	−24.555	−5.638
	3	0.332	4.740	0.172	−2.197	11.678	0.117	16.108	0.273	−13.362	45.579	0.338	−15.274	**0.003**	−25.116	−5.431
	4	0.365	3.708	0.341	−4.186	11.602	0.183	10.427	0.495	−20.504	41.359	0.411	−16.465	**0.002**	−26.546	−6.385
	5	0.399	4.551	0.392	−6.300	15.401	0.490	10.357	0.469	−18.745	39.458	0.455	−17.147	**0.003**	−27.829	−6.464

Table 3.3 *Cont.*

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Nitrogen (g)	1	0.001	0.747	0.837	−6.634	8.128	0.030	−19.306	0.321	−58.323	19.711	0.017	3.968	0.440	−6.356	14.293
	2	0.297	−4.643	0.407	−15.959	6.673	0.048	−24.332	0.472	−92.587	43.924	0.119	0.040	0.996	−17.873	17.952
	3	0.297	−4.622	0.438	−16.695	7.450	0.092	−21.690	0.520	−89.766	46.385	0.125	0.611	0.946	−17.734	18.956
	4	0.366	−5.911	0.327	−18.122	6.301	0.169	−6.075	0.872	−82.534	70.384	0.184	−0.280	0.977	−19.817	19.257
	5	0.402	−6.015	0.366	−19.565	7.535	0.487	21.821	0.536	−50.047	93.689	0.227	0.707	0.944	−19.774	21.187
Phosphorous (mg)	1	0.010	1.936	0.593	−5.384	9.255	0.029	−20.931	0.329	−63.886	22.025	0.028	5.931	0.322	−6.066	17.928
	2	0.280	−1.931	0.777	−15.783	11.921	0.047	−28.990	0.485	−112.750	54.770	0.125	7.100	0.627	−22.399	36.598
	3	0.281	−1.597	0.824	−16.252	13.058	0.090	−24.752	0.550	−108.475	58.970	0.136	9.891	0.523	−21.318	41.100
	4	0.341	−2.105	0.776	−17.217	13.006	0.178	−23.107	0.582	−108.193	61.980	0.205	14.626	0.389	−19.608	48.860
	5	0.381	−2.991	0.706	−19.313	13.331	0.478	−5.990	0.885	−90.846	78.867	0.244	13.957	0.448	−23.277	51.190
Potassium (mg)	1	0.007	1.337	0.662	−4.851	7.526	0.036	−19.541	0.274	−55.273	16.190	0.001	1.188	0.845	−11.066	13.442
	2	0.278	0.318	0.935	−7.579	8.216	0.054	−24.484	0.404	−83.561	34.593	0.172	−14.573	0.160	−35.223	6.077
	3	0.280	0.700	0.867	−7.806	9.207	0.093	−19.581	0.507	−79.212	40.049	0.172	−14.359	0.190	−36.204	7.486
	4	0.342	1.503	0.721	−7.086	10.093	0.187	−22.375	0.442	−81.154	36.405	0.212	−11.737	0.321	−35.497	12.022
	5	0.378	0.938	0.838	−8.489	10.366	0.495	−22.591	0.387	−75.593	30.410	0.261	−13.299	0.286	−38.402	11.804
Selenium (μg)	1	0.040	2.931	0.282	−2.541	8.404	0.001	−3.726	0.836	−40.123	32.672	0.028	3.654	0.321	−3.718	11.025
	2	0.283	1.851	0.674	−7.101	10.803	0.042	15.057	0.575	−39.189	69.303	0.123	2.239	0.697	−9.372	13.850
	3	0.285	1.978	0.661	−7.198	11.155	0.117	31.274	0.272	−25.844	88.391	0.130	2.706	0.646	−9.201	14.612
	4	0.343	1.688	0.710	−7.586	10.963	0.215	39.157	0.218	−24.592	102.907	0.186	1.519	0.799	−10.596	13.633
	5	0.379	1.311	0.784	−8.516	11.139	0.487	17.826	0.540	−41.505	77.158	0.237	3.642	0.569	−9.322	16.607
Sodium (mg)	1	0.088	4.275	0.104	−0.940	9.490	0.040	−14.905	0.248	−40.714	10.904	0.052	5.413	0.175	−2.519	13.345
	2	0.334	5.458	0.150	−2.114	13.030	0.056	−21.295	0.389	−71.052	28.463	0.128	4.165	0.575	−10.800	19.130
	3	0.352	6.607	0.107	−1.542	14.757	0.102	−21.094	0.390	−70.514	28.327	0.134	4.312	0.567	−10.871	19.495
	4	0.390	5.738	0.179	−2.828	14.305	0.216	−31.273	0.214	−81.738	19.192	0.191	3.797	0.619	−11.648	19.243
	5	0.438	6.639	0.153	−2.688	15.966	0.480	−7.151	0.770	−57.207	42.906	0.235	4.181	0.597	−11.894	20.256
Zinc (mg)	1	0.000	0.059	0.986	−6.747	6.865	0.033	−19.770	0.295	−57.549	18.010	0.026	4.984	0.343	−5.549	15.517
	2	0.327	−6.886	0.179	−17.132	3.360	0.062	−29.825	0.329	−91.235	31.585	0.120	2.044	0.817	−15.812	19.899
	3	0.327	−7.089	0.193	−18.004	3.826	0.124	−36.619	0.231	−97.872	24.634	0.126	2.199	0.806	−15.918	20.315
	4	0.401	−8.146	0.134	−19.009	2.716	0.188	−25.215	0.431	−89.980	39.550	0.185	1.313	0.886	−17.316	19.943
	5	0.464	−12.169	0.085	−26.193	1.856	0.480	8.802	0.779	−55.273	72.876	0.227	0.970	0.919	−18.434	20.375

Abbreviations: HbA1c = glycated haemoglobin. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

Table 3.4 Associations between Habitual Mineral Intake and Fasting Plasma Glucose in the Study Groups.

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Calcium (mg)	1	0.004	0.097	0.753	−0.527	0.720	0.021	−2.219	0.404	−7.561	3.124	0.090	2.072	0.071	−0.191	4.334
	2	0.151	0.149	0.703	−0.648	0.947	0.049	−2.695	0.492	−10.614	5.225	0.228	1.495	0.354	−1.740	4.730
	3	0.222	0.185	0.630	−0.598	0.967	0.088	−2.608	0.505	−10.511	5.296	0.234	1.722	0.311	−1.688	5.131
	4	0.225	0.192	0.651	−0.675	1.058	0.283	−3.788	0.302	−11.177	3.601	0.268	1.659	0.335	−1.799	5.117
	5	0.232	0.163	0.730	−0.814	1.140	0.545	−3.188	0.386	−10.646	4.271	0.303	1.746	0.339	−1.941	5.432
Chloride (mg)	1	0.025	0.302	0.399	−0.421	1.025	0.052	−2.620	0.187	−6.575	1.335	0.068	1.224	0.119	−0.331	2.780
	2	0.164	0.410	0.472	−0.745	1.565	0.091	−5.102	0.181	−12.716	2.513	0.209	−0.488	0.728	−3.329	2.352
	3	0.270	0.771	0.188	−0.402	1.945	0.129	−5.068	0.182	−12.658	2.521	0.210	−0.467	0.745	−3.364	2.431
	4	0.280	0.854	0.180	−0.424	2.132	0.340	−6.499	0.070	−13.578	0.579	0.247	−0.497	0.735	−3.465	2.471
	5	0.295	0.905	0.192	−0.497	2.308	0.553	−3.676	0.284	−10.607	3.256	0.283	−0.630	0.680	−3.732	2.471
Copper (mg)	1	0.022	−0.242	0.439	−0.875	0.390	0.032	−2.426	0.308	−7.187	2.336	0.025	0.677	0.347	−0.766	2.119
	2	0.277	−1.073	**0.044**	−2.113	−0.033	0.050	−2.194	0.480	−8.463	4.074	0.249	−1.382	0.187	−3.469	0.706
	3	0.320	−0.977	0.065	−2.021	0.066	0.079	−1.322	0.683	−7.884	5.241	0.249	−1.380	0.200	−3.530	0.770
	4	0.329	−1.084	0.069	−2.262	0.093	0.264	−1.868	0.537	−7.989	4.254	0.292	−1.577	0.173	−3.883	0.730
	5	0.416	−1.901	**0.023**	−3.508	−0.294	0.535	−1.471	0.585	−6.964	4.023	0.333	−1.754	0.154	−4.208	0.699
Iodine (µg)	1	0.008	0.154	0.637	−0.508	0.816	0.046	−3.572	0.214	−9.309	2.165	0.058	1.392	0.151	−0.533	3.316
	2	0.147	0.073	0.856	−0.749	0.895	0.061	−3.252	0.361	−10.412	3.909	0.219	0.838	0.464	−1.468	3.144
	3	0.219	0.147	0.711	−0.664	0.958	0.084	−2.203	0.559	−9.821	5.415	0.231	1.288	0.337	−1.405	3.980
	4	0.223	0.176	0.681	−0.701	1.054	0.274	−3.022	0.391	−10.129	4.084	0.254	0.919	0.526	−2.011	3.850
	5	0.230	0.118	0.811	−0.902	1.138	0.562	−3.979	0.200	−10.211	2.254	0.280	0.392	0.807	−2.878	3.663
Iron (mg)	1	0.004	−0.110	0.745	−0.793	0.574	0.070	−3.652	0.126	−8.384	1.079	0.031	0.843	0.294	−0.763	2.448
	2	0.186	−0.536	0.276	−1.527	0.456	0.130	−7.646	0.079	−16.241	0.950	0.232	−1.264	0.302	−3.721	1.193
	3	0.240	−0.430	0.381	−1.425	0.565	0.162	−7.387	0.090	−15.990	1.216	0.234	−1.268	0.308	−3.766	1.229
	4	0.254	−0.564	0.307	−1.683	0.555	0.296	−5.258	0.211	−13.683	3.166	0.265	−1.186	0.369	−3.842	1.470
	5	0.280	−0.830	0.254	−2.308	0.647	0.533	−1.636	0.675	−9.604	6.332	0.300	−1.215	0.377	−3.992	1.562
Magnesium (mg)	1	0.060	−0.533	0.193	−1.350	0.285	0.031	−2.638	0.316	−7.904	2.629	0.032	1.051	0.288	−0.927	3.030
	2	0.358	−1.611	**0.008**	−2.764	−0.457	0.056	−3.446	0.411	−11.880	4.988	0.249	−2.229	0.184	−5.574	1.116
	3	0.370	−1.470	**0.023**	−2.717	−0.224	0.094	−3.321	0.426	−11.741	5.099	0.249	−2.254	0.197	−5.739	1.230
	4	0.376	−1.485	**0.027**	−2.790	−0.181	0.274	−3.379	0.385	−11.234	4.477	0.284	−2.378	0.214	−6.208	1.453
	5	0.402	−1.658	**0.030**	−3.132	−0.183	0.541	−2.652	0.457	−9.899	4.595	0.315	−2.340	0.245	−6.386	1.707
Manganese (mg)	1	0.036	−0.313	0.315	−0.939	0.314	0.004	0.612	0.724	−2.888	4.111	0.000	0.020	0.978	−1.440	1.479
	2	0.216	−0.670	0.148	−1.595	0.255	0.070	2.447	0.286	−2.151	7.044	0.318	−2.065	**0.029**	−3.905	−0.225
	3	0.259	−0.548	0.243	−1.492	0.397	0.110	2.437	0.286	−2.147	7.020	0.319	−2.116	**0.031**	−4.029	−0.202
	4	0.261	−0.603	0.268	−1.702	0.496	0.258	0.917	0.683	−3.649	5.484	0.374	−2.394	**0.020**	−4.386	−0.403
	5	0.300	−1.023	0.177	−2.551	0.505	0.531	0.672	0.751	−3.650	4.994	0.403	−2.436	**0.027**	−4.579	−0.294

Table 3.4 *Cont.*

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Nitrogen (g)	1	0.000	0.029	0.951	−0.925	0.983	0.079	−4.872	0.102	−10.761	1.017	0.069	1.529	0.116	−0.396	3.455
	2	0.159	−0.492	0.540	−2.124	1.140	0.151	−9.958	0.051	−19.945	0.028	0.207	0.307	0.849	−2.949	3.564
	3	0.217	−0.232	0.775	−1.892	1.428	0.182	−9.612	0.059	−19.620	0.395	0.209	0.363	0.826	−2.979	3.706
	4	0.219	−0.201	0.816	−1.965	1.564	0.290	−6.283	0.249	−17.236	4.670	0.244	0.055	0.976	−3.551	3.660
	5	0.227	−0.073	0.941	−2.088	1.943	0.539	−3.647	0.482	−14.194	6.899	0.279	−0.286	0.878	−4.078	3.506
Phosphorous (mg)	1	0.002	0.113	0.809	−0.834	1.059	0.040	−3.794	0.252	−10.412	2.823	0.079	1.913	0.091	−0.325	4.150
	2	0.150	−0.317	0.743	−2.289	1.654	0.080	−7.676	0.228	−20.427	5.075	0.206	0.152	0.954	−5.234	5.538
	3	0.214	−0.017	0.986	−2.004	1.971	0.113	−7.102	0.266	−19.910	5.705	0.208	0.352	0.901	−5.375	6.080
	4	0.217	0.019	0.985	−2.116	2.155	0.279	−5.937	0.332	−18.279	6.405	0.244	0.307	0.922	−6.092	6.706
	5	0.227	0.046	0.968	−2.321	2.414	0.544	−5.139	0.396	−17.430	7.152	0.278	−0.356	0.917	−7.329	6.617
Potassium (mg)	1	0.093	−0.631	0.101	−1.395	0.132	0.041	−3.221	0.244	−8.742	2.301	0.034	1.259	0.276	−1.051	3.569
	2	0.343	−1.289	**0.011**	−2.260	−0.318	0.074	−5.037	0.265	−14.094	4.021	0.249	−2.497	0.187	−6.267	1.273
	3	0.359	−1.165	**0.029**	−2.199	−0.131	0.103	−4.377	0.338	−13.563	4.810	0.249	−2.577	0.197	−6.564	1.410
	4	0.369	−1.203	**0.031**	−2.289	−0.117	0.292	−5.001	0.238	−13.501	3.499	0.278	−2.493	0.252	−6.853	1.866
	5	0.390	−1.305	**0.036**	−2.518	−0.092	0.571	−5.495	0.147	−13.061	2.070	0.308	−2.391	0.301	−7.047	2.265
Selenium (μg)	1	0.001	0.070	0.844	−0.649	0.788	0.034	−2.930	0.290	−8.476	2.616	0.088	1.241	0.074	−0.127	2.609
	2	0.154	−0.296	0.630	−1.548	0.955	0.050	−2.893	0.486	−11.263	5.476	0.212	0.502	0.631	−1.608	2.611
	3	0.219	−0.223	0.713	−1.458	1.012	0.076	−1.390	0.756	−10.438	7.658	0.214	0.550	0.609	−1.619	2.720
	4	0.221	−0.210	0.741	−1.513	1.092	0.254	−0.467	0.921	−10.095	9.161	0.246	0.352	0.749	−1.882	2.586
	5	0.231	−0.221	0.747	−1.638	1.195	0.548	−4.096	0.336	−12.718	4.526	0.278	0.059	0.960	−2.358	2.475
Sodium (mg)	1	0.026	0.298	0.396	−0.410	1.006	0.043	−2.386	0.233	−6.379	1.606	0.070	1.203	0.114	−0.303	2.709
	2	0.167	0.429	0.440	−0.696	1.553	0.071	−4.127	0.279	−11.770	3.516	0.208	−0.339	0.802	−3.072	2.394
	3	0.269	0.733	0.193	−0.397	1.864	0.110	−4.098	0.280	−11.719	3.522	0.209	−0.327	0.812	−3.108	2.454
	4	0.278	0.805	0.186	−0.417	2.026	0.316	−5.590	0.128	−12.890	1.711	0.245	−0.350	0.804	−3.209	2.510
	5	0.303	0.938	0.166	−0.426	2.302	0.537	−2.196	0.541	−9.513	5.121	0.282	−0.535	0.716	−3.521	2.451
Zinc (mg)	1	0.002	0.104	0.811	−0.777	0.985	0.037	−3.221	0.270	−9.062	2.621	0.092	1.805	0.068	−0.144	3.754
	2	0.151	−0.285	0.705	−1.818	1.247	0.084	−5.927	0.208	−15.327	3.474	0.210	0.639	0.691	−2.604	3.881
	3	0.215	−0.045	0.952	−1.594	1.504	0.141	−6.936	0.142	−16.332	2.459	0.211	0.653	0.689	−2.645	3.951
	4	0.217	−0.027	0.973	−1.659	1.605	0.272	−3.872	0.410	−13.369	5.625	0.245	0.416	0.806	−3.019	3.851
	5	0.229	0.244	0.820	−1.971	2.459	0.530	0.535	0.908	−8.905	9.975	0.279	0.273	0.877	−3.320	3.866

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression) and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

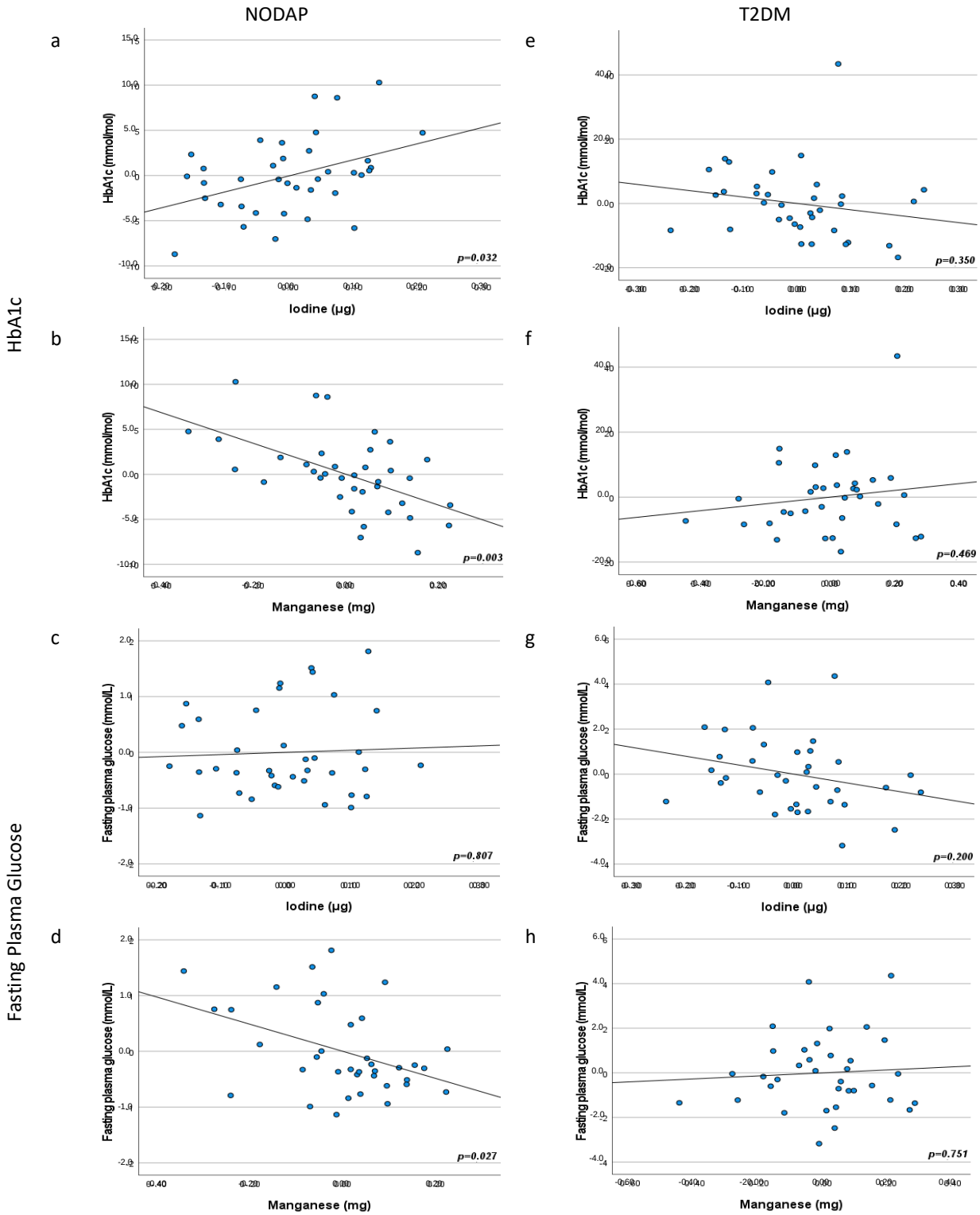

Figure 3.1 Associations between Iodine and Manganese Intake and Markers of Glucose Metabolism in NODAP (**a-d**) and T2DM (**e-h**).

Abbreviations: HbA1c = glycated haemoglobin. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis.

Footnotes: Iodine and manganese data were log transformed. Partial regression plots were adjusted for age, sex, daily energy intake, V/S fat volume, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$.

3.3.4. Associations between Habitual Mineral Intake and Insulin Traits in the Study Groups

Fasting insulin levels were associated with two minerals (chloride and sodium) in the NODAP group (Table 3.5). Chloride intake was significantly directly associated with fasting insulin levels in the unadjusted model only ($p = 0.044$). Sodium was significantly directly associated with fasting insulin levels in the unadjusted model only ($p = 0.043$).

In the T2DM group, fasting insulin was associated with seven minerals (calcium, chloride, iodine, iron, nitrogen, sodium, and zinc) (Table 3.5). Calcium intake was inversely associated with fasting insulin levels in the most adjusted model ($p = 0.048$) (Figure 3.2). Chloride intake was significantly inversely associated with fasting insulin in the unadjusted model ($p = 0.043$) and adjusted models 2 and 3 ($p = 0.035$ in model 2 and $p = 0.039$ in model 3). Iodine intake was significantly associated in the most adjusted models 4 and 5 ($p = 0.042$ in model 4 and $p = 0.041$ in model 5) (Figure 3.2). Iron intake was inversely associated with fasting insulin levels in adjusted model 4 only ($p = 0.028$). Nitrogen intake was significantly inversely associated with fasting insulin in both the unadjusted model ($p = 0.032$) and all adjusted models ($p = 0.026$ in model 2, $p = 0.028$ in model 3, $p = 0.010$ in model 4, and $p = 0.043$ in model 5) (Figure 2). Sodium intake was significantly inversely associated with fasting insulin in the unadjusted model ($p = 0.022$) and adjusted models 2 and 3 ($p = 0.008$ in model 2 and $p = 0.010$ in model 3). Zinc intake was significantly inversely associated with fasting insulin levels in both the unadjusted model ($p = 0.007$) and all adjusted models ($p = 0.001$ in model 2, $p = 0.001$ in model 3, $p < 0.001$ in model 4, and $p < 0.001$ in model 5) (Figure 3.2).

