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Stress Hyperglycaemia in the Acute Care Setting

A Thesis Submitted to Imperial College London for the Degree of Doctor of Philosophy

by

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Abstract

Introduction

Stress hyperglycaemia (SH), defined as transient hyperglycaemia during illness, is seen in up to 50% of inpatients and may progress to glucose intolerance in a significant proportion. SH is also associated with increased mortality. Despite this, there is no consensus on definition and management. Existing work focuses on single disease groups, frequently reporting adverse outcomes and variable success with therapies. There is, however, a scarcity of work profiling individuals with SH in detail. It is hoped that this approach may contribute to individualised management and improved outcomes for people with the condition.

Methods

The central hypotheses of this work focus on metabolic profiling and were examined through a prospective observational study. Participants were allocated into study groups based on glucose levels. A 30-day follow-up was organised for people with SH. Novel biomarkers, tools and a diabetes risk calculator were employed to provide the most detailed profile currently available of individuals with stress hyperglycaemia. Finally, results from the first multicentre trial to bear on the effect of metformin in SH are presented.

Results

The prevalence of SH was 34% and 31% in prospective (n=62) and metformin (n=52) studies respectively. People with SH had lower fasting insulin levels and insulin resistance. Otherwise, few differences were found. Metabolic profile, glycaemic variability, and HbA1c values were similar in both groups. Metabolic abnormalities and marked glycaemic excursions were also seen in both groups. Metformin was well tolerated but did not result in significantly reduced glucose variability or levels during the study period.

Conclusions

People with SH do not appear to be phenotypically different from people without the condition. Marked hyper- and hypoglycaemia are common in hospital patients despite apparent normal glucose levels. Increased vigilance as well as timely and appropriate interventions could significantly improve outcomes for these individuals.

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Abbreviations

AAU	Acute Assessment Unit
AC	Alternating Current
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AMU	Acute Medical Unit
ASA	American Stroke Association
BFD	Biochemical Features of Diabetes
BGL	Blood Glucose Levels
BIVA	Bioelectrical Impedance Vector Analysis
BM	Boehringer Mannheim
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BP	Blood Pressure
BRAMS	Brazilian Metabolic Syndrome Study
BTS	British Thoracic Society
βhCG	Human Chorionic Gonadotropin
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CBG	Capillary Blood Glucose
CE	Conformité Européene
CEWS	Chelsea Early Warning Score
CG	Clinical Guideline
CGM	Continuous Glucose Monitor/Monitoring
CGMS	Continuous Glucose Monitoring System
CI	Chief Investigator
CLAHRC	Collaborations for Leadership in Applied Health Research and Care
COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
CREATE-ECLA	The Clinical Trial of MEtabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica
CRF	Case Report Form
CRP	C-Reactive Protein
DCCT	The Diabetes Control and Complications Trial
DBP	Diastolic Blood Pressure
d.f.	Degrees of Freedom
DIGAMI/2	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FDA	Food and Drug Administration
F/up	Follow-up

GCP	Good Clinical Practice
GE	Greater or Equal to
GI	Gastrointestinal
GIH	Glucocorticoid-Induced Hyperglycaemia
GREAT2DO	Graded Resistance Exercise And Type 2 Diabetes in Older adults
GUARD	Glucose on Unselected Admissions and Risk of Diabetes
HAD	Hospital Anxiety and Depression
HbA1c	Glycated Haemoglobin
HI-5	Intensive Insulin In Infarction
HOMA2	Homeostatic Model Assessment
(HOMA2) %B	Estimated steady state beta cell function
(HOMA2) %S	Estimated insulin sensitivity
HOMA2-IR	Homeostatic Model Assessment Insulin Resistance
HPA	Hypothalamic-Pituitary-Adrenal Axis
HRD	High Risk for Diabetes
HTN	Hypertension
IBM	International Business Machines
ICD	International Classification of Diseases
ID	Identifier
IDF	International Diabetes Federation
IFCC	International Federation of Clinical Chemistry
IFG	Impaired Fasting Glycaemia
IGR	Impaired Glucose Regulation
IGT	Impaired Glucose Tolerance
IL-1	Interleukin-1
IMP	Investigational Medicinal Product
IR	Insulin Resistance
IRAS	Integrated Research Application System
ITU	Intensive Care Unit
LFT	Liver Function Tests
LOS	Length of stay
LT	Less Than
MA	Metabolic Abnormality (including IFG, IGT, high risk HbA1c)
Max	Maximum
MHRA	Medicines and Healthcare Products Regulatory Agency
Min	Minimum
MUST	Malnutrition Universal Screening Tool
N	Number
N/A	Not Applicable
NASH	Non-alcoholic Steatohepatitis
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
NSTEMI	Non ST-Elevation Myocardial Infarction
OGTT	Oral Glucose Tolerance Test
One-way ANOVA	One-way Analysis of Variance
PhD	Doctor of Philosophy

PI	Principal Investigator
PMH	Past Medical History
proADM	Proadrenomedullin
R&D	Research and Development
RCT	Randomised Controlled Trial
Rheum	Rheumatological
RPG	Random Plasma Glucose
rpm	Revolutions Per Minute
SBP	Systolic Blood Pressure
SD/Std Deviation	Standard Deviation
SDSG	Standard Deviation of Sensor Glucose
SG	Sensor Glucose
SH	Stress Hyperglycaemia
Sig.	Significance
SNK	Student-Newman-Keuls
SPSS	Statistical Package for the Social Sciences
STEMI	ST Elevation Myocardial Infarction
TGC	Tight Glycaemic Control
TNF- α	Tumour Necrosis Factor-α
Tukey's-HSD	Tukey's Honestly Significant Difference
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UO	Urine Output
WHO	World Health Organisation
Yrs.	Years

Table 1: Table of abbreviations used throughout thesis 'Stress Hyperglycaemia in the Acute Care Setting'

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participants who generously donated their time and energy despite the many challenges of hospitalisation.

I dedicate this thesis to my family, especially Ben, Lily and BZ.. 'A la la'.

‘The investigator should have a robust faith –and yet not believe.’

Claude Bernard, 1865

Declarations

Declaration of Originality

I declare that the work contained within this PhD thesis is my own and any other material is appropriately referenced.

Copyright Declaration

Publications & Presentations

Relevant Publications

- A Balasanthiran (Section editor for invited article), C Patterson, J Soong, T Woodcock, M Kaur, J Dixon, S Hancox, J Wolrich, J Reed, S Green, D Bell. A Beginner's Guide to Research. *Junior Dr Magazine* March 2012.

- A Balasanthiran, B Zalin, K Shotliff, EH Baker Hyperglycaemia in the Acute Care Setting (invited article). *Clinical Medicine* 2012;3:272

- J Soong, A Balasanthiran, D C MacLeod, D Bell. National Survey of Patients With AF in the Acute Medical Unit. *A Day in the Life Survey*. *Br J Cardiol*. 2013;20(3):106

- A Balasanthiran, K Shotliff, The History of Stress Hyperglycaemia. *Journal of the Royal College of Physicians Edinburgh*, Article in Press 2015

  NB: Maiden name 'Balasanthiran'

Relevant Posters

Poster Title (Abbreviated)	**Meeting**
Stress Hyperglycaemia in Acute Care	Society of Acute Medicine, ABCD 2012
National Survey of AF	Society of Acute Medicine, 2012 Quality and Safety in Healthcare 2013
Hydration & Nutrition on the AMU	Society of Acute Medicine, 2012
Diabetes Research & Self-Care	Diabetes UK 2013
Prevalence of Hyperglycaemia in the AMU	Society of Acute Medicine, 2013

Table 2: Posters related to PhD research with presentation dates and meeting description

Relevant Presentations

Research findings presented at the Society of Acute Medicine International research meeting in Oct 2012 and at the NIHR Northwest London team meeting in Dec 2014.

Chapter 1: Introduction

1.1 The History of Stress Hyperglycaemia

(Section 1.1 reproduced with kind permission from the Journal of the Royal College of Physicians Edinburgh, Article in Press)

Stress hyperglycaemia, defined as 'transient hyperglycaemia during illness' (Dungan, Braithwaite, & Preiser, 2009), is a common condition (Umpierrez et al., 2002). Hyperglycaemia typically resolves as the illness dissipates, although in a proportion of people, it may indicate unrecognised diabetes mellitus (Husband, Alberti, & Julian, 1983).

A number of studies have shown that stress hyperglycaemia is associated with poor outcomes across a wide range of conditions. (Baker et al., 2006; Capes, Hunt, Malmberg, & Gerstein, 2000; Umpierrez et al., 2002) Despite this, best management of the condition is unclear and remains the subject of active research.

This article explores views on hyperglycaemia, stress and disease as they emerge in antiquity and evolve through to the current day. The story incorporates aspects from the modern fields of biochemistry, mechanics, physiology and medicine.

A glimpse into the history of this intriguing condition provides insights into the evolution of major themes in medicine such as homeostasis, as well as the challenges involved in converting research, even conducted by the world's most eminent thinkers, into direct patient benefit. The staggered accumulation of knowledge described is perhaps not surprising given the diversity of research conducted and the substantial clinical concepts involved.

The first written descriptions relating to the symptoms of hyperglycaemia appear to have been found in the Ebers Papyrus, an ancient Egyptian text relating to the practice of

medicine, written about 1550BCE. In ancient Greece, Hippocrates, 'the father of medicine' described polyuria and wasting of the body. His disciple Aretaeus of Cappadocia, a Greek physician, was the first to use the term 'diabetes', derived from the Greek word for 'siphon' in relation to these symptoms (Sanders, 2002; Tattersall, 2009).

In parallel, concepts relating to homeostasis, stress and disease were beginning to emerge. Ancient Greeks such as Heraclitus (540-480BC) and Empedocles (495-435 BC) used terms such as balance and equilibrium to define the basic characteristics of life; the emerging view being that the ability to change or react to threatening forces was pivotal in restoring harmony and enabling survival of the organism. Hippocrates elaborated further by describing health as harmony and disease as disharmony (Le Moal, 2007).

It took until the 17th century for the clinical features of diabetes and glycosuria to be well documented. A variety of clinicians across the globe had described the urine of polyuric patients as sweet, honey-tasting and attractive to flies and ants. (MacFarlane, 1990; Tattersall, 2009). Despite this, it was some time before hyperglycaemia was identified.

In Europe, Thomas Willis (1621-75), who studied medicine at Oxford, referred to diabetes as the 'pissing evil'(Feudtner, 2003) but also went a step further to suggest that the condition was primarily a disease of the blood (Sanders, 2002).

Matthew Dobson (1734-1784) advanced understanding further by experimenting on the urine and blood of Peter Dickonson, a 33 year old man with symptoms of uncontrolled diabetes (Tattersall, 2009). As well as confirming that his urine contained a substance indistinguishable from sugar, (Sanders, 2002) he also identified that the blood serum was sweet to taste. Following further experimentation, he concluded that diabetic urine always contains sugar which is not formed in the kidney as previously thought but, 'existed in the

serum of the blood' (Tattersall, 2009). This important observation, obvious as it may seem now, paved the way for the modern understanding of diabetes and hyperglycaemia.

Particularly important here, as is typical of this narrative and many others in medicine, the flow of knowledge was staggered. Dobson published his research in the journal of a London medical society with a handful of members who 'met on alternate Monday evenings at the Mitre Tavern in Fleet street' and the findings were debated for some time (MacFarlane, 1990). Despite this, Dobson's discovery was, amongst many things, pivotal in the progress of diagnostics for hyperglycaemia.

1.1.1 The 19th Century

Major developments in the concept of stress hyperglycaemia occurred during the 19th century with the beginning of the experimental period in diabetes and work defining modern medical views of stress conducted by Claude Bernard[FIG1] (1813-1878) and Walter Cannon (1871-1945).

Bernard is often described as the greatest physiologist of his time and founder of experimental medicine. He was born in 1813 in the village of Saint-Julien in France (Wilson, 1914) and originally pursued a career in literature. Having been dissuaded from this course by a literary critic (Gross, 1998), he eventually trained in medicine instead. When he died, his distinguished contribution to the field accorded him a public funeral – an honour that France had never before bestowed on a man of science (Wilson, 1914).

Figure 1: *'The investigator should have a robust faith - and yet not believe', Claude Bernard (PD-1923)- published before 1923 and public domain in the US*

Early in his career as a medical student, Bernard developed respect for clinicians such as François Magendie, (Gross, 1998; Wilson, 1914) who cultivated his interest in nutrition, and Pierre Rayer (Theodorides, 1968) who had a particular expertise in diabetes. It is perhaps these influences, which encouraged Bernard closely to scrutinise glucose metabolism. His discovery, that gastric juices were capable of digesting cane sugar and starch into glucose, was eventually to form part of his thesis (Young, 1957).

Some 5 years later in 1848 he expanded his research into this field, developing a particular interest in the distribution of glucose through the body. He was intrigued to detect glucose in the blood of fasting humans and concluded, through rigorous experimentation and careful deduction that the liver was capable of synthesising glucose, even in fasting humans (Tattersall, 2009). He named the substance responsible for this 'glycogene' (Wilson, 1914; Young, 1957).

That the liver was capable of synthesising glucose was a controversial observation, in direct opposition to two commonly held beliefs: the inability of animals to synthesise nutrients (Tattersall, 2009) and 'one-organ one-function'. In disproving both these theories, Bernard

set the scene for a new way of thinking which ultimately led to the discovery of further 'glands of internal secretion' and the definition of the modern endocrine system (Heilbron, 2003).

Bernard also contributed significantly to modern medical views on stress by appreciating that, whilst organisms are closely responsive to their external environment, they also strive to maintain a stable and independent internal environment or 'Milieu Interieur' (Gross, 1998). This was encapsulated in his statement, 'constancy and stability of the internal environment is the condition that life should be free and independent' (M. Jackson, 2013; Le Moal, 2007). Applying these principles to medicine, Bernard was the first to report data relating to hyperglycaemia in critically ill patients in 1855 (Bernard, 1855).

The other great 19th century master of this field was Walter Bradford Cannon[FIG2] who was born in Wisconsin in 1871 (Benison, Barger, & Wolfe, 1987), towards the end of Bernard's life. As Claude Bernard before him, he was credited with an open, enquiring mind and his lifetime achievements eventually led to him being recognised as one of the America's leading physiologists.

Figure 2*: Walter Bradford Canon, circa 1908, Image in public domain. Courtesy of the National Library of Medicine*

From an early age, Cannon displayed an interest in the biological sciences and absorbed himself in debates between traditionalists and Darwinists. He struggled with a conflict between his religious and scientific beliefs, eventually leading him to reject the ideals of his family's faith. He reports being challenged by the church following this decision; 'he wanted to know what right I had, as a mere youth, to set up my opinion against the opinion of great scholars' (Bhattacharyya, 2011).

Despite this early discouragement, Cannon went on to distinguish himself academically, and was accepted into Harvard medical school in 1896 (Brown & Fee, 2002). Here, he sought out opportunities for research and was enrolled by the professor of physiology to use x-rays, a new discovery, to explore the mechanism of swallowing (Brown & Fee, 2002; B. Cannon, 1994; Cooper, 2008). During the course of this research, an astute observation, that anxiety led to a change in stomach motility, piqued an interest in the relationship between emotion and physiology (M. Jackson, 2013). This culminated in the discovery that major emotions involve the excitation of the sympathetic nervous system, increased secretion of adrenaline and a collection of physiological changes, now recognised as the 'stress response' (Brown & Fee, 2002). Cannon coined the term 'fight or flight' in a 1915 publication (W. Cannon, 1920) to describe these changes.

1.1.2 The 20th Century

Some 20 years later, and with the benefit of a significant body of work measuring blood variables, Cannon expanded Bernard's concept of the milieu interieur to 'homeostasis' (Goldstein & Kopin, 2007; M. Jackson, 2013; Le Moal, 2007), a maintenance of physiological variables within acceptable, narrow ranges, rather than more precise fixed values (Cooper, 2008). Laying the foundations for modern understanding of stress hyperglycaemia, a section of Canon's successful 1932 publication, 'The Wisdom of the

Body' (W. Cannon, 1932) describes how a state of 'pseudo or sham rage' was induced through the abrupt cessation of anaesthesia in decorticate animals. In addition to the signs of sympathetic innervation associated with this stressful event, an increase in blood glucose to five times the normal percentage was observed.

During this period, Cannon's research programme grew considerably and by the end of his 36-year professorship at Harvard Medical School, he would work with over 400 graduate students and colleagues. He died 3 years after retirement, a major public and political figure, described by Ralph W Gerard, a fellow former president of the American Physiological Association, as 'the greatest American physiologist' (Brooks, Koizumi, & Pinkston, 1975).

The next important development originates from the world-renowned endocrinologist Hans Seyle who was born in Vienna in 1907. Seyle trained in medicine at the German University of Prague where he graduated first in his class. As a medical student, he noted a constellation of signs and symptoms common to sick patients, regardless of the disease and subsequently popularised the term 'stress' within this context, using it to describe the response of the body to a wide range of stressors (Goldstein & Kopin, 2007).

Following extensive research, he refined his observations to propose the 'General Adaptation Syndrome' (GAS), a description of three stages in the response to a stressor:

- The alarm reaction
- Stage of resistance
- Stage of exhaustion

As highlighted by the 'stage of exhaustion', Seyle concluded that, 'the ability of living organisms to adapt themselves to changes in their surroundings is a finite quality' (Seyle, 1951).

During this period, the term ‘adaptation’ was widely used in physiological, psychological and sociological literature. The English biologist Herbert Spencer (1820-1903) claimed that all ‘evil results from the non-adaptation of constitution to conditions’. Seyle himself appeared to shift his vocabulary around 1950 to ‘reconceptualise stress, referring to it not merely as an external trigger of internal processes but also as a physiological or pathological process itself’. It is thought that this shift in language from adaptation to stress may have been preferred by Seyle for various reasons, including that it positioned his work more closely to that of Walter Cannon, as well as those studying anxiety and illness in occupational settings where the term ‘stress’ was already popularised (M. Jackson, 2013).

A large amount of Seyle’s work is relevant to modern understanding of stress hyperglycaemia. Aside from popularising the term ‘stress’ within the medical vocabulary, he also described how physiological features of ‘defense’ to and ‘damage’ from stress may coexist, noting that ‘some of the hormones produced during stress have definitely toxic effects’. The key role of the hypothalamic-pituitary-adrenal (HPA) axis in orchestrating responses was also highlighted (Seyle, 1951).

Seyle dedicated most of his life to researching stress in medicine and by the time of his death in 1982, had left an incredible legacy of over 1700 papers and 39 books. His two major books *The Stress of Life* (1956) and *Stress Without Distress* (1974) sold millions of copies worldwide.

The early 20th century also saw an increasing number of reports reporting hyperglycaemia to extreme stressors such as asphyxia (Kellaway, 1919) and pontine decerebration (Forster, 1933). Amongst other things, these early experiments highlighted the importance of counter-regulatory hormones such as epinephrine and hepatic gluconeogenesis in such scenarios.

During this period, various terminologies that could be considered precursors to the modern term 'stress hyperglycaemia' began to emerge (Figure 3). In these cases, hyperglycaemia was often precipitated during animal experimentation through the use of various stressors (De Bodo, Bloch, & Gross, 1942; Mylon, Cashman, & Winternitz, 1944).

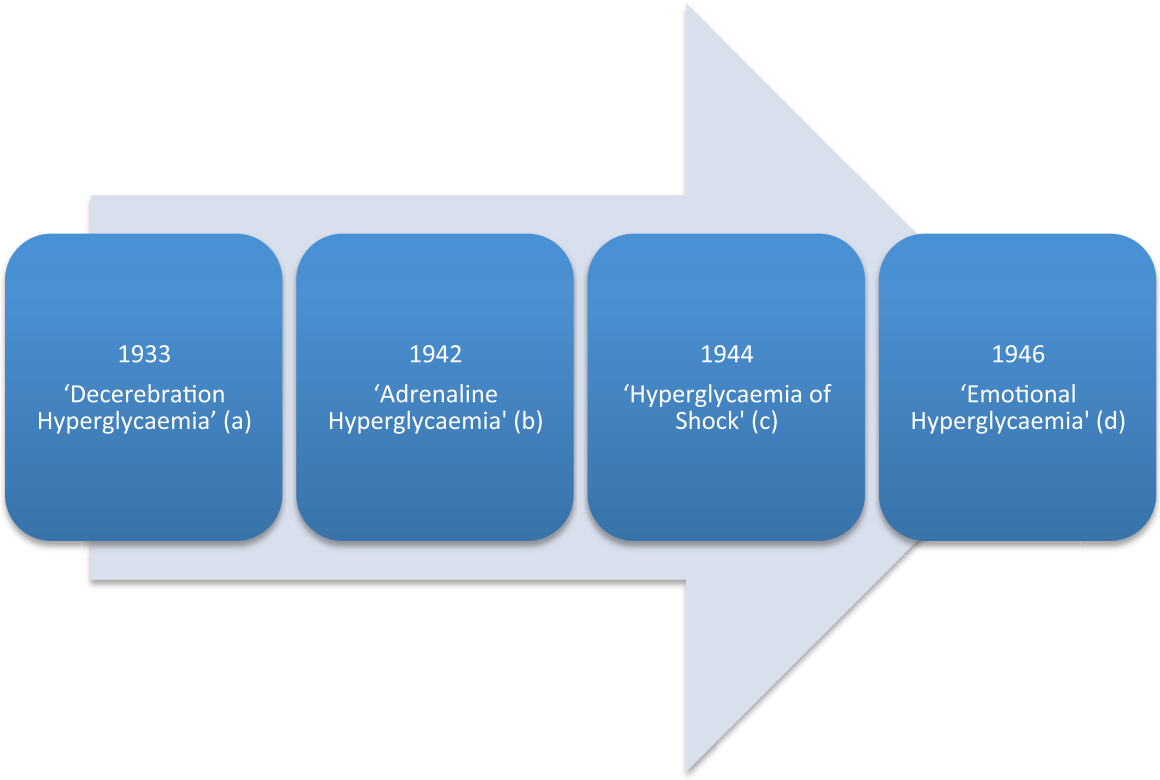


Figure 3: Various precursors to the term 'Stress Hyperglycaemia'. References: a-(Forster, 1933) **b-**(De Bodo et al., 1942) **c-**(Mylon et al., 1944)**, d-**(Mirsky, 1946)

As described earlier, Claude Bernard was the first to report stress hyperglycaemia in association with an acute human illness (Bernard, 1855). An American physician and Professor, Franklin McLean then published a paper in 1914 entitled 'The sugar content of the blood and its clinical significance'. Within this he described various cases of 'transitory hyperglycaemia and glycosuria' which he said 'are not to be regarded as diabetic symptoms' (McLean, 1914).

Eight years later, it was observed that 'coronary artery disease produces by itself a glycosuria that need not be indicative of diabetes' (Levine, 1922). This was followed by a number of publications reporting 'transient glycosuria' in association with coronary thrombosis (Cruickshank, 1931; Eckerstrom, 1951; Levine, 1922; Raab, 1936). In one case, 12 patients were followed up 10 years after their coronary event and found to have normal glucose tolerance curves (Eckerstrom, 1951).

Although the distinction was clearly made between this apparent 'transient glycosuria' syndrome and diabetes, it was another 25 years before the term 'stress hyperglycaemia' appeared in the title of a (PubMed) medical publication (Gitelson, 1956). In this paper, 26 patients with stress hyperglycaemia are described and a number of important observations, illustrative of 20th century knowledge into this condition, are made.

Firstly, a variety of acute illnesses including myocardial infarction and cerebral haemorrhage are mentioned in association with stress hyperglycaemia. Secondly, 'hyperglycaemia and glycosuria disappeared with clinical improvement', in all but 3 of these patients, within a few days of the acute episode. This statement is closely aligned to modern definitions of stress hyperglycaemia. Follow-up studies of this nature are now an established investigative tool in this condition. Thirdly, the 3 patients in whom hyperglycaemia did not resolve were described as 'latent diabetes that became manifest following the acute disorder'. This was also reported by other authors during this period (Datey & Nanda, 1967; Eckerstrom, 1951; Raab, 1936), and is now a well-recognised outcome. Finally, having previously reported raised pyruvic acid levels in association with emotional stress (Gitelson & Tiberin, 1952), the authors noted that levels are 'markedly elevated' in people with stress hyperglycaemia compared to those with diabetes.

Since this publication, other biomarkers have been examined in stress hyperglycaemia and reported for their ability to demonstrate a stress response or predict development of future diabetes (Carmen Wong et al., 2010).

Another important paper to emerge during this period (1951) was co-authored by Max Ellenburg, a former president of the American Diabetes Association. In this paper, '75 consecutive autopsied cases of coronary thromboses were studied and associations between hyperglycaemia, clinical course and histological findings were reported. Of note, people with stress hyperglycaemia (reported as 'nondiabetic cases with hyperglycaemia') suffered more profound shock and a 'stormier' clinical course (Ellenberg, Osserman, & Pollack, 1952).

Although it is now well recognised, this was one of the first papers to highlight links between stress hyperglycaemia and adverse clinical outcomes, reporting a higher incidence of conduction pathway defects and arrhythmias and an average survival of 6.3 days as compared to 20.3 days for those with normoglycaemia. Histological findings also indicated more extensive areas of infarct in the hyperglycaemic group as well as central liver cell necrosis.

Based on contemporary knowledge, largely gained through animal experimentation, the authors presented their 'crude picture' of the mechanisms leading to stress hyperglycaemia highlighting adrenaline-driven hepatic glycogenolysis and gluconeogenesis. In fact, gluconeogenesis was later recognised as one of the most important contributing factors to stress hyperglycaemia (Dungan et al., 2009).