In the NAP group, fasting insulin was not significantly associated with the investigated minerals.

HOMA-S was associated with four minerals (chloride, iron, selenium, sodium) in the NODAP group (Table 3.6). Chloride intake was significantly inversely associated with HOMA-S in the unadjusted model ($p = 0.044$) and the most adjusted model ($p = 0.044$) (Figure 3.3). Iron intake was significantly inversely associated with HOMA-S in the un- adjusted model ($p = 0.040$) and adjusted models ($p = 0.020$ in model 4 and $p = 0.001$ in model 5) (Figure 3.3). Selenium intake was significantly inversely associated with HOMA-S in both the unadjusted ($p = 0.015$) and all adjusted models ($p = 0.010$ in model 2, $p = 0.010$ in model 3, $p = 0.014$ in model 4, and $p = 0.042$ in model 5) (Figure 3.3). Sodium intake was significantly inversely associated with

HOMA-S in the unadjusted model ($p = 0.033$) and the most adjusted model ($p = 0.035$) (Figure 3.3).

In the T2DM group, HOMA-S was associated with one mineral (Table 3.6). Zinc intake was significantly directly associated with HOMA-S in two adjusted models ($p = 0.023$ in model 4 and $p = 0.037$ in model 5) (Figure 3.3).

HOMA-S was not significantly associated with any of the investigated minerals in the NAP group.

HOMA-β was associated with one mineral in the NODAP group (Table 3.7). Magnesium was significantly directly associated with HOMA-β in the most adjusted models ($p = 0.035$).

HOMA-β was not significantly associated with any of the investigated minerals in the T2DM or NAP group (Table 3.7).

Table 3.5 Associations between Habitual Mineral Intake and Fasting Insulin in the Study Groups.

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Calcium (mg)	1	0.000	0.682	0.944	−18.900	20.265	0.000	3.095	0.966	−144.004	150.194	0.025	11.785	0.352	−13.594	37.164
	2	0.003	1.530	0.908	−25.514	28.575	0.093	94.086	0.370	−117.360	305.531	0.140	0.416	0.982	−36.564	37.396
	3	0.006	1.318	0.923	−26.345	28.981	0.095	94.223	0.378	−121.278	309.724	0.154	4.158	0.828	−34.648	42.963
	4	0.055	−1.750	0.905	−31.605	28.104	0.345	151.133	0.123	−43.802	346.068	0.233	4.652	0.806	−33.719	43.023
	5	0.169	−4.304	0.779	−35.829	27.222	0.554	211.928	**0.048**	2.380	421.476	0.305	3.631	0.853	−36.272	43.535
Chloride (mg)	1	0.000	−0.396	0.971	−22.804	22.013	0.125	−115.711	**0.043**	−227.763	−3.659	0.111	16.935	**0.044**	0.477	33.394
	2	0.003	−1.419	0.940	−39.663	36.826	0.205	−250.464	**0.035**	−482.368	−18.559	0.165	15.112	0.338	−16.512	46.736
	3	0.006	−3.765	0.856	−46.016	38.486	0.206	−249.783	**0.039**	−486.616	−12.949	0.181	16.096	0.312	−15.873	48.066
	4	0.054	0.348	0.987	−44.621	45.316	0.325	−157.937	0.202	−405.953	90.079	0.248	12.594	0.430	−19.553	44.740
	5	0.167	3.869	0.865	−42.829	50.567	0.468	−74.265	0.573	−344.241	195.710	0.316	10.893	0.501	−21.922	43.708
Copper (mg)	1	0.001	−1.361	0.890	−21.340	18.619	0.051	−77.657	0.206	−200.404	45.090	0.015	5.743	0.463	−9.966	21.452
	2	0.005	−4.421	0.814	−42.569	33.727	0.087	−62.201	0.431	−221.550	97.148	0.175	−13.480	0.255	−37.185	10.225
	3	0.008	−5.274	0.785	−44.670	34.123	0.094	−73.003	0.383	−242.022	96.016	0.182	−12.505	0.302	−36.818	11.809
	4	0.057	−6.079	0.775	−49.572	37.413	0.309	−78.894	0.304	−233.561	75.772	0.239	−7.103	0.579	−33.004	18.797
	5	0.166	−0.005	1.000	−58.549	58.538	0.469	−43.971	0.561	−198.733	110.791	0.313	−7.846	0.555	−34.827	19.134
Iodine (μg)	1	0.015	6.774	0.508	−13.910	27.458	0.011	44.089	0.559	−108.095	196.274	0.003	−3.376	0.751	−24.832	18.080
	2	0.028	10.929	0.421	−16.526	38.385	0.145	139.849	0.119	−38.148	317.846	0.183	−16.155	0.207	−41.723	9.412
	3	0.029	10.675	0.444	−17.574	38.924	0.149	149.525	0.121	−42.249	341.299	0.183	−15.662	0.296	−45.737	14.413
	4	0.064	7.312	0.619	−22.663	37.287	0.391	177.429	**0.042**	7.071	347.788	0.262	−17.142	0.276	−48.728	14.444
	5	0.167	2.035	0.898	−30.667	34.737	0.560	173.350	**0.041**	7.943	338.758	0.389	−30.162	0.069	−62.806	2.482
Iron (mg)	1	0.003	3.297	0.755	−18.119	24.712	0.099	−115.820	0.075	−243.956	12.315	0.065	13.101	0.129	−3.999	30.202
	2	0.011	7.683	0.648	−26.530	41.897	0.160	−200.167	0.088	−432.286	31.952	0.141	1.804	0.897	−26.366	29.974
	3	0.012	7.195	0.679	−28.208	42.597	0.162	−201.193	0.092	−437.755	35.369	0.153	1.665	0.906	−26.784	30.113
	4	0.066	10.265	0.592	−28.802	49.333	0.407	−245.327	**0.028**	−462.181	−28.472	0.242	9.479	0.512	−19.738	38.695
	5	0.219	26.432	0.260	−21.085	73.948	0.506	−162.179	0.177	−403.620	79.263	0.316	9.995	0.496	−19.730	39.721
Magnesium (mg)	1	0.004	4.215	0.745	−22.047	30.478	0.031	−69.528	0.325	−211.363	72.307	0.064	16.067	0.131	−5.016	37.150
	2	0.013	11.065	0.615	−33.550	55.680	0.070	−38.358	0.729	−262.673	185.957	0.142	4.207	0.826	−34.552	42.967
	3	0.013	10.442	0.663	−38.328	59.212	0.072	−38.529	0.732	−267.158	190.100	0.157	7.364	0.710	−32.652	47.381
	4	0.064	11.718	0.631	−38.103	61.538	0.279	−13.693	0.895	−225.423	198.038	0.264	23.641	0.260	−18.415	65.697
	5	0.178	13.735	0.599	−39.821	67.291	0.467	56.533	0.604	−166.590	279.656	0.346	27.072	0.205	−15.765	69.909
Manganese (mg)	1	0.011	5.508	0.569	−14.050	25.066	0.041	−51.721	0.256	−142.781	39.339	0.021	6.635	0.395	−9.016	22.286
	2	0.027	12.556	0.426	−19.325	44.437	0.074	−29.026	0.632	−151.707	93.654	0.145	−4.331	0.695	−26.653	17.990
	3	0.027	12.358	0.457	−21.338	46.054	0.076	−28.812	0.640	−153.877	96.254	0.155	−2.854	0.803	−25.954	20.246
	4	0.063	8.552	0.651	−30.036	47.141	0.282	−21.648	0.713	−141.639	98.343	0.232	1.811	0.878	−22.102	25.723
	5	0.191	18.914	0.446	−31.778	69.606	0.464	23.069	0.710	−104.147	150.285	0.308	4.983	0.685	−20.009	29.976

Table 3.5 *Cont.*

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Nitrogen (g)	1	0.006	6.296	0.667	−23.334	35.925	0.141	−164.493	**0.032**	−313.440	−15.546	0.023	9.547	0.371	−11.829	30.923
	2	0.026	20.629	0.436	−32.961	74.219	0.220	−290.208	**0.026**	−543.873	−36.544	0.149	−10.206	0.574	−46.762	26.350
	3	0.026	20.417	0.469	−36.755	77.589	0.224	−293.149	**0.028**	−551.738	−34.560	0.159	−8.631	0.641	−45.969	28.707
	4	0.067	16.507	0.572	−43.109	76.122	0.449	−354.028	**0.010**	−616.299	−91.757	0.231	−2.819	0.885	−42.203	36.565
	5	0.205	29.712	0.336	−33.177	92.601	0.557	−302.235	**0.043**	−594.534	−9.936	0.309	−8.424	0.670	−48.642	31.795
Phosphorous (mg)	1	0.005	5.317	0.715	−24.217	34.852	0.064	−124.221	0.154	−297.555	49.113	0.030	12.826	0.303	−12.057	37.708
	2	0.028	26.005	0.417	−38.750	90.760	0.104	−176.359	0.291	−511.914	159.195	0.154	−21.636	0.470	−81.865	38.594
	3	0.028	25.670	0.448	−42.882	94.222	0.106	−180.110	0.290	−522.839	162.618	0.161	−17.082	0.589	−80.946	46.783
	4	0.065	17.927	0.614	−54.521	90.374	0.294	−120.851	0.458	−451.367	209.664	0.231	2.698	0.938	−67.235	72.630
	5	0.181	21.602	0.558	−53.968	97.173	0.461	−38.232	0.840	−427.352	350.887	0.306	2.698	0.938	−67.235	72.630
Potassium (mg)	1	0.006	5.082	0.680	−19.831	29.995	0.004	−25.770	0.734	−179.222	127.681	0.038	14.536	0.245	−10.432	39.504
	2	0.014	9.796	0.592	−27.342	46.933	0.077	67.976	0.576	−177.997	313.950	0.147	−10.519	0.626	−54.057	33.018
	3	0.014	9.292	0.637	−30.771	49.355	0.078	65.721	0.599	−187.360	318.802	0.156	−6.998	0.758	−52.818	38.823
	4	0.063	9.372	0.643	−31.888	50.632	0.294	83.250	0.466	−148.104	314.604	0.234	8.031	0.738	−40.624	56.686
	5	0.177	10.860	0.609	−32.768	54.489	0.486	115.795	0.314	−117.857	349.446	0.312	13.207	0.594	−37.094	63.508
Selenium (µg)	1	0.009	5.761	0.602	−16.608	28.130	0.098	−125.002	0.076	−263.713	13.708	0.057	10.798	0.155	−4.281	25.877
	2	0.034	18.588	0.369	−23.220	60.395	0.114	−127.226	0.229	−339.267	84.815	0.144	4.334	0.713	−19.488	28.156
	3	0.035	18.255	0.389	−24.650	61.159	0.132	−160.099	0.169	−392.384	72.187	0.159	5.725	0.634	−18.588	30.037
	4	0.076	15.940	0.464	−28.303	60.183	0.287	−66.978	0.582	−314.052	180.097	0.236	5.128	0.670	−19.252	29.508
	5	0.187	15.431	0.485	−29.824	60.687	0.489	−126.832	0.291	−370.420	116.757	0.304	0.815	0.949	−24.893	26.523
Sodium (mg)	1	0.001	−1.545	0.887	−23.518	20.428	0.159	−130.487	**0.022**	−240.412	−20.562	0.112	16.517	**0.043**	0.577	32.457
	2	0.005	−4.201	0.818	−41.446	33.043	0.275	−299.924	**0.008**	−516.198	−83.650	0.167	15.217	0.315	−15.142	45.576
	3	0.010	−6.605	0.740	−47.140	33.930	0.276	−299.407	**0.010**	−520.277	−78.537	0.182	15.680	0.305	−14.964	46.323
	4	0.056	−4.007	0.848	−46.888	38.874	0.359	−212.348	0.089	−459.386	34.690	0.247	11.938	0.437	−19.015	42.891
	5	0.167	2.849	0.898	−42.868	48.566	0.489	−142.541	0.288	−414.470	129.388	0.314	9.383	0.547	−22.242	41.008
Zinc (mg)	1	0.004	4.532	0.737	−22.804	31.869	0.213	−197.213	**0.007**	−336.116	−58.310	0.035	12.018	0.270	−9.755	33.791
	2	0.018	15.253	0.535	−34.560	65.067	0.382	−373.530	**0.001**	−575.644	−171.417	0.143	−5.245	0.772	−41.851	31.362
	3	0.018	14.702	0.573	−38.378	67.781	0.386	−380.543	**0.001**	−589.288	−171.797	0.155	−4.778	0.794	−41.776	32.220
	4	0.066	14.441	0.590	−40.152	69.033	0.657	−445.092	**<0.001**	−619.351	−270.832	0.231	−1.635	0.930	−39.212	35.941
	5	0.260	50.565	0.128	−15.779	116.909	0.724	−443.991	**<0.001**	−650.255	−237.727	0.305	−4.170	0.824	−42.378	34.037

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

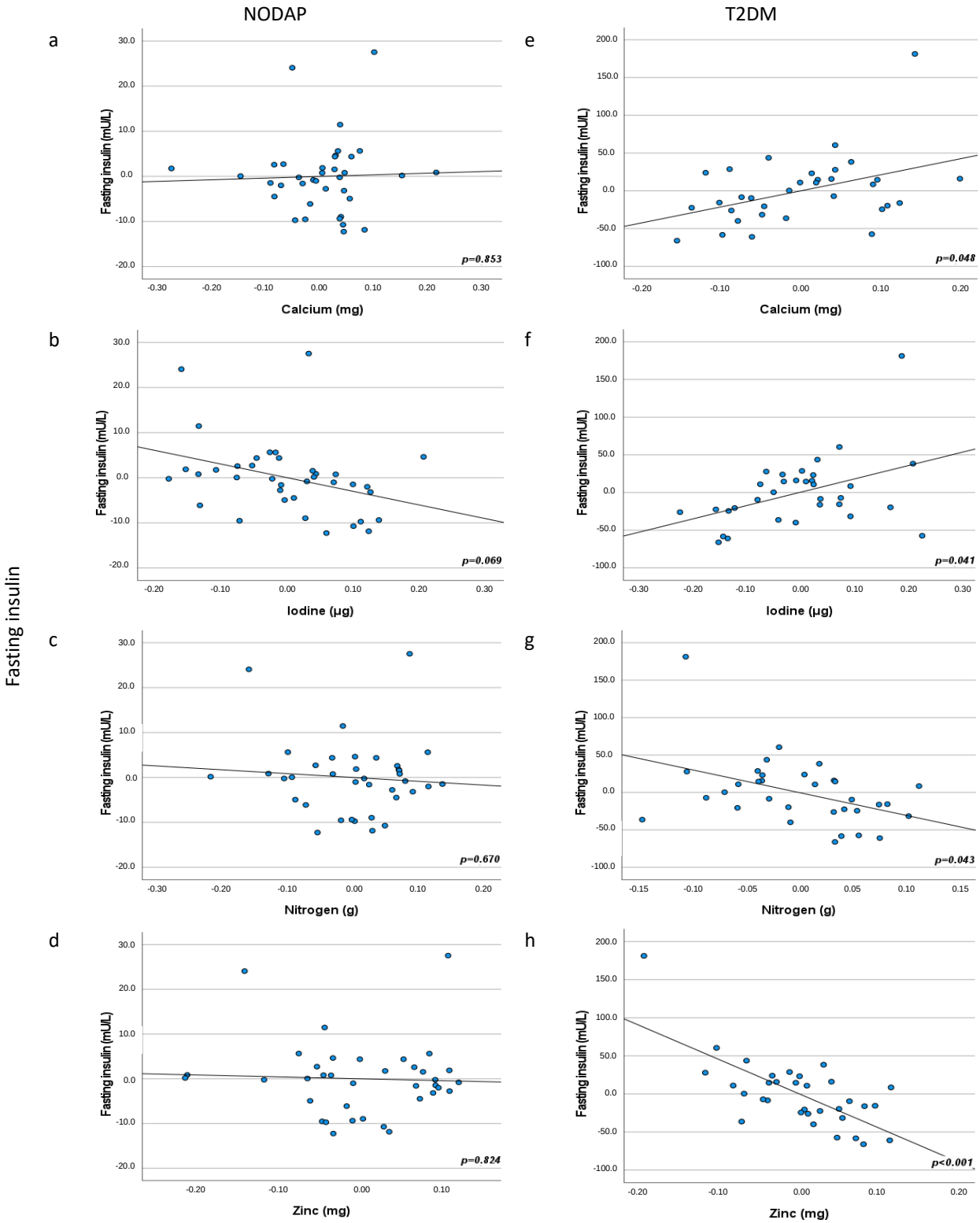

Figure 3.2 Associations between Calcium, Iodine, Nitrogen, and Zinc Intake and Fasting Insulin in NODAP (**a-d**) and T2DM (**e-h**).

Abbreviations: HbA1c = glycated haemoglobin. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis.

Footnotes: Calcium, iodine, nitrogen, and zinc data were log transformed. Partial regression plots were adjusted for age, sex, daily energy intake, V/S fat volume, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$.

Table 3.6 Associations between Habitual Mineral Intake and HOMA-S in the Study Groups.

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Calcium (mg)	1	0.000	4.245	0.926	−88.813	97.302	0.001	−8.964	0.867	−117.484	99.556	0.001	−20.276	0.881	−293.772	253.221
	2	0.073	23.013	0.706	−101.166	147.192	0.067	−18.272	0.817	−179.031	142.487	0.107	114.173	0.563	−283.789	512.134
	3	0.073	22.983	0.713	−104.289	150.254	0.192	−16.230	0.829	−168.916	136.457	0.110	132.410	0.526	−288.485	553.304
	4	0.154	41.110	0.533	−93.534	175.754	0.223	−5.025	0.950	−169.995	159.946	0.229	139.137	0.489	−267.284	545.558
	5	0.247	66.633	0.345	−77.518	210.784	0.420	−88.801	0.348	−281.674	104.072	0.709	57.731	0.667	−215.061	330.524
Chloride (mg)	1	0.033	−51.011	0.339	−158.443	56.421	0.004	15.765	0.737	−79.199	110.730	0.111	−180.055	**0.044**	−355.117	−4.993
	2	0.086	−63.180	0.477	−243.526	117.166	0.086	77.326	0.432	−121.453	276.104	0.178	−289.538	0.086	−622.669	43.594
	3	0.089	−72.394	0.452	−268.015	123.228	0.216	82.758	0.374	−105.362	270.879	0.178	−289.377	0.092	−629.320	50.567
	4	0.181	−104.669	0.298	−308.129	98.790	0.264	111.304	0.256	−86.304	308.911	0.280	−261.122	0.121	−594.969	72.724
	5	0.246	−98.220	0.355	−315.089	118.648	0.400	49.419	0.637	−165.851	264.689	0.750	−217.292	**0.044**	−428.069	−6.514
Copper (mg)	1	0.031	−43.362	0.352	−137.263	50.538	0.009	24.564	0.599	−69.756	118.884	0.099	−154.495	0.057	−314.111	5.122
	2	0.092	−69.511	0.416	−242.574	103.551	0.102	60.255	0.299	−56.496	177.005	0.146	−170.409	0.186	−427.502	86.684
	3	0.093	−71.292	0.418	−249.976	107.392	0.199	30.092	0.604	−87.746	147.929	0.146	−171.753	0.196	−436.630	93.124
	4	0.165	−78.492	0.413	−273.392	116.408	0.228	22.564	0.707	−99.655	144.782	0.309	−253.252	0.058	−515.926	9.422
	5	0.212	−31.411	0.815	−308.032	245.211	0.283	10.249	0.871	−119.765	140.263	0.745	−167.033	0.061	−342.373	8.307
Iodine (μg)	1	0.004	−15.292	0.755	−114.575	83.990	0.010	30.916	0.579	−81.679	143.511	0.020	−94.323	0.404	−320.836	132.190
	2	0.067	4.789	0.939	−123.720	133.298	0.087	56.379	0.421	−85.043	197.802	0.108	−85.555	0.543	−368.826	197.716
	3	0.067	4.607	0.943	−127.926	137.140	0.192	14.082	0.842	−129.786	157.951	0.109	−100.274	0.542	−432.233	231.685
	4	0.146	28.682	0.670	−109.020	166.384	0.226	24.852	0.743	−130.091	179.795	0.220	−62.038	0.715	−405.720	281.644
	5	0.238	60.435	0.415	−91.349	212.218	0.282	3.760	0.964	−165.192	172.712	0.730	166.340	0.149	−63.802	396.482
Iron (mg)	1	0.051	−59.579	0.231	−159.174	40.016	0.000	−1.752	0.973	−107.430	103.927	0.115	−185.833	**0.040**	−363.132	−8.535
	2	0.109	−82.280	0.286	−237.781	73.220	0.067	24.843	0.789	−164.093	213.779	0.165	−233.936	0.116	−528.950	61.077
	3	0.111	−85.085	0.287	−246.254	76.083	0.192	14.699	0.868	−165.163	194.562	0.166	−234.282	0.121	−534.284	65.720
	4	0.206	−114.133	0.186	−287.501	59.234	0.226	30.623	0.755	−169.964	231.209	0.352	−346.007	**0.020**	−633.371	−58.643
	5	0.254	−115.084	0.302	−342.302	112.134	0.282	3.634	0.972	−211.245	218.513	0.815	−311.717	**0.001**	−476.081	−147.352
Magnesium (mg)	1	0.003	−19.157	0.758	−145.201	106.887	0.000	−2.214	0.967	−110.488	106.061	0.037	−129.590	0.256	−357.405	98.225
	2	0.068	12.933	0.899	−194.469	220.335	0.065	2.267	0.978	−163.449	167.982	0.102	−83.355	0.690	−505.305	338.596
	3	0.068	13.362	0.904	−212.038	238.763	0.191	0.629	0.994	−156.748	158.006	0.102	−80.624	0.711	−520.302	359.053
	4	0.138	6.492	0.953	−221.286	234.269	0.223	9.332	0.906	−152.865	171.528	0.251	−255.197	0.258	−707.649	197.254
	5	0.217	48.798	0.688	−201.321	298.916	0.288	−38.814	0.670	−225.826	148.199	0.744	−270.454	0.062	−556.016	15.109
Manganese (mg)	1	0.033	−44.415	0.337	−137.646	48.815	0.025	−29.789	0.387	−99.021	39.444	0.018	−64.901	0.434	−231.423	101.621
	2	0.107	−75.452	0.299	−221.969	71.064	0.085	−34.271	0.443	−124.527	55.986	0.097	−8.935	0.941	−252.480	234.611
	3	0.110	−80.190	0.292	−233.884	73.504	0.210	−33.277	0.432	−118.905	52.352	0.098	−5.432	0.965	−259.170	248.305
	4	0.157	−58.269	0.495	−232.216	115.678	0.259	−47.567	0.288	−137.956	42.823	0.219	−38.405	0.761	−294.475	217.665
	5	0.210	0.653	0.996	−240.491	241.797	0.369	−82.329	0.102	−182.399	17.741	0.708	−27.175	0.749	−199.621	145.271