Of interest, the authors also drew parallels between deteriorating diabetes and stress hyperglycaemia: 'the mechanism of increased severity of the diabetes in cases with coronary thrombosis is identical with the mechanism of hyperglycaemia in non-diabetics with coronary thrombosis'. Deteriorating glycaemic control in acutely unwell people with established

diabetes, now considered by some as a version of stress hyperglycaemia, is often under-recognised.

During this period, the term 'latent diabetes' began to emerge to describe individuals in whom evidence of impaired glucose tolerance only appeared with the administration of cortisone (Camerini-Dávalos & Cole, 2013; Fajans & Conn 1954). In addition to such provocation, a publication in 1970 suggested that 'stress situations' such as infection, pregnancy and obesity may also unmask latent diabetes (Camerini-Dávalos & Cole, 2013). In this context, it is suggested that 'stress' acts as a catalyst toward the development of 'overt diabetes'. Whilst the modern definition of stress hyperglycaemia refers to a 'transient' phenomenon, some research suggests that a proportion of those with SH go on to develop overt diabetes during follow-up (Dave et al., 2010; C. S. Gray, Scott, French, Alberti, & O'Connell, 2004).

Another important condition that came to light in parallel with SH was gestational diabetes (GDM). A transient diabetes, associated with pregnancy, was described as far back as 1882 (Duncan, 1882). Subsequent work demonstrated various similarities between GDM and SH: i) a clear association with adverse outcomes (Coustan, 2013; W. Jackson, 1952); ii) a propensity to develop diabetes in the years following pregnancy/period of stress (Damm, 2009; Sutherland & Stowers, 1984). SH and GDM differ, however, in that the latter has recognised definitions, endorsed by speciality societies, established screening procedures and well-rehearsed modes of treatment (Coustan, 2013). In addition, unlike SH, the pathophysiology of GDM was examined as far back as 1898 with dedicated experimentation (McCance, Maresh, & Sacks, 2013; J. W. Williams, 1909).

By the early 1970s, more information relating to the pathogenesis of SH had emerged. A paper investigating the metabolic response to myocardial infarction, described as a 'severe

trauma…an acute emotional stress' drew parallels between the hormonal changes found in this condition and other 'medical and surgical diseases' outlining:

- Increased plasma concentrations of ACTH and cortisol
- High levels of urinary adrenaline and noradrenaline
- Failure of response of plasma immunoreactive insulin to intravenous glucose
- Failure of rise in plasma insulin level in spite of stress hyperglycaemia (Opie, 1971)

Over the years, it has become recognised that this picture is considerably more complex (Dungan et al., 2009).

Other key articles of the 20th century examined clinical outcomes (Sewdarsen, Jialal, Vythilingum, Govender, & Rajput, 1987), prediction tools (Greci et al., 2003) and factors involved in the aetiology of stress hyperglycaemia (Yudkin & Oswald, 1987). Myocardial infarction was a major area of interest up to this point and a paper published in 2000 (Capes et al., 2000) identified 15 studies (1966-1998) suitable for inclusion into a meta-analysis. The findings consolidated earlier suspicions: people *without* diabetes and stress hyperglycaemia on admission for acute myocardial infarction are at increased risk of in-hospital mortality and congestive heart failure or cardiogenic shock. A number of mechanisms were proposed to explain this including:

- Relative insulin deficiency, increased lipolysis and excess circulating free fatty acids, toxic to ischaemic myocardium
- Osmotic diuresis leading to interference with normal compensatory mechanisms for failing left ventricle (increased end-diastolic volume leading to increased stroke volume)

Stress hyperglycaemia was also associated with an increased risk of mortality in people with diabetes although the effect was smaller than in those without diabetes.

Within this period, interest also grew in stress hyperglycaemia and stroke. From the mid 1970s, studies began to emerge reporting poor neurological outcomes and increased mortality in the context of hyperglycaemia (Melamed, 1976; Pulsinelli, Levy, Sigsbee, Scherer, & Plum, 1983; E. Woo, Chan, Yu, & Huang, 1988). Similar reports were published in the 90s (Kiers et al., 1992; O'Neill, Davies, Fullerton, & Bennett, 1991; Weir, Murray, Dyker, & Lees, 1997; J. Woo et al., 1990) and biomarker studies suggested a vital role for 'stress hormones' notably cortisol, in the intensity of hyperglycaemia as well as the overall outcome post-stroke (Murros, Fogelholm, Kettunen, & Vuorela, 1993). Other studies demonstrated elevated plasma catecholamine levels although no clear link with outcomes was reported (Myers, Norris, Hachniski, & Sole, 1981).

A high prevalence of hyperglycaemia, recognised and unrecognised in the period preceding stroke was also reported (Riddle & Hart, 1982). Finally, towards the end of the century, a small randomised controlled trial concluded that glucose-lowering therapy for mild to moderate hyperglycaemia (plasma glucose 7.0-17.0mmol/L) was a safe intervention in the acute phase of stroke (Scott et al., 1999).

1.1.3 The 21st Century

More recently, stress hyperglycaemia has been studied in a wide range of conditions including COPD (Baker et al., 2006), pneumonia (McAlister et al., 2005), stroke (Capes, Hunt, Malmberg, Pathak, & Gerstein, 2001), heart failure (Mebazaa et al., 2013) and sepsis (Leonidou et al., 2007). In almost all cases, adverse outcomes have been identified in association with stress hyperglycaemia. In response, further work has aimed to improve

outcomes through risk stratification and proactive management (G van den Berghe et al., 2001).

1.1.4 Hyperglycaemia in Intensive Care

Several studies suggest that people with stress hyperglycaemia have worse outcomes at a given degree of hyperglycaemia than people with diabetes (Dungan et al., 2009; Moritoki Egi et al., 2008; Rady, Johnson, Patel, Larson, & Helmers, 2005).

A landmark interventional study in 2001 randomly assigned 1548 patients on a surgical intensive care unit to either intensive insulin therapy (maintaining blood glucose 4.4-6.1mmol/L) or conventional treatment (maintaining blood glucose 10-11.1 mmol/L with infusion of insulin only if blood glucose rose to >11.9mmol/L). It was concluded that intensive insulin therapy reduced mortality (G van den Berghe et al., 2001).

Various studies following failed to reproduce this finding (Arabi et al., 2008; Greet Van den Berghe et al., 2006) and several meta-analyses (Griesdale et al., 2009; Wiener, Wiener, & Larson, 2008) concluded that tight glycaemic control was not associated with significantly reduced hospital mortality (Preiser, 2009). Included in the analysis was a large, international trial of 6104 intensive care patients which concluded that intensive glucose control actually *increased* mortality (Finfer et al., 2009).

A few studies specifically aimed to identify patients with stress hyperglycaemia in the intensive care setting. Of these, one found that a target glucose of 6.9mmol/L led to a significantly reduced mortality in patients with stress hyperglycaemia but *not* diabetes. In concordance with this, mortality began to rise when mean glucose was greater than 7.8mmol/L in patients without diabetes, compared to a higher threshold of 10mmol/L in people with diabetes (Krinsley, 2006).

Similar findings have been reported in other settings and disease states and various hypotheses have been suggested to explain this (Capes, Hunt, Malmberg, & Gerstein, 2000). In 2002 an American group studied a mixed population of general medical patients and grouped them according to blood glucose levels and medical history (normoglycaemia, new hyperglycaemia or pre-existing diabetes). When compared to those with normoglycaemia, mortality was significantly higher in those with 'new hyperglycaemia' compared to those with diabetes (Umpierrez et al., 2002).

1.1.5 Hyperglycaemia in Acute Myocardial Infarction

Recent work in cardiovascular disease supports findings of the earlier mentioned meta-analysis. In a large sample of elderly patients with acute myocardial infarction (AMI) it was found that higher glucose levels were associated with a greater risk of 30-day mortality in patients without diabetes compared to patients with diabetes (Kosiborod et al., 2005). Longer follow-up periods have, however, resulted in variable results (Ishihara et al., 2007; Petursson et al., 2007; Schiele et al., 2006).

In addition to previous hypotheses on mechanisms of harm, recent studies have concluded that stress hyperglycaemia is an independent predictor of left ventricular remodelling after anterior MI (Bauters et al., 2007) and may also contribute to arrhythmias (Sanjuán et al., 2011).

There has also been a recent focus on biomarkers and tools to predict the risk of stress hyperglycaemia, future diabetes and outcomes from intervention. For example, higher cortisol levels have been found to be predictive of the onset of stress hyperglycaemia (Bronisz et al., 2012) as well as of subsequent normalisation of blood glucose levels(Carmen Wong et al., 2010). In the case of the latter, it was suggested that higher cortisol levels reflect stress-precipitated hyperglycaemia whereas lower cortisol levels suggest 'underlying glucose

intolerance' as the most likely explanation for hyperglycaemia. Glycated haemoglobin (HbA1c) has also been studied with varying results. One study found that hyperglycaemia and non-elevated HbA1c was associated with a poor prognosis following AMI whereas another study did not find any association between mortality and HbA1c (Hadjadj et al., 2004).

A number of recent studies examine the role of insulin intervention in MI. This was first suggested as a treatment for AMI in the early 60s (Sodi-Pallares et al., 1962) and subsequent trials have examined effects on mortality (Malmberg et al., 1995). More recently, DIGAMI-2 (Malmberg et al., 2005), HI-5 (Cheung et al., 2006) and CREATE-ECLA (S. R. Mehta et al., 2005) studies did not find a benefit to this approach.

Future work may focus on the role of Glucagon-like peptide 1 (GLP-1) in the setting of AMI (Egom, 2012) as well as the role of percutaneous coronary intervention in the treatment and risk reduction of patients with stress hyperglycaemia and AMI (McGregor, Leech, Purcell, & Edwards, 2012).

1.1.6 Hyperglycaemia in Respiratory Disease

Another recent field of interest has been pulmonary disease. Stress hyperglycaemia is seen in up to 50% of patients hospitalised with exacerbations of chronic obstructive pulmonary disease (COPD) and each 1mmol/L increase in blood glucose has been shown to increase the absolute risk of death or prolonged hospital stay by 15% (Baker et al., 2006). Prospective studies are currently underway to determine whether blood glucose control can improve COPD exacerbation outcomes (see Chapter 5).

A similar picture has been identified with pneumonia. A study of 6891 adults (2003-9) reported hyperglycaemia in 40% of patients presenting with community acquired pneumonia

(CAP). Hyperglycaemia was found to be an independent predictor of 28-, 90- and 180- day mortality with increasing glucose levels corresponding to increased risk (Lepper et al., 2012). Of interest, a separate study identified an association between hyperglycaemia (in 'non-diabetic CAP patients'), a more pronounced inflammatory response and adverse clinical outcomes (Schuetz et al., 2014).

1.1.7 Hyperglycaemia in Stroke

More evidence is now available to demonstrate how hyperglycaemia and insulin resistance exacerbate brain injury and induce cell lysis (Lindsberg & Roine, 2004; Parsons et al., 2002; Shao & Bayraktutan, 2013).

The glucose profile of patients with post-stroke hyperglycaemia has also been investigated in more detail using continuous glucose monitoring. 'Early' hyperglycaemia (≥7.0mmol/L, 8 hours post-stroke) was reported in 50% of people without diabetes followed by a later hyperglycaemic phase in 27% at between 48-88 hours post-stroke (Allport et al., 2006).

Longer term outcomes were studied in a retrospective analysis of 433 patients and it was concluded that hyperglycaemia (>10.0 mmol/L) but not diabetes *per se* is an independent predictor of dependency 1 year post-stroke (Vibo, Kõrv, & Roose, 2007). As with myocardial infarction, further evidence accumulates to suggest that hyperglycaemia is associated with worse outcomes in people *without* diabetes compared to those with the condition (Capes et al., 2000, 2001; Farrokhnia, Björk, Lindbäck, & Terent, 2005; Fogelholm, Murros, Rissanen, & Avikainen, 2005; Samiullah, Qasim, Imran, & Mukhtair, 2010). Interestingly, in lacunar stroke, studies have reported that hyperglycaemia may have a protective effect (Bruno et al., 1999, 2002; Uyttenboogaart et al., 2007) and is not associated with functional outcome, irrespective of diabetic status (Fang, Zhang, Wu, & Liu, 2012).

As with other conditions, controversy exists over whether acute hyperglycaemia directly leads to worsening pathology or whether it is, in fact an epiphenomenon. Some question why, 'glucose, the main energy substrate for the brain, causes demise of brain tissue at the time of cerebral ischaemia' (McCormick, Muir, Gray, & Walters, 2008). Recent magnetic resonance imaging studies, however, seem to support a causative role for hyperglycaemia in neurological deterioration (Parsons et al., 2002).

Another area of contention in stroke is whether stress hyperglycaemia is a separate entity or, in fact, unmasked glucose intolerance. It has been reported that two thirds of those with post-stroke hyperglycaemia (but not diabetes) are diagnosed with impaired glucose tolerance or diabetes at 12 weeks (C. S. Gray et al., 2004) whilst another study reports that hyperglycaemia in the setting of an acute stroke is transient in the majority of patients (Dave et al., 2010).

1.1.8 Hyperglycaemia in Heart Failure

Although links between diabetes and heart failure have been recognised for some time (Kannel, Hjortland, & Castelli, 1974) and there are many studies linking SH to mortality in AMI, the heart failure story is not as clear. Blood glucose values have been shown to be predictive of short-term mortality in a number of studies (Barsheshet et al., 2006; Helfand et al., 2015; Mebazaa et al., 2013; Sud et al., 2015) but a large (n=50 532) study did not find associations between admission glucose and mortality (Kosiborod et al., 2009).

The result of a study examining the effect of insulin on outcomes is awaited (ClinicalTrials.gov identifier: NCT00812487).

1.1.9 Conclusions on the History of Stress Hyperglycaemia

The history of stress hyperglycaemia is complex and fascinating. The body of knowledge accumulates over centuries and across continents, incorporating major themes such as homeostasis and 'fight or flight'. Despite the involvement of a large number of eminent thinkers, the spread and acceptance of valuable clinical knowledge was often suboptimal. This problem continues today.

Enquiring minds opened up the possibility of a new disease entity, separate to diabetes. It is now established to be a common condition with studies reporting 16-79% affected depending on the disease group and population examined (O'Sullivan, Duignan, O'Shea, Griffin, & Dinneen, 2013).

It was initially believed that hyperglycaemia during stress was a benign response or epiphenomenon. As more evidence has been presented, thinking has largely (but not entirely) shifted towards viewing stress hyperglycaemia as a mediator of harm and a marker of poor outcomes. It is notable that Hans Seyle, observed that 'some of the hormones produced during stress have definitely toxic effects' as far back as the early 20th century. Knowledge of the underlying mechanisms of pathogenesis and harm has evolved greatly since then. (Dungan et al., 2009; Van Cromphaut, 2009).

The medical definition of 'stress' has also evolved considerably. It is now recognised that there is no 'stereotyped response pattern' to a stressor and an 'understanding of the health consequences of stress requires an integrative approach'(Goldstein & Kopin, 2007).

Despite this, all these years later, basic gaps in knowledge remain. In particular, there is no consensus definition for stress hyperglycaemia, and best management in the acute care setting remains unclear. Understandably, there has been a focus on outcomes but a lack of detailed profiling of individuals with the condition. Future researchers may be inspired by Claude

Bernard's quote from so many years ago, *'The investigator should have a robust faith - and yet not believe'*.

1.2 Modern Views on the Pathophysiology of Stress Hyperglycaemia

Figure 4 illustrates the current understanding of glucose metabolism in stress hyperglycaemia. Gluconeogenesis is thought to be the most important contributing factor (Jeevanandam, Young, & Schiller, 1990; Lang, Bagby, Blakesley, & Spitzer, 1989) although the aetiology also involves various other counter-regulatory hormones, cytokines and hospital related factors (e.g. exogenous glucocorticoids). An individual's pancreatic reserve and degree of insulin resistance also play an important role in the development of stress hyperglycaemia (although the latter, to our knowledge, has not been measured in all-comers with stress hyperglycaemia in the acute care setting, see section 4.2.3). A vicious cycle then develops with hyperglycaemia exacerbating metabolic disturbance and contributing to further hyperglycaemia (Dungan et al., 2009).

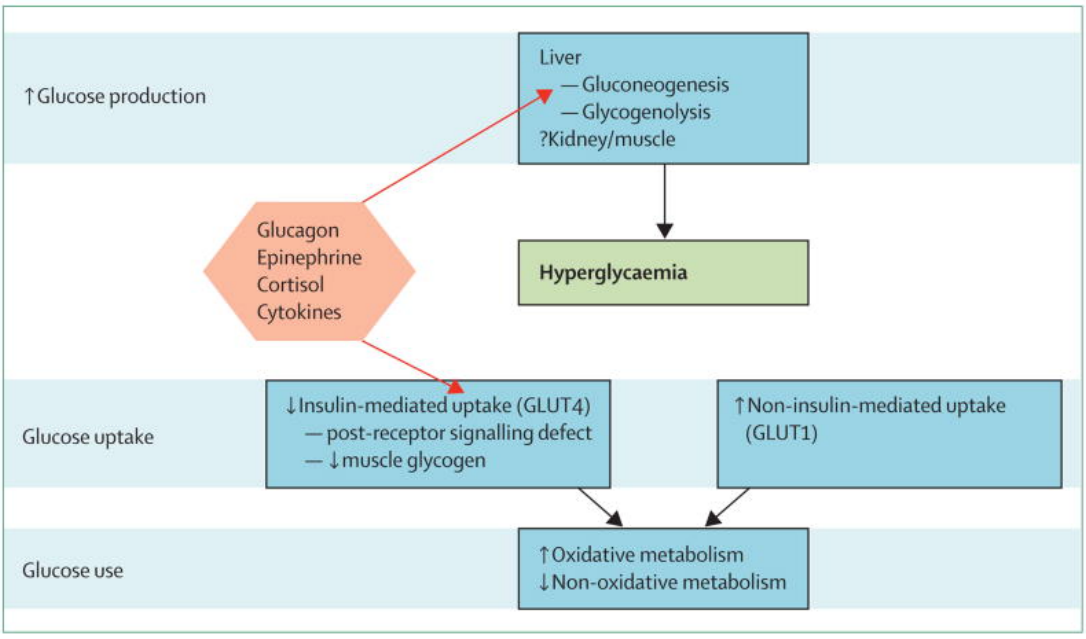


Figure 4: Glucose metabolism in stress hyperglycaemia. Reprinted from the Lancet, volume 373, KM Dungan, SS Braithwaite, JC Preiser. 'Stress Hyperglycaemia', Figure 3, page 6, Copyright 2009, with permission from Elsevier (Appendix 7)

Once developed, it is clear that stress hyperglycaemia is related to poor outcomes across a range of conditions (section 1.1). Figure 5 illustrates the mechanisms by which both acute *and* chronic hyperglycaemia may cause harm to an individual. This poses a few questions:

- Why do people with Stress Hyperglycaemia often have worse outcomes compared to similar people with diabetes? (Kosiborod et al., 2005)
- How does harm develop so rapidly in Stress Hyperglycaemia whereas complications in people with diabetes may take years to develop? (Dungan et al., 2009)

Various theories and evidence have been presented in response to these questions. Glycaemic variability or acute glucose fluctuations is one such example. This is covered in more detail in section 4.3.

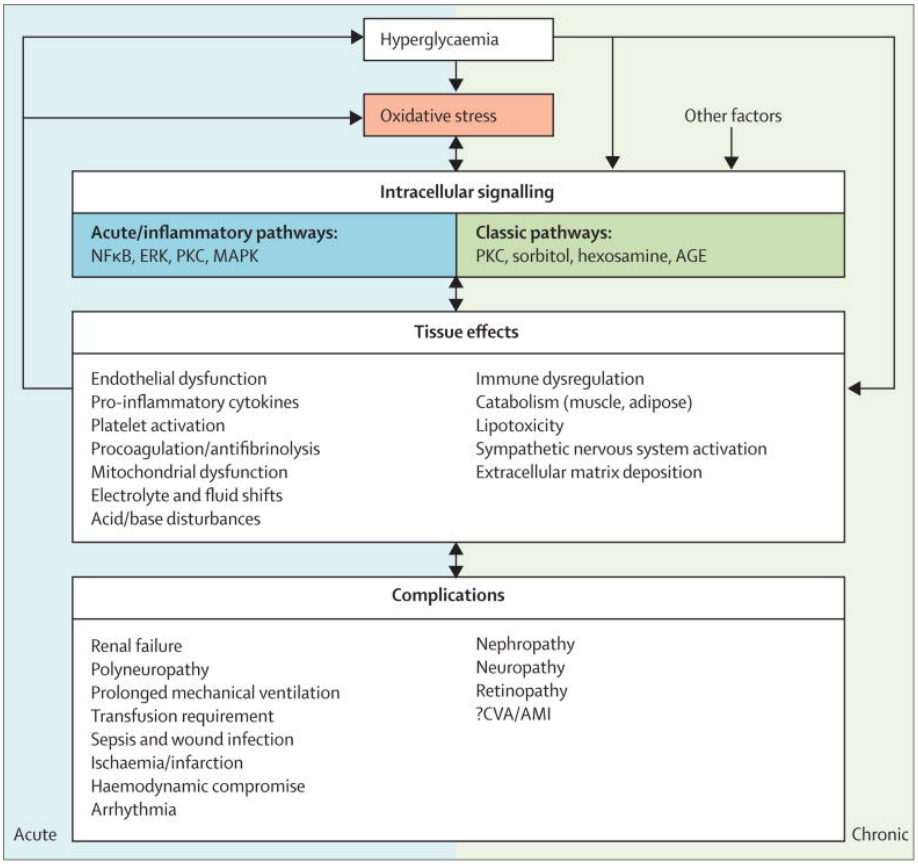


Figure 5: Overlapping mechanisms of harm in hyperglycaemia. Reprinted from the Lancet, volume 373, KM Dungan, SS Braithwaite, JC Preiser. 'Stress Hyperglycaemia', Figure 4, page 7, Copyright 2009, with permission from Elsevier (Appendix 7)

1.3 Modern Views on Management of Stress Hyperglycaemia

Large randomised-controlled trials, predominantly in the MI (Malmberg et al., 2005) and critically unwell populations (Finfer et al., 2009) have sought to clarify the best management for stress hyperglycaemia. Some studies have noted that in striving for tight glycaemic control (TGC) or normoglycaemia with insulin therapy, damaging episodes of hypoglycaemia have occurred (Finfer et al., 2009). Recent guidelines propose that less intensive glycaemic targets be implemented (Dellinger et al., 2013; Moghissi et al., 2009) and most UK (ITU) units now aim for a blood glucose of between 6-10mmol/L.

Outside of the intensive care setting, various aspects have complicated the picture, making management decisions difficult for a practising clinician on the shop floor.

- Lack of a consensus clinical/biochemical definition for SH
- Lack of detailed profiling of people with SH, particularly unselected AMU patients
- Lack of evidence-base for management decisions

A number of organisations have, however, issued disease-specific guidelines for the management of hyperglycaemia in the acute setting. These frequently relate to individuals with pre-existing DM, a scenario which many would consider to fall under the umbrella of SH (Dungan et al., 2009).

The UK National Institute for Health and Clinical Excellence (NICE) recommends initiating treatment with a dose-adjusted insulin infusion to manage hyperglycaemia in patients admitted with Acute Coronary Syndrome (ACS). Hyperglycaemia requiring treatment is defined as a blood glucose level >11.0mmol/L noted within 48 hours of admission (NICE, 2011). Of interest, a recent study suggests that an intravenous insulin infusion may only be of

benefit to patients with STEMI, and associated with poor outcomes in patients with NSTEMI (Birkhead, Weston, Timmis, & Chen, 2014).

International guidelines for the management of hyperglycaemia in stroke vary. NICE in the UK recommend that 'people with acute stroke should be treated to maintain a blood glucose concentration between 4 and 11 mmol/L'(NICE, 2008). The European Stroke Organization recommends treating levels >10mmol/L (European Stroke Organisation, 2008) whereas American associations (AHA/ASA) suggest treatment to maintain serum glucose concentrations between 7.8 and 10.0 mmol/L (Jauch et al., 2013).

Aside from acute management, the NICE ACS guideline (NICE, 2011) also addresses follow-up. As with the maternal condition, Gestational Diabetes Mellitus (GDM), it is probably prudent to follow up all hyperglycaemic patients to establish/exclude underlying glucose intolerance. As described previously, it has been shown that a certain proportion of patients with SH will go on to develop Diabetes Mellitus (C. S. Gray et al., 2004).

1.4 Gaps in Knowledge and Dilemmas

Despite the body of work described, there remain significant gaps in knowledge/areas of controversy with regards stress hyperglycaemia. To summarise:

1. Why do people with Stress Hyperglycaemia often have worse outcomes compared to similar people with diabetes? (Kosiborod et al., 2005)
2. How does harm develop so rapidly in Stress Hyperglycaemia whereas complications in people with diabetes may take years to develop? (Dungan et al., 2009)
3. Do people with Stress Hyperglycaemia actually have underlying glucose intolerance, unmasked during acute illness, rather than a genuinely transient disorder?

4. Does stress hyperglycaemia directly lead to worsening pathology or it is, in fact, an epiphenomenon?
5. What is the best management for stress hyperglycaemia in the acute care setting?

The most pertinent question for the practising clinician is the latter (question 5). Aside from a few conditions, there is little in the way of evidence-based guidance. Best management may not, however, involve pharmaceutical treatment. Considering the various outcomes for a patient with stress hyperglycaemia, (Figure 6) perhaps more appropriate management could be more aggressive treatment of the underlying condition or earlier follow-up to exclude glucose intolerance. Stress Hyperglycaemia could, in this way, serve as a signpost to raise awareness for potential adverse outcomes. Question 3 is also of interest here -further information on metabolic outcomes for patients with stress hyperglycaemia could also support management and follow-up decisions.

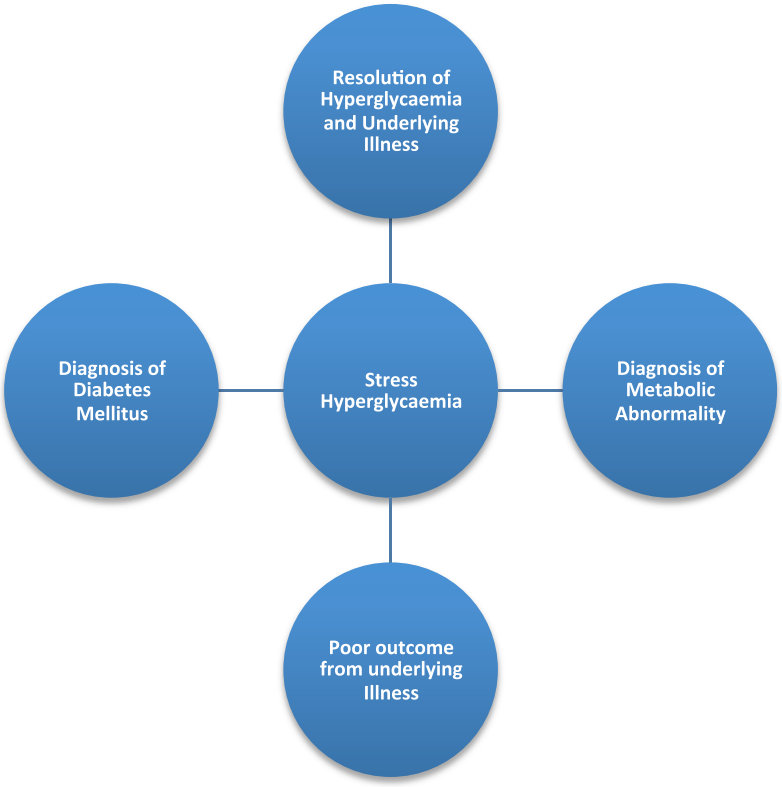


Figure 6: Various clinical outcomes for a patient with stress hyperglycaemia. Outcomes are not mutually exclusive

1.5 Research Objectives

The research in this thesis aims to address questions 3 and 5 through the detailed study of individuals with Stress Hyperglycaemia. Various metabolic parameters (including BMI, waist circumference, BP, Epworth score for obstructive sleep apnoea and copeptin values) were considered to be of most interest given established aetiological links with Type 2 Diabetes (question 3) as well as their relevance to an individualised treatment approach for SH (question 5). These selected parameters are summarised as the 'metabolic profile' for the purposes of this study and are described in more detail in section 3.1.1.

The main research objective, addressed through a prospective observational study, investigates whether there is a difference between the metabolic profile of people with and without Stress Hyperglycaemia (section 3.3). Five separate null hypotheses related to this objective are described below:

NULL HYPOTHESIS 1: There is no statistically significant difference between the mean Body Mass Index (BMI) values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 2: There is no statistically significant difference between the mean waist circumference values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 3: There is no statistically significant difference between the mean (systolic and diastolic) blood pressure values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 4: There is no statistically significant difference between the mean Epworth score of people with and without stress hyperglycaemia

NULL HYPOTHESIS 5: There is no statistically significant difference between the mean Copeptin values of people with and without stress hyperglycaemia

In addition to the main research question and hypotheses, a number of other novel measures will be described for interest only (see sections 3.1.1 and 4.1.1). Additionally, relevant data from a separate randomised controlled study is included in this thesis to compliment the main body of work and provide insight into a sub-population with SH (see section 2.2.1 for study objectives and Chapter 5 for results).

It is hoped that these comparisons will provide new insights into the differences between people with and without the condition, ultimately, and with subsequent work, enabling practising clinicians to make decisions on how best to manage patients with stress hyperglycaemia in the acute care setting.

For the purposes of this study, Stress Hyperglycaemia has been defined as a random plasma glucose 7.1-11.0 mmol/L in an individual without diabetes. Expert opinion and relevant clinical trials have informed this definition. (Baker et al., 2006)

Chapter 2: Materials and Methods

2.1 Prospective Observational Study

2.1.1 Ethical Approval

Application was made through the Integrated Research Application System (IRAS) and approved by the National Research Ethics Service (NRES) Committee-South East Coast, Surrey on the 11th July 2011 (now Surrey Borders NRES). Local approvals to conduct the research at Chelsea and Westminster Hospital NHS Foundation Trust were granted on the 30th August 2011. A substantial amendment requesting the addition of biomarkers copeptin and proADM as well as BIVA assessment was approved on the 4th January 2012.

2.1.2 Overall Trial Design

This project was designed as a prospective observational study with a baseline visit and follow-up visits at 90 and 180 days. Early on in the recruitment process, it became clear that many participants found the proposed follow-up schedule challenging and so a single follow-up visit at 30 days was proposed. We do not believe that the scientific aspects of this study were compromised by a shortened follow-up period. These challenges are discussed in more detail in section 6.12.2.

2.1.3 Study population

Participants were recruited from a population of patients admitted to the Acute Assessment Unit (AAU) at Chelsea and Westminster Hospital, London who were able to enter the study within 72 hours of admission. Nationally, the term AMU is more commonly used. In this thesis, the terms AAU, AMU and 'acute care setting' are used interchangeably.

2.1.4 Inclusion and exclusion criteria

Inclusion criteria:

1. All patients >18 years admitted to AAU
2. Able to enter the study within 72 hours of admission

Exclusion criteria:

1. Age <18 years
2. Pregnancy (based on history as β-hCG will not be routinely performed)
3. Inability to give informed consent
4. Moribund or not for active treatment
5. Critical illness requiring high dependency or intensive care
6. Prior or new diagnosis of diabetes mellitus (Type 1/Type 2) at/during admission
7. Patients on a Dextrose infusion

2.1.5 Subject Recruitment Process*

Eligible patients were informed that a research project was underway and they were offered the opportunity to participate. If they expressed interest, they were provided with an overview of the project, including its objectives, nature, burdens and risks. It was emphasised that participation was entirely voluntary.

If they remained keen to proceed, they were provided with a copy of the participant information leaflet, which was also explained to them. Time was provided to consider the contents of the leaflet and ask as many questions as necessary. If patients remained positive about participation, and no exclusion criteria were identified, informed consent was sought.

The participant leaflet was reviewed by 'Drive' a local (diabetes) patient involvement group. A number of changes were made to the leaflet based on their suggestions.

** -Parts of this section reproduced with kind permission of Metformin in COPD study team (see section 2.2)*

2.1.6 Informed Consent*

Informed consent was obtained by the Investigator who received training in Good Clinical Practice (GCP) and was familiar with the study protocol. The Investigator explained that there was no obligation to enter the study and withdrawal was possible at any time without having to give a reason. A copy of the signed Informed Consent was given to the participant and a second copy placed in the clinical notes. The original was securely stored at the study site.

2.1.7 Screening assessments*

A more detailed assessment of eligibility for inclusion was obtained by reviewing the clinical history and examination, obtained as part of routine care. Any components required to determine eligibility but not contained in the clinical notes were obtained directly from the patient during the screening assessment.

2.1.8 Study Group Formation

Following successful screening and recruitment, standard peripheral venipuncture was used to obtain a random plasma glucose (RPG) sample. Participants were placed into study group 1 or 2 based on their random plasma glucose (RPG) value. Participants diagnosed with DM during this process (group 4) were excluded from the study and clinical follow-up plans were made (Figure 7).

2.1.9 Study Measures

Group 1: Baseline visit

Identified through:

- 1st random plasma glucose (RPG) reading 7.1-11.0mmol/L
- 1st RPG ≥11.1 mmol/L, no symptoms of diabetes, and repeat RPG <11.1 mmol/L.

A baseline assessment was completed for participants during their admission. All relevant study information was handwritten into a case report form (CRF) and then scanned directly into IBM SPSS Statistics (versions 21 and 22) using the TELEform© program (version 8.2, see section 2.1.16). Table 3 contains the study measures collected during the baseline assessment. The rationale for these measures is discussed in section 3.1.1. Where possible, information was collected with minimum disruption to the participant. In some occasions, more than one visit was required.

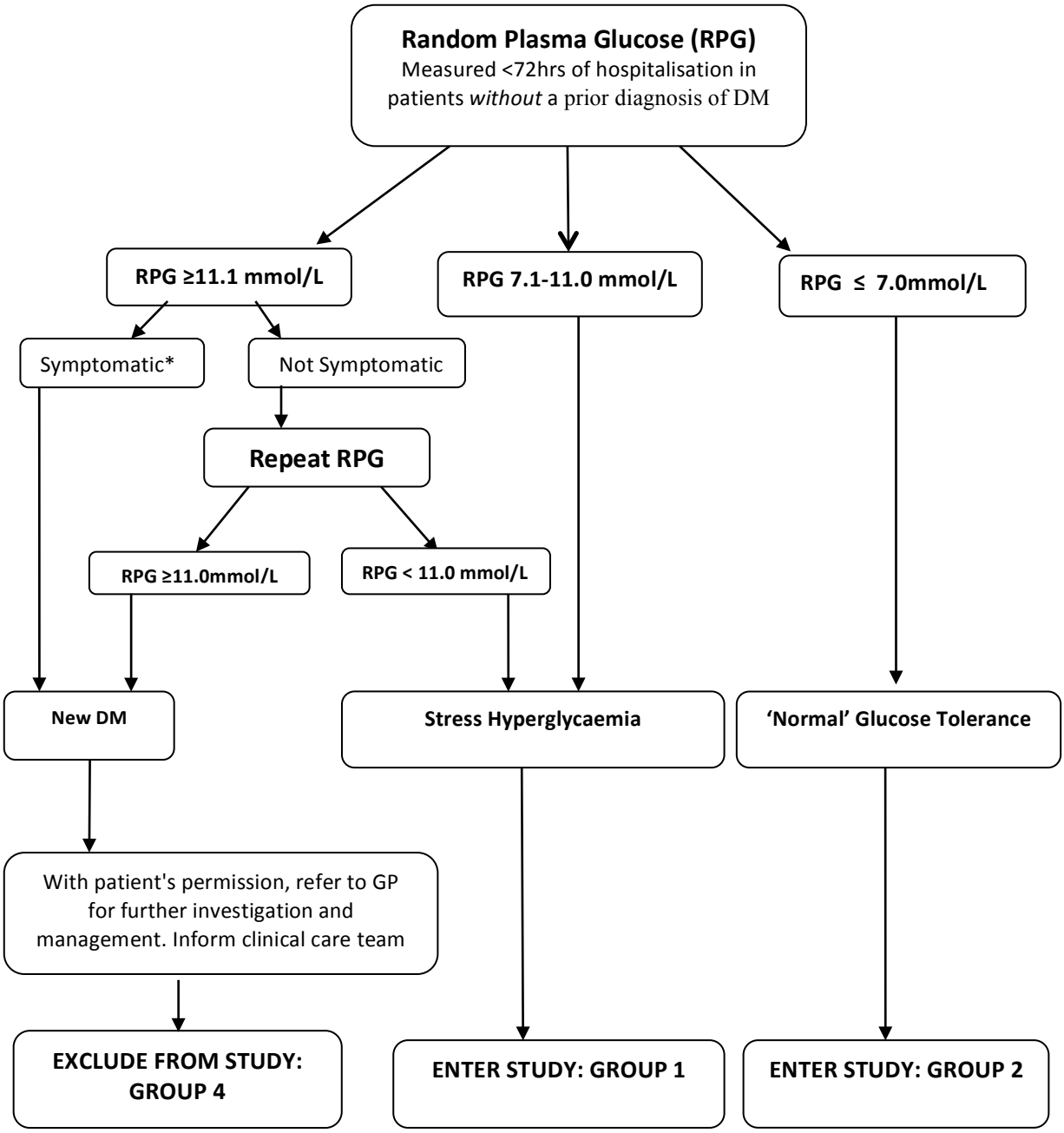


Figure 7: Schematic of Study Group Formation, prospective study

***Symptomatic refers to classic symptoms of DM such as polyuria, polydipsia and weight loss**

Demographics	Date of birth, gender, ethnicity
Admission Details	Primary/secondary/other diagnosis, illness severity (CEWS), presenting RPG* (time of sample and duration since last meal), baseline visit date
Associated Conditions	Family history, drug history, steroid treatment, history of HTN* & NASH*
Anthropometrics	Height, weight, *BMI*, BP**, neck and *waist circumference*, BIVA*
Clinical Score	*Epworth score,* Depression score
Blood tests	Fasting glucose & insulin, (HOMA-2*), HbA1c*, urea, Cr*, eGFR*, lactate, morning cortisol, CRP*, troponin I, BNP*, blood ketones, *copeptin,* pro-ADM*
Short-Term Outcomes	LOS*, metabolic abnormalities (including T2DM risk)

Table 3: Study information collected in Case Report Form (CRF) during baseline assessment for group 1 participants. *See Abbreviation Section. Measures in italics relate to primary study hypotheses.

A letter was sent to the participant and the GP following baseline visit 1 if any abnormal results were identified (see section 3.10.2).

Group 1:Visit 1

All group 1 participants were invited to a follow up visit (visit 1) at 30 days post-discharge. Following discharge, participants were contacted by telephone to check if they were still happy and well enough to attend. If so, a date was booked in for visit 1. The hospital electronic patient data and management system (Last Word Client version 4.1, IDX system©) was checked before contacting participants to ensure that only living participants were contacted.

Participants who agreed to attend visit 1 were reminded that they would be having an OGTT and what this involved, including 12 hours of preparatory fasting. Participants were advised

to take their normal medication with water and contact the investigator on the 24 hour study phone should they have any questions or concerns.

On arrival, participants were met at the entrance to the phlebotomy department and introduced to the phlebotomist who was expecting them. Following the ingestion of a 75g glucose solution for the OGTT, and acquisition of selected blood samples using a standard peripheral venepuncture technique, the participant was taken to a dedicated study area nearby and the remaining study measures were checked/requested (Table 4).

Anthropometrics	Height, weight, BMI*, waist and neck circumference, BP*, BIVA*
Clinical Score	Epworth score
Blood tests	OGTT* -0hr plasma glucose, 2hr glucose, fasting insulin, HOMA2*, HbA1c*, 9am cortisol, CRP*, BNP*, Troponin I, proADM*, copeptin
Outcome	Diagnosis of Diabetes, IGR*

Table 4: Study information collected in Case Report Form (CRF) during visit 1 for group 1 participants. *See abbreviation section.

During this period, the participant was asked to keep as still as possible to avoid any interference with the OGTT. They were then provided with reading material, a glass of water and asked to rest until it was time to return to phlebotomy for the final OGTT glucose test. The waiting time was generally about 30 minutes.

After 2 hours, the participant was accompanied back to the phlebotomy department and placed in contact with the same phlebotomist they had seen 2 hours previously. Whilst they were having their final blood test taken (OGTT, 2 hour glucose), the investigator purchased a hot drink and some lunch for them to end their fast. Finally, they were thanked for their kind participation and a letter was sent to both the patient and their GP with the results of visit 1.

Group 2: Baseline visit

Identified through:

- Random glucose <7.0mmol/L

All the same study measures were collected for group 2 as group 1 participants. Notably, no visit 1 was requested for this group. Figure 8 summarises the study processes for group 1 and 2 participants.

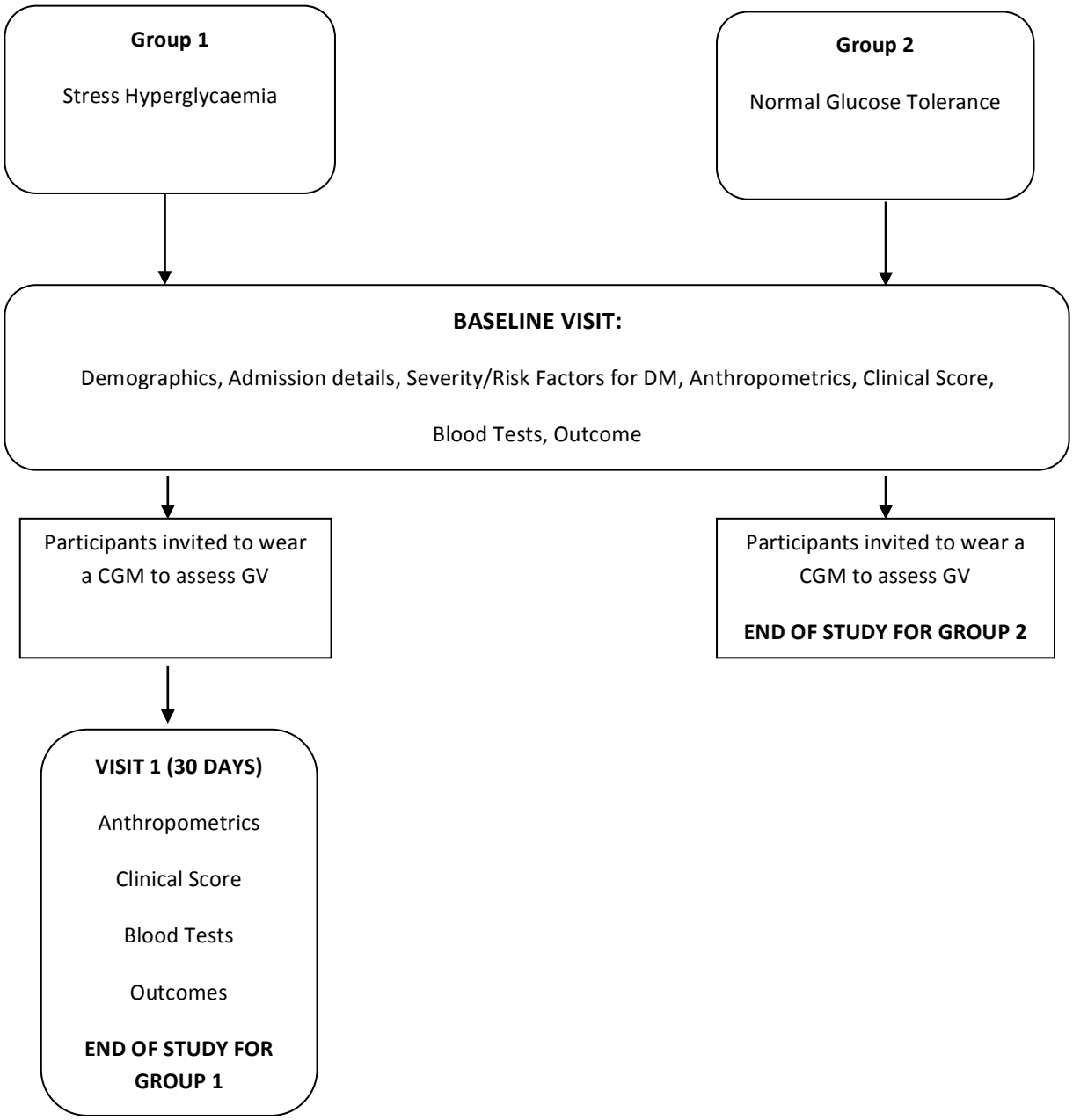


Figure 8: Schematic of Prospective Study Design

CGM patients

All participants were invited to wear a Medtronic iPro2™ Continuous Glucose Monitor (CGM) during the study to assess Glycaemic Variability (a novel measure of interest, see section 1.5 and also section 4.1.1). Those who expressed an interest, were provided with written information (included in the participant leaflet) and given time to consider the potential disadvantages and risks, notably a small amount of discomfort on sensor insertion and a very low risk of infection/inflammation related to the adhesive used to hold the sensor in place.

For participants happy to proceed, the CGM sensor was inserted using a sensor insertion device. An abdominal insertion site, at least 1 inch away from the umbilicus was selected. Following insertion, the introducing needle was disposed of in a sharps container and a transparent dressing was applied to the CGM sensor. After a period of 15 minutes, the CGM monitor was attached to the sensor and appropriate placement (flashing of ipro2 green light) was confirmed. An aseptic technique was used throughout. The staff nurse caring for the participant and the participant were given advice on its basic management and provided with the investigator's 24hr study phone number for any queries or concerns.

Participants were asked to wear the CGM for a minimum of 24 hours and a maximum of 6 days if possible. They were also provided with the iPro2™ 'Patient Instruction' leaflet. Whilst they wore the monitor, the following occurred:

- Participants were asked to keep a food diary outlining daily meals and snacks
- Capillary blood glucose (CBG)/BM was measured 4 times a day by the investigator or staff nurse for calibration purposes

- The CGM insertion site was inspected regularly by the investigator for any signs of inflammation
- Blood samples were taken for 25-OH Vitamin D and C-peptide

A removal date/time for the CGM was proposed based on the participant's experience with the monitor and anticipated discharge date. CGM removal was completed using an aseptic technique and a transparent dressing was applied. The whole process was documented in the clinical notes along with the investigator's phone number. The participant and staff nurse were advised to contact the investigator if there were any concerns with the CGM site.

The CGM was taken back to the clinical study area and sterilised according to manufacturer's guidelines. It was then taken to the study office and connected to the study computer. Sensor glucose values were uploaded into the CareLink ipro2™ programme and subsequently downloaded into Microsoft excel. The standard deviation around the mean SG value was used to express glycaemic variability (Kohnert, Lutz, & Salzsieder, 2010). All data were anonymised. Finally, the CGM was attached to the iPro2™ dock to be fully charged.

The initial plan was to recruit 35 patients to wear a continuous glucose monitor (CGM) during admission. Once again, the practical aspects of conducting this within the AAU setting made it clear that this would not be possible. A total of 12 participants were recruited. The challenges encountered during recruitment are discussed in more detail in section 2.1.20 and 6.12.2.

2.1.10 Newly Diagnosed Diabetes Mellitus: Group 4

Identified through:

- One random venous plasma glucose ≥11.1 and symptoms of DM including polyuria, polydipsia, unexplained weight loss
- Two random glucose levels ≥11.1 in the absence of any symptoms suggestive of DM

These patients were excluded from the study. With their permission, a letter was sent to their GP advising further investigation and management. The clinical team caring for the patient were also informed of the abnormal findings and advised to monitor CBG during admission.

A number of other metabolic abnormalities were noted during the course of the study, including IGT, IFG and 'High Risk for Diabetes'. Their diagnostic criteria are described in section 3.10.2. Of note, some participants fulfilled (single) biochemical criteria for diabetes but, for a number of reasons, it was not possible to assess for symptoms of diabetes/request a second test. For the purposes of the study they were described as having 'biochemical features of diabetes' and their GPs were advised to repeat a RPG/FPG and assess for symptoms following discharge to formally diagnose DM (Table 28).

2.1.11 Laboratory Procedures

All blood samples were taken using standard peripheral venipuncture technique. Venipuncture was coordinated with the clinical team wherever possible to avoid multiple procedures on one patient. All blood samples were handled according to standard hospital procedure. Of note, fasting insulin sample were placed on ice immediately after venipuncture and transported directly to the pathology laboratory by the investigator. A few blood samples required special procedures and handling:

BNP and Troponin I

Following specialist training, participant samples (taken in EDTA tubes) were processed in the clinical study area on a near-patient (Biosite Triage®) meter. The sample was inverted 7 times to enable mixing and then aspirated into a 250μl transfer pipette. The pipette was filled completely and slowly squeezed to dispense the participant's blood onto a test strip. The strip was then slotted inside the Biosite Triage® meter and a result for BNP and Troponin I was available in 15 minutes. The test strip was then disposed of appropriately.

The meter required a daily Quality Control (QC) procedure (using a QC device) as well as calibration with external control solutions for each new test cartridge lot. A log of these procedures and results was kept within a folder on the study site.

ProADM and Copeptin

A minor/non-substantial amendment was requested for external processing of these samples, as facilities for analysis were not available within the hospital. This amendment was approved by the NRES on the 24th July 2012. The blood samples were prepared for external processing in the following manner:

- Samples collected in 2 EDTA tubes
- Centrifuged within allied laboratory at 3000 rpm for 10 minutes to separate serum.
- Serum pipetted into cryotubes and stored in -20°C freezer within another allied laboratory. Cryotubes labelled with participant initials, study number, date of sample collection and study name.

- Frozen cryotube samples packaged in dry ice and sent by special courier (along with a material transfer agreement and signature of hospital Caldicott guardian) to Thermo Fisher Scientific laboratory in Hennigsdorf, Germany for analysis.

Samples were analysed using B.R.A.H.M.S™ KRYPTOR automated immunofluorescent assays. Four Samples for 2 participants (participants 057 and 065 at baseline and visit 1) were processed at the University of Oxford, using the same techniques and assays. No patient identifiable data were sent and all samples were destroyed in Germany and Oxford after analysis.

HOMA2

Several methods have been developed to assess insulin resistance. The Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was used in this study, as it is a simple and inexpensive method, frequently utilised in clinical trials. HOMA2 is an updated version of the HOMA-IR model and considers variations in hepatic and peripheral glucose resistance, increases in the insulin secretion curve for plasma glucose concentrations above 10 mmol/L and the contribution of circulating proinsulin in its calculation (Levy, Matthews, & Hermans, 1998; T. Wallace, Levy, & Matthews, 2004).

In this study, a validated computer programme (HOMA2 calculator: http://www.dtu.ox.ac.uk/homacalculator/index.php, released by the Oxford Centre for Diabetes, Endocrinology and Metabolism) was used to calculate HOMA2-IR, %B and %S values from measured variables (fasting insulin and glucose). It is worth noting that HOMA-IR measures correspond well, but are not necessarily equivalent to, non-steady state estimates

of insulin sensitivity derived from models such as the hyperglycaemic clamp (see link above).

Blood Ketones

Blood ketones were predominantly checked as a study safety measure (see section 6.10.7). A lancing device was used to obtain a CBG sample from the participant's fingertip. The sample was applied to a (Abbott) blood β-ketone test strip that had been inserted into an (Optium Xceed) blood ketone meter. A beeper and status bar on the meter indicated when ketone testing had begun. The test strip was left undisturbed until a blood ketone value was displayed on the meter screen, typically within minutes. The lancet was then disposed of appropriately. An aseptic technique was used throughout. The blood ketone meter was calibrated by using a calibrator test strip. This was performed when the meter was used for the first time and each time a new lot of β-ketone test strips were opened.