Table 3.6 *Cont.*

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Nitrogen (g)	1	0.038	−71.506	0.304	−211.519	68.508	0.015	42.746	0.499	−84.772	170.264	0.070	−177.381	0.113	−398.803	44.041
	2	0.112	−137.456	0.271	−389.188	114.275	0.111	124.875	0.248	−92.253	342.003	0.146	−258.927	0.184	−647.304	129.451
	3	0.116	−146.926	0.263	−411.659	117.807	0.223	105.339	0.308	−102.865	313.543	0.147	−260.240	0.193	−659.486	139.006
	4	0.174	−127.030	0.343	−399.145	145.084	0.314	213.001	0.087	−33.151	459.154	0.281	−317.497	0.119	−721.219	86.225
	5	0.259	−157.445	0.278	−452.534	137.643	0.370	224.107	0.101	−47.412	495.625	0.732	−202.711	0.129	−468.542	63.121
Phosphorous (mg)	1	0.012	−39.950	0.563	−179.722	99.821	0.004	22.295	0.741	−114.093	158.684	0.029	−133.702	0.311	−397.468	130.064
	2	0.072	−51.373	0.734	−359.027	256.282	0.080	84.240	0.504	−170.846	339.326	0.102	−132.413	0.687	−794.890	530.063
	3	0.072	−54.417	0.729	−375.257	266.423	0.200	65.482	0.585	−178.166	309.130	0.102	−129.617	0.710	−833.766	574.532
	4	0.138	−7.089	0.965	−340.158	325.981	0.243	98.521	0.432	−156.148	353.190	0.241	−353.553	0.340	−1099.203	392.097
	5	0.212	31.093	0.857	−325.047	387.233	0.286	56.721	0.713	−259.758	373.200	0.720	−269.348	0.284	−775.847	237.152
Potassium (mg)	1	0.003	−16.429	0.781	−136.370	103.512	0.004	18.905	0.736	−94.355	132.165	0.027	−128.753	0.334	−395.441	137.936
	2	0.067	3.992	0.962	−168.705	176.690	0.082	64.340	0.479	−119.569	248.249	0.097	−1.281	0.996	−478.077	475.515
	3	0.067	3.486	0.969	−182.688	189.661	0.198	40.995	0.639	−136.289	218.279	0.098	9.198	0.971	−496.937	515.333
	4	0.138	2.516	0.978	−186.768	191.800	0.233	49.116	0.585	−133.876	232.109	0.229	−172.371	0.502	−691.495	346.753
	5	0.215	35.293	0.723	−170.311	240.896	0.282	13.879	0.892	−195.396	223.154	0.723	−206.074	0.222	−544.658	132.510
Selenium (μg)	1	0.082	−79.157	0.126	−181.980	23.665	0.002	−11.955	0.832	−126.209	102.300	0.156	−190.212	**0.015**	−341.928	−38.496
	2	0.174	−161.698	0.084	−346.864	23.467	0.065	−9.716	0.905	−175.647	156.215	0.270	−316.557	**0.010**	−550.548	−82.565
	3	0.175	−163.257	0.089	−353.246	26.733	0.225	−88.172	0.294	−257.424	81.081	0.272	−321.541	**0.010**	−562.267	−80.815
	4	0.229	−150.724	0.121	−344.671	43.224	0.239	−65.983	0.483	−256.883	124.918	0.365	−301.402	**0.014**	−538.260	−64.544
	5	0.284	−136.762	0.178	−341.488	67.963	0.287	−41.705	0.682	−250.337	166.927	0.751	−170.803	**0.042**	−334.944	−6.663
Sodium (mg)	1	0.045	−58.808	0.260	−163.574	45.959	0.004	16.363	0.733	−80.536	113.262	0.124	−184.187	**0.033**	−352.486	−15.889
	2	0.106	−88.626	0.307	−263.553	86.301	0.091	87.005	0.384	−114.584	288.594	0.199	−311.853	0.052	−626.458	2.752
	3	0.111	−98.167	0.289	−285.097	88.764	0.221	93.598	0.322	−97.008	284.204	0.199	−311.400	0.056	−631.659	8.858
	4	0.203	−124.509	0.194	−317.339	68.320	0.281	137.051	0.176	−65.969	340.071	0.298	−283.647	0.077	−599.697	32.403
	5	0.271	−126.663	0.223	−336.940	83.615	0.343	144.558	0.175	−69.341	358.456	0.754	−218.425	**0.033**	−418.330	−18.520
Zinc (mg)	1	0.023	−51.834	0.420	−181.514	77.846	0.025	55.468	0.385	−72.923	183.859	0.073	−183.978	0.105	−408.329	40.372
	2	0.085	−78.844	0.495	−313.081	155.394	0.112	125.731	0.243	−90.458	341.919	0.145	−252.328	0.191	−637.361	132.704
	3	0.086	−83.949	0.488	−329.674	161.776	0.273	169.479	0.098	−33.648	372.607	0.145	−251.641	0.200	−643.524	140.241
	4	0.158	−86.306	0.480	−335.522	162.909	0.377	289.421	**0.023**	43.866	534.977	0.264	−258.584	0.182	−645.443	128.275
	5	0.229	−105.373	0.507	−431.429	220.683	0.419	309.600	**0.037**	20.715	598.485	0.742	−224.960	0.070	−469.860	19.940

Abbreviations: HOMA-S = homeostasis model assessment of insulin sensitivity. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

Table 3.7 Associations between Habitual Mineral Intake and HOMA-β in the Study Groups.

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Calcium (mg)	1	0.000	−5.939	0.924	−131.853	119.975	0.026	59.501	0.375	−75.352	194.355	0.002	−14.743	0.801	−132.376	102.890
	2	0.012	−6.229	0.942	−179.720	167.261	0.073	77.512	0.436	−123.813	278.838	0.045	−38.284	0.665	−216.884	140.317
	3	0.026	−9.389	0.914	−185.937	167.158	0.082	78.258	0.439	−126.297	282.813	0.045	−36.058	0.700	−224.993	152.877
	4	0.096	−29.370	0.750	−218.038	159.298	0.199	100.850	0.333	−109.921	311.621	0.122	−31.336	0.736	−219.349	156.676
	5	0.207	−49.778	0.609	−249.916	150.361	0.323	212.290	0.108	−51.282	475.862	0.242	−36.731	0.696	−227.639	154.177
Chloride (mg)	1	0.000	−6.794	0.926	−154.426	140.838	0.015	39.754	0.501	−79.372	158.881	0.054	54.184	0.166	−23.594	131.962
	2	0.012	−3.849	0.975	−257.061	249.363	0.062	68.869	0.583	−185.206	322.944	0.143	141.793	0.058	−5.019	288.606
	3	0.028	−31.997	0.811	−305.099	241.105	0.071	71.013	0.577	−187.234	329.259	0.147	144.009	0.058	−5.501	293.518
	4	0.092	−3.160	0.982	−292.529	286.208	0.174	61.822	0.633	−201.737	325.382	0.201	128.137	0.095	−23.649	279.924
	5	0.197	17.586	0.904	−284.210	319.383	0.239	81.685	0.583	−223.503	386.873	0.304	116.500	0.126	−35.158	268.159
Copper (mg)	1	0.001	7.765	0.903	−121.090	136.620	0.017	41.359	0.482	−77.394	160.112	0.004	14.096	0.695	−58.279	86.471
	2	0.016	34.751	0.772	−209.890	279.392	0.053	17.738	0.812	−134.068	169.543	0.039	6.490	0.911	−110.693	123.673
	3	0.027	24.732	0.841	−226.887	276.350	0.060	7.625	0.923	−153.952	169.202	0.041	8.557	0.886	−112.062	129.176
	4	0.093	19.065	0.887	−256.912	295.043	0.168	16.570	0.833	−143.875	177.016	0.136	46.493	0.458	−79.998	172.984
	5	0.201	64.828	0.724	−314.034	443.690	0.228	11.032	0.897	−164.469	186.533	0.251	42.761	0.502	−86.363	171.884
Iodine (μg)	1	0.008	30.782	0.640	−102.706	164.271	0.046	81.841	0.240	−57.529	221.212	0.022	−42.133	0.386	−139.513	55.247
	2	0.029	56.302	0.518	−120.504	233.109	0.098	101.984	0.249	−75.679	279.648	0.072	−64.920	0.297	−189.764	59.923
	3	0.039	50.674	0.570	−130.679	232.027	0.098	98.086	0.303	−93.617	289.789	0.076	−78.239	0.285	−224.781	68.303
	4	0.095	23.215	0.803	−167.908	214.337	0.225	127.661	0.189	−67.401	322.723	0.141	−66.715	0.389	−222.844	89.415
	5	0.197	−15.199	0.881	−225.146	194.748	0.309	158.222	0.140	−56.457	372.901	0.322	−137.836	0.084	−295.371	19.699
Iron (mg)	1	0.007	30.044	0.658	−107.487	167.575	0.035	66.164	0.308	−64.121	196.449	0.035	44.412	0.265	−35.151	123.976
	2	0.034	79.261	0.461	−138.613	297.135	0.076	98.022	0.403	−138.853	334.898	0.079	77.703	0.245	−55.889	211.295
	3	0.043	70.665	0.523	−154.431	295.761	0.083	95.313	0.424	−145.887	336.513	0.081	77.519	0.253	−58.319	213.357
	4	0.123	104.201	0.387	−140.508	348.909	0.168	30.333	0.813	−231.155	291.821	0.202	117.228	0.091	−20.114	254.570
	5	0.276	206.316	0.165	−92.421	505.054	0.230	35.933	0.801	−258.075	329.941	0.323	119.810	0.081	−15.689	255.309
Magnesium (mg)	1	0.012	47.893	0.566	−121.097	216.883	0.010	37.288	0.578	−98.261	172.836	0.018	39.442	0.424	−59.480	138.364
	2	0.048	134.307	0.338	−148.960	417.574	0.054	27.146	0.794	−183.772	238.064	0.074	100.091	0.277	−84.314	284.497
	3	0.051	120.287	0.429	−188.080	428.655	0.062	26.630	0.800	−187.738	240.998	0.080	109.211	0.254	−82.253	300.675
	4	0.122	130.433	0.395	−181.386	442.253	0.167	16.960	0.870	−195.391	229.310	0.228	195.903	**0.052**	−1.449	393.255
	5	0.225	137.590	0.405	−200.651	475.831	0.231	34.706	0.778	−219.204	288.617	0.359	209.968	**0.035**	15.617	404.319
Manganese (mg)	1	0.028	55.427	0.378	−71.380	182.235	0.005	16.415	0.707	−71.921	104.751	0.010	21.010	0.558	−51.092	93.113
	2	0.071	123.704	0.221	−79.364	326.773	0.052	−3.069	0.957	−119.040	112.901	0.050	32.472	0.544	−75.283	140.227
	3	0.075	116.172	0.271	−96.576	328.920	0.060	−2.711	0.963	−120.579	115.156	0.054	36.441	0.512	−75.538	148.420
	4	0.115	87.295	0.463	−155.219	329.809	0.174	26.902	0.649	−93.552	147.355	0.161	67.896	0.235	−46.563	182.354
	5	0.233	148.215	0.348	−174.149	470.580	0.228	6.949	0.921	−136.888	150.786	0.301	86.001	0.137	−29.129	201.130

Table 3.7 *Cont.*

Mineral	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
Nitrogen (g)	1	0.009	45.855	0.628	−145.675	237.384	0.028	72.596	0.361	−87.307	232.498	0.001	10.020	0.838	−89.000	109.040
	2	0.059	187.715	0.277	−160.518	535.947	0.079	122.556	0.377	−157.318	402.431	0.039	−2.024	0.982	−179.990	175.943
	3	0.063	173.300	0.338	−192.896	539.496	0.085	117.196	0.407	−168.841	403.233	0.040	0.506	0.996	−182.241	183.252
	4	0.117	144.646	0.436	−233.597	522.889	0.167	−23.512	0.888	−365.757	318.734	0.127	48.643	0.609	−143.703	240.989
	5	0.253	229.907	0.243	−169.685	629.500	0.228	−24.832	0.898	−421.984	372.320	0.239	19.193	0.840	−174.203	212.590
Phosphorous (mg)	1	0.003	27.993	0.766	−162.724	218.710	0.015	57.456	0.499	−114.202	229.114	0.000	7.146	0.901	−108.600	122.893
	2	0.045	188.086	0.367	−233.295	609.466	0.060	78.072	0.627	−247.944	404.089	0.039	−13.901	0.924	−308.039	280.237
	3	0.051	169.357	0.435	−271.236	609.950	0.067	71.617	0.662	−261.259	404.493	0.040	−5.683	0.971	−318.630	307.265
	4	0.103	113.980	0.613	−346.970	574.930	0.167	17.031	0.918	−321.290	355.353	0.134	117.914	0.484	−222.170	457.998
	5	0.208	126.685	0.590	−356.433	609.803	0.234	85.992	0.685	−349.189	521.173	0.240	54.466	0.755	−300.687	409.619
Potassium (mg)	1	0.018	56.300	0.477	−103.819	216.419	0.006	30.712	0.663	−111.969	173.394	0.008	29.688	0.607	−86.520	145.896
	2	0.047	109.673	0.347	−125.983	345.328	0.051	−1.282	0.991	−235.386	232.821	0.047	51.782	0.620	−159.087	262.650
	3	0.051	97.860	0.434	−155.787	351.506	0.060	−8.590	0.942	−248.425	231.244	0.050	62.325	0.572	−160.321	284.971
	4	0.119	101.462	0.425	−157.261	360.184	0.166	−2.926	0.980	−241.369	235.517	0.161	138.053	0.236	−95.225	371.330
	5	0.222	105.443	0.434	−170.771	381.657	0.228	18.263	0.892	−259.878	296.404	0.293	162.286	0.165	−71.287	395.858
Selenium (μg)	1	0.013	43.158	0.544	−100.802	187.119	0.069	102.133	0.146	−37.525	241.791	0.017	26.818	0.445	−43.726	97.362
	2	0.068	157.873	0.231	−107.040	422.786	0.132	155.801	0.125	−45.927	357.530	0.065	52.255	0.358	−61.844	166.354
	3	0.078	152.266	0.257	−118.360	422.893	0.133	162.882	0.151	−63.501	389.264	0.068	55.403	0.343	−61.864	172.670
	4	0.132	135.082	0.323	−142.104	412.269	0.215	144.228	0.235	−99.935	388.390	0.151	60.494	0.302	−57.238	178.226
	5	0.232	128.958	0.356	−156.548	414.464	0.268	141.726	0.305	−139.159	422.612	0.249	37.843	0.530	−84.499	160.185
Sodium (mg)	1	0.001	−12.310	0.863	−156.880	132.261	0.007	27.329	0.651	−94.818	149.477	0.056	53.368	0.159	−21.949	128.684
	2	0.013	−17.939	0.882	−264.710	228.832	0.051	4.073	0.975	−256.284	264.431	0.145	137.731	**0.055**	−3.231	278.693
	3	0.030	−43.199	0.737	−305.709	219.310	0.060	5.845	0.964	−258.847	270.537	0.147	138.601	0.058	−4.721	281.923
	4	0.094	−24.835	0.854	−300.837	251.166	0.167	−18.877	0.889	−295.000	257.246	0.199	121.615	0.100	−24.696	267.927
	5	0.196	14.467	0.919	−280.912	309.846	0.228	−20.252	0.897	−341.472	300.969	0.297	105.786	0.150	−40.874	252.447
Zinc (mg)	1	0.003	27.139	0.756	−150.344	204.621	0.002	22.001	0.786	−141.899	185.901	0.002	11.563	0.818	−89.887	113.012
	2	0.038	131.442	0.418	−197.461	460.345	0.051	−2.183	0.987	−284.797	280.430	0.039	6.272	0.943	−171.268	183.813
	3	0.045	115.778	0.494	−228.626	460.181	0.060	9.784	0.946	−281.729	301.297	0.041	6.966	0.938	−173.654	187.585
	4	0.111	115.634	0.501	−235.095	466.363	0.204	−180.999	0.299	−533.080	171.082	0.123	34.254	0.706	−149.606	218.113
	5	0.296	335.168	0.117	−91.712	762.049	0.256	−180.723	0.394	−613.285	251.839	0.239	18.785	0.835	−164.458	202.028

Abbreviations: HOMA-β = homeostasis model assessment of β-cell dysfunction. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

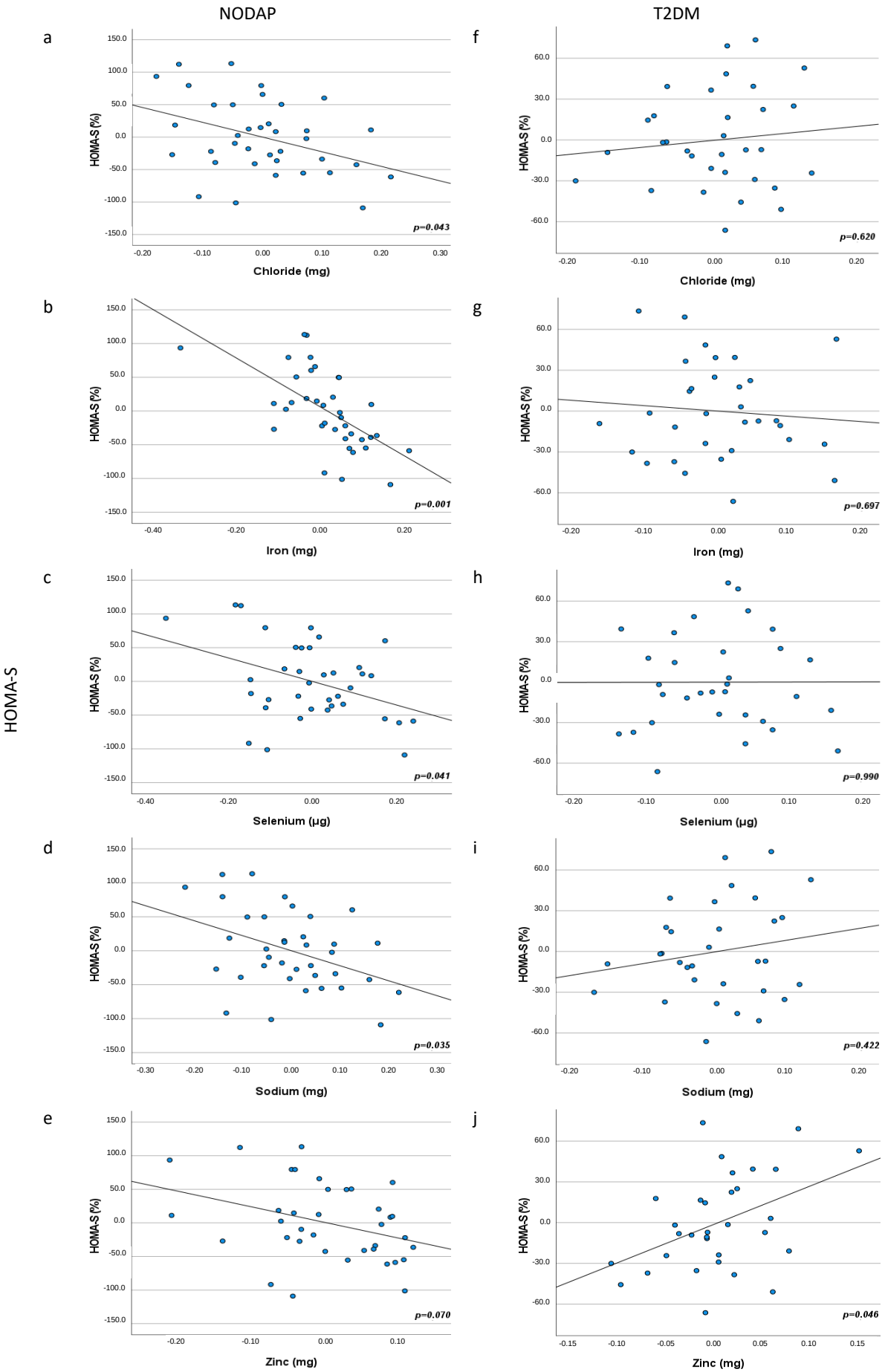

Figure 3.3 Associations between Chloride, Iron, Selenium, Sodium, and Zinc Intake and HOMA-S in NODAP (**a-e**) and T2DM (**f-j**).

Abbreviations: NODAP = New-onset diabetes or prediabetes after acute pancreatitis. T2DM = Type 2 diabetes or prediabetes prior to acute pancreatitis. HbA1c = glycated haemoglobin.

Footnotes: Chloride, iron, selenium, sodium, and zinc data were log transformed. Partial regression plots were adjusted for age, sex, daily energy intake, V/S fat volume, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$.

3.4 Discussion

The present study was the first to investigate habitual mineral intake in people with NODAP. This chapter compared the mean habitual intake of 13 minerals between the NODAP and NAP groups and assessed associations between habitual mineral intake and markers of glucose metabolism, as well as insulin traits, in these groups. A key finding was significant associations between iron, nitrogen, phosphorous, and zinc intakes and the NODAP group, but not the T2DM group. Another key finding was significant associations between manganese, iodine, and markers of glucose metabolism in the NODAP group. Specifically, a significant inverse relationship was observed between manganese intake and both HbA1c and FPG, whereas iodine was significantly directly related to HbA1c levels. Five minerals were also significantly associated with insulin traits in the NODAP group. Specifically, magnesium intake was directly associated with HOMA-β whereas chloride, iron, selenium, and sodium intakes were significantly inversely associated with HOMA-S in people with NODAP.

3.4.1 Manganese Intake and Glucose Metabolism

Manganese is an essential trace element primarily obtained through the dietary intake of grain and cereal products, vegetables, and beverages (tea) (107). Absorption of manganese is limited, with only 1–5% of ingested intake being absorbed through the small intestine (108,109). Once absorbed, manganese is transported to mitochondria-rich organs (such as the liver, pituitary gland, and pancreas) (108,109). Manganese is involved in many processes throughout the body, including enzyme synthesis and activation, metabolism of glucose and lipids, haematopoiesis, endocrine regulation, and immune function (109).

Previous studies have investigated the association between manganese and type 2 diabetes using varying methods of assessing manganese status. Du et al. observed an inverse relationship between manganese intake and type 2 diabetes (independent of total antioxidant capacity) in two prospective cohort studies of Chinese individuals (97). Similar results were observed by Mancini et al. and Gong et al., who investigated manganese intake and risk of type 2 diabetes in all women and postmenopausal women, respectively (95,110). Eshak et al. examined these associations in a Japanese cohort, observing only a significant inverse association between manganese intake and risk of type 2 diabetes in women (but not men) (96).

The sex difference in these observed results was attributed to women's higher absorption, bioavailability, and retention of manganese. Women typically have lower iron intake and an increased risk of low ferritin levels and iron deficiency; therefore, manganese does not have to compete with iron for absorption (96). Other studies have examined relationships between manganese and type 2 diabetes using blood, urine, and serum manganese. Koh et al. observed that low blood manganese levels were associated with increased prevalence of type 2 diabetes in a cross-sectional study in a Korean population (111). Yang et al. investigated associations between both blood and urinary manganese levels and markers of glucose metabolism and insulin traits (112). Results showed a positive linear relationship between urinary manganese (but not blood manganese) with FPG and HbA1c among women, while a J-shaped nonlinear relationship of blood manganese with HOMA-IR and insulin among men (112). Interestingly, Shan et al. observed a U-shaped association between serum manganese and type 2 diabetes in a Chinese population, suggesting that both low and high levels of manganese increase the risk of type 2 diabetes (113). Evidence suggests that there is likely a link between decreased habitual manganese intake and increased risk of type 2 diabetes, which appears to be stronger in women and Asian populations (96,97,111,112). The present study was the first to investigate the associations of dietary manganese intake and glucose metabolism/insulin traits in the unique cohort of individuals after an attack of AP. We found that manganese intake had an inverse relationship with both HbA1c and FPG in those with NODAP. Specifically, every 1 mg decrease in manganese intake was significantly associated with a 0.17 mmol/mol increase in HbA1c and a 0.02 mmol/L increase in FPG in people with NODAP. By studying the associations of both HbA1c and FPG, we were able to investigate the relationship between manganese intake and glucose metabolism comprehensively. HbA1c measures blood glucose levels over the past 90–120 days and therefore mitigates any day-to-day variation in plasma glucose levels. However, HbA1c can be affected by abnormal haemoglobin levels (114). FPG is specific to plasma glucose after a fasted period (8 hours in the present study) and remains unaffected by these abnormalities (115).

The mechanistic link between manganese and HbA1c and FPG is not fully understood; however, there is a possible role of the involvement of superoxide dismutase (SOD) enzymes (109,116,117). There are three forms of SOD in mammals and manganese is a crucial component of manganese SOD (MnSOD) (it is worth noting that two of the other studied minerals—copper and zinc—are structural components of copper/zinc and extracellular SOD) (118). SODs contribute to metabolic processes and protect cells against oxidative damage

(109,116). It has been hypothesised that MnSOD can affect glucose metabolism and insulin secretion (109). MnSOD acts as an antioxidant to reduce oxidative stress and free radicals by catalysing the disproportionation of superoxide anion radicals to hydrogen peroxide and molecular oxygen (109,116,117). Reactive oxidant species and oxidative stress can result in impaired islet β-cell function, cause insulin resistance, and finally lead to impaired glucose metabolism (109). Animal models have observed that manganese supplementation can increase MnSOD activity and improve glucose tolerance (119,120). There are few studies on these associations in humans. Hope et al. observed that moderate to high intake of black tea (which is high in manganese) did not significantly alter circulating manganese levels or expression of leucocyte MnSOD (121). However, an inverse relationship was noted between blood manganese and leucocyte MnSOD expression, which suggests that low levels of manganese may lead to overcompensation of MnSOD expression (121). AP is a disease characterised by acute inflammation and oxidative stress, with subclinical low-grade inflammation persisting after the initial attack (30,122). This leads to elevated oxidant levels and, consequently, MnSOD may be upregulated to manage oxidative damage (123). Ściskalska et al. observed that patients with AP had a 3-fold increased MnSOD in erythrocytes compared with healthy controls and decreased plasma MnSOD, suggesting migration of MnSOD from other cells circulating in plasma (e.g., leukocytes and platelets) in the state of oxidative stress induced by AP (118). Gut hormones (e.g., gastric inhibitory peptide and peptide YY) appear to increase circulating levels of pro-inflammatory cytokines, leading to persistent subclinical inflammation following an attack of AP (30,122). As inverse associations between manganese intake and HbA1c and FPG were observed in the present study, there may be a link between manganese intake and MnSOD levels in patients after AP, perpetuating glucose metabolism dysfunction. Purposely designed studies are now warranted to investigate the exact mechanism behind the association between manganese intake and NODAP.

In the present study, the mean manganese intakes were 2.91 and 2.46 mg/day for men and women, respectively. These mean manganese intakes are 47.1% and 50.8% lower than the New Zealand and Australia adequate intake guidelines of 5.5 and 5 mg/day (for men and women, respectively) (107). Therefore, manganese intake meeting the adequate intake may be beneficial for people after an attack of AP. Manganese is present in a wide range of foods and food groups, including shellfish (1.1–6.8 mg/100 g), nuts (3.8–13 mg/100 g), whole grains (3.1–7 mg/100 g), legumes (0.40–2.5 mg/100 g), vegetables (0.7–1.5 mg/100 g), and black tea (0.4–1.9 mg/100 g) (124,125).

3.4.2 Iron Intake and Glucose Metabolism

Iron is a mineral that is an essential component of proteins (e.g., haemoglobin, myoglobin, and cytochromes) and a cofactor for enzymes involved in redox reactions (107). Dietary iron has two forms (haem and non-haem) that differ in chemical structure, food sources, and absorptive properties. Non-haem iron, primarily derived from plant sources, is less bioavailable than haem iron (derived from meat products) as it is not as readily absorbed in the small intestine (126). Iron absorption occurs via the apical brush border membrane of the small intestine by haem carrier protein (HCP1) and divalent metal transporter (DMT1), which enable transmembrane transport of haem iron into enterocytes, where iron is transported into plasma via ferroportin (127,128). These transporters allow haem iron to be efficiently absorbed in the small intestine; however, non-haem iron forms insoluble non- absorbable complexes in an alkaline environment, thus requiring ferric iron to be reduced to ferrous iron to be absorbed (128,129). The bioavailability of non-haem iron can also be limited by the presence of oxalates, phytates, polyphenols, phosphates, and calcium, which interfere with iron absorption. These compounds are present in most non-meat sources of iron; therefore, they primarily inhibit non-haem iron absorption (128). Iron homeostasis is tightly regulated. A peptide hormone, hepcidin, is the primary regulator of iron homeostasis by maintaining the systemic balance of iron storage, distribution, and utilisation (129). Hepcidin negatively controls iron efflux by inactivating ferroportin in macrophages, enterocytes, and other cells to decrease plasma iron levels (127). Hepcidin is upregulated in response to high iron levels and is down-regulated during iron deficiency, anaemia, or hypoxia to increase iron uptake (130). Inflammatory states also lead to upregulation of hepcidin, triggered by proinflammatory cytokines such as interleukin-6 (127).

There is evidence to suggest a relationship between increased iron intake and impaired glucose metabolism resulting in an increased risk of type 2 diabetes (98–103), gestational diabetes (131–133), and metabolic syndrome (134,135). Increased frequency of diabetes has also been observed in iron overload disorders (haemochromatosis and β-thalassemia), attributed to insulin resistance and destruction of pancreatic β-cells (127,136,137). However, there is limited research on the effects of iron on glucose metabolism in individuals after pancreatitis. A previous ANDROMEDA study by the COSMOS group investigated associations between dietary iron and markers of glucose metabolism in individuals after pancreatitis (138). Kimita et al. found that total and non-haem iron were significantly inversely associated with FPG in individuals following AP (138). These results contrast previous findings from studies

investigating non-haem iron intake and glucose metabolism that found positive associations or no associations (134,135,139). The present study found total iron intake in the NODAP group was significantly less than in the NAP group and was inversely associated with insulin sensitivity (HOMA-S). Every 1mg increase in total iron intake was significantly associated with a 3.12% decrease in HOMA-S in people with NODAP. These findings provide new insight into the role of iron intake on insulin sensitivity in people with NODAP. As our previous study focused on iron metabolism and hyperglycaemia in all individuals following AP, the subgroup analysis by diabetes type in the present study uncovered novel insights into iron's role in NODAP.

However, the mechanism of this association is not fully understood (140). In the context of type 2 diabetes, elevated levels of serum ferritin were associated with an increased risk of diabetes and were significantly associated with elevated levels of insulin, glucose, and HbA1c (141–143). It has also been suggested that elevated ferritin levels in type 2 diabetes are due to inflammatory mechanisms rather than iron overload as there were no differences in transferrin receptor levels (144,145). A comprehensive review of iron metabolism and the exocrine pancreas provided evidence for crosstalk between iron metabolism and the exocrine pancreas (146). Chand et al. found that hepcidin levels were significantly increased and ferritin levels significantly decreased in participants with prediabetes/diabetes after AP, providing further evidence that iron may be involved in the pathogenesis of NODAP (140).

In the present study, the mean iron intake for men was 10.51 mg/day, which is 75% higher than the New Zealand and Australia EAR of 6 mg/day for men (107). The mean intake of women in our study cohort was 8.87 mg/day, which is 77.4% higher than the New Zealand and Australia EAR of 5 mg/day for women over 51 (107). Dietary sources of haem iron include seafood (1.1–16.9 mg/100 g) and meat (2.3–21 mg/100 g), while sources of non-haem iron include fortified grain products (2.6–15.4 mg/100 g), legumes (5.3–6.4 g/100 g), nuts (3.5–9.2 mg/100 g), and vegetables (0.6–4.4 mg/100 g) (124). In New Zealand, whole grain cereals, meat, fish, and poultry are significant contributors to iron intake (107,147). Therefore, iron intake within the recommended range may be beneficial for people after an attack of AP.

3.4.3 Iodine and Selenium Intakes and Glucose Metabolism

The pairing of selenium and iodine and their involvement in glucose metabolism has been suggested (148). Iodine plays an important role in the synthesis of thyroid hormones—

triiodothyronine (T3) and thyroxine (T4)—and is therefore crucial for the regulation of basal metabolic rate, macronutrient metabolism, redox reactions, and normal growth and development within the body (149,150). Iodine is ingested in different chemical forms, which are absorbed differently. Up to 90% of iodide is absorbed in the stomach and duodenum, while iodate is reduced to iodide for absorption. The rate of iodine absorption is dependent on the iodine status of an individual. In individuals with adequate iodine levels, up to 10% of absorbed iodine is taken up by the thyroid, whereas as much as 80% can be taken up in iodine deficiency (124). In the thyroid, thyroperoxidase and hydrogen peroxide oxidise iodide bind with thyroglobulin to produce thyroid hormone precursors, monoiodotyrosine and diiodotyrosine, which then form T3 and T4 (150). Iodine not taken up by the thyroid is excreted from the body in urine (151). Due to its role in thyroid hormone synthesis, dietary iodine intake is closely related to thyroid function (152,153). Both iodine deficiency and iodine excess have been associated with an increased risk of thyroid disorders including iodide-induced hyperthyroidism, autoimmune thyroid disease, iodine-induced hypothyroidism (153,154).

There is a clear link between thyroid function, diabetes, and glucose metabolism due to thyroid hormones' role in regulating carbohydrate metabolism and pancreatic function (155,156). Studies have found both hypo- and hyperthyroidism have been associated with insulin resistance and impaired glycaemic control, leading to hyperglycaemia (155–158). Therefore, a link between iodine intake and type 2 diabetes is plausible. However, few studies focused on associations between dietary iodine intake and type 2 diabetes. Mancini et al. found iodine intake above 160 µg/day was significantly associated with an increased risk of type 2 diabetes in French women (159). Other studies have investigated the same association using urinary iodine—a commonly used indicator of iodine intake (151). Liu et al. examined the associations between excessive iodine intake on blood glucose levels in Chinese adults (149). The cross-sectional study assessed median water iodine concentration (MWIC) and median urinary iodine concentration (MUIC) in in three geographical areas classed as iodine-adequate (MWIC 6.3 µg/L MUIC 126.6 µg/L), iodine-sufficient (MWIC 79.8 µg/L, MUIC 221.2 µg/L), and iodine-excess (MWIC 506.0 µg/L, MUIC 421.3 µg/L) (149). The authors found that blood glucose of adults in iodine-sufficient and iodine-excess areas was increased, compared with the iodine-adequate area. Urinary iodine, thyroid stimulating hormone (TSH), and free T4 also had a nonlinear correlation with blood glucose (149). Therefore, it was concluded that excessive iodine intake might result in elevated blood glucose and contribute to the development of diabetes. The present study found iodine intake is significantly associated with HbA1c levels

in people with NODAP. Every 1 μg increase in iodine intake was significantly associated with a 0.17 mmol/mol increase in HbA1c in those with NODAP.

Selenium plays structural and enzymatic roles in antioxidant defence systems throughout the body (105,160,161). It is a component of selenoproteins that is a cofactor for many enzymes, including glutathione peroxides, thyroid peroxidases, thioredoxin reductases, and iodothyronine deiodinidases (105,160). Selenium's role in diabetes has been debated. It was previously hypothesised that selenium might prevent the development of diabetes due to its antioxidant properties (162). Selenate has also been observed to act as an effective insulin-mimetic by stimulating glycolysis, fatty acid synthesis and, in some cases, glycogen synthesis in animal models (163,164). However, in human studies, there is evidence to suggest that increased selenium intake has a positive relationship with the risk of type 2 diabetes. Siddiqi et al. observed a significant direct association between dietary selenium intake and HbA1c and FBG (105). These results were consistent with Wei et al., who found a significant positive association between dietary selenium and the prevalence of diabetes in a Chinese population (106). A prospective study involving 7182 Italian women also found that dietary selenium had a strong association with type 2 diabetes (104). Selenium supplementation has also been studied in the context of diabetes. Stranges et al. examined the effect of long-term selenium supplementation and diabetes in low-selenium regions of eastern United States (165). Results showed that increased selenium intake (via 200 μg supplementation) significantly increased the cumulative incidence of T2DM in this population compared with the placebo group (165). Therefore, evidence suggests limited usefulness of selenium supplementation in the prevention of T2DM. One study showed a U-shape association between dietary selenium intake and type 2 diabetes, which indicates that low intake may also increase the risk of T2DM (166). Behar et al. observed that high and low dietary selenium intake could impact glycaemic control in women from Algeria (166). In that population, both the lowest and highest quintiles of selenium intake were associated with a significant increase in HbA1c (166). However, a systematic review and meta-analysis of selenium exposure (measured in serum, plasma, whole blood, nail, urine, hair, tears, and dietary intake) and risk of diabetes found a consistent pattern of a positive association in both nonexperimental and experimental studies, with limited evidence for associations between low selenium exposure and diabetes (167). Our study found an inverse relationship between habitual selenium intake and insulin sensitivity (but not HbA1c or FPG) in people with NODAP. Every 1 μg increase in selenium intake was significantly associated with a 1.71% decrease in HOMA-S (%).

Overall, our results suggest that selenium and iodine intake were significantly associated with markers of insulin sensitivity, which may be involved with the progression of NODAP. A possible mechanism for this is their respective roles in the synthesis of thyroid hormones. Thyroid hormones are efficient modulators of catabolism of energy sources (including carbohydrates) and both hyperthyroidism and hypothyroidism have been associated with the development of diabetes (168). A positive relationship has been observed between thyroid stimulating hormone and HOMA-IR, indicating hypothyroidism has a role in insulin resistance and diabetes (169,170). In AP, serum free T3 and T4 are reduced and TSH levels are increased. It has also been observed that levels of TSH are related to severity of AP (171–173). Therefore, it is possible that iodine and selenium requirements may be altered for people with a history of AP. Dietary intake of both selenium and iodine varies greatly and is often dependent on geographical location and soil composition. Mean iodine intake in the present study was 120 μg/day in men and 105 μg/day in women, which is 20% and 5% higher than the New Zealand and Australia EAR of 100 μg/day for men and women (107). The native iodine content of most foods and beverages is low due to the lack of iodine in New Zealand soil. Therefore, the majority of iodine intake is from fortified foods (commercially made bread 30.1–53.5 μg/100 g and iodised salt 32–64 μg/100 g) (107,174). Seafood (12–370 μg/100 g), eggs (61 μg/100 g), and milk products (10–50.4 μg/100 g) are also sources of iodine (107,124,175). The iodine content of meat products (4.2–50 μg/100 g) is reflective of the iodine content of animal feed used (124,150). The use of processing aids (e.g., calcium iodate, potassium iodate, potassium iodide, and cuprous iodide) also increases iodine content in processed foods (107,150). In our study population, mean selenium intake was 60 μg/day in men and 50 μg/day in women—in line with the New Zealand and Australia EAR of 60 μg/day and 50 μg/day for men and women, respectively (107). Dietary sources of selenium include brazil nuts (1270 μg/100g), seafood (46.7–142 μg/100 g), meat (21–110 μg/100 g), whole grains (7.6–28.7 μg/100 g), and vegetables (0.9–16.1 μg/100 g) (124). However, plant sources of selenium are not as efficient as animal products due to their high water content and the varying soil content of selenium (107,160). Dietary factors such as vitamins, fat, protein, and some heavy metals also alter the bioavailability of selenium (176). Therefore, the requirements of these minerals for people after AP may be different than for the general population.

3.4.4 Limitations

Findings of the present study must be considered with several limitations. First, habitual dietary intake of minerals was ascertained using a self-reported FFQ, which relies on the ability of respondents to recall their usual intake of foods. Therefore, FFQ data might be biased due to omission or addition of foods, and over- or under-estimating frequency and portion of foods (177). However, the EPIC-Norfolk FFQ has been extensively validated and it provides a more accurate estimation of long-term habitual intake of minerals compared with other dietary assessment methods (e.g., 3-day food records) (76,178). Second, the possibility of changes in the habitual intake after an attack of AP must not be discounted. However, the FFQ assesses habitual intake in the 12 months before the study visit and our study participants were recruited, on average, in 26 months since the last attack of AP (hence, the data captured in the FFQ focused on the period after the AP attack). Also, they were not encouraged to make any dietary changes after hospital discharge. Third, the present study investigated intake of each mineral in isolation and did not account for all dietary covariates associated, including but not limited to intake of other minerals, protein, fat, and carbohydrates. Due to the complex composition of food, individuals consume various macronutrients and micronutrients at one time, some of which may interact with absorption or utilisation of another. For example, iron absorption is known to be influenced by many factors that inhibit (calcium, zinc, manganese, phytates, polyphenols, and vegetable protein) or enhance (meat, fish, poultry factor, vitamin C and citric, lactic, and malic acids) it (126). Various minerals are also known to compete for absorption. For example, manganese bioavailability is influenced by dietary iron intake, as they compete for binding to transferrin in serum and transport by DMT1 (179). Calcium, phosphate, and zinc are also known to interact with manganese absorption (107,108,180). Considering the relatively small sample size of the present study, including these covariates might have resulted in the overfitting of statistical models. However, energy intake was included in statistical models to encompass most dietary variables as a single factor, along with other covariates (age, sex, V/S fat volume ratio, smoking status, alcohol intake, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications) to provide robust models. It is also worth noting that V/S fat volume ratio was used instead of traditional measures of adiposity (BMI and waist circumference) as it is a more comprehensive measure of relative body fat distribution and is correlated superbly to metabolic risk (181). Fourth, use of oral pharmacologic agents and/or insulin therapy was exclusive to those in the T2DM group and not in the NODAP group. Therefore, use of these medications has the potential to confound

results, particularly between markers of glucose metabolism and mineral intake in the T2DM group. By adjusting for antidiabetic medication use in statistical models' internal validity of results is maintained and results are comparable between study groups. Future research should further investigate the impact of antidiabetic medications on mineral intake and markers of glucose metabolism. This study also did not assess other possible confounders (such as enzyme activity, levels of hormones or inflammatory markers), which may have implications on glucose metabolism and insulin traits following AP. They should be addressed in further research. Fifth, dietary supplements were not included in this study due to limitations of the FETA software (76). Hence, results in the present study can only be applied to habitual intake of minerals, which may be altered by supplement use. Future studies should investigate the associations of supplements on people with NODAP. Sixth, our study only investigated dietary intake of minerals, which is not reflective of mineral status. Therefore, we cannot assess whether participants nutritional status is sufficient, deficient, or excessive. As mineral status of an individual may affect glucose metabolism and insulin traits, future research should use appropriate methods of assessment (plasma, whole blood, urine, nail and/or hair tests). Last, due to the cross-sectional design of this study, a causal relationship between dietary mineral intake and markers of glucose metabolism and insulin traits cannot be inferred. However, this was the first study investigating this relationship in individuals with NODAP. Insights from the present study will help design future prospective longitudinal studies of dietary mineral intake in people after an attack of pancreatitis.

3.5 Chapter Summary

Of the 13 minerals investigated in the present study, intake of iron, nitrogen, phosphorous, and zinc was significantly altered in people with NODAP. These people were also characterised by significant inverse associations between intake of manganese and both HbA1c and FPG, as well as intake of iron and HOMA-S. Iodine intake was significantly directly associated with HbA1c levels whereas intake of selenium was significantly inversely associated with HOMA-S. These findings give light to the possible role of mineral intake in NODAP. Longitudinal studies and randomised controlled trials are now warranted to investigate possible causal relationships and mechanisms of mineral intake on NODAP to provide evidence for nutritional interventions specifically for people at risk of NODAP.

CHAPTER 4. RELATIONSHIP BETWEEN HABITUAL VITAMIN INTAKE AND PREDIABETES/DIABETES AFTER ACUTE PANCREATITIS

4.1 Background

Vitamins and vitamers are essential micronutrients required to maintain metabolic health (107,182). There are 13 known vitamins and several vitamers required in small quantities for metabolic health (e.g., energy metabolism, antioxidant function, and enzymatic functions) (107,183–188). There are two subtypes of vitamins classified by their solubility – fat-soluble and water-soluble vitamins. Most vitamins (such as vitamins A, C, E, and K, majority B-complex vitamins) are not endogenously synthesised by the body and are predominantly obtained through the diet (185). The structural differences between the groups of vitamins influence their method of absorption (183). Low intake of vitamin-rich foods or reduced vitamin absorption can cause oxidative stress-driven disorders such as insulin resistance (189,190), β-cell dysfunction (191), and metabolic syndrome (188,192). Reduced fat- and water-soluble vitamin intake is also associated with type 2 diabetes. For instance, a large prospective cohort study showed that low intake of fat-soluble vitamins E and K increased risk of this type of diabetes (193). Other studies demonstrated that low intake of water-soluble vitamins C, B2, and B9 was associated with increased risk of type 2 diabetes (194,195).