2.1.12 Non-Laboratory Study Procedures

With the participant's permission, the clinical notes and hospital Lastword database were searched to obtain as much study information as possible. The participants were directly questioned for any information not recorded in these locations.

Clinical questionnaires (Epworth and Hospital Anxiety and Depression HAD), measurement of height, weight, BP, waist and neck circumference were undertaken according to standard methods based on published recommendations and local guidelines (Ben-Noun, Sohar, & Laor, 2001; Johns, 1991; WHO, 2008; Zigmond & Snaith, 1983).

A relatively novel measure (see section 1.5 and 3.1.1) – BIVA (Bioelectrical Impedance Vector Analysis) -was used to describe hydration and nutrition status in participants. The BIVA scores were obtained by attaching 2 disposable, adhesive electrodes or 'BIVAtrodes' to the participant's upper and lower limb. Specifically, the apex of one electrode was attached to a line bisecting the ulnar head on the upper limb, whilst the second electrode was attached to the medial malleolus on the lower limb. The participant was asked to remain in a still, supine position if possible. The BIVAtrodes were then connected to the BIVA machine using 'patient cables' and the machine was switched on.

Before taking the reading, the individual's study ID, height and gender were entered into the machine. Following this, the participant was pre-warned that they might feel a small 'tingle' and an AC microcurrent (typically 50 KHz ±1%) was introduced through the BIVAtrodes. Impedance to the current, measured as Resistance (R) and Reactance (Xc) values were divided by the participant's height (h) and resultant 'R/h' 'Xc/h' values were plotted on a BiaVector® plot, displayed on the BIVA screen to provide a nutrition and hydration status for each participant. The ellipses shown on the plot (Figure 9) represent 50%, 75% and 95% confidence intervals derived from the 'R/h' and 'Xc/h' data of, '18 000 healthy male and female volunteers of various body shapes, gender and heights.' (*Copyright EFG Diagnostics, version 2.02, March 2012*)

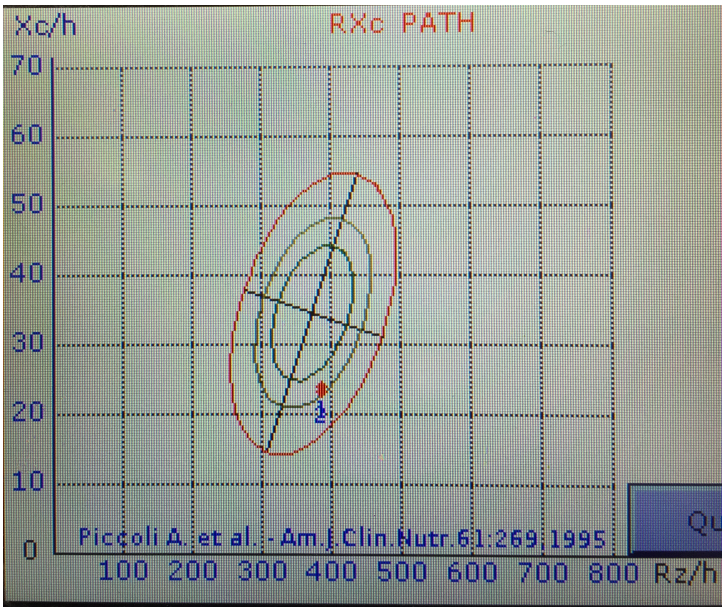


Figure 9: Anonymised BiaVector ® plot for prospective study participant as displayed on the BIVA screen (taken by investigator).

Participants' illness severity was assessed through the Chelsea Early Warning Score (CEWS), a physiological scoring system analogous to the NHS Early Warning Score in widespread use (NEWS). Scores were obtained directly from the participants' nursing notes and recorded in the CRF. Components of the CEWS score included: temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, conscious level and urine output (Austen et al., 2012).

2.1.13 Definition of end of trial*

This trial concluded when the last participant attended their follow-up appointment and reasonable steps had been taken to contact all participants due a follow-up visit.

2.1.14 Subject withdrawal procedure*

Participants were withdrawn from the study if they were unable or unwilling to continue the study and/or follow-up arrangements. Where possible, consent was sought to analyse the data

and samples already collected although participants were not asked to attend for follow-up. Attempts were then made to enrol a replacement subject.

2.1.15 Confidentiality*

All data were handled in accordance with the Data Protection Act 1998. The Case Report Forms (CRFs) did not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and study identification number were used for identification. All data pertaining to identifiable persons were regarded as confidential.

2.1.16 Data Collection Tool

Case report forms (CRFs) were designed by the investigator and produced on the Cardiff TELEform© Design program (version 8.2) with the assistance of Mrs Sylvia Chalkley, research coordinator. It was the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log identified all those personnel with responsibilities for data collection and handling.

2.1.17 Data handling and analysis*

All CRFs and person-identifiable study data were kept in a locked room within a keypad-accessed area of the study site, protected by 24-hour on-site security personnel, fire detection and alarm system.

Data were transferred to IBM SPSS Statistics (versions 21 and 22) by scanning of the CRFs using the TELEform© Scan and Verify programs (version 8.2). The resulting SPSS database was scrutinised to identify missing and spurious data. Such data were corrected with

reference to the Case Report Forms. Some data were also transferred from SPSS to Microsoft Excel (2010) for further analysis.

Electronic data were kept in encrypted databases, on a restricted access area of the study site computer network. This was backed up locally on a daily basis, and monthly backups were held securely in an offsite location. No patient identifiable data were stored on laptop computers, portable storage devices, or sent by electronic mail. The computer network was protected by an intrusion detection system. Data held within SPSS were anonymised, compressed and password-protected.

2.1.18 Archiving arrangements*

The trial documents (including case report forms and consent forms) will be kept for a minimum of five years. They will be stored in locked offices at the study site or in an archiving site as recommended and/or approved by the local Research and Development (R&D) office. The trial database will be kept electronically on the Imperial College computer network at the Chelsea and Westminster site, for a minimum of five years.

2.1.19 Statistical input in trial design

The trial design and statistical analysis plan have been constructed with input from Dr Tom Woodcock, principal information analyst/programme lead for NIHR CLAHRC North West London and Mrs Sylvia Chalkley, research coordinator.

2.1.20 Feasibility Study

A feasibility study was undertaken before the commencement of the prospective observational study. During this period, an exploratory hypothesis (related to glycaemic variability and insulin resistance) was examined. It soon became apparent that a formal power calculation would not be possible for this hypothesis due to a lack of published studies relating to the selected measures in people with SH. As an alternative, some exploratory calculations using linear regression (Dupont & Plummer, 1998) were performed using information on the selected measures in people with diabetes. This suggested that an optimal number of participants for recruitment would be n=125 with n=35 wearing a CGM.

It was initially thought that this would be feasible: local informatics revealed that a total of 5877 patients (>18 years) were admitted to Chelsea and Westminster Hospital between April 2010 and March 2011. In addition, a previous local study identified 245 patients with SH in a 6 month period (defined as RPG>7.8mmol/L). Upon commencing a practical trial of recruitment, however, it became apparent that a sole investigator would not be able to recruit to these numbers in the busy AAU environment. In particular, assessment of GV required consenting participants to wear a CGM for at least 24 hours – a challenge given the rapid patient turnover observed. Therefore, the exploratory hypothesis was deemed unfeasible.

Following further consideration, discussion and review of the literature, the five central hypotheses (originally considered as research questions) described in section 1.5 were selected for study. The experiences of the feasibility study informed the final prospective study –measures chosen for study were deemed to make a significant contribution to the field whilst also being feasible for collection by one investigator in the challenging environment and timeframe. Once again, there was insufficient published evidence to enable a formal

power calculation. A pragmatic approach was hence taken: attempts were made to recruit as many participants as reasonably possible within the available timeframe (whilst operating safely within GCP and ethical frameworks). It was also considered that given the absence of related literature, any number of participants would inform future power calculations and make an unique contribution to the field of stress hyperglycaemia.

2.1.21 Statistical Analysis

Descriptive statistics (including correlations), inferential statistics (one-way Analysis of Variance post-hoc tests and independent samples/paired samples t-tests) were all performed using the SPSS database. Glycaemic Variability (GV) was represented as a Standard Deviation (see sections 4.3.9 and 5.7) and was also calculated using SPSS. Assumptions for all tests were carefully checked before their application (Altman, Gore, Gardner, & Pocock, 1983; Bland, 1987). Additionally, an online tool, the GUARD Type 2 Diabetes Risk Calculator (http://www.cphs.mvm.ed.ac.uk/diabetes-risk/), was used to predict an individual's 3-year risk of developing Type 2 Diabetes (McAllister et al., 2014). This tool was validated in a country with a relatively small non-white population, similar to the prospective study population (Figure 13).

*2.2 Methodology for the 'Stress Hyperglycaemia in COPD' (Metformin) Study

Data for this study were obtained from the adopted, multicentre study: 'A randomised, double-blind, placebo-controlled trial of metformin in chronic obstructive pulmonary disease (COPD) exacerbations: a pilot study' (Metformin in COPD, EudraCT number 2010-020818-28). In total, 9 UK study sites were involved in recruitment. Co-investigator, Dr Anjali Balasanthiran and local collaborators collected data at the Chelsea and Westminster study site. Relevant sections of the study protocol* (version 4.0, 29th June 2012) have been

reproduced with the kind permission of Dr Andrew Hitchings, Co-Investigator at St George's, University of London (study sponsor).

Full details of this study including study governance and pharmacovigilance are contained within the metformin in COPD study protocol. Certain broad sections (e.g.: informed consent, confidentiality) are applicable to both the metformin in COPD and the prospective study. These sections have been included within the prospective study methodology and marked with '* ' to indicate that they apply to both studies (and are reproduced with kind permission of the metformin in COPD team). Results from this study are reported in chapter 5.

2.2.1 Overall trial design and objectives

This was a randomised, double-blind, parallel-group, placebo-controlled trial. An overview of the study is provided in Figure 10. A double-blinded design was adopted to provide the best possible evidence for the efficacy of metformin in this context by minimising the risk of bias. Blinding was implemented by means of visually identical active and placebo treatments. The primary study objective was to determine whether, 'in patients hospitalised for COPD exacerbations and receiving conventional treatment, the addition of metformin, as compared with placebo, ameliorates hyperglycaemia'. The objectives of the secondary analysis differ and focus on examining the following in the recruited COPD population:

i) Prevalence of stress hyperglycaemia

ii) Characteristics of people with SH

iii) Glucose patterns and glycaemic variability (GV)

iv) The effect of metformin on GV

v) Diabetes risk

2.2.2 Study population

Based on existing literature and primary study objectives, the sample size was set at 69 patients, randomised to metformin or placebo in a 2:1 ratio. The patients were drawn from the population of patients admitted to the study sites with an exacerbation of COPD, and who were able to enter the study within 48 hours of admission. Data for 52 patients were available for the secondary analysis.

2.2.3 Schematic of trial design

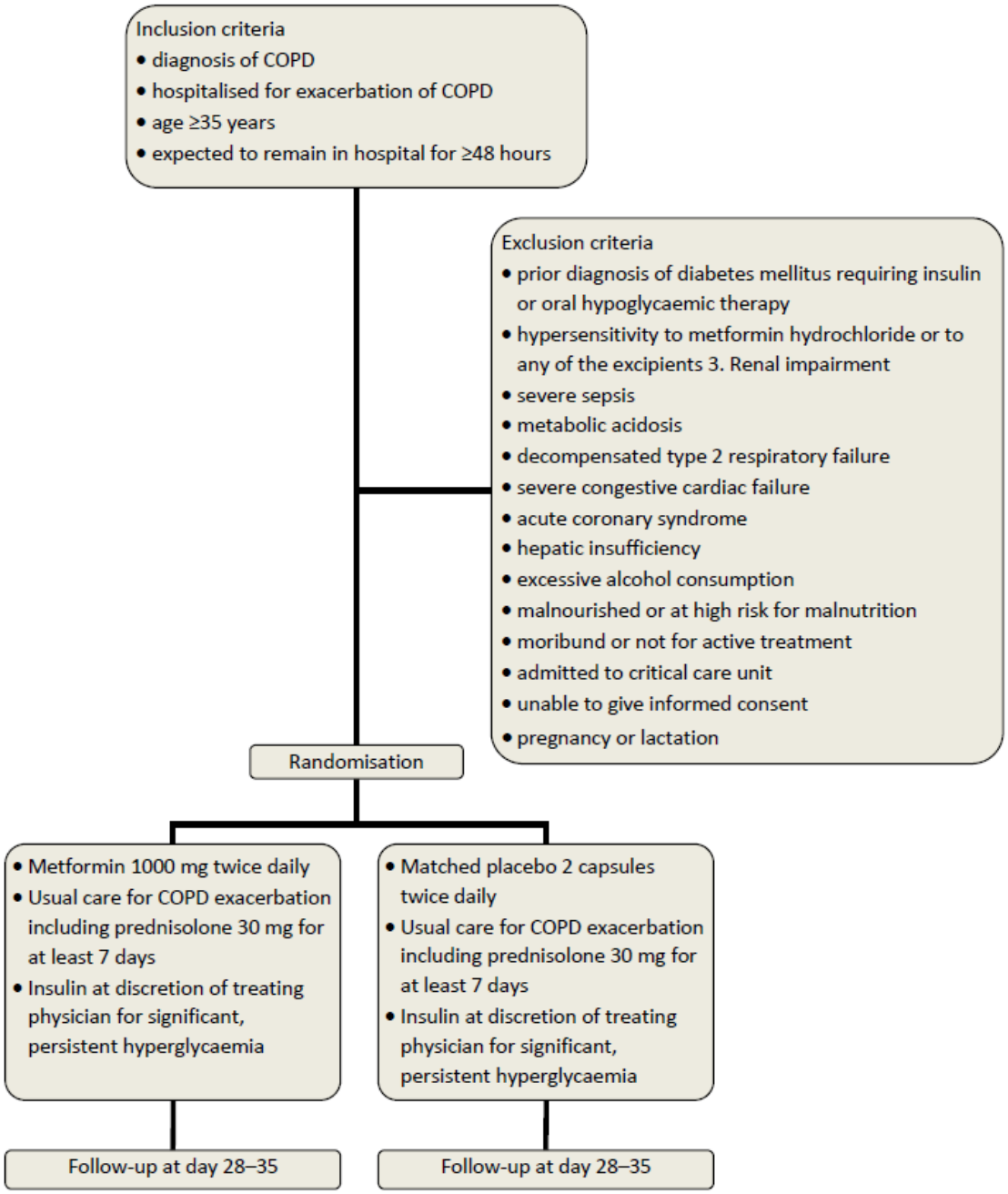


Figure 10: Schematic of metformin in COPD trial design (including up to 28-35 day follow-up). Image reproduced, with permission, from original study protocol

2.2.4 Subject recruitment process

Process as per section 2.1.5 (Prospective study) although there was no involvement of 'Drive' patient involvement group in this study

2.2.5 Randomisation procedure

Patients were allocated in a 2:1 ratio to metformin or placebo in blocks of six. Randomisation was performed by the IMP manufacturer, in accordance with the method agreed by the study team. The randomisation list was produced electronically by the drug manufacturer (Bilcare [GCS] Europe Ltd). Following allocation to a study treatment, patients were given a trial participant card, which contained the study title, IMP details, patient trial number and contact details for advice and emergency unblinding.

2.2.6 Summary flow chart of study assessments

Day	IMP administration	Assessments
1	One capsule	Capillary glucose concentration (thereafter repeated before and 2 hours after each mealtime, and at approximately 22:00) COPD Assessment Test (CAT) Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Malnutrition Universal Screening Tool (MUST) Renal profile, liver profile, CRP, lactate, random glucose, HbA1c Serum sample saved
2	One capsule twice daily	Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Capillary glucose (as above) CRP Food chart if admission MUST score 1 (medium risk)
3	Two capsules morning, one capsule evening	Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Capillary glucose (as above) CRP measured daily to day 7 Food chart if admission MUST score 1 (medium risk)
Day 4 until discharge	Two capsules twice daily	Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Capillary glucose (as above) CRP measured daily to day 7 Safety parameters (renal function, liver enzymes, plasma lactate, venous glucose) measured at least every 72 hours until day 7 (more often if deemed necessary by study team or clinical team), then at a frequency appropriate for the clinical condition of the patient (no less often than once-weekly)
Day of discharge	Two capsules twice daily	Capillary glucose (as above, until time of discharge) Exacerbations of Chronic Pulmonary Disease Tool (EXACT) COPD Assessment Test Spirometry CRP Serum sample saved
Day of discharge until follow-up	Two capsules twice daily	Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
Follow-up (day 28–35)	Two capsules in the morning	Structured interview and pill count COPD Assessment Test (CAT) Weight, height and waist circumference Spirometry Venous glucose, HbA1c, lactate, CRP Serum sample saved
12 weeks	None	Vital status (electronic patient record) Hospital admissions (self-reported and electronic patient record) COPD Assessment Test (returned by post) Antibiotic and steroid courses (self-reported) Diagnosis and/or treatment for diabetes (self-reported)

Table 5: Summary flow chart of study assessments for metformin in COPD study. Image reproduced, with permission, from original study protocol

2.2.7 Practical Procedures and Study Assessments

All blood samples were taken using standard peripheral venepuncture technique.

Measurement of height, weight, and waist circumference were undertaken according to published guidelines (University of Leicester, 2008). The COPD Assessment Test (CAT), Exacerbations of Chronic Pulmonary Disease Tool (EXACT), and Malnutrition Universal Screening Tool (MUST) were administered in accordance with their user instructions. Spirometric measurements were performed in accordance with published guidelines (BTS, 2005). Blood glucose measurements were taken using a CE-marked device licensed for this purpose. A summary flow chart of study assessments is presented in Table 5.

2.2.8 Subject withdrawal procedure

Process as per section 2.1.14 (Prospective study) with the exception that patients withdrawn from the metformin study were invited to attend study follow-up to establish health status and occurrence of any further COPD exacerbations

2.2.9 Data handling and analysis

Similar to section 2.1.21 except that data were transferred to an electronic database in the Excel software programme by double entry (rather than transferred to SPSS using theTELEform© program).

The prospective study definition of SH was used in this study (see section 1.5). As per section 2.1.21, descriptive statistics (including correlations), inferential statistics (one-way Analysis of Variance post-hoc tests and independent samples t-tests) were all performed using the SPSS database. Again, the GUARD risk calculator was used to calculate an

individual's 3-year risk for T2DM (McAllister et al., 2014). Additional analyses performed for this study include:

- Mann-Whitney U non-parametric test –performed due to data distribution, section 5.7
- Glycaemic Variability, (again expressed as a SD and calculated using SPSS), was compared between all study groups (section 5.7) by calculating the GV for each individual participant and obtaining a mean GV value for each study group (prospective study groups 1 and 2 and metformin study groups A and B). The mean values were then compared using one-way ANOVA

As before, assumptions for all statistical tests were carefully checked before their application (Altman et al., 1983; Bland, 1987).

Chapter 3: Prospective Study Results, Part 1

3.1 Introduction

3.1.1 Study Measures

As described in section 1.5, the main research objective relates to the metabolic profile of people with stress hyperglycaemia and differences between individuals with and without the condition. These results are presented in section 3.3. A number of variables, linked to the development of DM were examined in the metabolic profile including: BMI (Looker, Knowler, & Hanson, 2001), waist circumference (Diabetes Prevention Program Research Group, 2006), blood pressure (Conen, Ridker, Mora, Buring, & Glynn, 2007), Epworth score for OSA (Idris et al., 2009) and copeptin (Enhörning et al., 2010).

In addition to the hypotheses-related data, a few further measures, related to the metabolic profile, were also included to provide a fuller picture. Participants were asked about their family history of diabetes as well as past medical history of hypertension (HTN) and Non-alcoholic steatohepatitis (NASH). The IDF definition of metabolic syndrome (Alberti, Zimmet, & Shaw, 2006) was also considered (section 3.3) but could not be formally diagnosed on a single study assessment.

As well as the metabolic profile, a number of additional measures are described in people with SH (see section 2.1.9). Comparisons are made between people with and without the condition. Such detailed profiling of people with SH is novel work. The following sections describe the rationale for the selection of these measures and how they may, with further work, address the broader questions (3 and 5) described in section 1.4.

Demographics and Primary Diagnosis of People with SH (section 3.2):

Although a number of different diagnostic populations with SH have been described, there is little work describing all-comers in an acute care setting (Umpierrez et al., 2002). Building a fuller profile of people with the condition could support the practising clinician in identifying at-risk individuals (perhaps demonstrating conditions particularly associated with SH) as well as focusing management.

Glucose Values in People with SH (section 3.4)

There is currently no biochemical definition of SH but notably, modest levels of hyperglycaemia have been associated with harm in several common conditions (>7.0mmol/L in respiratory disease (Baker et al., 2006) and >6.1 mmol/L in AHF (Sud et al., 2015). A local study identified 245 patients with a RPG>7.8mmol/L in a 6 month period. Otherwise, there is a scarcity of data examining SH glucose values in the acute care setting and, in particular, fasting glucose values have not been examined in this context. This information would be of interest when considering management options.

Steroids in people with SH (section 3.5)

Glucocorticoids are frequently prescribed in the acute care setting, particular for patients with acute exacerbations of COPD (Lindenauer et al., 2010). Resultant glucocorticoid-induced hyperglycemia (GIH) is common (Katsnelson et al., 2013), and considered by many to fall under the umbrella of SH. The odds ratio for new-onset diabetes mellitus in patients treated with glucocorticoids ranges from approximately 1.5 to 2.5 (Perez et al., 2014) with steroid dose and duration strong predictors of diabetes induction (Clore & Thurby-Hay, 2009). A

comparison was made between the steroid-treated proportions of participants with and without SH and metabolic abnormalities (section 3.10.2).

Nutrition and Hydration Status in people with SH (section 3.6)

BIVA has been used to predict outcomes (Peacock, 2010) as well as to assess nutritional and hydration status in a variety of situations (Tuy & Peacock, 2011; Valle et al., 2011; Walter-Kroker, Kroker, Mattiucci-Guehlke, & Glaab, 2011). Methodology for measurement and analysis is described in section 2.1.12. Within the context of this study, it is anticipated that the measurement will add an extra dimension to the metabolic profile of patients with stress hyperglycaemia.

Anxiety & Depression in people with SH (section 3.7)

Depression is a common, under-diagnosed condition which has also been proposed as a risk factor for the development of T2DM (M. M. Williams, Clouse, & Lustman, 2006). Possible aetiological mechanisms include activation of the immune system and HPA axis, leading to increased insulin resistance. To provide a different perspective on 'stress' and further flesh out the profile of the individual with SH, the HAD questionnaire was used to determine anxiety and depression scores in people with and without stress hyperglycaemia.

Stress Profile in people with SH (section 3.8)

Whilst the pathogenesis of SH has been reasonably well elucidated, (section 1.2) there is little work investigating the contribution of (scored) illness severity to the development of SH in the acute setting. This addition could enhance real-world risk stratification and management.

Biomarkers in people with SH (section 3.9)

The association between SH and poor outcomes is well established (Chapter 1). One particular outcome of interest is the development of a metabolic abnormality (see section 3.10.2). Various biomarkers have been shown to have prognostic utility in a number of common conditions (John et al., 2010; Maisel et al., 2011; Martins, Rodrigues, Miranda, & Nunes, 2009) and, in particular, several have been associated with glucose intolerance in SH (Carmen Wong et al., 2010). Despite this interesting work, there is a scarcity of similar research and it is not clear what, if any, popular biomarkers may add to the prognostic utility of glucose.

To start, biomarker values in participants with and without SH were investigated. Values at baseline and follow-up were also scrutinised in group 1 participants. Biomarkers selected for study are presented in results section 3.9 and discussed in more detail in discussion section 6.10.

Short-term outcomes in people with SH (section 3.10):

The question, 'do people with Stress Hyperglycaemia actually have underlying glucose intolerance, unmasked during acute illness, rather than a genuinely transient disorder?' was

considered. Metabolic abnormalities were screened for and recorded (see section 3.10.2). Given the relatively short duration of study follow-up, a risk calculator was utilised to estimate an individual's 3-year risk of developing Type 2 Diabetes (see section 2.1.21). Additionally, as hyperglycaemia has been suggested as a risk factor for prolonged length of stay, (Takada et al., 2012) these results are presented in section 3.10.1. Further information on LOS in people with SH could enhance triage and decision-making.

3.1.2 Recruitment Statistics

Participants were suitable for inclusion if there were >18 years of age, admitted to the Acute Assessment Unit (AAU) at Chelsea and Westminster hospital and able to enter the study within 72 hours of admission. Full inclusion/exclusion criteria are described within the methods chapter (section 2.1.4)

A total of 196 patients (16%) were formally screened and found to be eligible for inclusion. Type 1 or 2 Diabetes Mellitus was the most frequently encountered exclusion criterion. Of those eligible (n=196), the investigator was able to approach n=93 to discuss participation in the study - a total of 64 patients agreed to participate whilst 29 declined (Figure 11)

Of those recruited within the available time-frame, 21 were allocated to group 1 (Stress Hyperglycaemia) and 41 to group 2 ('normal' glucose tolerance). Two patients who were recruited to the study were subsequently withdrawn –one with DM and another on request (see section 3.10.2). Recruitment took place between 11/7/2012 and 16/05/2013.

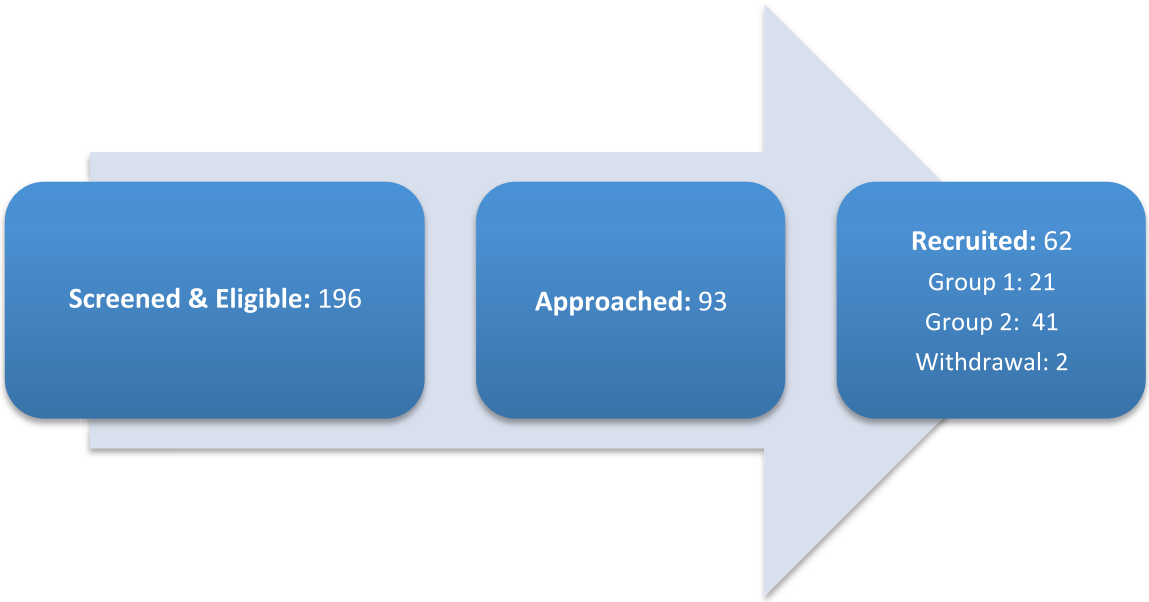


Figure 11: Screened, elgible, approached and recruited participants for prospective observational study

Following recruitment, 11 patients from group 1 (50%) were lost to follow-up (Table 6).

Outcome	Number of Patients
Recruited	21
Follow-up completed	10
Unable to contact /no response to contact despite initial agreement*	6
Declined follow-up*	4
Withdrawn from f/up by investigator (clinically unsuitable for recall) *	1

Table 6: Follow-up outcomes for group 1 participants, prospective study *summarised as 'lost to follow-up'

3.2 Demographics and Primary Diagnosis

The mean age for all participants was 68 years. Using an independent samples t-test (Table 8), no statistically significant difference was found between the age distribution (Table 7) of participants from group 1 and 2 at baseline.

Descriptive Statistics	Group 1	Group 2
Mean Age in years (± SD)	67.6 (± 16.04)	67.5 (± 16.07)
Minimum Age (yrs.)	27	22
Maximum Age (yrs.)	91	89
N	21	41

Table 7: Descriptive statistics of age for group 1 and 2 participants, prospective study

Equal Variances Assumed	t	df	Sig. (2-tailed)
Yes	0.014	60	0.989
No	0.014	40	0.989

Table 8: Independent samples t-test of age, group 1 and 2 participants (prospective study)

Figure 12 displays skewing of the age distribution in all participants towards an older age.

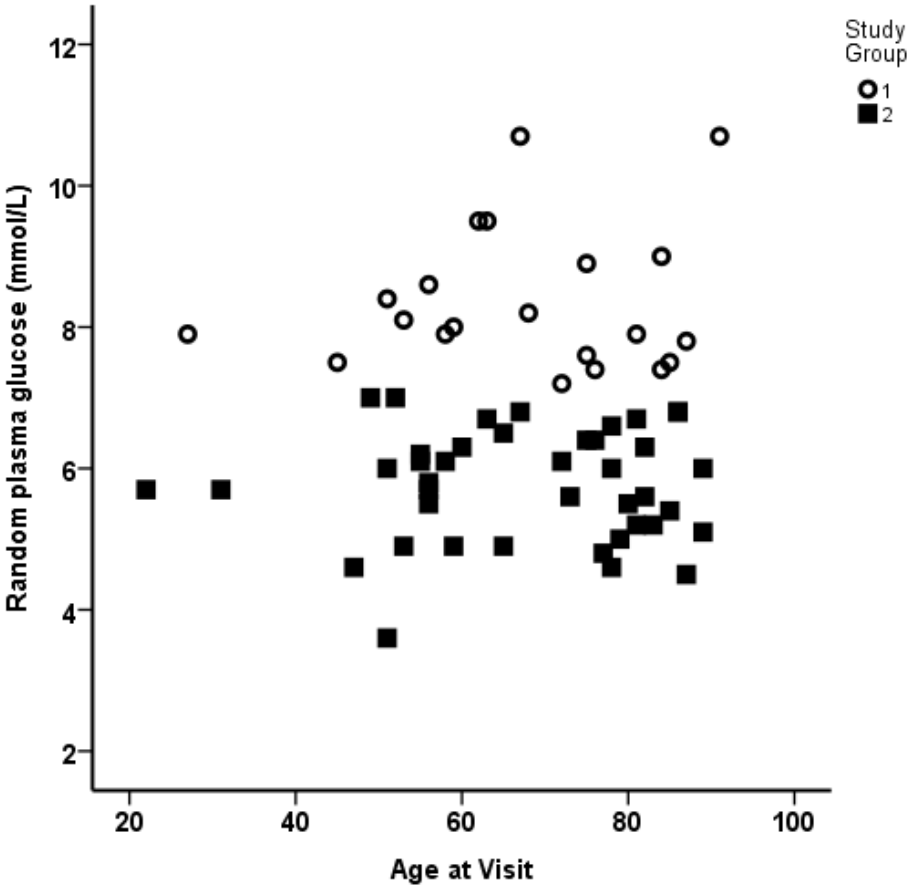


Figure 12: Age distribution and random plasma glucose levels by study group, prospective study

Sixty percent of all participants were men. Gender distribution was also similar in group 1 and 2 participants. (Table 9)

Descriptive Statistics	Group 1	Group 2
Gender, male/female (%)	14/7 (66.7/33.3)	23/18 (56.1/43.9)
N	21	41

Table 9: Gender distribution of participants recruited to group 1 and 2, prospective study

In keeping with the local AAU population (local informatics), the majority of participants in both study groups were of White British ethnicity (Table 10, Figure 13)

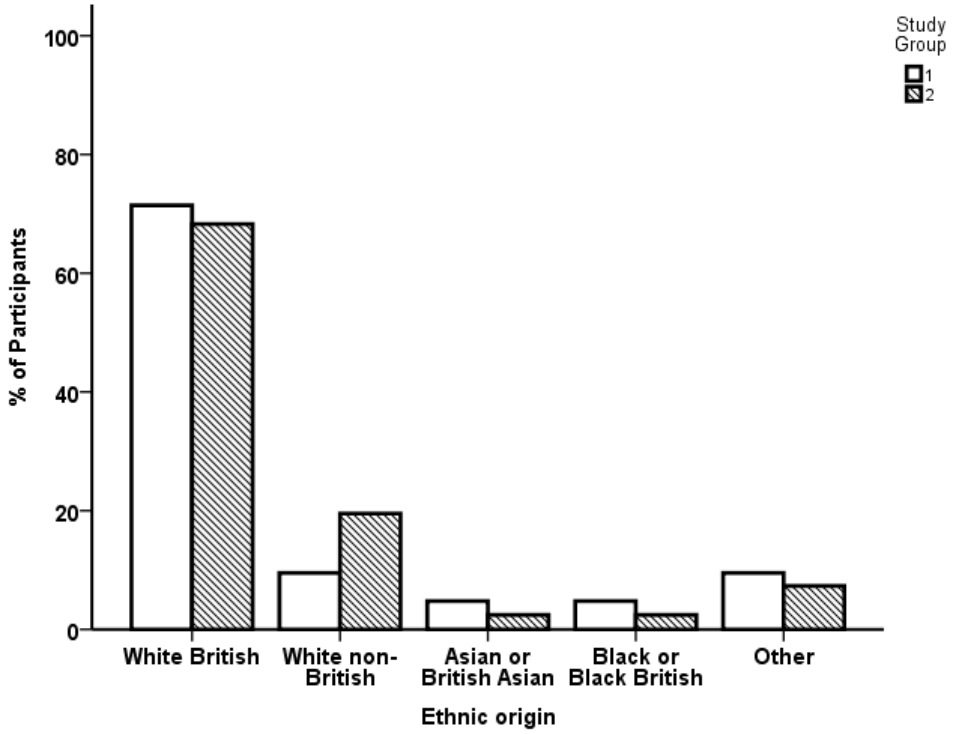


Figure 13: Percentage distribution of ethnicity between participants of group 1 and 2, prospective study

Ethnicity	Group 1 % (N)	Group 2 % (N)
White British (A)	71.4 (15)	68.3 (28)
White Non-British (B/C)	9.5 (2)	19.5 (8)
Asian/British Asian (H,J,K,L)	4.8 (1)	2.4 (1)
Black/Black British (M,N,P)	4.8 (1)	2.4 (1)
Mixed/Other (D,E,F,G,R, S)	9.5 (2)	7.3 (3)
Total	100 (21)	100 (41)

Table 10: Distribution of ethnicity between participants of group 1 and 2, prospective study (% and frequencies)

41 different primary diagnoses (ICD codes) were recorded across 62 patients. Figure 14 and Table 11 display these diagnoses within broad categories for participants from both study groups (for a full breakdown of all ICD-10 diagnoses, see Appendix 1). Respiratory disease was the primary diagnosis for the majority of participants from group 1 and 2.

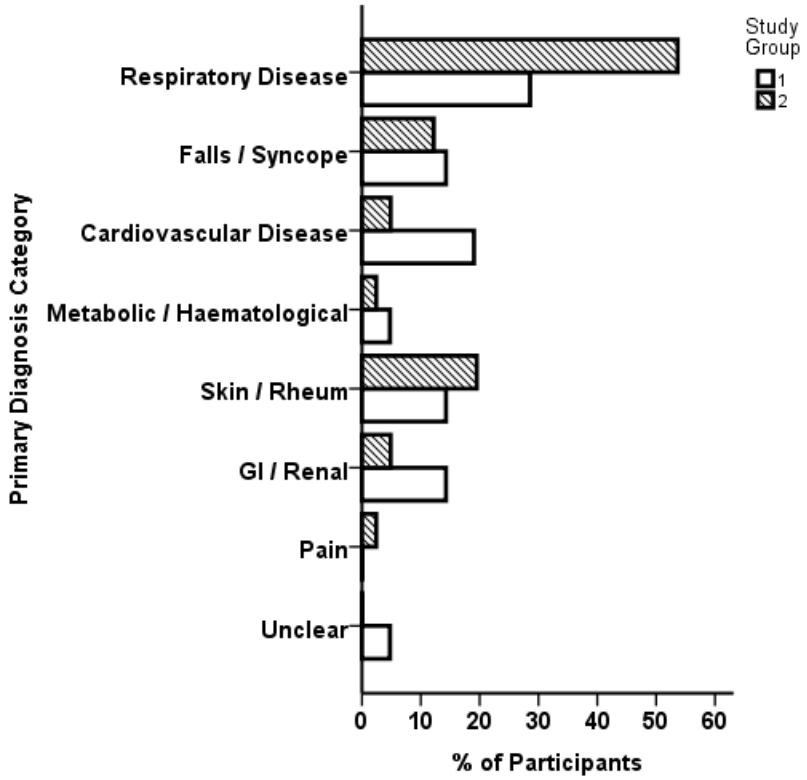


Figure 14: Percentage distribution of primary diagnoses categories, group 1 and 2 participants (prospective study)

Primary Diagnosis	Number of Participants	Group 1/2 Participants
Respiratory Disease	28	6/22
Falls/Syncope	8	3/5
Cardiovascular Disease	6	4/2
Metabolic/Haematological	2	1/1
Skin/Rheum Disease	11	3/8
GI and Renal	5	3/2
Pain	1	0/1
Unclear	1	1/0

Table 11: Frequency distribution of primary diagnoses categories, group 1 and 2 participants (prospective study)

3.3 Metabolic profiling

Participants from group 1 and 2 had similar (mean) values for BMI (hypothesis 1), waist circumference (hypothesis 2), weight, blood pressure (hypothesis 3), Epworth score (hypothesis 4) and neck circumference. (Table 12). Of note, a similar proportion of group 1 and 2 participants were treated with anti-hypertensives (38% and 39& respectively). An Independent samples t-test revealed no statistically significant differences in the mean or variance of these variables between group 1 and 2 participants (Table 13).

	Group 1	**Group 2**
BMI (kg/m^2)*		
Mean (± SD)	25.7 (± 4.77)	26.7 (±5.78)
Min/Max	17.6/33.9	16.6/43.4
N	20	39
Waist circumference (cm)*		
Mean (± SD)	101.4 (±10.54)	101.6 (±16.27)
Min/Max	84.0/124.0	77.0/157.0
N	19	36
Weight (kg)		
Mean (±SD)	73.3 (±16.44)	74.9 (±22.74)
Min/Max	47.7/112.5	42.0/160.0
N	20	40
SBP (mmHg)*		
Mean (±SD)	125 (±14.49)	133 (±19.28)
Min/Max	105/154	101/173
N	20	41
DBP (mmHg)*		
Mean (±SD)	72 (±7.70)	75 (±11.17)
Min/Max	56/85	54/97
N	20	41
Epworth Score*		
Mean (±SD)	5.5 (±5.02)	4.7 (±3.43)
Min/Max	0/19	0/11
N	21	41
Neck Circumference (cm)		
Mean (±SD)	39.9 (±5.74)	39.1 (±5.46)
Min/Max	29.0/53.0	28.0/51.0
N	19	38

Table 12: Descriptive statistics of Body Mass Index, weight, systolic blood pressure, diastolic blood pressure, waist circumference, neck circumference and Epworth score for group 1 and 2 participants (prospective study)

	Equal Variances Assumed	Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Sig. (2-tailed)
BMI	Yes	0.672	0.416	-0.665	57	0.509
	No			-0.707	45.457	0.483
Waist circumference	Yes	1.737	0.193	-0.056	53	0.956
	No			-0.064	50.586	0.949
Neck circumference	Yes	0.099	0.755	0.499	55	0.619
	No			0.491	34.506	0.627
Weight	Yes	1.763	0.189	-0.277	58	0.783
	No			-0.308	50.317	0.760
SBP	Yes	3.590	.063	-1.668	59	0.101
	No			-1.839	48.714	0.072
DBP	Yes	4.512	0.038	-.976	59	0.333
	No			-1.106	52.016	0.274
Epworth Score	Yes	1.390	0.243	0.711	60	0.480
	No			0.631	29.868	0.533

Table 13: Independent samples t-test of selected metabolic variables, group 1 and 2 participants (prospective study)

Table 14 describes copeptin values for group 1 and participants (hypothesis 5). An independent samples t-test did not reveal a statistically significant difference in the mean value between group 1 and 2 participants (Table 15). However, a highly statistically significant difference was found in the variance of copeptin between group 1 and 2 (Table 15, Figure 15).

	Study Group	N	Mean	SD	Min	Max
Copeptin (pmol/L)	1	20	8.88	6.49	2.3	24.5
	2	34	15.19	18.13	1.6	86.1

Table 14: Descriptive statistics of copeptin values for group 1 and 2 participants, prospective study

	Equal variances Assumed	Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Sig. (2-tailed)
Copeptin (pmol/L)	Yes	7.435	0.009**	-1.497	52	0.140
	No			-1.840	45.216	0.072

Table 15: Independent samples t-test for copeptin, group 1 and 2 participants (prospective study) * statistically significant p<0.05, ** statistically highly significant p<0.01

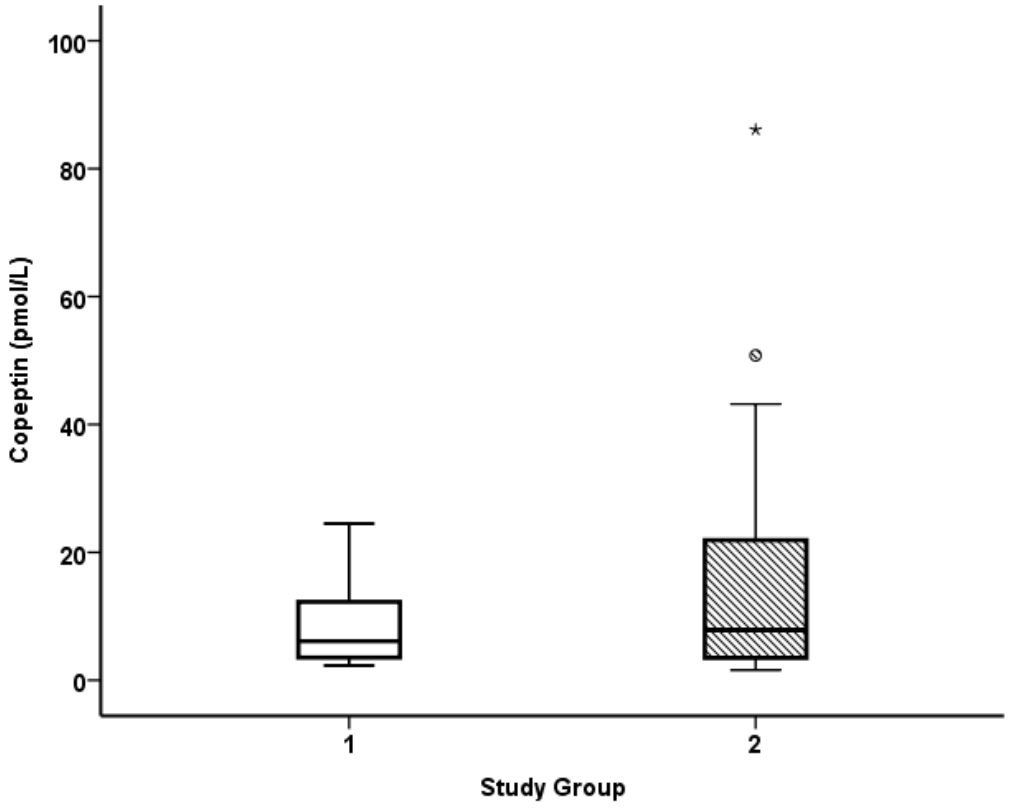


Figure 15: Copeptin values in n=54 group 1 and 2 participants, prospective study

As described in section 3.1.1, a number of further questions were asked of participants to complete their metabolic profile:

- Do you have a family history of diabetes?
- Do you have a Past Medical History (PMH) of hypertension?
- Do you have a PMH of Non-alcoholic Steatohepatitis (NASH)?

Only 1 participant from group 2 reported a history of NASH. Responses to the questions on diabetes and hypertension are displayed in Figure 16 and Figure 17 respectively.

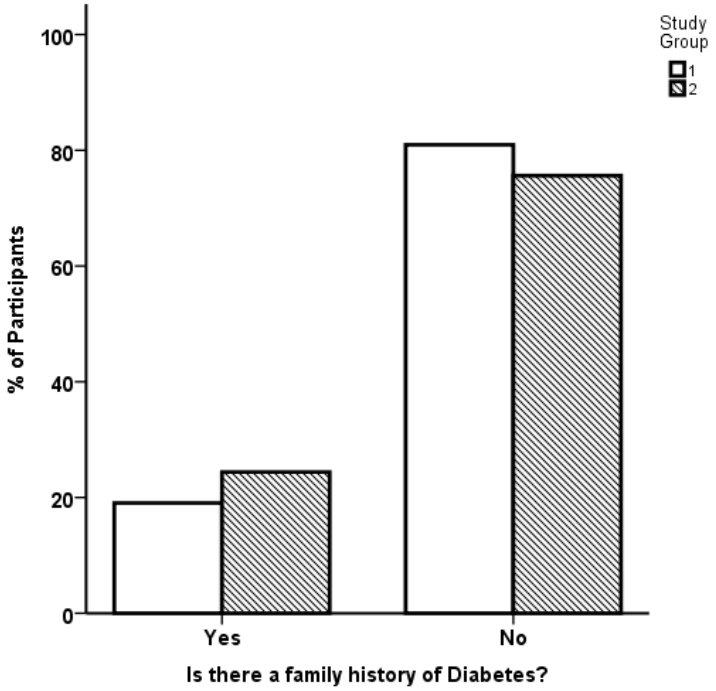


Figure 16: Percentage of participants with a family history of diabetes mellitus in group 1 and 2, prospective study

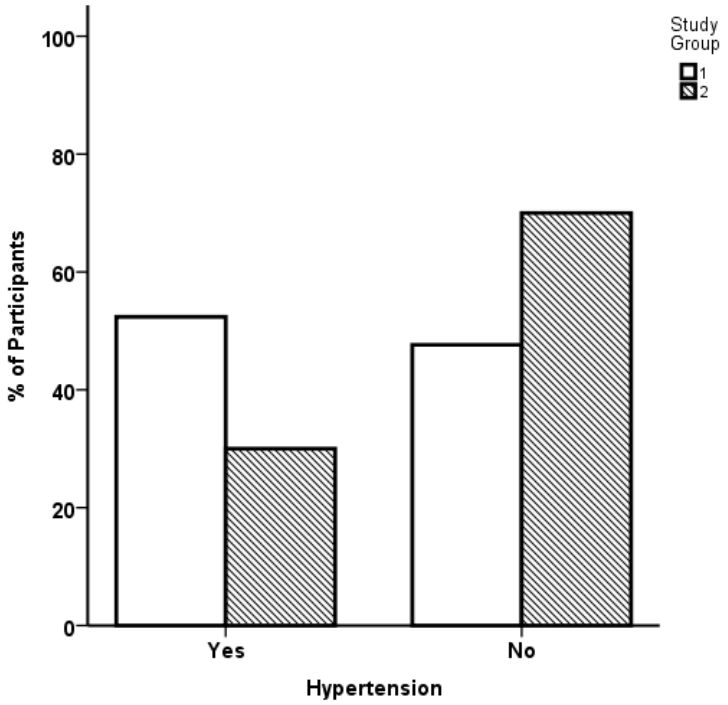


Figure 17: Percentage of participants reporting a past medical history of hypertension in group 1 and 2, prospective study

Considering the IDF definition of metabolic syndrome (see section 3.1.1), four participants from group 1 (27% of n=15) and 10 participants from group 2 (34% of n=29) loosely met the diagnostic criteria at baseline visit. Notably, this is only a estimate given lack of follow-up data in all participants (to assess persistence of hypertension) and lipid values. In addition, it is important to note that, although a higher proportion of participants in group 1 self-reported a history of hypertension, similar proportions of participants from groups 1 and 2 were actually prescribed anti-hypertensives (38% and 39% respectively).

3.4 Glucose values

The mean (baseline) plasma glucose for all prospective study participants was 6.7mmol/L. Recruited participants were placed into group 1 if their initial random plasma glucose (RPG)

was 7.1-11.0 mmol/L. The prevalence of SH was 34% in the prospective study population (as recruited within the available time-frame).

As described in section 2.1.10, participants with a RPG ≥11.1 were screened for diabetes and excluded as appropriate. Table 16 contains descriptive statistics for RPG whilst Figure 18 displays 95% confidence intervals and demonstrates clear separation between the 2 study groups as per study group definition (see section 2.1.8).

RPG Descriptors	Group 1	Group 2
N	21	41
Mean random plasma glucose in mmol/L (±SD)	8.4 (±1.02)	5.8 (±0.80)
Min/Max random plasma glucose in mmol/L	7.2/10.7	3.6/7.0

Table 16: Random plasma glucose levels (mean/SD/min/max) in group 1 and 2 participants, prospective study

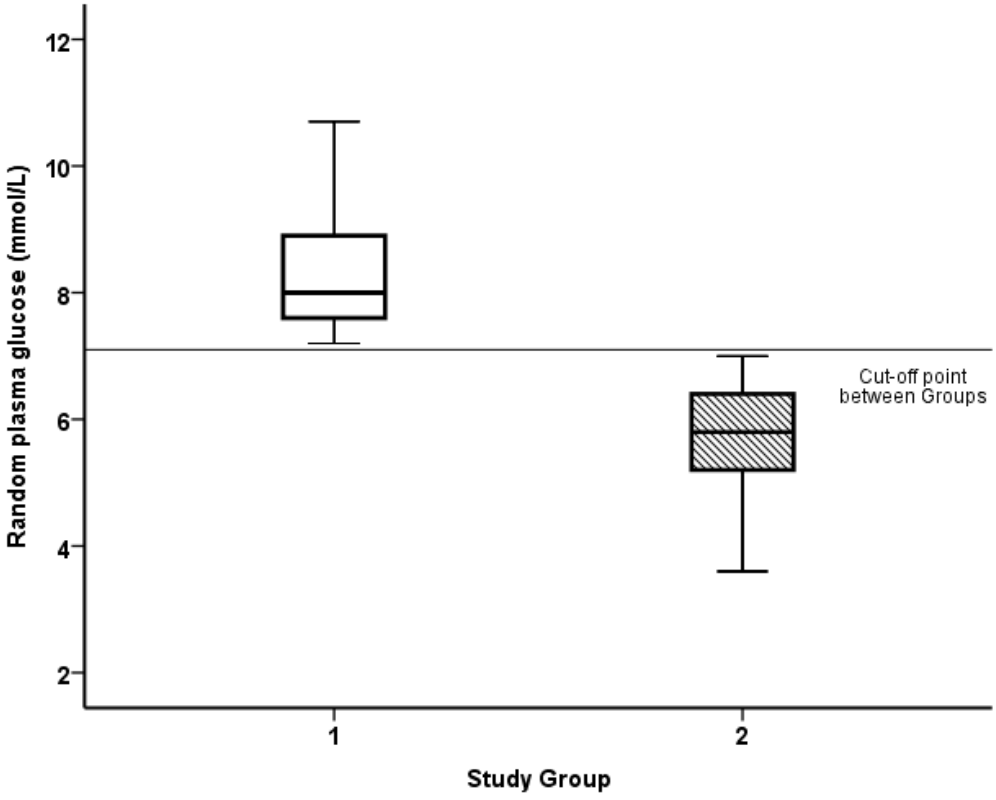


Figure 18: Random plasma glucose values in group 1 and 2 prospective study participants (n=62)

One-way Analysis of Variance (one-way ANOVA) post-hoc tests were performed to investigate any differences in mean RPG value between diagnostic categories for participants in groups 1 and 2. Categories 'metabolic/haematological', 'unclear' and 'pain' (with the lowest frequencies) were removed to allow the analysis to proceed.