Another example of a disease marked by oxidative stress is acute pancreatitis (AP). AP is an inflammatory disorder of the pancreas. Damage to pancreatic cells during an attack of AP can cause subsequent endocrine and exocrine dysfunctions (27,196). A systematic literature review and meta-analysis by the COSMOS group showed that exocrine pancreatic dysfunction occurs in 29% of patients following an episode of AP (34). Exocrine pancreatic insufficiency impairs digestion and absorption of food and nutrients, resulting in deficiency of vitamins (197). A large cohort study conducted by the COSMOS group demonstrated that individuals after AP with exocrine pancreatic insufficiency had a significantly increased risk of new-onset diabetes after AP, irrespective of the disease severity and mechanical destruction of the pancreas (40). NODAP develops in about 40% of individuals after an episode of AP and individuals with NODAP are characterised by chronic low-grade inflammation, impaired lipid metabolism, iron metabolism, and insulin secretion (27,33,79). NODAP is a clinically distinct entity to type 2

diabetes, yet often misclassified and misdiagnosed as type 2 diabetes (10,13,79). Individuals with NODAP have worse glycaemic control (79), increased need for insulin therapy (79), higher incidence of pancreatic cancer (36), and higher hospitalisations and mortality than individuals with type 2 diabetes (35). Nonetheless, there are no specific guidelines for optimal nutrition therapy for NODAP, with patients typically receiving generalised type 2 diabetes nutrition advice focusing on macronutrient distribution, portion sizes, and intake of minimally processed foods (85,198). Chapter 3 investigated the role of mineral intake in the development of NODAP; yet intake of other micronutrients (specifically vitamin intake) has never been investigated in the context of new-onset diabetes after AP.

Therefore, this chapter aimed to investigate the associations between habitual intake of vitamins/vitamers and glycaemic status after AP (aim 2.1). Additionally, the associations between habitual fat- and water-soluble vitamin intake and FPG, HOMA-IR, and HOMA-β index in individuals after AP were also investigated (aims 2.2 and 2.3).

4.2 Methods

4.2.1 General Methods

General methods specific to this chapter (study design, study population, covariates, and laboratory assays) are described in Chapter 2.

4.2.2 Ascertainment of Vitamin Intake Data

Habitual dietary intake data of study participants in the 12 months prior to recruitment was collected using the EPIC-Norfolk FFQ (76). The extensively validated, semi-quantitative, and self-administered FFQ assesses the frequency of intake of 130 commonly and less commonly consumed foods and collected information on types and brands of commonly consumed foods (breakfast cereal, milk, meat, and cooking fats). Data gathered from the FFQ were then analysed using the FETA software to ascertain daily intake of seven fat-soluble vitamins and vitamers (α-carotene (µg), β-carotene (µg), retinol (µg), total carotene (µg) vitamin A/ total retinol equivalents (µg), vitamin D (µg), and vitamin E (mg)) and seven water-soluble vitamins (vitamin B1 (mg), vitamin B2 (mg), vitamin B3 (mg), vitamin B6 (mg), vitamin B9 (µg), vitamin B12 (µg), vitamin C (mg)). Habitual vitamin intake was measured from food sources only and intake from vitamin supplements was excluded from this study. FFQ data were excluded from the study if ten or more questions were left unanswered as this level of missing

data would lead to significant underestimation of intake (76). Additionally, FFQ data were excluded if the ratio of total energy intake (estimated from the FFQ data) and estimated basal metabolic rate (determined by the Harris-Benedict equation) were more than two SD outside the mean ratio (i.e., <0.28 and >1.82) (76).

4.2.3 Statistical analyses

All statistical analyses were performed using SPSS 27.0 (IBM Corporation, Armonk, NY, USA). One-way ANOVA was used to investigate differences in participants' characteristics between the study groups (NODAP, T2DM, and NAP). Data were presented as mean (SD) or frequency (percentage), and *p* values were deemed statistically significant if less than 0.05. ANCOVA analysis between the NODAP, T2DM, and NAP groups (reference group) was undertaken to assess variance in mean intakes of the investigated fat-soluble and water-soluble vitamins between the groups while adjusting for the effect of covariates. All investigated vitamins/vitamers were log-transformed to account for non-normal distribution (based on the Shapiro-Wilk test). Five models were built for ANCOVA analysis. Model 1 was unadjusted; model 2 was adjusted for age, sex, and daily energy intake; model 3 was adjusted for age, sex, daily energy intake, and V/S fat volume ratio; model 4 was adjusted for age, sex, daily energy intake, V/S fat volume ratio, smoking status, and daily alcohol intake; model 5 was adjusted for age, sex, daily energy intake, V/S fat volume ratio, smoking status, daily alcohol intake, aetiology of AP, number of AP episodes, cholecystectomy, and use of antidiabetic medications. Data were presented as a β coefficient, *p* value, and 95% confidence interval. Second, associations between the habitual intake of the investigated fat-soluble and water-soluble vitamins and FPG, HOMA- β, and HOMA-IR were examined for each study group. FPG, HOMA-β, and HOMA-IR were the dependent variables and the vitamin variables were the independent variables. Multiple linear regression analyses were conducted using the same five statistical models as the ANCOVA analysis. Data were presented as R^2, unstandardised B, *p* value, and 95% confidence interval. *P* values less than 0.05 were considered statistically significant in all analyses, and data were not corrected for multiple tests.

4.3 Results

4.3.1 Study Cohort

Of the 117 individuals who enrolled in the study, 106 participants were used for analyses. 11 participants were excluded for more than 10 unanswered FFQ questions and estimated basal

metabolic rate exceeding two SD outside the mean ratio. Of the 106 included participants, 37 participants made up the NODAP group, 37 the T2DM group, and 32 the NAP group. The mean ± SD time elapsed after an attack of AP was of 26 ± 20 months. Other descriptive characteristics are presented in Table 4.1.

Table 4.1 Characteristics of the Study Cohort

Characteristic	Total (*n* = 106)	NODAP (*n* = 37)	T2DM (*n* = 37)	NAP (*n* = 32)	*p* *
Age (years)	56.1 (14.5)	58.9 (14.4)	57.2 (15.0)	51.6 (13.3)	0.094
Men, n (%)	69 (65.1)	26 (70.3)	28 (75.7)	15 (46.9)	**0.031**
Daily energy intake (kcal)	1686 (609)	1776 (692)	1728 (534)	1534 (575)	0.226
V/S fat volume ratio	0.77 (0.43)	0.81(0.40)	0.87 (0.46)	0.61 (0.40)	**0.035**
Alcohol intake (g/day)	11.08 (17.91)	13.43 (21.90)	8.65 (13.05)	11.08 (17.70)	0.527
Tobacco smoking					0.052
Yes	23 (21.7)	10 (27.0)	4 (10.8)	9 (28.2)	
No	82 (77.3)	27 (72.9)	32 (86.5)	23 (71.9)	
Aetiology of AP					0.563
Biliary	40 (37.7)	14 (37.8)	14 (37.8)	12 (37.5)	
Non-biliary	66 (62.3)	23 (62.1)	23 (62.1)	20 (62.5)	
Number of AP episodes	1.85 (2.77)	2.27 (3.76)	1.43 (1.04)	1.84 (2.82)	0.434
Cholecystectomy					0.538
Yes	39 (36.8)	13 (35.1)	12 (32.4)	14 (43.8)	
No	66 (62.3)	24 (64.9)	25 (67.6)	17 (53.1)	
Anti-diabetic medication usage					**<0.001**
None	92 (86.8)	37 (100)	23 (62.2)	32 (100)	
Oral medication	8 (7.5)	0 (0)	8 (21.6)	0 (0)	
Insulin	6 (5.7)	0 (0)	6 (16.2)	0 (0)	
Fasting plasma glucose (mmol/L)	5.86 (1.74)	5.86 (0.92)	6.61 (2.55)	4.96 (0.34)	**<0.001**
HOMA-β (%)	106.97 (56.87)	95.74 (45.63)	103.24 (57.12)	125.07 (65.87)	0.098
HOMA-IR (mIU/L-mmol/L)	1.76 (1.28)	1.73 (1.29)	1.97 (1.31)	1.55 (1.22)	0.408

Abbreviations: AP = acute pancreatitis. HOMA-IR = homeostasis model assessment of insulin resistance. HOMA-β = homeostasis model assessment of β-cell dysfunction. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. V/S fat volume ratio = visceral to subcutaneous fat volume ratio. Footnotes: Data are presented as mean (standard deviation) or frequency(percentage). **p* values were calculated from one way ANOVA. Significance was set at $p < 0.05$. Significant values are shown in bold.

4.3.2 Associations between Habitual Fat-Soluble Vitamin Intake and Diabetes

In the NODAP group, intake of the investigated vitamins/vitamers did not differ significantly when compared with the NAP (reference) group.

In the T2DM group, two vitamers (α-carotene and β-carotene) were significantly different when compared with the NAP group (Table 4.2). The mean α-Carotene intake was significantly different in the adjusted models 2 and 4 ($p = 0.048$ in model 2 and $p = 0.030$ in model 4). However, the difference in mean intake became insignificant in the most adjusted model ($p = 0.292$). The mean β-carotene intake was significantly different in adjusted model 4 ($p = 0.024$).

Intake of other investigated vitamins/vitamers in the T2DM group did not differ significantly from the reference group.

Table 4.2 Associations between Habitual Fat-Soluble Vitamin/Vitamer Intake and the Study Groups

Mineral	Model	T2DM				NODAP			
		β	*p*	95% CI		β	*p*	95% CI	
				Lower	Upper			Lower	Upper
α-Carotene (μg)	1	-0.222	0.105	-0.492	0.048	-0.042	0.757	-0.310	0.226
	2	-0.277	**0.048**	-0.552	-0.002	-0.112	0.417	-0.384	0.160
	3	-0.261	0.061	-0.534	0.013	-0.111	0.415	-0.381	0.158
	4	-0.317	**0.030**	-0.602	-0.032	-0.104	0.446	-0.373	0.165
	5	-0.178	0.292	-0.512	0.155	-0.096	0.502	-0.378	0.186
β-Carotene (μg)	1	-0.121	0.188	-0.302	0.060	-0.034	0.709	-0.214	0.146
	2	-0.140	0.138	-0.325	0.046	-0.061	0.511	-0.244	0.122
	3	-0.130	0.165	-0.315	0.054	-0.061	0.511	-0.243	0.122
	4	-0.216	**0.024**	-0.402	-0.029	-0.060	0.498	-0.236	0.116
	5	-0.182	0.104	-0.402	0.038	-0.067	0.477	-0.253	0.119
Retinol (μg)	1	0.179	0.063	-0.010	0.368	0.182	0.057	-0.006	0.370
	2	0.112	0.205	-0.062	0.285	0.085	0.329	-0.087	0.257
	3	0.126	0.146	-0.045	0.296	0.085	0.317	-0.083	0.254
	4	0.095	0.299	-0.085	0.274	0.086	0.317	-0.084	0.256
	5	0.091	0.388	-0.118	0.300	0.101	0.259	-0.076	0.278
Total carotene (μg)	1	-0.085	0.336	-0.260	0.089	-0.028	0.753	-0.201	0.146
	2	-0.093	0.300	-0.271	0.084	-0.045	0.615	-0.221	0.131
	3	-0.083	0.354	-0.260	0.094	-0.044	0.614	-0.219	0.130
	4	-0.149	0.108	-0.331	0.033	-0.044	0.609	-0.216	0.127
	5	-0.120	0.271	-0.336	0.095	-0.047	0.610	-0.229	0.135
Total retinol equivalents (μg)	1	0.075	0.295	-0.066	0.216	0.090	0.206	-0.050	0.231
	2	0.055	0.418	-0.079	0.189	0.048	0.472	-0.084	0.181
	3	0.065	0.332	-0.067	0.197	0.048	0.463	-0.082	0.179
	4	0.026	0.705	-0.111	0.163	0.051	0.438	-0.079	0.180
	5	0.038	0.639	-0.124	0.201	0.053	0.450	-0.085	0.190
Vitamin D (μg)	1	0.036	0.581	-0.093	0.165	0.044	0.500	-0.085	0.172
	2	-0.008	0.882	-0.119	0.103	-0.016	0.776	-0.126	0.094
	3	-0.007	0.906	-0.119	0.105	-0.016	0.778	-0.126	0.095
	4	-0.032	0.581	-0.148	0.083	-0.022	0.687	-0.131	0.087
	5	0.001	0.990	-0.135	0.136	-0.009	0.873	-0.124	0.106
Vitamin E (mg)	1	0.074	0.202	-0.041	0.190	0.105	0.070	-0.009	0.220
	2	0.017	0.661	-0.060	0.095	0.028	0.475	-0.049	0.104
	3	0.022	0.575	-0.055	0.099	0.028	0.469	-0.048	0.104
	4	0.002	0.965	-0.078	0.082	0.025	0.505	-0.050	0.101
	5	0.018	0.692	-0.073	0.110	0.014	0.717	-0.063	0.092

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as β coefficients, 95% CI and *p* values (from ANCOVA analysis). NAP group was used as the reference group. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

4.3.3 Fat-soluble Vitamin Intake and Markers of Glucose Metabolism in the Study Groups

4.3.3.1 Fasting Plasma Glucose

In the NODAP and T2DM groups, associations between FPG and the investigated fat-soluble vitamins/vitamers were not statistically significant (Table 4.3).

In the NAP group, FPG was significantly associated with two fat-soluble vitamins/vitamers (retinol and vitamin E). Retinol intake was significantly directly associated with FPG in the most adjusted models (model 4: $p = 0.046$, model 5: $p = 0.038$). Vitamin E intake was significantly inversely associated with FPG in model 2 ($p = 0.040$).

4.3.3.2 HOMA-β

In the NODAP group, HOMA-β was significantly associated with three fat-soluble vitamins/vitamers (α-carotene, β-carotene, and total carotene) (Figure 4.1). α-carotene was significantly directly associated with HOMA-β in the unadjusted model (model 1: $p = 0.034$) and adjusted models (model 3: $p = 0.042$, model 4: $p = 0.023$, model 5: $p = 0.013$). β-carotene was significantly directly associated with HOMA-β in the most adjusted models (model 4: $p = 0.044$, model 5: $p = 0.035$). Total carotene was significantly directly associated with HOMA-β in the most adjusted models (model 4: $p = 0.039$, model 5: $p = 0.029$).

In the T2DM or NAP groups, HOMA-β was not significantly associated with any of the investigated fat-soluble vitamins/vitamers (Table 4.4).

4.3.3.3 HOMA-IR

In the NODAP, T2DM and NAP groups, associations between HOMA-IR and the investigated fat-soluble vitamins/vitamers were not statistically significant (Table 4.5).

Table 4.3 Associations between Habitual Fat-Soluble Vitamin/Vitamer Intake and Fasting Plasma Glucose in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
α-Carotene (μg)	1	0.025	-0.116	0.400	-0.393	0.162	0.062	-0.839	0.149	-1.993	0.315	0.032	-0.341	0.292	-0.987	0.306
	2	0.157	-0.083	0.571	-0.381	0.215	0.085	-0.887	0.206	-2.287	0.514	0.268	-0.486	0.110	-1.089	0.116
	3	0.233	-0.107	0.458	-0.400	0.186	0.105	-0.729	0.317	-2.194	0.736	0.269	-0.507	0.115	-1.145	0.131
	4	0.233	-0.111	0.510	-0.456	0.233	0.260	-0.334	0.638	-1.776	1.107	0.298	-0.478	0.146	-1.134	0.177
	5	0.247	-0.137	0.488	-0.543	0.269	0.533	0.266	0.690	-1.098	1.630	0.330	-0.474	0.167	-1.159	0.211
β-Carotene (μg)	1	0.039	-0.169	0.293	-0.491	0.154	0.004	-0.339	0.716	-2.215	1.537	0.037	-0.633	0.252	-1.737	0.471
	2	0.162	-0.117	0.499	-0.467	0.234	0.034	-0.107	0.926	-2.446	2.232	0.254	-0.715	0.164	-1.737	0.306
	3	0.229	-0.113	0.505	-0.456	0.231	0.075	0.283	0.814	-2.152	2.719	0.254	-0.714	0.176	-1.765	0.337
	4	0.231	-0.124	0.538	-0.536	0.288	0.264	0.735	0.528	-1.622	3.092	0.286	-0.697	0.201	-1.789	0.394
	5	0.243	-0.154	0.539	-0.668	0.361	0.556	1.230	0.248	-0.918	3.378	0.324	-0.751	0.193	-1.905	0.403
Retinol (μg)	1	0.089	0.296	0.110	-0.071	0.663	0.024	-0.863	0.370	-2.794	1.068	0.083	0.666	0.084	-0.094	1.425
	2	0.221	0.318	0.134	-0.104	0.740	0.056	-0.943	0.413	-3.261	1.375	0.250	0.582	0.180	-0.282	1.446
	3	0.321	0.385	0.064	-0.025	0.794	0.081	-0.604	0.618	-3.056	1.847	0.257	0.633	0.160	-0.263	1.530
	4	0.350	0.458	**0.046**	0.009	0.907	0.260	-0.540	0.635	-2.851	1.771	0.289	0.652	0.184	-0.328	1.632
	5	0.387	0.568	**0.038**	0.033	1.103	0.538	-0.672	0.520	-2.803	1.458	0.307	0.545	0.309	-0.535	1.624
Total carotene (μg)	1	0.037	-0.168	0.308	-0.499	0.163	0.011	-0.585	0.549	-2.554	1.383	0.043	-0.690	0.218	-1.806	0.426
	2	0.161	-0.117	0.516	-0.481	0.248	0.037	-0.376	0.750	-2.767	2.014	0.262	-0.790	0.128	-1.821	0.241
	3	0.229	-0.117	0.506	-0.474	0.241	0.073	0.045	0.971	-2.477	2.568	0.262	-0.794	0.138	-1.859	0.271
	4	0.231	-0.127	0.542	-0.551	0.298	0.256	0.377	0.748	-2.006	2.760	0.294	-0.771	0.161	-1.866	0.325
	5	0.243	-0.160	0.536	-0.692	0.372	0.537	0.657	0.533	-1.490	2.804	0.333	-0.831	0.153	-1.991	0.330
Total retinol equivalents (μg)	1	0.013	-0.115	0.541	-0.496	0.266	0.058	-1.812	0.162	-4.386	0.762	0.014	0.471	0.492	-0.904	1.845
	2	0.149	-0.062	0.769	-0.492	0.368	0.082	-1.960	0.219	-5.150	1.230	0.207	0.133	0.858	-1.374	1.640
	3	0.216	-0.038	0.853	-0.462	0.385	0.098	-1.515	0.377	-4.973	1.942	0.209	0.191	0.808	-1.399	1.781
	4	0.218	-0.021	0.930	-0.498	0.457	0.272	-1.309	0.414	-4.550	1.931	0.247	0.300	0.735	-1.493	2.093
	5	0.227	-0.018	0.955	-0.689	0.652	0.541	-1.085	0.446	-3.980	1.809	0.278	0.125	0.898	-1.855	2.104
Vitamin D (μg)	1	0.101	0.394	0.087	-0.061	0.849	0.016	-1.374	0.468	-5.184	2.436	0.009	0.276	0.587	-0.746	1.299
	2	0.182	0.314	0.304	-0.302	0.931	0.040	-1.025	0.651	-5.610	3.559	0.213	-0.341	0.603	-1.663	0.981
	3	0.262	0.365	0.223	-0.237	0.967	0.078	-0.858	0.705	-5.447	3.731	0.214	-0.343	0.606	-1.687	1.001
	4	0.266	0.373	0.238	-0.265	1.011	0.254	-0.225	0.917	-4.595	4.145	0.256	-0.454	0.504	-1.828	0.919
	5	0.276	0.375	0.271	-0.318	1.069	0.533	0.908	0.659	-3.295	5.110	0.304	-0.704	0.332	-2.167	0.760
Vitamin E (mg)	1	0.079	-0.429	0.133	-0.998	0.139	0.025	-1.469	0.368	-4.742	1.804	0.053	0.888	0.169	-0.396	2.173
	2	0.280	-0.691	**0.040**	-1.349	-0.033	0.043	-1.594	0.599	-7.725	4.537	0.226	-1.049	0.373	-3.415	1.317
	3	0.308	-0.600	0.085	-1.288	0.088	0.080	-1.369	0.652	-7.506	4.768	0.226	-1.052	0.395	-3.540	1.436
	4	0.308	-0.597	0.104	-1.325	0.132	0.277	-2.726	0.357	-8.697	3.245	0.277	-1.454	0.254	-4.011	1.103
	5	0.320	-0.673	0.124	-1.549	0.202	0.529	-0.156	0.959	-6.341	6.029	0.299	-1.183	0.387	-3.947	1.582

Abbreviations: NAP = Normoglycaemia after acute pancreatitis. NODAP = New-onset diabetes or prediabetes after acute pancreatitis. T2DM = Type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval. Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

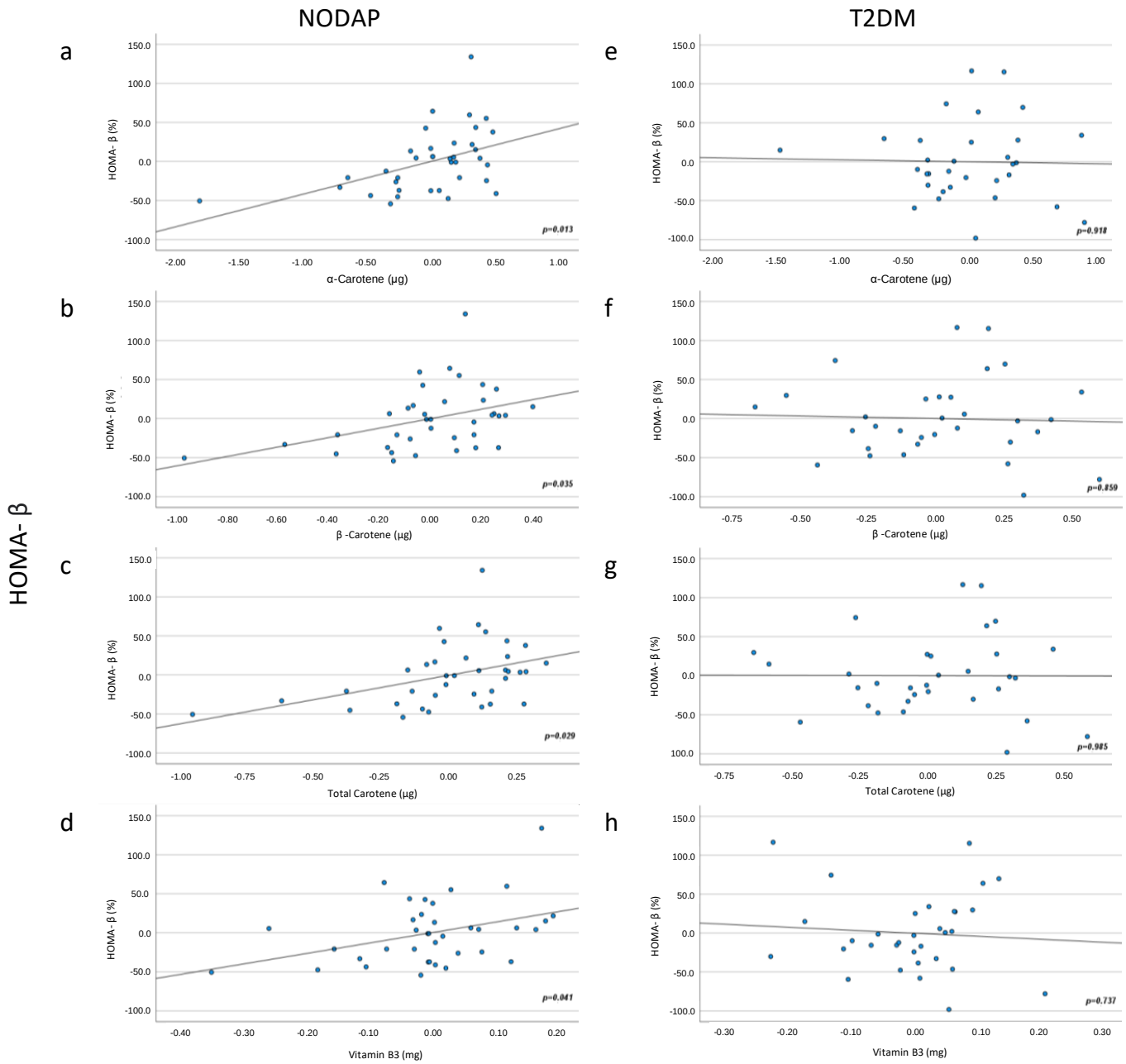

Figure 4.1 Associations between α-Carotene, β-Carotene, Total Carotene, Vitamin B3 and HOMA-β in NODAP (**a, b, c, d**) and T2DM **(e, f, g, h**).

Abbreviations: HOMA-β = homeostasis model assessment β-cell function index, NODAP = new-onset diabetes or prediabetes after acute pancreatitis, T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis.

Footnotes: α-carotene, β-carotene, total carotene, and vitamin B3 data were log-transformed. Partial regression plots were adjusted for age, sex, daily energy intake, V/S fat volume, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$.

Table 4.4 Associations between Habitual Fat-Soluble Vitamin/Vitamer Intake and HOMA-β in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper	R^2	Unstandardised B	*p*	95% CI Lower	95% CI Upper
α-Carotene (μg)	1	0.085	42.654	0.118	-11.525	96.833	0.026	12.369	0.380	-15.993	40.730	0.122	33.125	**0.034**	2.563	63.688
	2	0.097	46.408	0.137	-15.817	108.633	0.067	11.596	0.509	-23.970	47.162	0.144	31.487	0.056	-0.863	63.836
	3	0.120	49.019	0.123	-14.212	112.250	0.071	9.963	0.592	-27.775	47.701	0.161	35.211	**0.042**	1.280	69.143
	4	0.149	42.815	0.238	-30.423	116.053	0.167	2.010	0.916	-37.064	41.083	0.265	39.096	**0.023**	5.803	72.390
	5	0.253	46.748	0.245	-34.802	128.298	0.228	-2.449	0.918	-51.174	46.277	0.400	41.584	**0.013**	9.383	73.785
β-Carotene (μg)	1	0.046	36.574	0.258	-28.244	101.392	0.017	16.025	0.479	-29.657	61.706	0.075	44.684	0.100	-9.036	98.405
	2	0.062	41.825	0.260	-32.875	116.526	0.059	12.900	0.648	-44.502	70.302	0.111	43.746	0.117	-11.620	99.112
	3	0.075	41.472	0.271	-34.421	117.365	0.064	9.766	0.744	-51.147	70.678	0.117	45.524	0.112	-11.213	102.261
	4	0.105	23.914	0.586	-65.736	113.565	0.166	-0.629	0.984	-65.396	64.139	0.235	57.657	**0.044**	1.591	113.723
	5	0.234	48.647	0.341	-55.638	152.933	0.229	-6.627	0.859	-83.196	69.942	0.360	60.440	**0.035**	4.672	116.209
Retinol (μg)	1	0.028	33.740	0.374	-42.742	110.222	0.001	4.373	0.856	-44.366	53.112	0.000	-2.031	0.917	-41.393	37.331
	2	0.048	44.359	0.341	-49.691	138.410	0.060	-14.040	0.628	-72.872	44.791	0.051	-14.781	0.537	-63.044	33.482
	3	0.055	40.772	0.396	-56.658	138.202	0.076	-20.059	0.515	-82.446	42.329	0.051	-14.404	0.564	-64.723	35.916
	4	0.124	45.228	0.382	-59.861	150.317	0.183	-20.912	0.488	-82.218	40.394	0.119	-0.939	0.972	-55.105	53.228
	5	0.235	56.332	0.340	-64.138	176.803	0.246	-22.664	0.498	-91.238	45.911	0.249	-16.912	0.539	-72.685	38.860
Total carotene (μg)	1	0.053	40.540	0.220	-25.715	106.796	0.013	15.205	0.527	-33.323	63.734	0.090	49.461	0.072	-4.580	103.502
	2	0.072	47.608	0.217	-29.735	124.951	0.058	12.827	0.667	-47.733	73.387	0.124	48.182	0.088	-7.591	103.956
	3	0.086	47.633	0.223	-30.889	126.155	0.063	9.133	0.775	-55.814	74.081	0.132	50.738	0.081	-6.625	108.102
	4	0.112	31.256	0.488	-60.620	123.132	0.166	2.405	0.942	-65.244	70.054	0.241	59.620	**0.039**	3.231	116.009
	5	0.247	58.189	0.269	-48.786	165.163	0.228	-0.725	0.985	-79.302	77.852	0.368	63.178	**0.029**	7.069	119.286
Total retinol equivalents (μg)	1	0.043	41.583	0.269	-33.984	117.150	0.027	29.823	0.371	-37.247	96.893	0.007	16.417	0.630	-52.062	84.896
	2	0.061	50.225	0.267	-40.850	141.300	0.055	13.194	0.755	-72.675	99.062	0.040	5.249	0.897	-77.085	87.583
	3	0.070	48.395	0.293	-44.571	141.360	0.061	6.655	0.885	-86.884	100.194	0.041	8.065	0.851	-78.824	94.955
	4	0.111	34.100	0.498	-68.523	136.723	0.166	1.319	0.977	-91.619	94.257	0.149	47.023	0.318	-47.582	141.628
	5	0.265	84.330	0.196	-47.518	216.178	0.228	-2.039	0.967	-102.177	98.099	0.254	36.814	0.456	-63.106	136.734
Vitamin D (μg)	1	0.003	13.246	0.781	-83.424	109.916	0.025	-44.015	0.390	-146.965	58.935	0.056	35.164	0.159	-14.385	84.712
	2	0.024	36.265	0.587	-99.552	172.082	0.116	-80.625	0.170	-197.999	36.749	0.127	60.927	0.082	-8.187	130.041
	3	0.035	32.472	0.634	-106.445	171.388	0.128	-82.399	0.167	-201.624	36.826	0.128	60.837	0.087	-9.439	131.113
	4	0.109	43.550	0.531	-98.202	185.303	0.291	-115.998	0.051	-232.456	0.460	0.192	56.521	0.114	-14.500	127.542
	5	0.216	48.852	0.491	-96.631	194.335	0.347	-122.811	0.071	-256.989	11.367	0.275	42.089	0.254	-32.052	116.231
Vitamin E (mg)	1	0.003	16.183	0.783	-103.121	135.488	0.066	61.903	0.156	-24.999	148.806	0.014	22.958	0.478	-42.091	88.007
	2	0.016	23.462	0.758	-131.794	178.719	0.107	100.700	0.205	-58.552	259.953	0.048	34.906	0.589	-95.343	165.154
	3	0.027	11.989	0.882	-152.544	176.522	0.113	98.254	0.225	-64.290	260.798	0.052	40.872	0.546	-95.836	177.580
	4	0.092	2.743	0.973	-165.515	171.002	0.225	105.902	0.191	-56.399	268.203	0.132	44.707	0.516	-94.467	183.881
	5	0.210	52.021	0.574	-138.296	242.338	0.258	92.114	0.374	-119.097	303.326	0.279	83.141	0.230	-56.011	222.293

Abbreviations: HOMA-β = homeostasis model assessment β-cell function. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

Table 4.5 Associations between Habitual Fat-Soluble Vitamin/Vitamer Intake and HOMA-IR in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
α-Carotene (μg)	1	0.058	0.654	0.200	-0.366	1.673	0.005	-0.131	0.694	-0.804	0.543	0.039	0.533	0.240	-0.372	1.437
	2	0.068	0.735	0.209	-0.437	1.907	0.139	-0.441	0.269	-1.244	0.361	0.175	0.368	0.411	-0.531	1.267
	3	0.077	0.767	0.200	-0.433	1.967	0.145	-0.395	0.349	-1.246	0.456	0.200	0.496	0.289	-0.442	1.434
	4	0.111	0.659	0.336	-0.729	2.046	0.202	-0.496	0.266	-1.395	0.402	0.293	0.620	0.180	-0.304	1.544
	5	0.232	0.709	0.345	-0.823	2.241	0.405	-0.187	0.701	-1.192	0.818	0.372	0.660	0.158	-0.273	1.592
β-Carotene (μg)	1	0.023	0.481	0.424	-0.735	1.697	0.002	0.141	0.792	-0.940	1.222	0.021	0.669	0.391	-0.896	2.234
	2	0.034	0.587	0.398	-0.818	1.993	0.101	-0.181	0.780	-1.500	1.137	0.172	0.569	0.449	-0.943	2.081
	3	0.039	0.583	0.409	-0.851	2.018	0.115	-0.061	0.929	-1.453	1.331	0.190	0.660	0.388	-0.878	2.197
	4	0.076	0.234	0.777	-1.455	1.922	0.166	-0.336	0.653	-1.858	1.187	0.290	0.985	0.198	-0.545	2.514
	5	0.215	0.659	0.490	-1.299	2.617	0.402	-0.151	0.845	-1.735	1.434	0.363	1.009	0.199	-0.565	2.583
Retinol (μg)	1	0.053	0.856	0.221	-0.544	2.256	0.007	-0.258	0.648	-1.400	0.884	0.004	0.193	0.727	-0.920	1.305
	2	0.064	1.049	0.223	-0.680	2.778	0.172	-0.981	0.132	-2.278	0.316	0.165	-0.355	0.576	-1.636	0.926
	3	0.065	1.027	0.250	-0.770	2.825	0.175	-0.928	0.180	-2.313	0.458	0.175	-0.269	0.682	-1.597	1.059
	4	0.137	1.199	0.212	-0.734	3.133	0.217	-0.913	0.194	-2.323	0.498	0.247	0.002	0.997	-1.414	1.419
	5	0.275	1.514	0.161	-0.659	3.687	0.446	-0.850	0.214	-2.231	0.530	0.326	-0.326	0.658	-1.821	1.169
Total carotene (μg)	1	0.030	0.562	0.362	-0.681	1.806	0.001	0.073	0.897	-1.074	1.221	0.027	0.771	0.329	-0.811	2.352
	2	0.043	0.698	0.333	-0.758	2.155	0.104	-0.262	0.702	-1.650	1.127	0.176	0.648	0.395	-0.883	2.179
	3	0.048	0.699	0.341	-0.787	2.184	0.116	-0.127	0.862	-1.610	1.356	0.196	0.765	0.326	-0.797	2.327
	4	0.081	0.376	0.657	-1.357	2.110	0.168	-0.402	0.606	-1.991	1.186	0.292	1.013	0.190	-0.529	2.555
	5	0.226	0.842	0.392	-1.170	2.853	0.402	-0.141	0.858	-1.767	1.484	0.366	1.049	0.187	-0.542	2.640
Total retinol equivalents (μg)	1	0.028	0.624	0.373	-0.788	2.036	0.001	-0.154	0.845	-1.750	1.443	0.009	0.524	0.586	-1.412	2.461
	2	0.040	0.783	0.354	-0.924	2.490	0.158	-1.279	0.180	-3.184	0.626	0.158	-0.167	0.877	-2.350	2.016
	3	0.043	0.764	0.376	-0.985	2.513	0.160	-1.195	0.248	-3.274	0.884	0.170	0.042	0.970	-2.246	2.330
	4	0.085	0.521	0.581	-1.410	2.451	0.215	-1.347	0.202	-3.467	0.772	0.266	1.028	0.405	-1.460	3.516
	5	0.253	1.439	0.237	-1.026	3.904	0.430	-0.982	0.323	-3.004	1.040	0.330	0.790	0.550	-1.890	3.470
Vitamin D (μg)	1	0.012	0.501	0.569	-1.283	2.286	0.011	-0.685	0.570	-3.122	1.751	0.045	0.896	0.205	-0.514	2.307
	2	0.020	0.750	0.546	-1.772	3.273	0.150	-1.692	0.210	-4.396	1.013	0.169	0.632	0.505	-1.277	2.541
	3	0.024	0.712	0.576	-1.879	3.303	0.164	-1.647	0.228	-4.390	1.097	0.182	0.623	0.515	-1.304	2.550
	4	0.094	0.930	0.475	-1.720	3.579	0.219	-1.892	0.187	-4.765	0.982	0.252	0.400	0.676	-1.535	2.334
	5	0.221	1.034	0.431	-1.655	3.724	0.472	-2.237	0.115	-5.071	0.597	0.321	-0.018	0.986	-2.050	2.014
Vitamin E (mg)	1	0.000	-0.113	0.918	-2.327	2.102	0.018	0.769	0.459	-1.324	2.862	0.075	1.481	0.101	-0.303	3.265
	2	0.007	-0.290	0.838	-3.182	2.601	0.106	-0.855	0.643	-4.600	2.890	0.157	-0.060	0.972	-3.530	3.409
	3	0.015	-0.466	0.757	-3.535	2.604	0.120	-0.763	0.684	-4.566	3.041	0.171	0.265	0.882	-3.353	3.883
	4	0.079	-0.621	0.686	-3.763	2.521	0.173	-1.253	0.518	-5.192	2.686	0.247	0.004	0.998	-3.664	3.671
	5	0.195	0.225	0.896	-3.336	3.786	0.401	-0.200	0.926	-4.660	4.261	0.325	0.721	0.701	-3.092	4.534

Abbreviations: HOMA-IR = homeostasis model assessment insulin resistance. NAP = Normoglycaemia after acute pancreatitis. NODAP = New-onset diabetes or prediabetes after acute pancreatitis. T2DM = Type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold

4.3.4 Associations between Habitual Water-Soluble Vitamin Intake and Diabetes Types

In the NODAP group, one vitamin was significantly different when compared with the NAP group (Table 4.6). The mean vitamin B6 intake was significantly different in the most adjusted model ($p = 0.023$). Intake of other investigated vitamins/vitamers in the NODAP group did not differ significantly from the reference group.

In the T2DM group, one vitamin was significantly different when compared with the NAP group (Table 4.6). The mean vitamin B6 intake was significantly different in the most adjusted model ($p = 0.024$). Intake of other investigated vitamins/vitamers in the T2DM group did not differ significantly from the reference group.

Table 4.6 Associations between Habitual Water-Soluble Vitamin/Vitamer Intake and the Study Groups

Mineral	Model	T2DM				NODAP			
		β	*p*	95% CI		β	*p*	95% CI	
				Lower	Upper			Lower	Upper
Vitamin B1 (mg)	1	0.035	0.426	-0.051	0.120	0.011	0.797	-0.074	0.096
	2	-0.009	0.778	-0.071	0.053	-0.042	0.177	-0.103	0.019
	3	-0.005	0.870	-0.067	0.056	-0.042	0.174	-0.103	0.019
	4	-0.013	0.679	-0.077	0.050	-0.043	0.158	-0.103	0.017
	5	0.002	0.964	-0.073	0.076	-0.049	0.127	-0.112	0.014
Vitamin B2 (mg)	1	0.032	0.425	-0.047	0.110	0.012	0.770	-0.067	0.090
	2	-0.014	0.639	-0.075	0.046	-0.041	0.177	-0.101	0.019
	3	-0.012	0.704	-0.073	0.049	-0.041	0.177	-0.101	0.019
	4	-0.015	0.632	-0.078	0.047	-0.039	0.199	-0.098	0.021
	5	-0.002	0.951	-0.075	0.071	-0.043	0.172	-0.105	0.019
Vitamin B3 (mg)	1	0.008	0.850	-0.075	0.091	-0.012	0.778	-0.094	0.071
	2	-0.036	0.271	-0.099	0.028	-0.062	0.053	-0.126	0.001
	3	-0.033	0.306	-0.097	0.031	-0.062	0.053	-0.125	0.001
	4	-0.046	0.170	-0.113	0.020	-0.061	0.055	-0.124	0.001
	5	-0.033	0.404	-0.112	0.045	-0.065	0.053	-0.132	0.001
Vitamin B6 (mg)	1	-0.002	0.951	-0.079	0.074	0.000	0.996	-0.076	0.076
	2	-0.048	0.078	-0.103	0.006	-0.053	0.053	-0.106	0.001
	3	-0.046	0.095	-0.100	0.008	-0.053	0.053	-0.106	0.001
	4	-0.056	0.049	-0.113	0.000	-0.052	0.055	-0.105	0.001
	5	-0.075	**0.024**	-0.141	-0.010	-0.064	**0.023**	-0.120	-0.009
Vitamin B9 (µg)	1	0.026	0.609	-0.076	0.129	0.021	0.678	-0.080	0.123
	2	-0.018	0.680	-0.105	0.069	-0.031	0.478	-0.117	0.055
	3	-0.017	0.705	-0.105	0.071	-0.031	0.480	-0.118	0.056
	4	-0.026	0.578	-0.118	0.066	-0.031	0.484	-0.118	0.056
	5	-0.055	0.317	-0.163	0.054	-0.044	0.339	-0.136	0.047
Vitamin B12 (µg)	1	0.060	0.298	-0.054	0.173	0.044	0.443	-0.069	0.156
	2	0.014	0.791	-0.089	0.116	-0.015	0.775	-0.116	0.087
	3	0.020	0.697	-0.082	0.122	-0.014	0.775	-0.115	0.086
	4	0.003	0.948	-0.100	0.107	-0.012	0.802	-0.111	0.086
	5	0.022	0.718	-0.099	0.143	-0.020	0.701	-0.122	0.082
Vitamin C (mg)	1	0.081	0.278	-0.066	0.228	0.023	0.759	-0.123	0.169
	2	0.064	0.385	-0.082	0.210	-0.001	0.992	-0.145	0.144
	3	0.071	0.338	-0.075	0.217	-0.001	0.993	-0.145	0.143
	4	0.042	0.584	-0.111	0.196	-0.005	0.944	-0.150	0.140
	5	0.002	0.984	-0.178	0.182	0.004	0.959	-0.148	0.156

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as β coefficients, 95% CI, and *p* values (from ANCOVA analysis). NAP group was used as the reference group. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

4.3.5 Water-soluble Vitamin Intake and Markers of Glucose Metabolism in the Study Groups

4.3.5.1 Fasting Plasma Glucose

In the NODAP group, associations between FPG and the investigated water-soluble vitamins were not statistically significant (Table 4.7).

In the T2DM group, FPG was significantly associated with three water-soluble vitamins (Vitamin B1, vitamin B2, and vitamin B12) (Table 4.7). Vitamin B1 was significantly inversely associated with FPG in adjusted model 4 only (p = 0.036). Vitamin B2 was significantly inversely associated with FPG in adjusted models (model 2: p = 0.030, model 3: p = 0.041, model 4: p = 0.046). Vitamin B12 was significantly inversely associated with FPG in the unadjusted model (model 1: p = 0.001) and adjusted models (model 2: p = 0.002, model 3: p = 0.003, model 4: p = 0.024).

In the NAP group, FPG was significantly associated with one water-soluble vitamin (vitamin B3). Vitamin B3 was significantly inversely associated with FPG in adjusted model 2 (p = 0.030).

4.3.5.2. HOMA-β

In the NODAP group, HOMA-β was significantly associated with one water-soluble vitamin (vitamin B3) (Table 4.8, Figure 4.1). Vitamin B3 was significantly directly associated with HOMA-β in the most adjusted models (model 4: p = 0.035, model 5: p = 0.041).

In the T2DM and NAP groups, associations between HOMA-β and the investigated water-soluble vitamins were not statistically significant.

4.3.5.3. HOMA-IR

In the NODAP group, T2DM and NAP groups, associations between HOMA-IR and the investigated water-soluble vitamins were not statistically significant (Table 4.9).