Tukey-HSD testing showed that within study group 2, the only statistically significant differences in mean RPG values were for participants with renal and cardiovascular disease. Of this small number of participants (n=4), mean RPG were found to be significantly lower ($p<0.05$) than for those group 2 participants with diagnoses of falls/syncope, respiratory and skin/rheum disease. There were no significant differences in mean RPG values between participants in different diagnostic categories within study group 1. (Table 17).

Random plasma glucose (mmol/L)

Groups/Primary Diagnosis		N	Subset for alpha = 0.05		
			1	2	3
Student-Newman-Keuls[a,b]	G2/GI/Renal	2	5.200		
	G2/Cardiovascular	2	5.550		
	G2/Falls/Syncope	5	5.700		
	G2/Respiratory Disease	22	5.745		
	G2/Skin/Rheum	8	5.938		
	G1/Skin/Rheum	3		7.800	
	G1/GI/Renal	3		8.200	
	G1/Cardiovascular	4		8.300	
	G1/Falls/Syncope	4		8.450	
	G1/Respiratory Disease	7		8.600	
	Sig.		0.812	0.763	
Tukey HSD[a,b]	G2/GI/Renal	2	5.200		
	G2/Cardiovascular	2	5.550		
	G2/Falls/Syncope	5	5.700	5.700	
	G2/Respiratory Disease	22	5.745	5.745	
	G2/Skin/Rheum	8	5.938	5.938	
	G1/Skin/Rheum	3		7.800	7.800
	G1/GI/Renal	3			8.200
	G1/Cardiovascular	4			8.300
	G1/Falls/Syncope	4			8.450
	G1/Respiratory Disease	7			8.600
	Sig.[c.]		0.984	0.085	0.972

Means for groups in homogeneous subsets are displayed. (a) Uses Harmonic Mean Sample Size = 3.731. (b) The group sizes are unequal . The harmonic mean of the group sizes is used. Type I error levels are not guaranteed. (c) This p value refers to all variables within the same column, demonstrating no difference between the values in the homogenous subset.

Table 17: One-way Analysis of Variance (one-way ANOVA) post-hoc tests to examine differences in mean Random Plasma Glucose (RPG) values between diagnostic categories for group 1 and 2 participants.

Figure 19 and Table 18 display the FPG, taken the morning after study entry, for participants in study group 1 and 2.

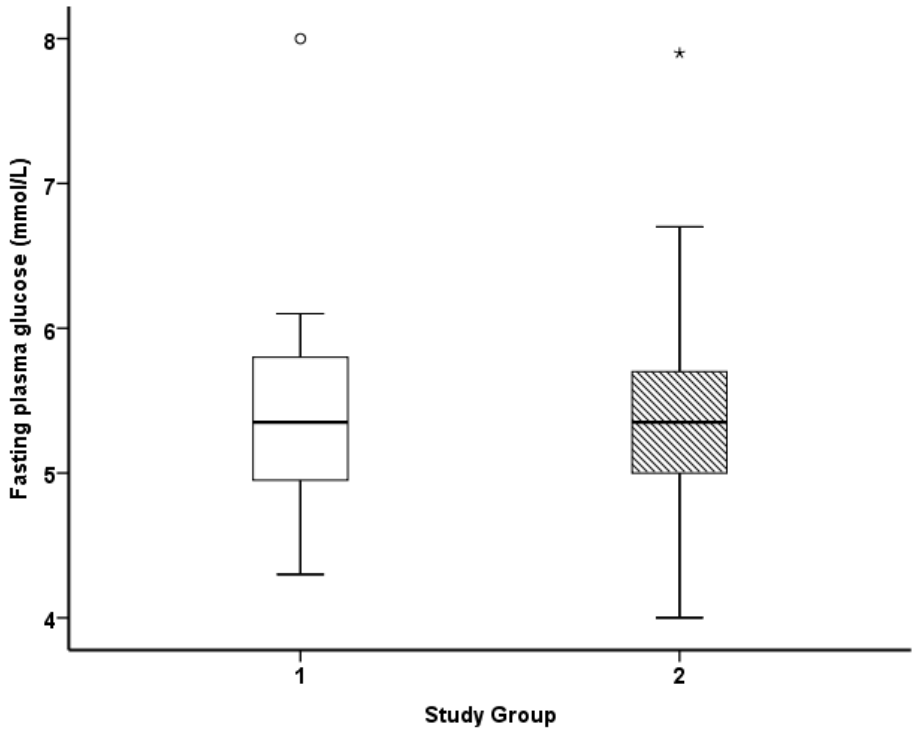


Figure 19: Fasting plasma glucose values in group 1 and 2 prospective study participants (n=46)

FPG Descriptors	Group 1	Group 2
N	16	30
Mean fasting plasma glucose (mmol/L) ±SD	5.4(±0.87)	5.5 (±0.78)
Min/Max fasting plasma glucose (mmol/L)	4.3/8.0	4.0/7.9

Table 18: Descriptive statistics of Fasting Plasma Glucose (FPG) values for group 1 and 2 participants

Figure 20 displays FPG and RPG on one figure for comparison:

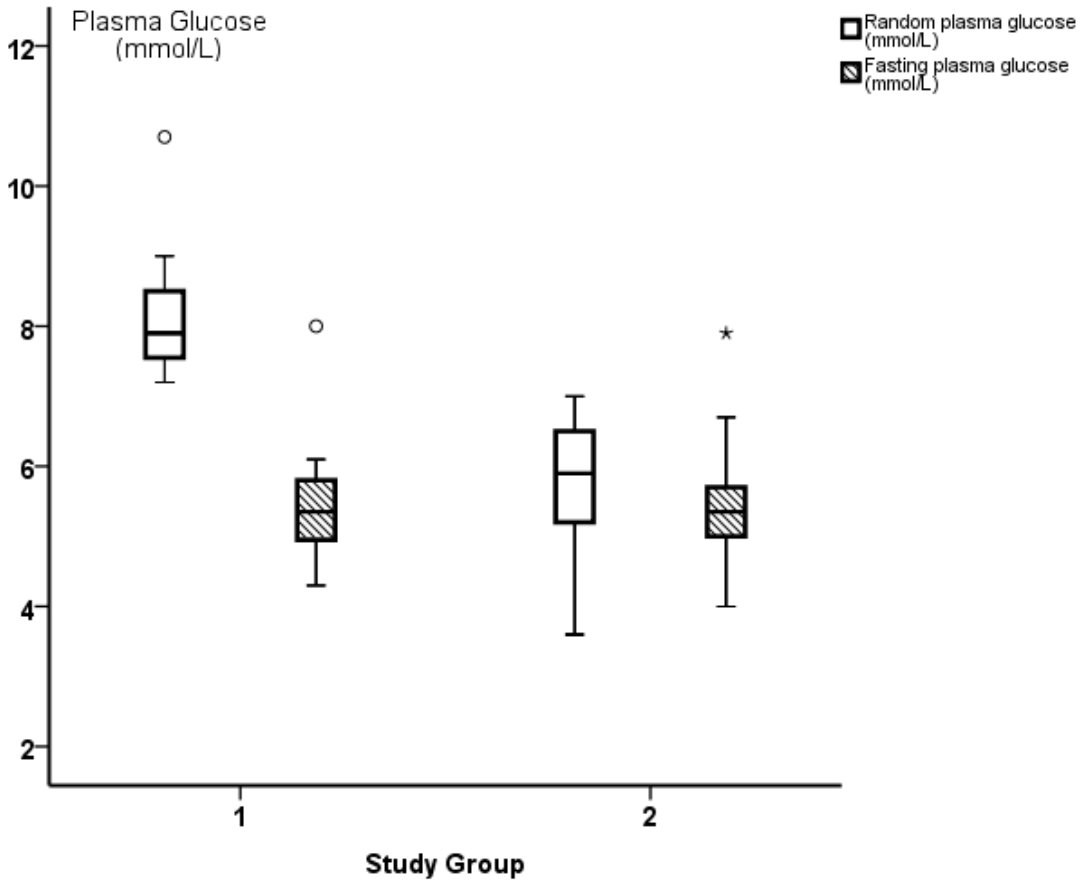


Figure 20: Random and fasting plasma glucose levels in group 1 and 2 prospective study participants

One-way Analysis of Variance (one-way ANOVA) post-hoc tests were performed to investigate any differences in the mean RPG and FPG values of participants in groups 1 and 2 (Table 19). As expected, mean RPG was significantly higher for participants in study group 1 compared to other glucose groups ($p < 0.05$). Mean FPG from both groups and RPG in group 2 were placed in the same homogenous subset and were not statistically different.

Plasma Glucose (mmol/L)

Study Group/Sample Type		N	Subset for alpha = 0.05	
			1	2
Student-Newman-Keuls[a,b]	Group 1/ Fasting Glucose	16	5.444	
	Group 2/ Fasting Glucose	31	5.561	
	Group 2/ Random Glucose	41	5.771	
	Group 1/ Random Glucose	21		8.410
	Sig.		0.449	1.000
Tukey HSD[a,b]	Group 1/ Fasting Glucose	16	5.444	
	Group 2/ Fasting Glucose	31	5.561	
	Group 2/ Random Glucose	41	5.771	
	Group 1/ Random Glucose	21		8.410
	Sig.		0.621	1.000

Means for groups in homogeneous subsets are displayed. (a) Uses Harmonic Mean Sample Size = 23.986 (b) The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

Table 19 One-way ANOVA post-hoc tests to examine differences in FPG and RPG values of group 1 and 2 prospective study participants

3.5 Steroid Prescriptions

48% of participants in group 1 (n=10) and 45% of participants in group 2 (n=18) were steroid treated at the time of study entry (Figure 21). The most frequent steroid prescribed in both

study groups was oral prednisolone at a dose of 30mg (12% of all prednisolone prescriptions in group 1 and 9.5% of all prednisolone prescriptions in group 2).

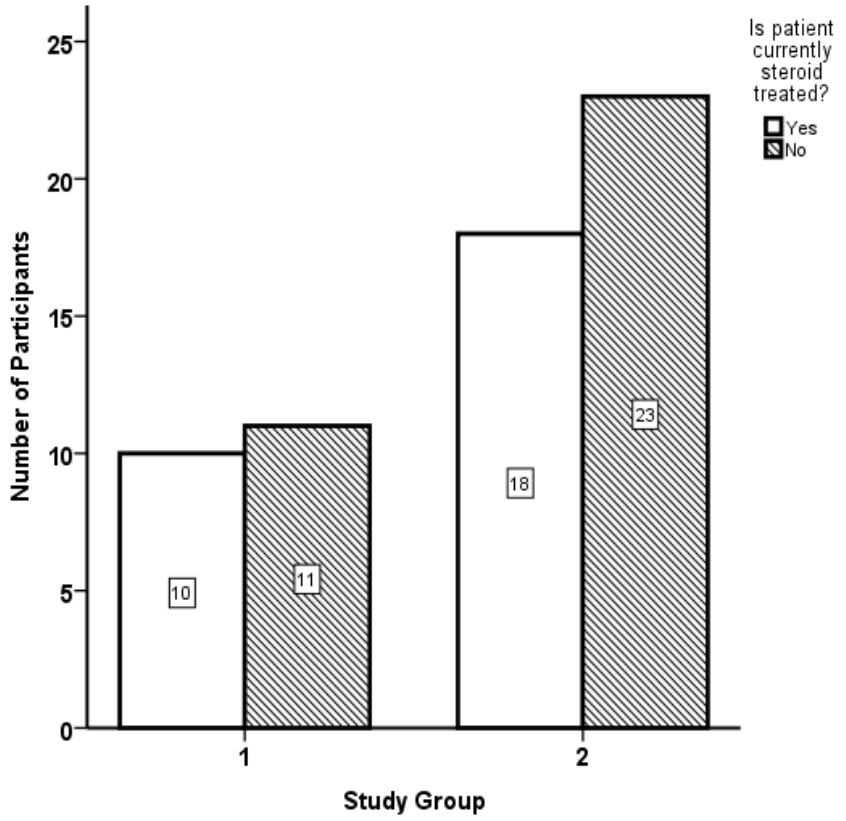


Figure 21: Steroid-treated participants in group 1 and 2, prospective study (n=62)

3.6 Nutrition and Hydration Status

An independent samples t-test did not reveal any statistically significant differences in the mean or variance of BIVA scores between group 1 and 2 participants (see methods section 2.1.12) Table 20 summarises the BIVA-derived hydration and body-type values for all participants.

Study Group	Hydration (Mean Value)	Nutrition (Body Type)
1	Mean value for this group was 77% defined as *'mildly wet'*	Obese 31% (n=5) Cachectic 25% (n=4) Muscular 25% (n=4) Lean 19% (n=3) **16 total**
2	Mean value for this group was 73% defined as *'normal hydration'*	Cachectic 61% (n=11) Obese 28% (n=5) Muscular 11% (n=2) Lean 0% **18 total**

Table 20: Mean BIVA-derived hydration scores for group 1 and 2 participants as well as proportions of group 1 and 2 participants with obese, cachectic, muscular and lean body types, prospective study (baseline visit)

3.7 Hospital Anxiety and Depression (HAD)

An independent samples t-test did not reveal any significant differences between the mean depression and anxiety scores (Table 21) of participants from group 1 and 2. All mean values were within the normal range (0-7).

	Study Group	N	Mean	Std. Deviation	Min/Max
Depression score	1	19	3.84	3.89	0/16
	2	41	2.88	2.40	0/9
Anxiety score	1	19	5.05	3.47	0/12
	2	41	4.34	3.62	0/16

Table 21: Descriptive statistics of Hospital Anxiety and Depression (HAD) scores for group 1 and 2 participants, prospective study

		Levene's Test for Equality of Variances		t-test for Equality of Means		
Equal Variances Assumed		F	Sig.	t	df	Sig. (2-tailed)
Depression score	Yes	2.736	0.104	1.180	58	0.243
	No			0.996	24.6	0.329
Anxiety score	Yes	0.175	0.678	0.716	58	0.477
	No			0.728	36.6	0.471

Table 22: Independent sample t-test of HAD scores, group 1 and 2 participants (prospective study) * statistically significant p<0.05, ** statistically highly significant p<0.01

3.8 Stress profiling

Descriptive statistics for participant CEWS scores at the time of study entry are contained in Table 23. The scoring system is described in more detail in section 2.1.12 and is scored out of 21. The CEWS score was '0' in all but 3 group 1 participants who had a score of '1'. A greater number of group 2 participants had a CEWS score of >0 (n=8). Independent sample t-testing did not demonstrate a statistically significant difference between the CEWS score for participants from group 1 and 2.

	Study Group	N	Mean	Std. Deviation	Min/Max
CEWS Score	1	21	0.14	0.36	0/1
	2	41	0.27	0.63	0/3

Table 23: Descriptive statistics of CEWS scores for group 1 and 2 participants, prospective study, n=62

3.9 Biomarkers

Table 24 summarises the biomarker values of group 1 and 2 participants taken at the baseline visit (with reference ranges where appropriate). Cortisol samples were taken between 07:30 and 09:00 on the morning after study entry. The mean cortisol value for all participants was 406nmol/L.

	Study Group	N	Mean	SD	Min	Max
HbA1c	1	20	39.75	4.63	33	52
(20-42 mmol/mol)	2	33	39.67	3.92	32	51
eGFR	1	21	78.38	17.05	39.0	91.0
(>59 ml/min/m^2)	2	40	78.70	18.87	17.0	91.0
Lactate	1	20	1.51	0.85	0.57	3.47
(0.6-2.5 mmol/L)	2	37	1.25	0.63	0.56	3.34
Cortisol	1	15	326.93	179.84	<20	569.0
(160-550 nmol/L)	2	30	432.23	301.14	<20	1650.0
hsCRP	1	21	72.21	71.96	0.5	224.4
(0.0-5.0mg/L)	2	41	75.53	96.73	0.3	339.9
Troponin 1	1	19	0.18	0.73	<0.05	3.18
(<0.05 ng/mL)	2	34	0.005	0.03	<0.05	0.17
BNP	1	19	149.37	198.69	<0.5	784.0
(0.0-100 pg/mL)	2	35	114.38	166.15	<0.5	774.0
Ketones	1	19	0.05	0.06	0.0	0.2
(<0.6 mmol/L)	2	39	0.47	1.16	0.0	5.1
Pro-ADM	1	20	1.00	0.48	0.41	2.00
(nmol/L)	2	34	1.07	0.63	0.23	2.97
25-OH-Vitamin D	1	5	23.38	8.91	9.9	33.7
(70-150 nmol/L)	2	8	52.84	33.45	13.8	118.7

Table 24: Descriptive statistics of biomarker values for group 1 and 2 participants, prospective study with local biomarker reference ranges. Cortisol reference range applies to samples take at approximately 9am.

An independent samples t-test (Table 25) demonstrated a statistically significant difference ($p < 0.05$) between mean blood ketone (Figure 22) and 25-OH-Vitamin D (Figure 23) values of group 1 and 2 participants. A statistically significant difference was also found in the variance between group 1 and 2 for blood ketones.

		Levene's Test for Equality of Variances		t-test for Equality of Means		
	Equal variances Assumed	F	Sig.	t	df	Sig. (2-tailed)
HbA1c	Yes	0.697	0.408	0.070	51	0.944
(mmol/mol)	No			0.067	35.128	0.947
eGFR	Yes	0.001	0.972	-0.065	59	0.949
(ml/min/m2)	No			-0.067	44.533	0.947
Lactate	Yes	2.426	0.125	1.283	55	0.205
(mmol/L)	No			1.172	30.415	0.250
Cortisol	Yes	0.353	0.556	-1.244	43	0.220
(nmol/L)	No			-1.463	41.446	0.151
hsCRP	Yes	1.581	0.214	-0.139	60	0.890
(mg/L)	No			-0.152	51.916	0.879
BNP	Yes	0.251	0.619	0.690	52	0.494
(pg/mL)	No			0.654	31.830	0.518
Ketones	Yes	6.324	0.015*	-1.562	56	0.124
(mmol/L)	No			-2.243	38.429	0.031*
Pro-ADM	Yes	0.054	0.816	-0.424	52	0.673
(nmol/L)	No			-0.455	48.371	0.651
25-OH-Vitamin	Yes	4.181	0.066	-1.899	11	0.084
D (nmol/L)	No			-2.361	8.487	0.044*

Table 25: Independent samples t-test for biomarkers, group 1 and 2 participants (prospective study) * statistically significant p<0.05, ** statistically highly significant p<0.01

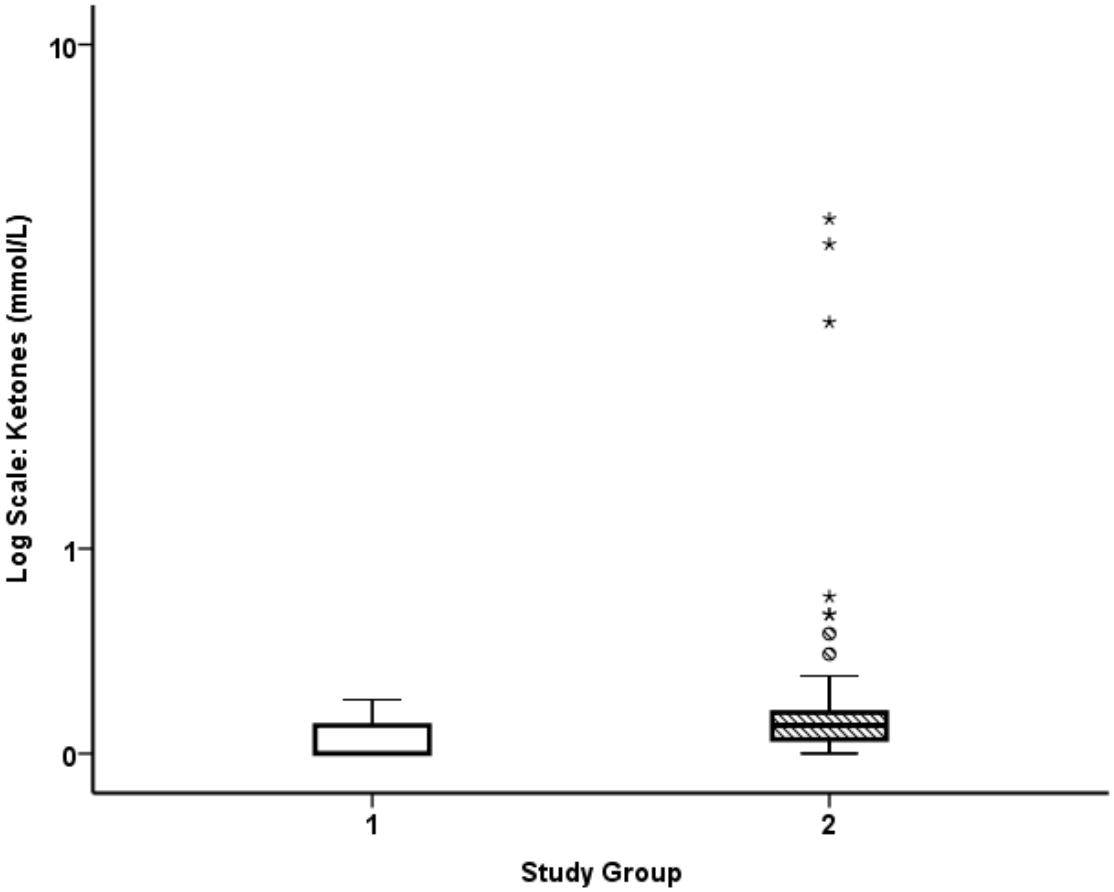


Figure 22: Blood ketone values (log scale) in group 1 and 2 participants, prospective study (n=58)

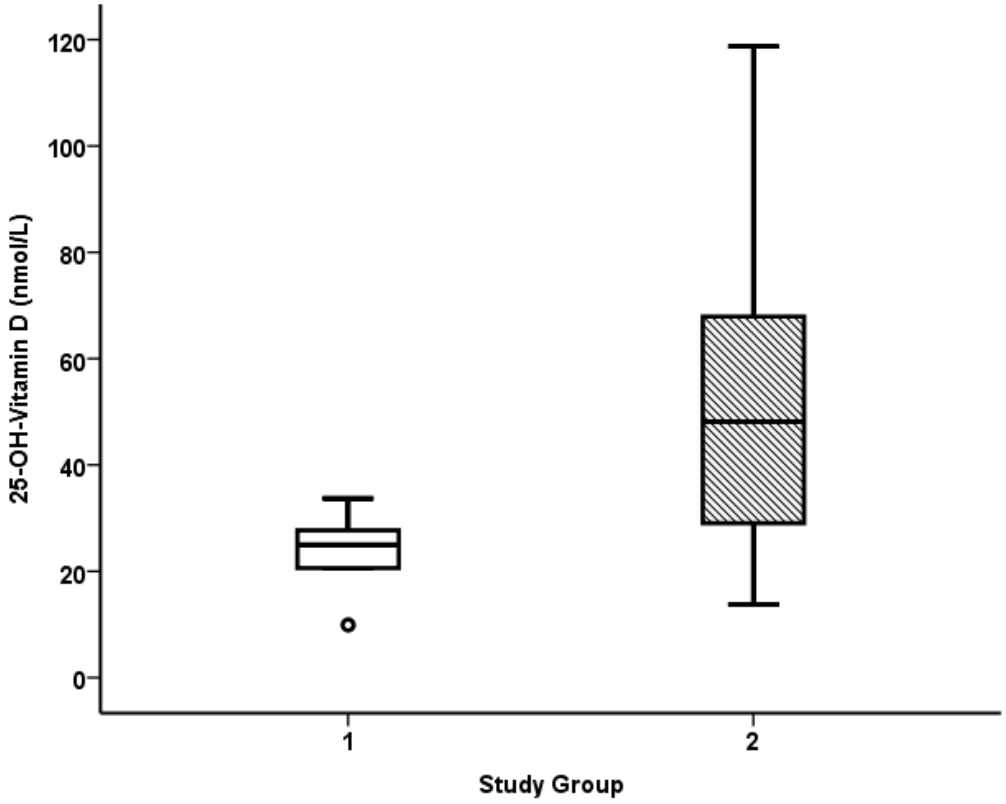


Figure 23: 25-OH Vitamin D values in group 1 and 2 participants, prospective study (n=13)

No differences were found between mean HbA1c (Figure 24) or cortisol values (Figure 25) for group 1 and 2 participants. All participants apart from n=3 had a troponin I value of <0.05 ng/mL.