Table 4.7 Associations between Habitual Water-Soluble Vitamin Intake and Fasting Plasma Glucose in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Vitamin B1 (mg)	1	0.002	-0.084	0.828	-0.867	0.700	0.089	-3.682	0.081	-7.847	0.483	0.052	1.227	0.177	-0.579	3.033
	2	0.181	-0.573	0.313	-1.716	0.571	0.121	-5.077	0.096	-11.104	0.950	0.216	-0.856	0.537	-3.649	1.937
	3	0.221	-0.282	0.648	-1.543	0.978	0.143	-4.615	0.136	-10.774	1.545	0.217	-0.875	0.535	-3.718	1.967
	4	0.222	-0.252	0.712	-1.648	1.144	0.368	-6.024	**0.036**	-11.612	-0.437	0.265	-1.321	0.365	-4.257	1.615
	5	0.234	-0.337	0.677	-2.003	1.329	0.573	-3.930	0.137	-9.206	1.346	0.311	-1.711	0.271	-4.836	1.414
Vitamin B2 (mg)	1	0.005	0.144	0.716	-0.656	0.943	0.106	-4.251	0.056	-8.613	0.111	0.091	1.965	0.069	-0.161	4.091
	2	0.146	0.019	0.972	-1.058	1.095	0.176	-6.653	**0.030**	-12.614	-0.691	0.211	0.718	0.648	-2.451	3.888
	3	0.219	0.193	0.716	-0.888	1.273	0.200	-6.313	**0.041**	-12.347	-0.279	0.213	0.769	0.632	-2.474	4.011
	4	0.221	0.184	0.741	-0.952	1.319	0.357	-5.771	**0.046**	-11.439	-0.104	0.275	2.198	0.272	-1.820	6.216
	5	0.229	0.194	0.744	-1.030	1.418	0.593	-5.056	0.070	-10.560	0.448	0.301	2.103	0.368	-2.610	6.816
Vitamin B3 (mg)	1	0.042	-0.442	0.277	-1.259	0.375	0.055	-3.346	0.173	-8.237	1.544	0.029	0.808	0.316	-0.804	2.421
	2	0.295	-1.100	**0.030**	-2.086	-0.115	0.095	-4.751	0.167	-11.594	2.092	0.224	-0.943	0.400	-3.194	1.308
	3	0.323	-0.972	0.062	-1.995	0.051	0.132	-4.694	0.170	-11.517	2.130	0.224	-0.930	0.415	-3.225	1.366
	4	0.331	-1.014	0.066	-2.098	0.071	0.276	-3.074	0.362	-9.881	3.733	0.255	-0.853	0.509	-3.459	1.754
	5	0.334	-1.058	0.096	-2.324	0.208	0.531	-1.020	0.750	-7.572	5.532	0.291	-0.931	0.488	-3.650	1.789
Vitamin B6 (mg)	1	0.019	-0.320	0.466	-1.208	0.567	0.051	-3.222	0.192	-8.141	1.696	0.026	0.916	0.336	-0.992	2.824
	2	0.242	-1.114	0.088	-2.404	0.176	0.098	-5.976	0.154	-14.314	2.362	0.239	-1.504	0.246	-4.096	1.089
	3	0.274	-0.920	0.172	-2.267	0.428	0.132	-5.717	0.172	-14.064	2.631	0.239	-1.492	0.261	-4.150	1.167
	4	0.275	-0.910	0.200	-2.337	0.517	0.280	-3.967	0.322	-12.036	4.101	0.268	-1.396	0.333	-4.297	1.505
	5	0.291	-1.025	0.205	-2.661	0.611	0.565	-4.942	0.183	-12.394	2.510	0.301	-1.355	0.365	-4.380	1.669
Vitamin B9 (µg)	1	0.016	-0.192	0.502	-0.770	0.386	0.002	-0.430	0.813	-4.103	3.242	0.003	0.270	0.742	-1.381	1.921
	2	0.174	-0.314	0.365	-1.015	0.387	0.035	0.530	0.836	-4.650	5.711	0.258	-1.391	0.143	-3.277	0.495
	3	0.237	-0.280	0.411	-0.971	0.411	0.076	0.727	0.776	-4.450	5.903	0.259	-1.385	0.151	-3.304	0.535
	4	0.237	-0.276	0.454	-1.028	0.475	0.254	0.251	0.917	-4.609	5.110	0.274	-1.182	0.284	-3.396	1.032
	5	0.259	-0.413	0.374	-1.362	0.536	0.530	-0.327	0.879	-4.715	4.061	0.316	-1.381	0.238	-3.728	0.967
Vitamin B12 (µg)	1	0.041	0.281	0.283	-0.245	0.808	0.270	-5.259	**0.001**	-8.326	-2.193	0.055	0.926	0.164	-0.397	2.250
	2	0.153	0.140	0.655	-0.497	0.777	0.310	-5.895	**0.002**	-9.372	-2.418	0.212	0.387	0.634	-1.253	2.026
	3	0.233	0.231	0.457	-0.400	0.863	0.319	-5.676	**0.003**	-9.262	-2.090	0.214	0.420	0.615	-1.263	2.102
	4	0.233	0.223	0.502	-0.455	0.902	0.384	-4.698	**0.024**	-8.723	-0.674	0.250	0.430	0.630	-1.378	2.239
	5	0.240	0.213	0.573	-0.564	0.990	0.593	-3.437	0.069	-7.169	0.295	0.281	0.318	0.734	-1.589	2.225
Vitamin C (mg)	1	0.052	-0.236	0.223	-0.625	0.152	0.005	-0.510	0.677	-2.974	1.955	0.005	-0.258	0.673	-1.486	0.971
	2	0.201	-0.284	0.202	-0.730	0.162	0.034	-0.129	0.926	-2.935	2.677	0.242	-0.708	0.229	-1.883	0.468
	3	0.255	-0.245	0.267	-0.690	0.200	0.074	0.197	0.889	-2.665	3.058	0.242	-0.703	0.240	-1.900	0.493
	4	0.258	-0.268	0.284	-0.773	0.238	0.253	-0.088	0.947	-2.778	2.602	0.284	-0.756	0.214	-1.973	0.461
	5	0.296	-0.441	0.190	-1.119	0.238	0.540	-0.866	0.466	-3.282	1.551	0.341	-1.034	0.127	-2.382	0.315

Abbreviations: NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

Table 4.8 Associations between Habitual Water-Soluble Vitamin Intake and HOMA-β in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Vitamin B1 (mg)	1	0.011	42.743	0.582	-114.512	199.998	0.010	32.893	0.577	-86.282	152.067	0.055	62.654	0.164	-26.869	152.178
	2	0.051	121.755	0.322	-126.508	370.018	0.053	19.778	0.811	-148.017	187.573	0.131	131.536	0.076	-14.439	277.511
	3	0.052	111.205	0.421	-169.103	391.512	0.061	13.557	0.873	-159.371	186.485	0.131	131.084	0.082	-17.611	279.778
	4	0.109	94.553	0.522	-206.688	395.793	0.170	28.241	0.739	-144.743	201.226	0.226	146.635	0.054	-2.996	296.265
	5	0.223	131.169	0.427	-207.308	469.646	0.234	40.247	0.677	-158.402	238.895	0.314	127.934	0.102	-26.982	282.850
Vitamin B2 (mg)	1	0.023	62.837	0.427	-96.935	222.609	0.059	76.867	0.180	-37.390	191.124	0.000	-1.518	0.978	-112.231	109.196
	2	0.068	135.116	0.231	-91.641	361.873	0.094	88.374	0.271	-72.907	249.655	0.042	-25.655	0.765	-199.099	147.790
	3	0.073	126.599	0.282	-110.736	363.935	0.099	85.231	0.298	-79.789	250.251	0.043	-23.939	0.785	-201.522	153.644
	4	0.140	128.952	0.278	-111.612	369.517	0.192	69.896	0.390	-94.709	234.501	0.131	69.627	0.519	-148.701	287.955
	5	0.233	119.315	0.347	-139.643	378.273	0.263	95.159	0.340	-107.822	298.141	0.238	10.611	0.930	-233.651	254.873
Vitamin B3 (mg)	1	0.025	68.587	0.405	-97.535	234.708	0.013	41.105	0.536	-92.863	175.072	0.032	42.527	0.287	-37.389	122.443
	2	0.076	144.887	0.202	-82.670	372.444	0.057	35.967	0.700	-153.789	225.723	0.079	70.447	0.247	-51.283	192.178
	3	0.079	136.725	0.253	-103.996	377.447	0.065	34.328	0.718	-158.689	227.345	0.082	71.752	0.247	-52.247	195.752
	4	0.169	167.720	0.168	-76.085	411.526	0.170	-32.271	0.750	-238.848	174.306	0.245	140.586	**0.035**	10.330	270.842
	5	0.342	249.197	0.054	-4.603	502.997	0.232	-38.662	0.737	-275.291	197.966	0.352	134.901	**0.041**	5.816	263.985
Vitamin B6 (mg)	1	0.029	79.794	0.367	-98.301	257.889	0.025	53.354	0.384	-70.034	176.742	0.004	18.678	0.695	-77.091	114.447
	2	0.106	222.157	0.118	-60.324	504.637	0.068	70.571	0.488	-135.447	276.589	0.040	14.355	0.841	-130.214	158.924
	3	0.107	215.652	0.153	-85.765	517.070	0.076	68.214	0.510	-141.538	277.965	0.042	16.470	0.822	-131.676	164.616
	4	0.164	215.652	0.153	-85.765	517.070	0.170	34.555	0.741	-178.907	248.017	0.138	61.693	0.426	-94.618	218.004
	5	0.283	240.804	0.145	-91.028	572.636	0.240	70.489	0.572	-185.510	326.487	0.259	65.964	0.388	-88.546	220.475
Vitamin B9 (μg)	1	0.030	52.984	0.356	-62.696	168.665	0.017	32.051	0.479	-59.229	123.332	0.016	30.339	0.454	-51.071	111.750
	2	0.066	87.722	0.240	-62.516	237.960	0.054	16.610	0.799	-115.882	149.103	0.057	40.811	0.437	-64.747	146.369
	3	0.076	84.973	0.264	-68.271	238.217	0.062	15.355	0.817	-119.424	150.133	0.059	41.402	0.438	-65.998	148.802
	4	0.120	65.458	0.413	-97.326	228.241	0.171	23.043	0.724	-110.081	156.167	0.173	79.214	0.178	-38.046	196.473
	5	0.235	91.910	0.335	-102.621	286.441	0.230	19.129	0.801	-137.147	175.405	0.284	75.258	0.206	-44.048	194.564
Vitamin B12 (μg)	1	0.000	-3.524	0.947	-111.910	104.863	0.070	66.147	0.144	-23.970	156.263	0.002	8.979	0.789	-58.525	76.483
	2	0.012	5.736	0.933	-133.002	144.475	0.094	56.737	0.272	-47.021	160.494	0.039	0.995	0.982	-88.885	90.874
	3	0.026	5.736	0.933	-133.002	144.475	0.097	53.918	0.312	-53.464	161.300	0.040	2.305	0.960	-89.975	94.585
	4	0.094	-1.786	0.980	-145.308	141.736	0.169	17.344	0.780	-109.359	144.048	0.130	29.526	0.537	-67.152	126.205
	5	0.197	9.464	0.903	-151.686	170.615	0.229	13.246	0.844	-125.424	151.916	0.241	17.287	0.718	-79.974	114.548
Vitamin C (mg)	1	0.049	45.996	0.240	-32.526	124.519	0.020	24.530	0.440	-39.475	88.536	0.068	46.339	0.120	-12.699	105.378
	2	0.078	62.628	0.194	-34.000	159.256	0.064	22.657	0.544	-53.029	98.344	0.120	52.901	0.096	-9.984	115.786
	3	0.085	59.848	0.226	-39.561	159.257	0.070	19.904	0.606	-58.556	98.364	0.122	53.264	0.099	-10.682	117.209
	4	0.116	41.520	0.447	-69.754	152.795	0.186	31.218	0.453	-53.300	115.736	0.183	47.746	0.141	-16.774	112.266
	5	0.236	67.759	0.332	-74.766	210.283	0.259	40.954	0.367	-51.682	133.591	0.290	46.795	0.178	-22.697	116.288

Abbreviations: HOMA-β = homeostasis model assessment β-cell function. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

Table 4.9 Associations between Habitual Water-Soluble Vitamin Intake and HOMA-IR in the Study Groups

Vitamin	Model	NAP					T2DM					NODAP				
		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI		R^2	Unstandardised B	*p*	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Vitamin B1 (mg)	1	0.010	0.768	0.594	-2.149	3.684	0.001	-0.272	0.845	-3.086	2.541	0.102	2.426	0.054	-0.044	4.895
	2	0.027	1.658	0.471	-3.003	6.320	0.139	-2.053	0.273	-5.814	1.709	0.170	1.419	0.479	-2.618	5.455
	3	0.027	1.607	0.535	-3.660	6.873	0.148	-1.892	0.324	-5.764	1.979	0.182	1.344	0.507	-2.739	5.427
	4	0.083	1.384	0.617	-4.283	7.052	0.207	-2.346	0.235	-6.319	1.626	0.257	1.258	0.540	-2.890	5.407
	5	0.213	2.025	0.510	-4.290	8.340	0.412	-1.231	0.537	-5.321	2.860	0.325	0.862	0.687	-3.486	5.210
Vitamin B2 (mg)	1	0.038	1.503	0.304	-1.437	4.442	0.000	-0.007	0.996	-2.775	2.761	0.021	1.325	0.392	-1.776	4.426
	2	0.073	2.751	0.189	-1.442	6.944	0.129	-1.759	0.340	-5.474	1.957	0.168	-1.455	0.522	-6.030	3.120
	3	0.073	2.721	0.214	-1.677	7.119	0.141	-1.647	0.379	-5.434	2.139	0.179	-1.284	0.578	-5.940	3.372
	4	0.136	2.741	0.217	-1.731	7.213	0.182	-1.556	0.418	-5.449	2.338	0.256	1.578	0.577	-4.143	7.299
	5	0.245	2.566	0.274	-2.199	7.332	0.417	-1.510	0.466	-5.753	2.733	0.322	0.686	0.831	-5.835	7.207
Vitamin B3 (mg)	1	0.010	0.813	0.596	-2.290	3.917	0.004	-0.529	0.735	-3.691	2.634	0.069	1.760	0.116	-0.459	3.978
	2	0.024	1.438	0.501	-2.898	5.774	0.142	-2.426	0.252	-6.679	1.826	0.160	0.539	0.741	-2.752	3.830
	3	0.025	1.333	0.554	-3.257	5.924	0.156	-2.376	0.267	-6.684	1.933	0.174	0.627	0.703	-2.701	3.955
	4	0.100	1.868	0.419	-2.837	6.572	0.196	-2.464	0.298	-7.240	2.312	0.291	2.329	0.193	-1.245	5.904
	5	0.268	3.273	0.184	-1.692	8.237	0.432	-2.391	0.310	-7.175	2.393	0.361	2.268	0.210	-1.360	5.897
Vitamin B6 (mg)	1	0.020	1.227	0.455	-2.090	4.545	0.005	0.554	0.702	-2.376	3.484	0.023	1.207	0.368	-1.479	3.892
	2	0.053	2.929	0.274	-2.461	8.319	0.105	-1.026	0.661	-5.771	3.719	0.175	-1.556	0.410	-5.350	2.238
	3	0.053	2.897	0.309	-2.858	8.651	0.120	-0.947	0.689	-5.757	3.862	0.185	-1.408	0.463	-5.276	2.460
	4	0.109	2.720	0.350	-3.194	8.634	0.161	-0.640	0.796	-5.684	4.404	0.248	-0.267	0.896	-4.400	3.866
	5	0.242	3.301	0.288	-3.025	9.627	0.407	-1.169	0.651	-6.484	4.146	0.321	-0.118	0.954	-4.306	4.070
Vitamin B9 (µg)	1	0.018	0.765	0.474	-1.393	2.923	0.014	0.679	0.523	-1.469	2.828	0.034	1.242	0.277	-1.042	3.526
	2	0.034	1.180	0.399	-1.654	4.013	0.100	-0.282	0.850	-3.319	2.755	0.157	-0.087	0.950	-2.913	2.738
	3	0.037	1.150	0.421	-1.750	4.050	0.115	-0.241	0.873	-3.317	2.834	0.170	-0.041	0.977	-2.896	2.814
	4	0.084	0.797	0.597	-2.282	3.876	0.161	-0.384	0.803	-3.531	2.763	0.261	1.134	0.466	-2.003	4.271
	5	0.212	1.146	0.520	-2.514	4.807	0.406	-0.666	0.671	-3.891	2.560	0.331	1.010	0.530	-2.253	4.274
Vitamin B12 (µg)	1	0.003	0.263	0.790	-1.744	2.270	0.031	-1.034	0.336	-3.195	1.128	0.010	0.568	0.549	-1.335	2.471
	2	0.008	0.306	0.809	-2.272	2.884	0.196	-2.022	0.082	-4.319	0.274	0.163	-0.574	0.626	-2.948	1.800
	3	0.012	0.231	0.860	-2.449	2.911	0.201	-1.939	0.105	-4.312	0.435	0.175	-0.466	0.698	-2.889	1.957
	4	0.079	0.526	0.699	-2.255	3.307	0.232	-2.101	0.143	-4.963	0.762	0.248	0.104	0.934	-2.441	2.650
	5	0.198	0.776	0.579	-2.091	3.642	0.439	-1.562	0.255	-4.341	1.217	0.321	-0.152	0.905	-2.757	2.452
Vitamin C (mg)	1	0.028	0.648	0.375	-0.824	2.119	0.007	0.343	0.647	-1.171	1.857	0.046	1.080	0.203	-0.610	2.771
	2	0.042	0.869	0.337	-0.957	2.694	0.099	0.052	0.952	-1.694	1.797	0.179	0.777	0.364	-0.943	2.496
	3	0.044	0.841	0.366	-1.042	2.724	0.116	0.168	0.849	-1.629	1.966	0.194	0.803	0.352	-0.931	2.538
	4	0.082	0.482	0.639	-1.621	2.585	0.162	-0.298	0.763	-2.313	1.718	0.261	0.620	0.471	-1.117	2.358
	5	0.211	0.821	0.529	-1.863	3.506	0.404	-0.309	0.745	-2.262	1.644	0.329	0.518	0.583	-1.395	2.430

Abbreviations: HOMA-IR = homeostasis model assessment insulin resistance. NAP = normoglycaemia after acute pancreatitis. NODAP = new-onset diabetes or prediabetes after acute pancreatitis. T2DM = type 2 diabetes or prediabetes prior to acute pancreatitis. 95% CI = 95% confidence interval.

Footnotes: Data are presented as R^2 values (from crude analysis), unstandardised B, *p* values (from linear regression), and 95% confidence intervals. All the variables were log-transformed. Model 1: unadjusted model. Model 2: age, sex, daily energy intake. Model 3: age, sex, daily energy intake, V/S fat volume ratio. Model 4: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status. Model 5: age, sex, daily energy intake, V/S fat volume ratio, alcohol intake, smoking status, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications. Significance was set at $p < 0.05$. Significant values are shown in bold.

4.4 Discussion

This chapter was the first to compare the mean habitual intake of 14 vitamins/vitamers between the NODAP and NAP groups and investigate the associations between a comprehensive vitamin profile and markers of glucose metabolism (FPG, HOMA-β, and HOMA-IR) in individuals after an attack of AP. A key finding was significant associations between vitamin B6 intake and both the NODAP and T2DM groups. Another key finding of this study was that, of the seven fat-soluble vitamins/vitamers, significant direct associations between habitual intake of fat-soluble vitamers α-carotene, β-carotene, and total carotene and HOMA-β were found in the NODAP group. Also, of the seven water-soluble vitamins, a significant direct association was observed between vitamin B3 and HOMA-β in individuals with NODAP.

4.4.1 Fat-Soluble Vitamins

Fat-soluble vitamins (vitamins A, D, E, and K) are hydrophobic compounds and, therefore, are insoluble in the aqueous environment of the gastrointestinal tract (183). To be absorbed, fat-soluble vitamins must be emulsified with dietary fats to form emulsion droplets (183). Pancreatic lipase enzyme binds to the surface of these emulsion droplets and breaks down triglycerides into fatty acids and monoglycerides, which then interact with long-chain hydrocarbons and bile salts to form mixed micelles with a hydrophobic core and hydrophilic exterior (183,199). These mixed micelles encase fat-soluble vitamins, fatty acids, bile salts, and phospholipids to be diffused across the brush border of the intestinal villi, absorbed into the lymphatic circulation, and transported throughout the body. Fat-soluble vitamins are stored in the liver and adipose tissue and, hence, are very slowly excreted from the body. Therefore, very high intakes of fat-soluble vitamins can be detrimental to health (183,200). Fat-soluble vitamin deficiencies are rare; however, insufficiency may occur in sub-populations including individuals with very low fat intake, low energy intake, or vegetarian/vegan diets (200). Due to the dependence on dietary fat intake for absorption of fat-soluble vitamins, individuals with malabsorptive conditions, such as EPD, may also develop subsequent deficiencies in these vitamins (197,201,202).

Vitamin A is available in the diet in two forms – retinol (preformed vitamin A) and provitamin carotenoids (203). There are many forms of carotenoids, with α-carotene and β-carotene being among the most abundant in the human diet and body (203). Carotenoids are endogenously

converted into retinol and contribute to overall vitamin A status. Carotenoids have potent antioxidant properties that have been found to have a beneficial role in eye health, cognitive function, and the prevention of several diseases including cardiovascular diseases and cancer (204,205). Dietary carotenoids have also been shown to be associated with the incidence of type 2 diabetes. Quansah et al. observed that increased intake of α-carotene had a 48% and 39% reduction in diabetes risk in Korean men and women, respectively (206). Additionally, β-carotene intake also reduced the risk of diabetes in men (though no association was found in women) (206). Another large prospective study showed that higher dietary intake of α-carotene (0.7 mg/day) was associated with a 15% lower risk of type 2 diabetes and β-carotene (3.5mg/day) was associated with a 22% reduced risk of diabetes, compared with the lowest quartile of the vitamins (207). A community based longitudinal study showed that increasing dietary intake of β-carotene by 1.4mg/day was associated with a 29–34% lower risk of incident diabetes in elderly Swedish men (208). Men in the highest tertile of β-carotene intake (>1.9 mg/day) at age 70 had a 49–50% lower risk of type 2 diabetes compared with the lowest tertile (<1.0mg/day) (208). Additionally, an 0.2 umol/L increase of serum β-carotene at age 50 years was associated with 0.08 units higher insulin sensitivity (determined with the use of euglycaemic–hyperinsulinaemic clamp) in nondiabetic participants at age 70 years. However, insulin secretion was not influenced significantly by serum β-carotene levels (208). Harari et al. found that serum α-carotene, β-carotene, and total carotenoids were inversely associated with fasting insulin and HOMA-IR in an Australian adult population (209). Mirmiran et al. also observed that increased dietary intake of β-carotene, but not other carotenoids, was significantly associated with a lower risk of HOMA-IR in Iranian adults (210). Serum β-carotene concentration was inversely associated with HOMA-IR in middle-aged Japanese individuals (211). A meta-analysis of prospective observational studies also concluded that dietary intake and circulating concentrations of total carotenoids have beneficial effects on reducing the risk of type 2 diabetes in a population at high risk of type 2 diabetes (211). In this meta-analysis, β-carotene intake was also consistently inversely associated with diabetes risk.