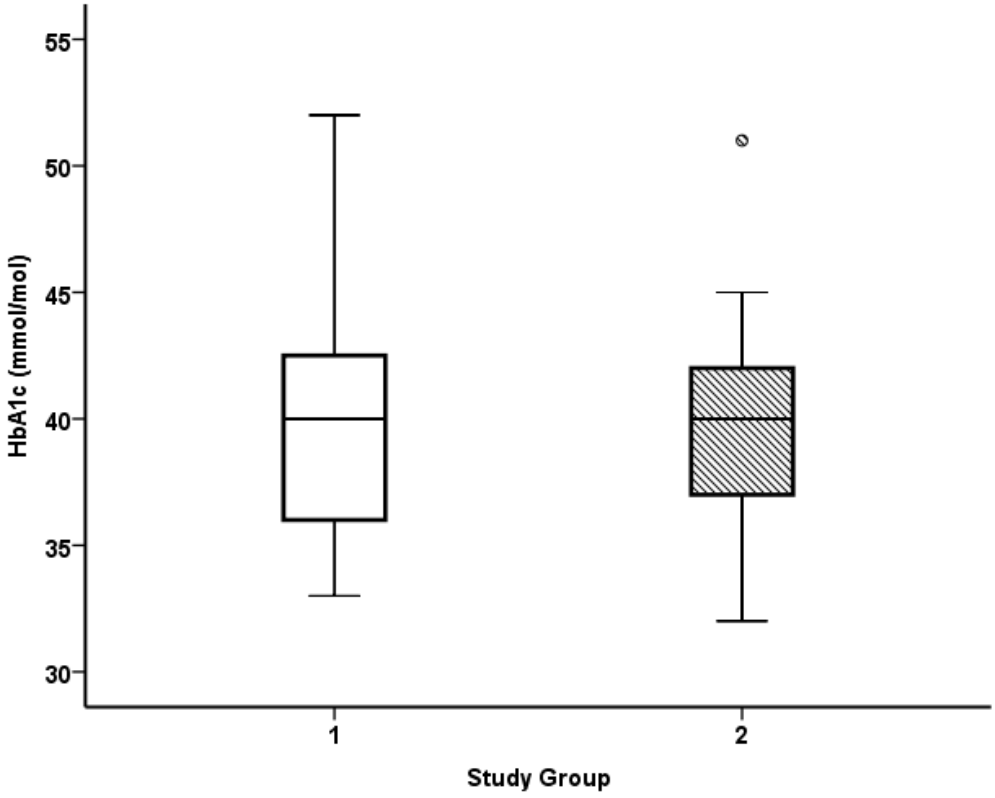


Figure 24: HbA1c values in group 1 and 2 participants, prospective study (n=53)

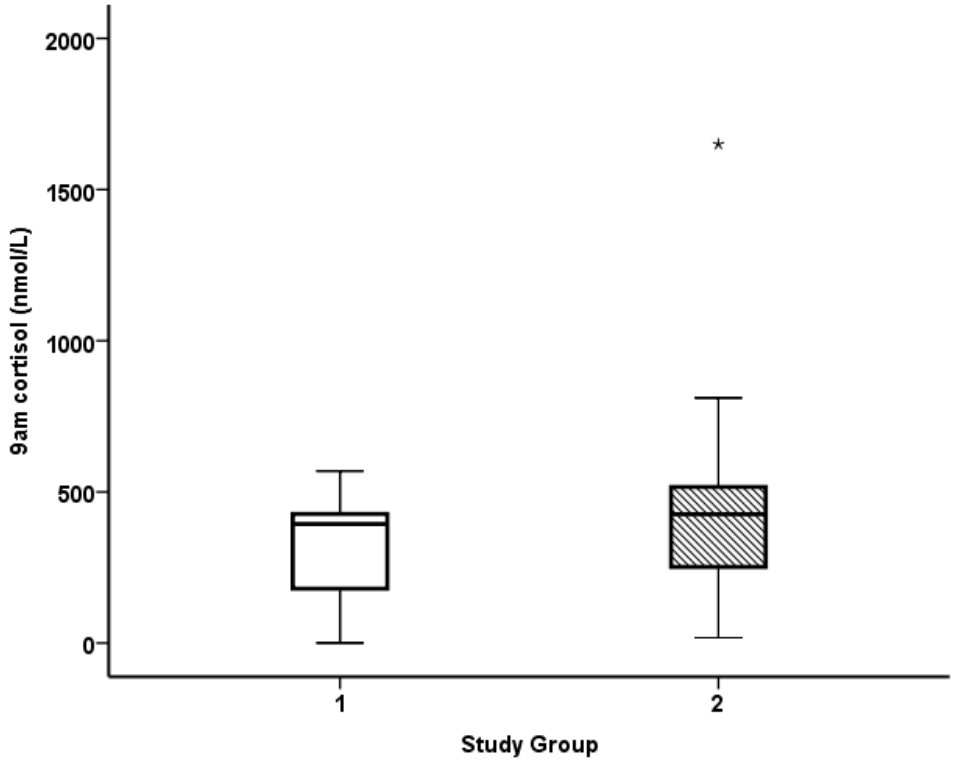


Figure 25: Cortisol values in group 1 and 2 participants, prospective study (n=45)

Table 26 describes significant and highly significant biomarker correlations noted in all participants (groups 1 and 2 combined).

Variable 1	Variable 2	Pearson Correlation	Sig.(2-tailed)	N
Fasting insulin (mIUL)	Copeptin (pmol/L)	0.376*	0.012	44
	hsCRP (mg/L)	0.321*	0.031	45
Pro-ADM (nmol/L)	Copeptin (pmol/L)	0.749**	0.000	54

Table 26: Notable statistically significant Pearson correlations between biomarkers - all prospective study participants (groups 1 and 2 combined)* statistically significant p<0.05, ** statistically highly significant p<0.01

3.10 Short-Term Outcomes

As described in section 2.1.9, a number of short-term outcomes were studied. They include:

- Length of stay
- Metabolic outcomes: new diagnoses of Impaired Glucose Regulation (IGR) and Diabetes Mellitus (DM)
- A selection of variables for consenting group 1 participants at dedicated follow-up

A description of these outcomes and relevant analyses are described in section 3.10.1 to 3.10.3.

3.10.1 Length of Stay

The mean Length of Stay (LOS) for all participants was 4.5 days (n=58, SD ±4.94, min/max 1/32 days). Table 27 contains descriptive data on LOS for each study group. An independent samples t-test did not show a statistically significant difference in length of stay between group 1 and 2 participants.

Variable	Study Group	N	Mean	Std. Deviation	Min/Max
LOS (days)	1	20	6.3	7.07	1/32
	2	38	3.6	3.06	1/18

Table 27: Descriptive statistics of Length of Stay for group 1 and 2 participants, prospective study

LOS was positively correlated with variable 'copeptin' in group 1 but not group 2 participants (Pearson correlation 0.472, $p<0.05$).

3.10.2 Metabolic Outcomes

Newly Diagnosed Diabetes Mellitus

As described in section 3.1.2, one participant was withdrawn from the study during the screening process. The reason for withdrawal was a new diagnosis of T2DM (RPG of 11.2mmol/L, HbA1c 51mmol/mol and symptoms of DM). Procedures outlined in section 2.1.10 were followed.

Metabolic Abnormalities: Introduction

The term 'metabolic abnormalities' is used by the investigator to describe a number of related disorders. Table 28 summarises the diagnostic criteria for these disorders, the majority of which did not necessitate participant withdrawal. Disorders 'IFG', 'IGT' and 'high risk for diabetes' may also be summarised as 'Impaired Glucose Regulation' or IGR (see section 6.3).

During the course of the study it became apparent that, due to the study design, rapid patient turnover in the recruitment setting and the timing of pathology results, a new category would have to be added to 'metabolic abnormalities'. This category was entitled 'biochemical features of DM' by the investigator and is used to describe participants in whom 1

biochemical value met the diagnostic criteria for DM but, for a number of reasons, it was not possible to assess for symptoms of DM/request a second test and formally diagnose DM. As per participants diagnosed with DM, a letter was sent to their GPs advising further follow-up (section 2.1.10).

Metabolic Abnormality	**Diagnostic Criteria**
Diabetes Mellitus (DM)	Diabetes symptoms plus: • RPG ≥ 11.1 mmol/l or FPG ≥ 7.0 mmol/l • *or* 2hr plasma glucose concentration ≥ 11.1 mmol/l after 75g oral glucose load In the absence of symptoms, at least one additional glucose test result on another day, with a value in the diabetic range, is required for diagnosis. (WHO/IDF, 2006), (Diabetes UK)
Biochemical features of DM (BFD)	Single biochemical value fulfilling the diagnostic criteria for DM but, due to study design/recruitment setting, a formal diagnosis of DM not made (defined by the study team)
Impaired Fasting Glucose (IFG)	Fasting Plasma Glucose (FPG) between 6.1-6.9mmol/L (WHO/IDF, 2006)
Impaired Glucose Tolerance (IGT)	FPG <7.0mmol/L and 2hr venous plasma glucose (after ingestion of 75g oral glucose load) 7.8-11.1mmol/L (NICE 2012, WHO/IDF, 2006)
High Risk for Diabetes (HRD)	HbA1c 42-47 mmol/mol (NICE 2012)
Impaired Glucose Regulation (IGR)	Term encompassing IFG, IGT and HRD (NICE 2012)

Table 28: Diagnostic criteria for metabolic abnormalities detected in the prospective and metformin studies.

Impaired Glucose Tolerance (IGT)

Considering the definitions in Table 28, one participant was diagnosed with IGT during study follow-up (Table 29):

Variable	Value
Patient ID & Study Group	011, Group 1
Admission RPG (mmol/L)	8.9
Admission FPG (mmol/L)	4.9
OGTT Glucose 0/2hr (mmol/L)	5.4/10.0
Admission HbA1c (mmol/mol)	39
HOMA2 IR	1.0

Table 29: Random plasma glucose, fasting plasma glucose, OGTT, HbA1c and HOMA2 values for participant 011 diagnosed with IGT during prospective study follow-up

Impaired Fasting Glycaemia (IFG)

Eight patients were diagnosed with Impaired Fasting Glycaemia (IFG) during the course of the study. Notable variables are described in Table 30.

Variable	Value
Study Group distribution (group 1/2)	2/6
Mean Admission RPG (mmol/L)	7.1
Min/Max RPG (mmol/L)	6.1/6.7
Mean Diagnostic FPG (mmol/L)	6.3
Mean Admission HbA1c (mmol/mol)	39
Min/Max HbA1c (mmol/mol)	33/45
Mean HOMA2 IR (n=7)	2.8
Min/Max HOMA2 IR	0.7/6.8

Table 30: Study group, random and fasting plasma glucose, HbA1c, HOMA2-IR (mean/min/max) values for n=8 prospective study participants diagnosed with Impaired Fasting Glycaemia (IFG)

OGTT results were only available for 1 participant with IFG (0hr: 6.1 mmol/L, 2hr: 6.2mmol/L) as some participants with IFG were from group 2 (no study follow-up/OGTT) and 1 participant from group 1 declined follow-up. GPs were advised that all participants diagnosed with IFG using FPG should have an OGTT to determine glucose tolerance status

(WHO/IDF, 2006). Three participants with IFG (054,056 and 059) consented to wear a CGMS -their detailed profiles are illustrated in section 4.3.

High risk for Diabetes Mellitus

The mean HbA1c for all participants was 40mmol/mol. Twelve participants were highlighted as 'high risk for DM' (Table 28). Notable variables are summarised in Table 31.

Variable	Value
Study Group distribution (group 1/2)	6/6
Mean Admission RPG (mmol/L)	7.0
Min/Max RPG (mmol/L)	4.6/10.7
Mean Admission FPG (mmol/L)	5.5 (n=9)
Min/Max FPG (mmol/L)	4.9/6.0
Mean Admission HbA1c (mmol/mol)	43
Min/Max HbA1c (mmol/mol)	42/45
Mean HOMA2-IR	1.0 (n=8)
Min/Max HOMA2-IR	0.5/1.5

Table 31: Study group, random and fasting plasma glucose, HbA1c, HOMA2IR (mean/min/max) values for 12 prospective study participants considered to be at high risk for Diabetes Mellitus based on HbA1c values

OGTT results were available for 3 participants highlighted as 'high risk for DM'. Mean glucose values for these patients were:

- 0hr: 4.9 mmol/L
- 2hr: 4.7 mmol/L

Two participants at high risk for diabetes (057 and 063) consented to wear a CGMS. These detailed profiles are illustrated in section 4.3.

Biochemical Features of DM

Four participants displayed 'biochemical features of DM' (Table 28). The characteristics of these participants are outlined in tables 32-35 with the variable suggestive of DM highlighted in bold font. Of note, participant 041 had pre-existing IGT. Participant 023 was defined as having 'biochemical features of DM' due to a HbA1c value of 51 mmol/mol which although meets the diagnostic criteria for DM (WHO, 2011), should not, according to UK guidance, be used solely for the diagnosis of DM in the acute setting (see section 6.4).

In addition, one participant (061) displayed SG readings of >20mmol/L on CGM (see section 4.3.2). This participant's biochemical characteristics are summarised in table 57 but are not further included within this section. Procedures for participants with 'newly diagnosed diabetes mellitus' were followed (see section 2.1.10).

Variable	**Value**
Study Group	1
Age (years)	53
Gender	Female
Ethnicity	Black
Weight (kg)	74.1
BMI ($kg/m^{2)}$	28.9
Waist circumference (cm)	102
Neck circumference (cm)	35.5
Epworth score	1
Admission RPG (mmol/L)	8.1
Admission FPG (mmol/L)	5.9
OGTT 0/2hr glucose (mmol/L)	**10.2/6.7**
Admission HbA1c (mmol/mol)	44
Admission HOMA2-IR	1.3

Table 32: Demographic, clinical and biochemical features of participant 002R

Variable	Value
Study Group	2
Age (years)	46
Gender	Male
Ethnicity	White British
Weight (kg)	90.0
BMI (kg/m$^{2)}$	29.7
Waist circumference (cm)	99
Neck circumference (cm)	39
Epworth score	4
Admission RPG (mmol/L)	4.6
Admission FPG (mmol/L)	**7.9**
OGTT 0/2hr glucose (mmol/L)	N/a
Admission HbA1c (mmol/mol)	42
Admission HOMA2-IR	1.2

Table 33: Demographic, clinical and biochemical features of participant 007

Variable	Value
Study Group	2
Age (years)	58
Gender	Female
Ethnicity	Black/Black British
Weight (kg)	84.6
BMI (kg/m$^{2)}$	33.0
Waist circumference (cm)	Not taken
Neck circumference (cm)	Not taken
Epworth score	10
Admission RPG (mmol/L)	4.9
Admission FPG (mmol/L)	4.5
OGTT 0/2hr glucose (mmol/L)	N/a
Admission HbA1c (mmol/mol)	**51**
Admission HOMA2-IR	0.9

Table 34: Demographic, clinical and biochemical features of participant 023

Variable	Value
Study Group	1
Age (years)	81
Gender	Male
Ethnicity	White British
Weight (kg)	74.3
BMI (kg/m$^{2)}$	30.9
Waist circumference (cm)	104
Neck circumference (cm)	45
Epworth score	5
Admission RPG (mmol/L)	7.9
Admission FPG (mmol/L)	**8.0**
OGTT 0/2hr glucose (mmol/L)	**6.1/11**
Admission HbA1c (mmol/mol)	**52**
Admission HOMA2-IR	1.0

Table 35: Demographic, clinical and biochemical features of participant 041

Metabolic Abnormalities: Summary

A total n=11 participants from group 1 and n=14 participants from group 2 were diagnosed with metabolic abnormalities giving a prevalence of 40% for all recruited prospective study participants. (Table 36). IGR (encompassing IFG, IGT, HRD) was diagnosed in 34% (n=21) of all participants. Individuals 024 and 042 had an HbA1c value which fell in the 'high risk for DM' category but, as they were formally diagnosed with IFG, they were only included in the latter category.

Fifty two percent of participants with metabolic abnormalities were steroid-treated (oral/topical/inhaled) at the time of study entry. Table 37 displays the metabolic profile and other selected variables in participants with and without MA. It should be noted that metabolic outcomes in group 1 and 2 are not directly comparable as only group 1 had a study follow-up phase.

Diagnosis	Group 1 (n=21)	Group 2 (n=41)
IGT	1	0
IFG	2	6
High risk for DM	6	6
Biochemical Features of DM	2	2
TOTAL (% of study group)	11 (52%)	14 (34%)

Table 36: Numbers and proportions of participants diagnosed with IGT, IFG, 'high risk for DM' and with 'biochemical features of DM' from study group 1 and 2

	Group 'MA' (n=25)	**Group 'no MA' (n=37)**
Age (mean, years)	68	68
Gender (% male)	64%	57%
BMI (mean, kg/m2)	28.6 (n=24)	24.8 (n=35)
Waist circumference (mean, cm)	106.9 (n=22)	97.9 (n=33)
SBP (mean, mmHg)	131 (n=24)	129
DBP (mean, mmHg)	74 (n=24)	73
Epworth score (mean)	4	5
Copeptin (mean,)	16.9 (n=18)	11.8 (n=28)
HbA1c (mean, mmol/mol)	42 (n=23)	38 (n=30)
Morning Cortisol (mean, nmol/L)	415 (n=19)	399 (n=25)
HOMA2-IR (mean)	1.7 (n=19)	1.1 (n=18)
LOS (mean, days)	4 (n=24)	5 (n=34)
BNP (pg/mL)	176 (n=21)	97.7 (n=34)
CRP (mg/L)	63 (n=25)	82 (n=37)
Lactate (mmol/L)	1.25 (n=23)	1.42 (n=35)

Table 37: Mean values for metabolic profile measures (in bold) and selected variables in participants with and without Metabolic Abnormalities (MA), prospective study

An independent samples t-test demonstrated statistically significant differences between BMI ($p<0.05$) and waist circumference ($p<0.01$) in participants with and without metabolic abnormalities. There were no statistical differences between the groups with regards copeptin, BP, Epworth score and CRP. Due to data distribution, BNP and lactate values were assessed using the nonparametric Mann-Whitney test. Again there was no statistically significant

difference between the groups for these 2 variables. Variables 'HbA1c', 'cortisol', 'HOMA2-IR' and 'LOS' were not tested.

Finally, half of the participants who wore a CGM (n=6) were diagnosed with a metabolic abnormality during the course of the study. No statistically significant differences were found in glycaemic variability between the groups with and without metabolic abnormalities (total n=12, Appendix 5).

Type 2 Diabetes Risk

Using the GUARD Type 2 Diabetes Risk Calculator, the 3 year risk of developing Type 2 Diabetes was calculated at a mean score of 5.4% for group 1 participants (n=19) and 1.7% for group 2 participants (n=31). Not all participants were included in this calculation as a number (n=12) had an age/admission glucose that fell outside of the calculator range. A GUARD score of 5% and over broadly corresponds to a 'high risk' category as described by NICE. Table 38 summarises the metabolic profile of participants with a GUARD score < and ≥ 5% as well as neck circumference, fasting insulin and HbA1c values. All Participants with a GUARD score **≥5%** were from group 1.

Variable	GUARD <5%	GUARD ≥5%
Mean BMI (kg/m^2)	26.4	25.8
Mean SBP (mmHg)	131	124
Mean DBP (mmHg)	74	74
Mean Waist circumference (cm)	100.9	104.9
Mean Neck circumference (cm)	39.1	41.1
Mean Epworth Score	5	7
Mean HbA1c (mmol/mol)	40	40
Mean Fasting Insulin (mIU/L)	12.8	7.1

Table 38: 'Metabolic profile', neck circumference, HbA1c and fasting insulin of participants with a GUARD score < and ≥ 5%, prospective study

3.10.3 Group 1 Study Follow-up

As described in section 3.1.2, n=10 participants from group 1 attended visit 1, whilst n=11 were lost to follow-up. The mean duration from discharge to visit 1 was 115 days (min 94, max 190 days).

Tables in Appendix 4 display selected baseline and follow-up study variables for participants with a full data set. 'Baseline' refers to variables measured during hospital admission and 'f/up' refers to variables measured at visit 1.

Table 39 summarises all 'paired' variables with values available at baseline and visit 1. A paired samples t-test did not demonstrate a statistically significant difference between baseline and visit 1 variables (Table 40).

Notably, given that an OGTT was performed at visit 1, a RPG could not be checked at this visit and is only available for the baseline visit.

Variable	Study Point	N	Mean	SD
Weight (kg)	Baseline	10	84.6	13.03
	Visit 1	10	86.1	14.52
FPG (mmol/L)	Baseline	8	5.7	0.99
	Visit 1	8	5.9	1.86
Fasting Insulin (mIU/L)	Baseline	8	6.9	1.88
	Visit 1	8	11.0	10.12
HbA1c (mmol/mol)	Baseline	10	41	4.85
	Visit 1	10	38	3.35
HOMA2-IR	Baseline	7	0.9	0.28
	Visit 1	7	1.4	1.37
Copeptin (pmol/L)	Baseline	10	9.28	6.87
	Visit 1	10	7.56	4.78
ProADM (nmol/L)	Baseline	10	1.05	0.47
	Visit 1	10	0.79	0.32

Table 39: Baseline and visit 1 variables for group 1 participants attending follow-up, prospective study

	Paired Differences		t	df	Sig. (2-tailed)
	Mean	Std. Deviation			
Weight (kg)	-1.56000	7.50840	-0.657	9	0.528
Fasting plasma glucose (mmol/L)	-.17500	1.87293	-0.264	7	0.799
Fasting insulin (mIU/L)	-4.06250	9.57168	-1.200	7	0.269
HbA1c (mmol/mol)	3.10000	4.70106	2.085	9	0.067
HOMA2-IR	-0.48571	1.31584	-0.977	6	0.366
Copeptin (pmol/L)	1.72100	4.72306	1.152	9	0.279
Pro-ADM	0.26100	.38757	2.130	9	0.062

Table 40: Paired samples t-test for paired baseline and visit 1 variables, group 1 participants

* statistically significant p<0.05, ** statistically highly significant p<0.01

3.11 Summary of Chapter 3

- The prevalence of SH was 34% in the recruited prospective study population.
- Participants from study group 1 and 2 were similar in terms of age, gender, and ethnicity.
- The most frequently occurring primary diagnosis within both study groups was 'respiratory disease'
- **Mean values of the metabolic profile (including BMI, waist circumference, BP and Epworth score, copeptin variables) were not statistically significantly different between group 1 and 2 participants (hypotheses 1-5). Proportions of participants treated with anti-hypertensives were similar in group 1 and 2**

- Despite this, group 1 did have a lower variance in copeptin compared to group 2 participants ($p \leq 0.01$)
- Group 1 and 2 contained similar proportions of participants with a positive family history of DM. There appeared to be a higher proportion of people with a PMH of hypertension in group 1 compared to group 2
- Although only a estimate, similar proportions of participants from group 1 and 2 met the IDF diagnostic criteria for metabolic syndrome
- The mean baseline RPG was 6.7mmol/L for all prospective study participants: 8.4mmol/L in group 1 and 5.8mmol/L in group 2 participants
- Mean RPG values were not statistically significantly different across different diagnostic categories of group 1 participants
- The mean FPG values for group 1 and 2 participants were 5.4 and 5.5 mmol/L respectively. One-way ANOVA testing did not demonstrate a statistically significant difference in the FPG of participants from group 1 and 2 or the FPG and RPG of participants from group 2. RPG was (statistically significantly) higher than FPG in group 1 participants
- Similar proportions of participants from group 1 and 2 were steroid treated at the time of study entry (48% and 45% respectively). Fifty two percent of participants diagnosed with metabolic abnormalities during the study were steroid-treated at the time of study entry.
- There were no statistically significant differences in the BIVA-related hydration and nutrition scores between participants in group 1 and 2
- There were no statistically significant differences in the HAD scores between participants in group 1 and 2

- CEWS score was low (0) in most participants. Participants from group 1 did not have significantly higher CEWS scores compared to participants in group 2.
- Group 1 participants had lower mean ketone values ($p \leq 0.05$) as well as lower variance in ketone values ($p \leq 0.01$) compared to group 2 participants. A greater proportion of group 2 participants also had a 'cachectic' body type (61% compared to 25% in group 1).
- Group 1 participants had lower mean 25-OH-Vitamin D values compared to group 2. Of note, numbers analysed were small (whole group n=13)
- No statistically significant differences were found between mean HbA1c or cortisol values for group 1 and 2 participants.
- A number of correlations were observed between biomarkers and other variables. Of note, in all participants (group 1 and 2 combined), a statistically significant positive correlation was noted between fasting insulin and copeptin ($p<0.05$)
- A highly significant positive correlation was noted between proADM and Copeptin for all participants ($p<0.000$)
- Copeptin was noted to be positively correlated with length of stay for group 1 but not group 2 participants
- An independent samples t-test did not show a statistically significant difference in length of stay between group 1 and 2 participants
- Although not strictly comparable, it is of interest to note that 52% of group 1 participants and 34% of group 2 participants (40% of all recruited participants) were diagnosed with metabolic abnormalities (including IGT, IFG, high risk for DM and biochemical features of DM) during the course of the study
- The 3-year risk of developing T2DM was calculated (using the GUARD calculator) at 5.4% for group 1 participants (n=19) and 1.7% for group 2 participants (n=31).

- There was no statistically significant difference in GV between participants who wore a CGM and were diagnosed with MA (n=6) compared to participants who wore a CGM and were not diagnosed with MA (n=6)
- There was no statistically significant difference between a number of variables, including copeptin, in participants with and without MA
- A paired samples t-test did not demonstrate a statistically significant difference between baseline and visit 1 variables (including HbA1c and HOMA2-IR) for group 1 participants attending study follow-up

Chapter 4: Prospective Study Results, Part 2

4.1 Introduction

4.1.1 Study Measures

As described in section 2.1.20, an exploratory hypothesis relating to associations between glycaemic variability and insulin resistance was initially considered. Despite the challenges encountered and subsequent shift in focus, it was decided that the emerging data would make a substantial contribution to the field of study and thereby justified ongoing recruitment. The following sections provide a brief introduction into insulin resistance and glycaemic variability in SH. Methodology is described in sections 2.1.9 and 2.1.11 and further discussion is continued in sections 6.6 and 6.8.