The present study was the first to investigate the associations between habitual carotenoid intake and insulin traits in individuals after an attack of AP. We found that dietary intake of α-carotene, β-carotene, and total carotene intake was significantly and directly associated with HOMA-β, indicating detrimental effects of deficient carotenoid intake on insulin secretion. Specifically, for every 1% decrease in α-carotene, β-carotene, and total carotene intake, HOMA-β decreased by 0.42%, 0.60%, and 0.63%, respectively. These results suggest that

increased intake of α-carotene, β-carotene, and total carotenoids may have beneficial effects on insulin secretion in individuals with NODAP. We found no association with other markers of glucose metabolism (FPG and HOMA-IR). Several intrinsic and extrinsic factors are associated with carotenoid status; therefore, dietary intake may not truly reflect carotenoid status in the body (212). In our unique cohort of individuals following an attack of AP, there may be mechanistic differences in the absorption or utilisation of fat-soluble vitamins, such as carotenoids, compared with those with type 2 diabetes (213). It is not uncommon for individuals to develop EPD following an attack of AP, which leads to maldigestion and malabsorption of nutrients, particularly of fat and fat-soluble vitamins (40,214). It has also previously been established that there is an association between EPD and NODAP, with individuals with EPD have a significantly increased risk of developing NODAP (40). It was suggested that deficiency in fat-soluble vitamins may have a role in this association as no significant correlation was found between EPD and NODAP when individuals were taking fat-soluble vitamin supplements (40). It is worth noting that pancreatic enzymes and serum carotenoid levels were not measured in the present study. Hence, we were not able to determine if EPD or low serum levels of these vitamins contributed to the observed results (215).

Vitamin D has two primary forms – vitamin D3 or cholecalciferol (which is endogenously synthesised in the skin after exposure to ultraviolet light) and vitamin D2 or ergocalciferol (which is predominantly obtained by dietary intake) (216). Vitamin D2 and D3 are hydroxylated in the liver by vitamin D-25-hydroxylase to produce the major circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D) (217,218). The serum concentration of 25(OH)D is one of the most reliable biomarkers of vitamin D status (218). There are few foods with naturally occurring vitamin D and only 10-50% of the body's vitamin D levels are obtained through dietary intake with the remainder being produced in the skin (219,220). Vitamin D deficiency has been associated with the increased risk of cancer, obesity, osteoporosis, infectious and immune-mediated diseases, and cardiovascular disease (221). It may also be involved with the onset of type 2 diabetes and impaired glucose metabolism. However, study results have been inconsistent. A large prospective case-control study found that dietary vitamin D intake was not significantly associated with the incidence of type 2 diabetes (222). The Nurses' Health Study found that there was no significant association between dietary vitamin D intake and type 2 diabetes (223). However, a significant inverse relationship was observed between vitamin D supplementation and incident diabetes in women who consumed ≥400UI/day of supplemental vitamin D (223). These women had a 13% lower risk of

developing diabetes, compared with those who consumed ≤100UI/day of supplemental vitamin D (223). A randomised controlled trial by Mitri et al. found that short-term cholecalciferol supplementation (2000 IU/day for 16 weeks), with or without calcium supplementation, improved β-cell function (as determined by a disposition index), insulin secretion, and attenuated the rise of HbA1c levels in adults at risk of type 2 diabetes (224). In contrast, Gagnon et al. found that daily supplementation of 2000-6000 IU/day of cholecalciferol and calcium for six months resulted in no significant effect on insulin sensitivity (as determined by HOMA-S and Matsuda index), insulin secretion (as determined by insulinogenic index and C-peptide), and β-cell function (as determined by a disposition index), despite a significant increase in circulating 25(OH)D (225). A study of prediabetic individuals with vitamin D deficiency showed that 1200 IU/d of cholecalciferol and 500mg of calcium for 16 weeks significantly increased mean serum 25(OH)D levels compared with the placebo. However, these did not improve insulin sensitivity (as determined by Stumvoll index and HOMA-IR), β-cell function (as determined by insulinogenic index), HbA1c, fasting glucose, or glucose tolerance (226). The effect of long-term vitamin D supplementation (2000IU/week for five years) also has shown no significant effect on glucose metabolism or insulin resistance (227). Therefore, evidence suggests that intake of vitamin D (either dietary or supplemental) has a limited effect on type 2 diabetes, glucose metabolism, and insulin resistance, irrespective of dosage or period of supplementation. Circulating vitamin D levels (25(OH)D) have been found to have an inverse association with the risk of type 2 diabetes in a meta-analysis of prospective studies (228). Baseline serum 25(OH)D ≥50nmol/L was significantly associated with decreased risk of type 2 diabetes (228). Results from Gao et al. also showed that circulating 25(OH)D had a positive association with insulin sensitivity (as determined by Matsuda index), a negative association with insulin resistance (as determined by HOMA-IR), and β-cell function (as determined by disposition index) in women (but not men) with newly diagnosed type 2 diabetes (229).

The present study was the first to investigate the associations between habitual vitamin D intake and markers of glucose metabolism in individuals after an attack of AP. No significant associations were observed between dietary vitamin D intake and FPG, HOMA-IR, or HOMA-β. These results are consistent with evidence from other disease states, suggesting that vitamin D intake has little effect on diabetes risk and insulin traits; however, circulating serum vitamin D levels may indicate risk of NODAP. Sunlight exposure is the primary determinant of circulating 25(OH)D and overall vitamin D status; therefore, dietary intake may not reflect

overall vitamin D status (219,220). Vitamin D levels of AP patients have been found to be insufficient, deficient, or severely deficient in up to 40% of AP patients during hospital admission (230). Serum 25(OH)D levels also decreased within the first two days of hospital admission (230). Similarly, the prevalence of vitamin D insufficiency and deficiency was 28.5% and 56.2% in patients with AP, increasing AP severity and risk of admission to the ICU (231). Emerging evidence also demonstrates the perpetuation of low-grade inflammation long after the initial AP attack (228,232). Therefore, the inflammatory state of AP may influence long term fat-soluble vitamin status and may be associated with altered insulin traits. It is suggested that upregulation 1a-hydroxylase alters the synthesis of 1,25(OH)D by macrophages and tumour necrosis factor-α during inflammation, thus depleting the reservoir of 25(OH)D (230,233). Therefore, further investigations on circulating vitamin D status and NODAP are warranted.

4.4.2 Water-Soluble Vitamins

Water-soluble vitamins are a group of structurally dissimilar, hydrophilic, organic compounds that include B vitamins and vitamin C (183,234). Most water-soluble vitamins are easily absorbed across the brush border membrane in the aqueous environment of the intestinal lumen due to their hydrophilic nature. This allows these vitamins to passively diffuse across the concentration gradient into the bloodstream (183). Once absorbed, these vitamins are transported to target organs and tissues. Humans have evolutionarily lost the ability to endogenously synthesise most water-soluble vitamins (except for vitamin B3, which can be synthesised by gut bacteria in small quantities) (235,236). Therefore, these vitamins must be obtained via dietary intake (234). Water-soluble vitamins are not stored in large quantities throughout the body and are readily excreted through urine (183). Therefore, short periods of inadequate water-soluble vitamin intake increases risk of vitamin deficiency (237). Several potential causes of B vitamin deficiency include inadequate intake, increased requirements, malabsorption, drug-nutrient interactions, and genetic disorders or medical conditions (238).

Vitamin B3, also known as niacin, plays a role in energy metabolism, redox reactions, and reduce oxidative stress (239,240). Dietary vitamin B3 is primarily in the form of nicotinic acid and nicotinamide; however, some foods may contain small amounts of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) (241). Nicotinamide can also be derived from the amino acid tryptophan, thus foods high in tryptophan are also considered sources of vitamin B3 (241). Vitamin B3 has a broad spectrum

of biological functions including serving as cofactors for redox reactions, a substrate for enzymes, and a ligand for purine receptors (241). Vitamin B3 also inhibits the production of the pro-inflammatory cytokines (hence, reducing inflammation) (236,242). Studies investigating associations between dietary intake of vitamin B3 and diabetes and insulin traits are scarce, with inconsistent results. Eshak et al. observed an inverse relationship between vitamin B3 intake and diabetes in men and women; however, this association was non-significant after adjusting for alcohol intake and magnesium intake (194). A study by Mancini et al. observed that dietary patterns with a positive loading for vitamin B3 and magnesium reduced the risk of developing type 2 diabetes, concluding that intakes high in vitamin B3 and magnesium may have a protective effect against type 2 diabetes when consumed together (95). Niacin therapy has also been investigated in individuals with type 2 diabetes. It was shown that ≤2.5g/day of niacin, alone or combined with statins, was effective in reducing cardiovascular events in those with diabetes (243). Glycaemic control in the study cohort was mildly impaired with an increase in fasting glucose by up to 5% and a 0.3% increase in HbA1c. However, these results were transient and reversible with adjustments to oral hypoglycaemic regimes (243). More recent studies have also suggested that niacin treatment has a more significant effect on glucose levels in individuals with diabetes and may increase the risk of developing diabetes. A meta-analysis of randomised controlled trials found a 34% increase in the risk of developing diabetes in individuals who received niacin therapy (244). Consistent results were observed in the HPS2-THRIVE study, with a 55% increase in significant disturbances in glycaemic control for individuals with diabetes taking extended-release niacin, compared with the placebo group (245). Additionally, those in the treatment group also had a 32% proportional increase in the diagnosis of diabetes compared with the placebo group (245). Overall, evidence suggests that dietary intake of vitamin B3 may have limited effects on type 2 diabetes, particularly in women. The use of niacin therapy and pharmacological doses of vitamin B3 appears to negatively impact glycaemic control.

The present study found that reduced dietary intake of vitamin B3 was significantly directly associated with HOMA-β. Specifically, with every 1% decrease in vitamin B3 intake, HOMA-β decreased by 1.35% in individuals with NODAP. Therefore, it appears that insulin secretion may be improved by increased vitamin B3 intake of individuals with NODAP. However, the mechanisms behind the observed results are unclear. Vitamin B3 (specifically nicotinic acid) is well known for regulating dyslipidaemia and its beneficial effects on cardiovascular disease risk factors (241,246–248). These effects are mediated by agonistic action of nicotinic acid on

nicotinic acid G-protein-coupled pathway receptor (GPR109a) (241). In adipocytes, activation of GPR109a suppresses the release of free fatty acids from adipose tissue, reducing free fatty acid flux to the liver, hence reducing the synthesis of triglyceride and VLDL production by substrate depletion (242). It is not yet clear whether the observed derangements in glycaemic control with high dose niacin therapy is a side effect of increased GRP109a activation; however, use of low dose niacin therapy and dietary intake of vitamin B3 appear to not impact glucose homeostasis (241,249,250). Chronically elevated lipid and lipoprotein profiles are associated with glucose intolerance, insulin resistance, and the onset of type 2 diabetes by inhibiting insulin-mediated glucose transporters in skeletal muscle (251–254). Therefore, there may be a link between the GPR109a receptor, improved lipid homeostasis, and improved insulin secretion, although further investigations are required to validate this hypothesis. A previous study by the COSMOS group observed associations between lipid metabolism and individuals with chronic hyperglycaemia after AP (29). In that study, chronic hyperglycaemia was significantly associated with elevated serum triglyceride and glycerol levels, consistent with individuals with type 2 diabetes, yet not free fatty acids or apolipoprotein-B levels. The study also found that insulin and HOMA-IR were associated with lipid metabolism in patients after AP (29). These results highlight the abnormal lipid profile of patients with chronic hyperglycaemia after an attack of AP and suggest that there may be a potential role for triglyceride-lowering pharmacotherapy in reducing the risk of NODAP (29). Dietary vitamin B3 may improve insulin secretion and abnormal lipid profile of individuals after AP, reducing the risk of NODAP. However, pharmacological doses of vitamin B3 may have detrimental effects on glycaemic control in individuals with (245) and without diabetes (244,245). Therefore, well-designed clinical studies are warranted to investigate these associations in people after an attack of AP.

4.4.3 Limitations

There are several limitations to consider within the present study. First, a self-administered FFQ was used to ascertain long-term habitual intake of vitamins. Therefore, the possibility of recall bias cannot be discounted due to requiring the respondent to recall their diet retrospectively. Additionally, intentional or accidental over- or under-reporting of portion sizes and/or food frequency may also impact the accuracy of data (255). However, the EPIC-Norfolk FFQ has been extensively validated in various populations, providing a more accurate representation of long-term vitamin intake compared with other dietary assessment methods

(76,178). Second, due to limitations of the EPIC-Norfolk FFQ and FETA software, intake of vitamin K and other vitamers and supplement intake were not able to be assessed (76). Future studies should consider investigating other vitamins and vitamers in individuals after AP. Third, it is possible that dietary changes were made after an attack of AP, altering participant nutrient intake. However, FFQ data were collected an average of 26 months post-AP attack and are representative of a participant's habitual intake of the past 12 months; therefore, data collected reflected vitamin intake after an attack of AP. Additionally, participants were not provided nutrition advice or encouraged to change their diet. Forth, vitamins/vitamers were investigated in isolation. Therefore, interactions between vitamins and other dietary confounders were not assessed. It is well known that nutrients and other dietary factors influence the bioavailability and absorption of other vitamins and impact glycaemic control and insulin traits (256–258). However, due to this study's relatively small sample size, accounting for each of these covariates would result in the overfitting of statistical models. Therefore, the use of average daily energy intake was used as a single covariate to account for most other dietary variables, along with other covariates (age, sex, V/S fat volume ratio, smoking status, alcohol intake, aetiology of AP, number of AP episodes, cholecystectomy, use of antidiabetic medications). The V/S fat volume ratio was also used instead of more commonly used markers of adiposity (BMI and waist circumference), as it is a more comprehensive measure of abdominal adiposity and metabolic risk (181,259). It is also worth noting that the use of hypoglycaemic agents was exclusive to the T2DM group and could affect results. Therefore, antidiabetic medications were included in statistical models. This study also did not assess other possible confounders (e.g., inflammatory markers, intra-pancreatic fat deposition), which may affect glucose metabolism and insulin traits following AP (84,260–264). They should be addressed in future research. Fifth, habitual vitamin intake was assessed in this study, which is not necessarily reflective of vitamin status, particularly in a population that may be prone to malabsorption (such as NODAP) (40). The vitamin status of an individual may affect insulin traits and glycaemic control; therefore, future studies should investigate vitamin levels in a post-pancreatitis population using more advanced assessment methods. Sixth, the hyperinsulinaemic-euglycaemic glucose clamp, the ‘gold standard’ for assessment of insulin traits, was not used in this study (265). Future studies may consider using this method in exploring the associations between vitamin intake and glucose metabolism after an attack of AP. Last, as this study had a cross-sectional design, a causal relationship between vitamin intake and NODAP cannot be established. However, in the first study investigating associations between vitamin intake and NODAP, we have provided insights that may assist the design of

future prospective, longitudinal studies of habitual vitamin intake in individuals after an attack of AP.

4.5 Chapter Summary

Of the 14 water-soluble and fat-soluble vitamins and vitamers investigated in the present study, intake of vitamin B6 was significantly altered in people with NODAP and T2DM group compared with the NAP group. Habitual intake of α-carotene, β-carotene, total carotenoids, and vitamin B3 were significantly directly associated with HOMA-β. The findings provide first evidence that intake of these vitamins/vitamers may have a role in NODAP. Longitudinal cohort and randomised controlled trials are now warranted to investigate causal relationships between these vitamins and NODAP as well as to uncover the mechanisms behind these associations, providing further evidence for nutrition interventions for individuals after an attack of AP.

EPILOGUE

There are few clinical studies investigating the effect of nutrition for those after an attack of AP. Dietary intake has been linked to the risk of metabolic diseases, including type 2 diabetes and metabolic syndrome. Previous studies have suggested the intake of vitamins and minerals to have a role in the onset of these metabolic disorders due to their roles in various metabolic pathways. There have been no investigations of micronutrient intake in individuals after AP. With this gap in evidence, this thesis had a primary aim to investigate the associations of habitual micronutrient intake and NODAP.

Chapter 3 investigated the associations of habitual mineral intake in individuals after AP (aim 1). Associations between habitual mineral intake and glycaemic status after AP were assessed (aim 1.1). Additionally, relationships between dietary intake of minerals and markers of glucose metabolism (aim 1.2) and insulin traits (aim 1.3) in individuals after AP were also assessed. Results showed that mean dietary intake of iron, nitrogen, phosphorous, and zinc were significantly altered in individuals with NODAP. Individuals with NODAP also had significant inverse associations between intake of manganese and both HbA1c and FPG and intake of iron and HOMA-S. Iodine intake was significantly directly associated with HbA1c levels, whereas selenium intake was significantly inversely associated with HOMA-S in the NODAP group. These findings suggest that adequate intake of manganese may be beneficial for those after an attack of AP, while required intake of iron, iodine and selenium may be altered.

Habitual vitamin/vitamer intakes in individuals after AP were also investigated and presented in Chapter 4 (aim 2). Associations between habitual vitamin/vitamer intake and glycaemic status after AP were investigated, with mean intake of vitamin B6 being significantly altered in the NODAP group compared with the NAP group (aim 2.1). The key findings of this chapter provide evidence that fat- and water-soluble vitamin/vitamer intake may have a role in NODAP (aims 2.2 and 2.3); habitual intake of fat-soluble vitamers α-carotene, β-carotene, and total carotene were observed to have significant direct associations with HOMA-β in the NODAP group. Additionally, results showed a significant direct association between vitamin B3 and HOMA-β in individuals with NODAP. These findings suggest that increased intake of α-carotene, β-carotene, total carotenoids, and vitamin B3 may benefit insulin secretion in individuals with NODAP.

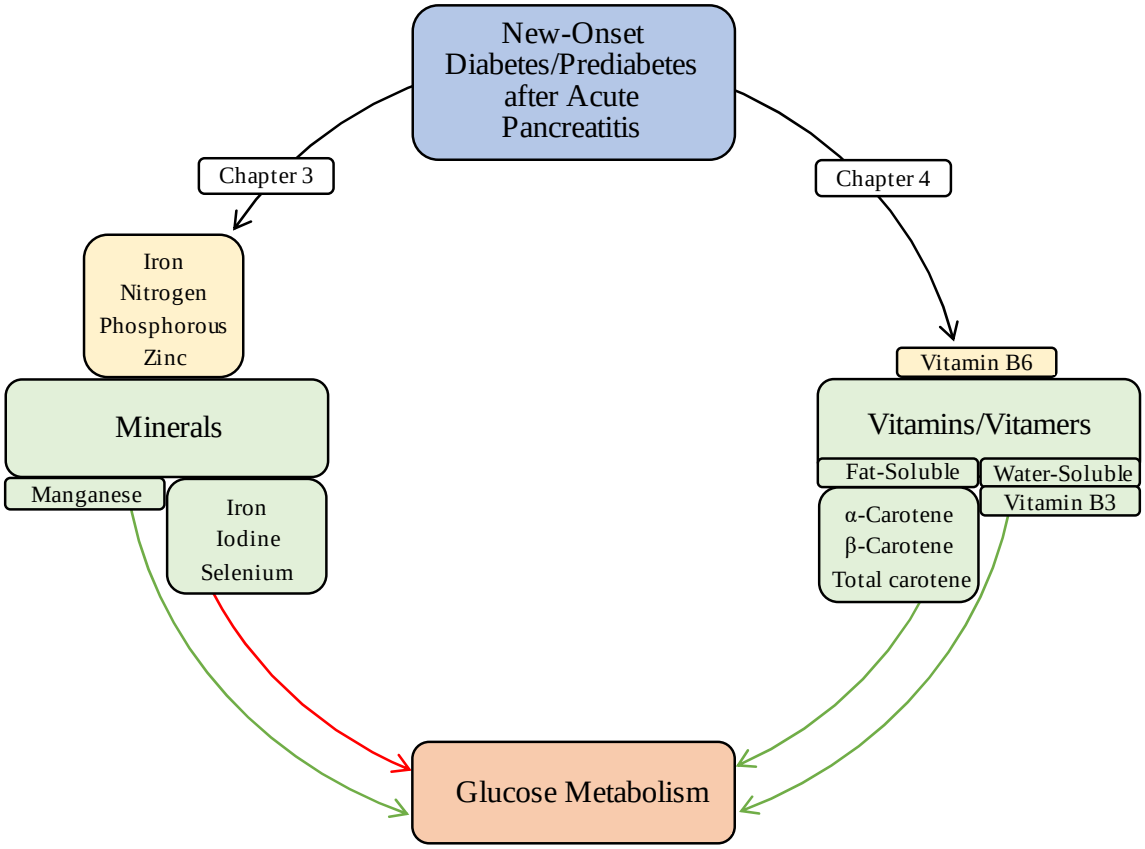

Figure 5.1 Summary of Associations between Micronutrients and Glucose Metabolism in Individuals with New-Onset Prediabetes/Diabetes
Key: Blue box = glycaemic status; green box = habitual micronutrient intake; yellow box = significantly altered intake compared with reference group; orange box = markers of glucose metabolism and insulin traits; arrow = significant association observed in this thesis; red = potential detrimental effect; green = potential beneficial effect.

The findings of Chapters 3 and 4 provide novel insights and the first evidence that intake of these micronutrients may have a role in NODAP, as shown in Figure 5.1. To date, there are no nutrition management guidelines for those at risk of or with. NODAP, with these individuals typically receiving a generalised type 2 diabetes advice. As discussed in Chapters 1, 3, and 4, studies from the COSMOS group have determined distinct differences in pathology, glycaemic response, and risk of complications between type 2 diabetes and NODAP. It is plausible that nutrition management may differ in effectiveness in individuals with different subtypes of diabetes; thus, highlighting the need for specific, evidence-based nutrition guidelines for those after AP and the possible role of dietitians in their management.

The findings of this thesis have identified new areas requiring further investigation. Due to the cross-sectional study design of studies in this thesis, no causal relationships can be inferred between the investigated micronutrients and NODAP. Purpose-built longitudinal cohort and

randomised controlled trials are now warranted to determine the causality of these associations and provide evidence for the nutritional management of individuals at risk of NODAP. Future randomised controlled trials may consider the use of supplementation or micronutrient-specific diets to determine causal relationships between micronutrients and glucose metabolism in individuals after AP. Alternatively, clinical biomarkers (serum, whole blood, urine, hair, and, nails testing) could be used to determine circulating micronutrient levels to give a more accurate representation of micronutrient status and identify individuals after AP as nutrient deficient, sufficient, or excessive. More comprehensive measures of glucose metabolism (e.g. the hyperinsulinaemic-euglycaemic glucose clamp) could be considered.

This thesis has provided preliminary evidence that habitual intake of micronutrients has a notable association on regulating glucose metabolism in those with NODAP. This indicates that nutrition management may be beneficial for individuals after AP to reduce the risk of developing NODAP. Therefore, it would be worthwhile to develop specific dietary guidelines for NODAP when future robust longitudinal studies and randomised controlled trials in post-pancreatitis settings are conducted.

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