Insulin levels (and resistance) in people with SH (section 4.2):

The central role of IR in SH is introduced in section 1.2. To our knowledge, however, this is the first study to compare IR in SH with that of a 'normoglycaemic', non-critically unwell population. The comparison is useful as any differences could predict future glucose intolerance (question 3, section 1.4); adverse outcomes (Das et al., 2009) and guide therapy (question 5, section 1.4). Insulin resistance in SH is discussed in more detail in section 6.8.

Glycaemic variability in people with SH (section 4.3):

Glycaemic variability, which may be defined as 'excursions of blood glucose around the mean' (Archer, Misra, Simmgen, Jones, & Baker, 2011), is estimated by computing characteristic indices from glucose profiles (Louis Monnier, Colette, & Owens, 2008) and is an emerging research interest. It has been identified as an independent predictor of mortality

in critically ill patients, (M Egi, Bellomo, Stachowski, French, & Hart, 2006; Krinsley, 2008) as well as those with heart failure (Dungan, Braithwaite, & Preiser, 2009) and sepsis (Ali et al., 2008) and has therefore been proposed as a confounder, correlating with both glucose levels and mortality. Such a confounder may explain the trial result variability described in section 1.1.4 and 1.1.5.

In vitro, increased GV has been linked to an increased production of reactive oxygen species and a detrimental effect on endothelial function (Kilpatrick, Rigby, & Atkin, 2010). This has led some investigators to examine GV in the context of micro-vascular complications (Bragd et al., 2008; Nalysnyk, Hernandez-Medina, & Krishnarajah, 2010) (DM) and endothelial dysfunction (metabolic syndrome) (Buscemi et al., 2009). These associations, although demonstrated in some studies, remain controversial.

GV has not been examined in all-comers in the acute care setting and could, in this context, advance understanding of the differences between people with and without SH as well as guide treatment. GV was examined in a small number of participants who consented to wear a CGM (see section 2.1.9). Associations with outcomes (LOS), metabolic abnormalities and any differences between participants in group 1 and 2 were noted. GV was also compared between this group and a separate, metformin-treated population (see section 5.7).

The CGM provided a unique opportunity to appreciate detailed fluctuations in blood glucose levels. The iPro2 model provided a maximum of 288 plasma glucose values in 24 hours, allowing the construction of detailed sensor glucose profiles for individual participants (section 4.3.2 and 4.3.2).

As both glycaemic variability and insulin resistance have been associated with adverse outcomes, it is worth considering whether IR is independently associated with GV – a scientifically plausible explanation. Only a small number of participants had data available

for this comparison but the limited results showing tight correlation, suggest further work would be of value (section 4.3.9).

4.1.2 Recruitment Statistics

Based on the availability of fasting insulin and glucose values, HOMA2 could be calculated in n=13 group 1 participants and n=24 group 2 participants. 12 participants wore a CGMS; 5 from group 1 and 7 from group 2 (Figure 26). All consenting participants were asked to wear the monitor for a minimum 24 hours and a maximum of 6 days.

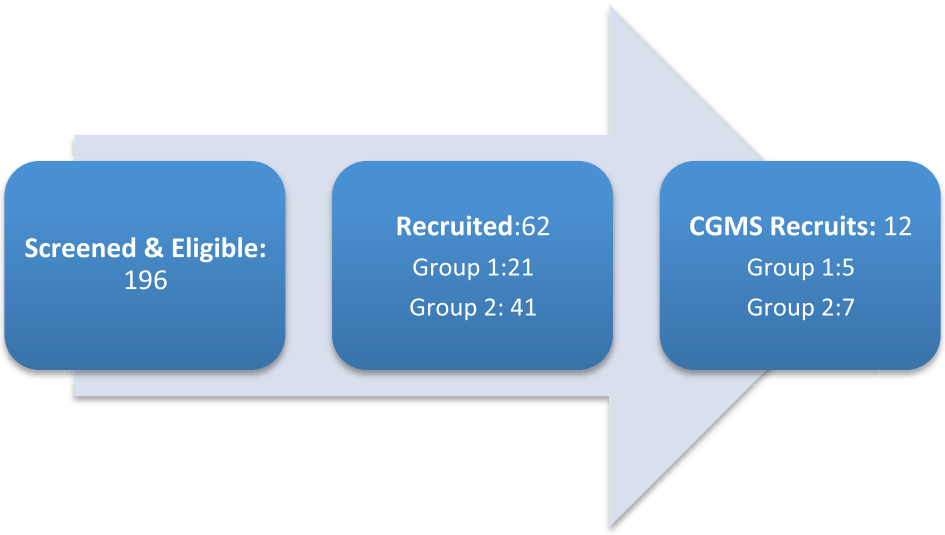


Figure 26: Screened, eligible and recruited participants to CGMS component of prospective observational study

4.2 Insulin and HOMA2 Values

4.2.1 Fasting Insulin

Fasting insulin levels were checked on the morning after study entry (Table 41, Figure 27). An independent samples t-test demonstrated a highly statistically significant difference in variance and a statistically significant difference in mean fasting insulin values between participants in group 1 and 2 (Table 42).

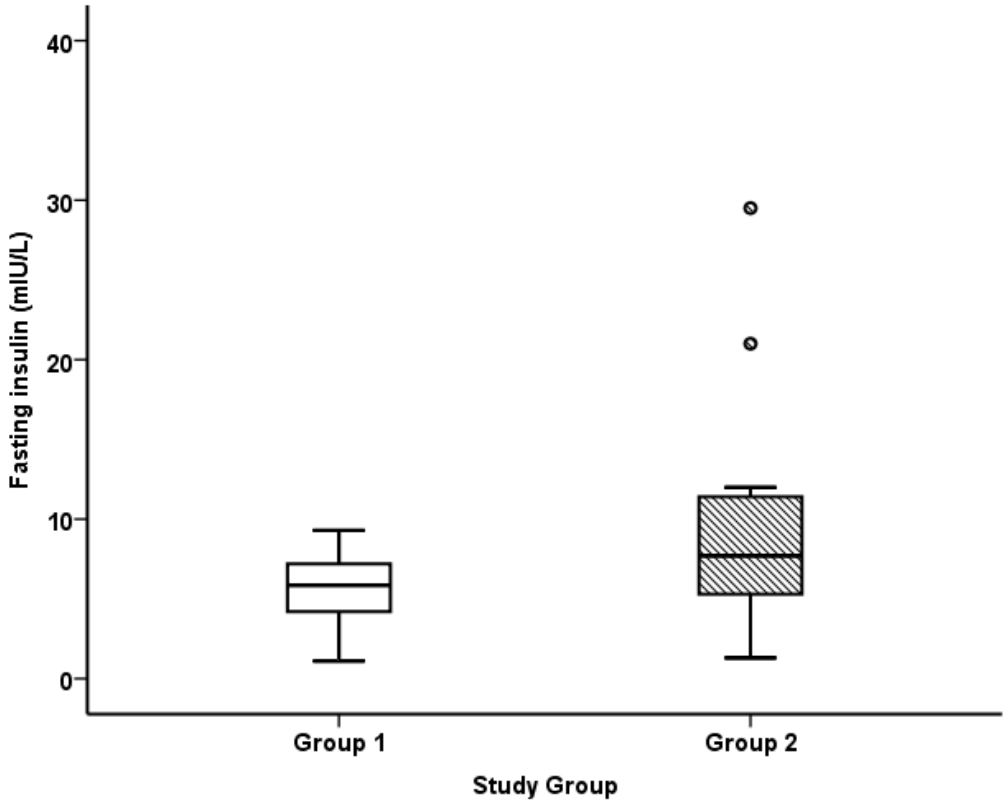


Figure 27: Fasting insulin values in group 1 and 2 participants, prospective study (n=45)

	Study Group	N	Mean	Std. Deviation	Min/Max
Fasting insulin (mIU/L)	1	16	5.76	2.32	1.1/9.3
	2	29	15.33	20.15	1.3/82.0

Table 41: Descriptive statistics of fasting insulin values for group 1 and 2 participants, prospective study

		Levene's Test for Equality of Variances		t-test for Equality of Means		
	Equal Variances Assumed	F	Sig.	t	df	Sig. (2-tailed)
Fasting insulin (mIU/L)	Yes	11.862	0.001**	-1.884	43	0.066
	No			-2.528	29.331	0.017*

Table 42: Independent samples t-test of fasting insulin values, group 1 and 2 participants (prospective study)

* Statistically significant p<0.05, ** statistically highly significant p<0.01

Figure 28 and Figure 29 display fasting insulin against RPG and FPG values in study group 1 and 2. They demonstrate lower fasting insulin values in study group 1 participants and clear separation between FPG and RPG values in study group 1 as described in section 3.4.

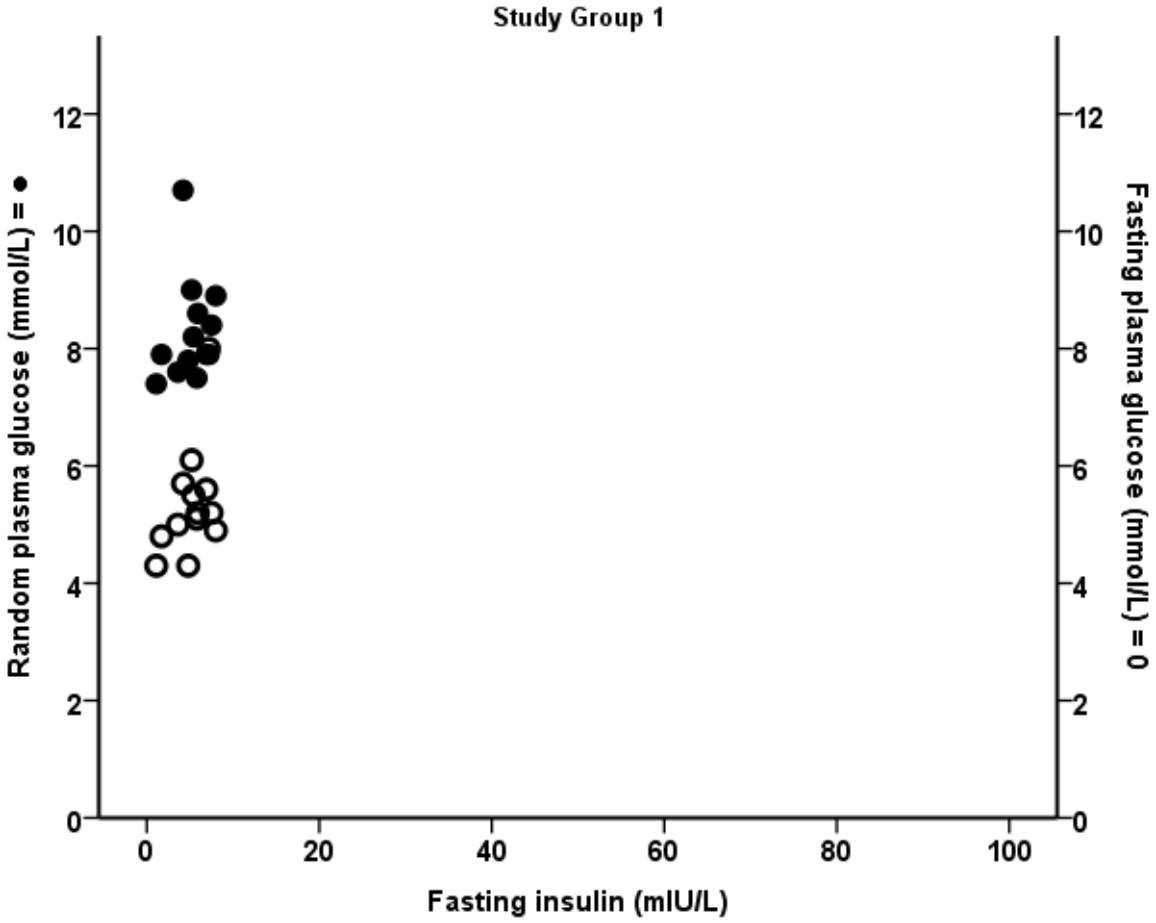


Figure 28: Study Group 1 – Random and Fasting Plasma Glucose compared to fasting insulin, prospective study

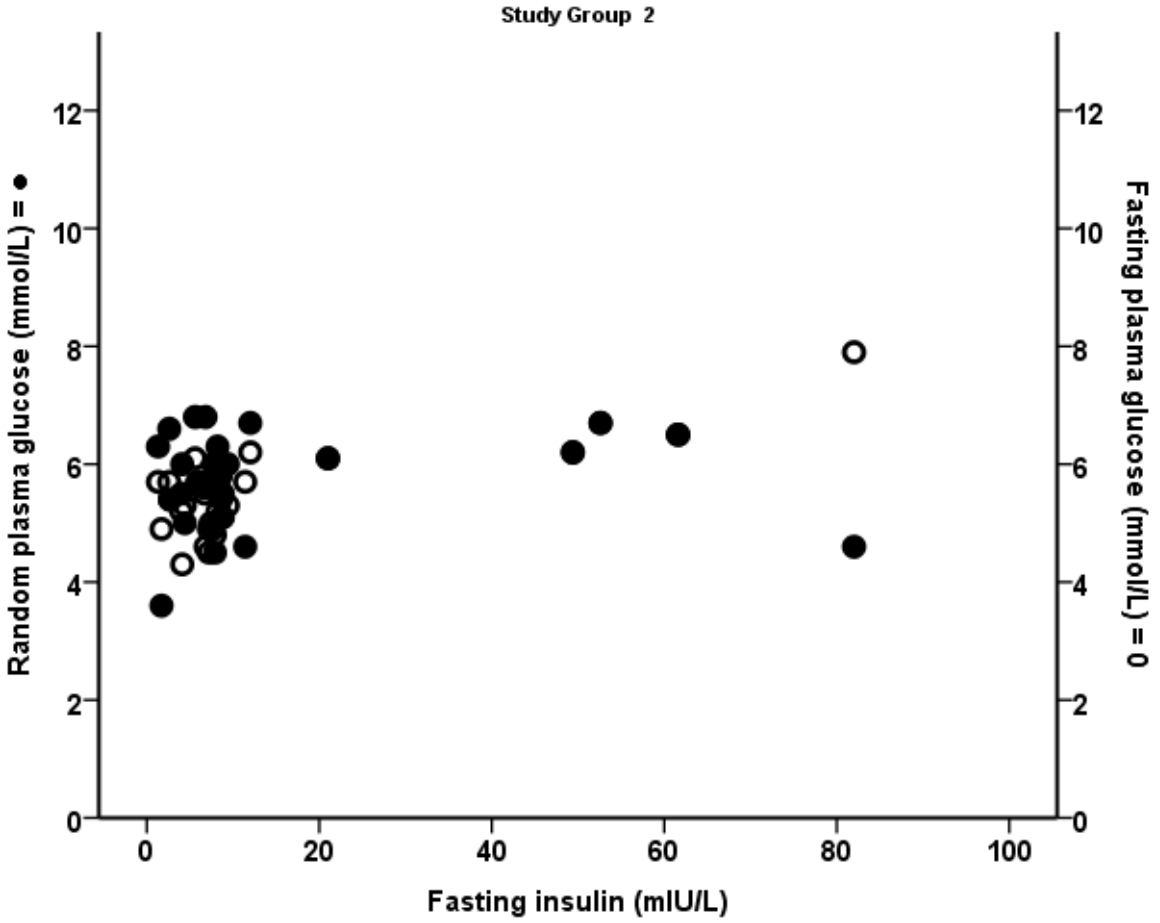


Figure 29: Study Group 2 – Random and Fasting Plasma Glucose compared to fasting insulin

4.2.2 C-Peptide

Local permissions were granted to measure (fasting) C-peptide values in all participants who wore a CGMS (see section 2.1.9). Results were available for 11 out of 12 participants. Table 43 describes the values obtained and Figure 30 displays them.

	Study Group	N	Mean	SD	Min/Max
C-peptide (pmol/L)	1	5	752.60	246.66	394/986
	2	6	1070.8	368.36	457/1513

Table 43: Descriptive statistics of C-peptide values for group 1 and 2 participants, prospective study

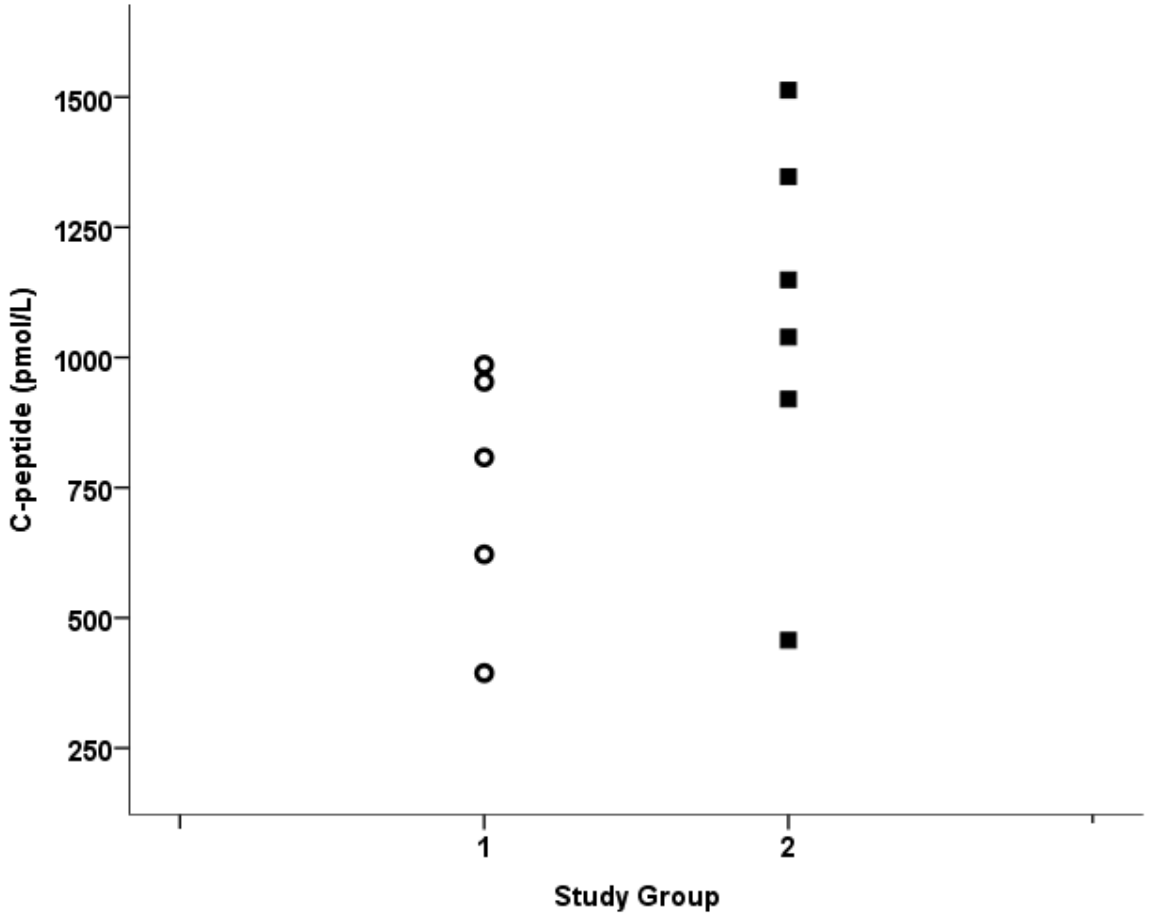


Figure 30: C-Peptide values in group 1 and 2 participants, prospective study, n=11

4.2.3 HOMA2

As described in more detail within section 2.1.11, HOMA2 values (%B, %S and IR) were calculated electronically by using fasting insulin and glucose samples obtained from participants on the morning after study entry. These values are displayed in Table 44. Figures displayed demonstrate a clear difference in HOMA2-IR (Figure 31), %B (Figure 32) and %S (Figure 33) values between group 1 and 2 participants. HOMA 2 could not be calculated in 6 participants whose fasting insulin levels which were out of range of the calculator (2.9-57.6 μU/ml).

Study Group		N	Min	Max	Mean	SD
1	HOMA2-IR	13	0.5	1.3	0.854	0.24
	%B	13	36.0	101.7	70.631	19.35
	%S	13	79.7	212.1	127.800	39.10
2	HOMA2-IR	24	0.5	6.8	1.650	1.70
	%B	24	40.5	228.5	96.417	43.13
	%S	24	14.8	194.3	97.267	48.34

Table 44: Descriptive statistics of HOMA2, %B and %S for group 1 and 2 participants, prospective study

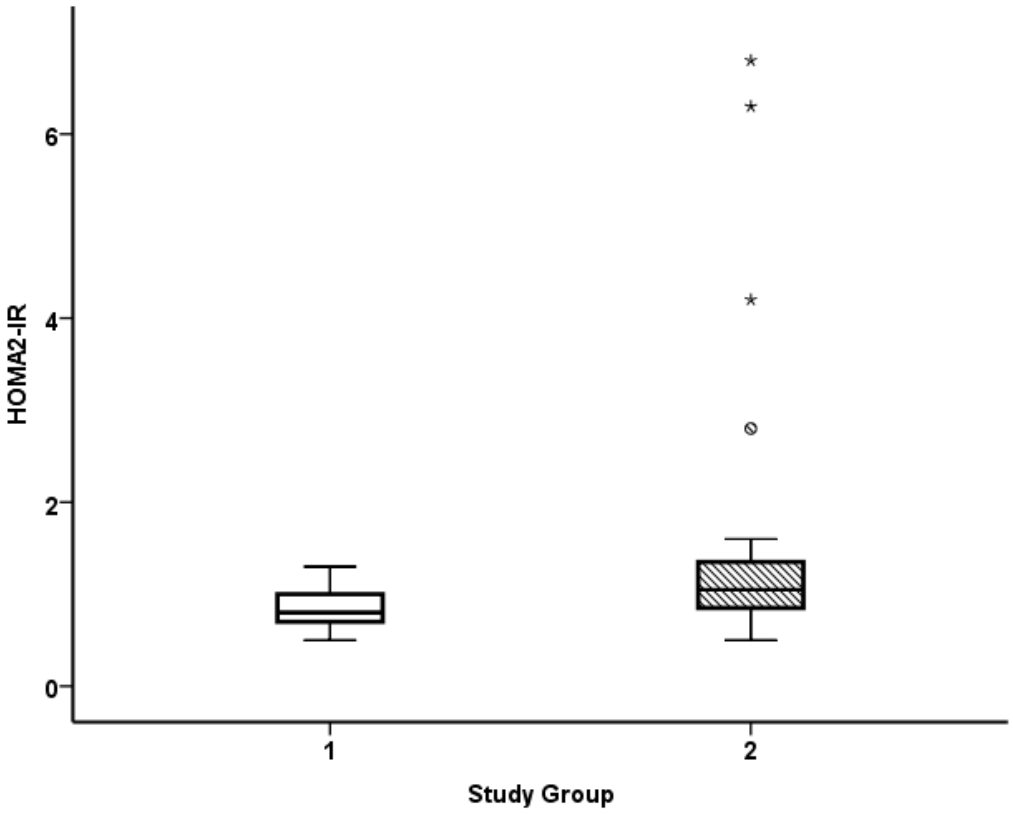


Figure 31: HOMA2-IR values in group 1 and 2 participants, prospective study (n=37)

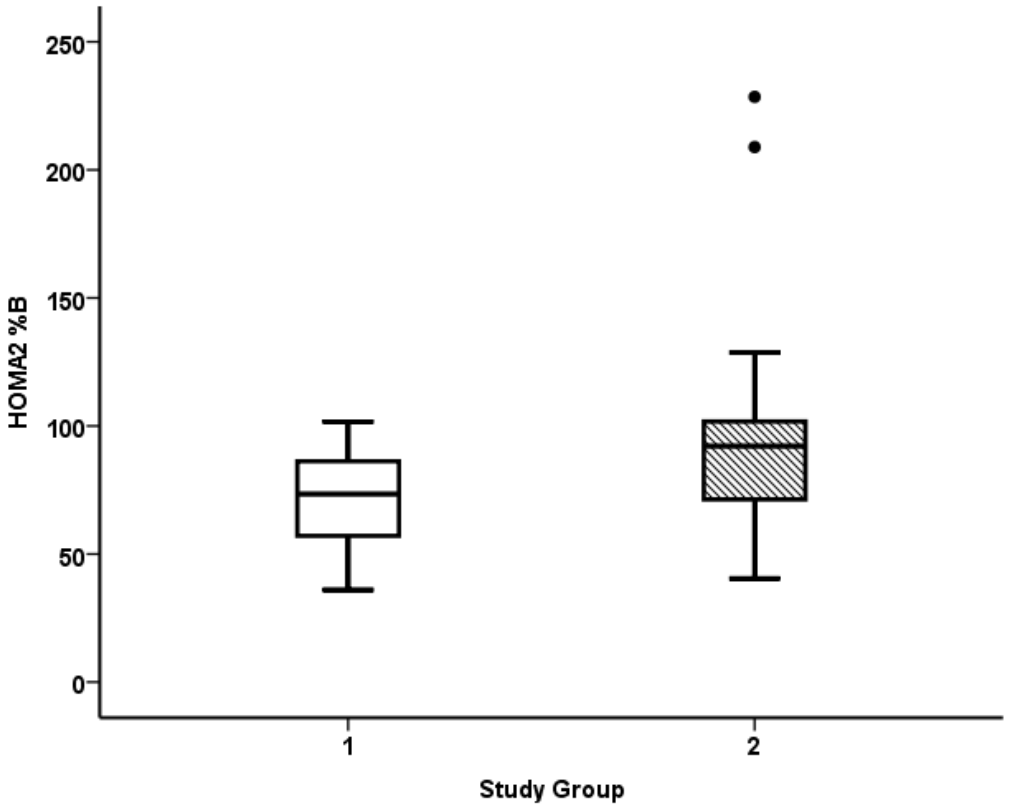


Figure 32: HOMA2 %B values in group 1 and 2 participants, prospective study (n=37)

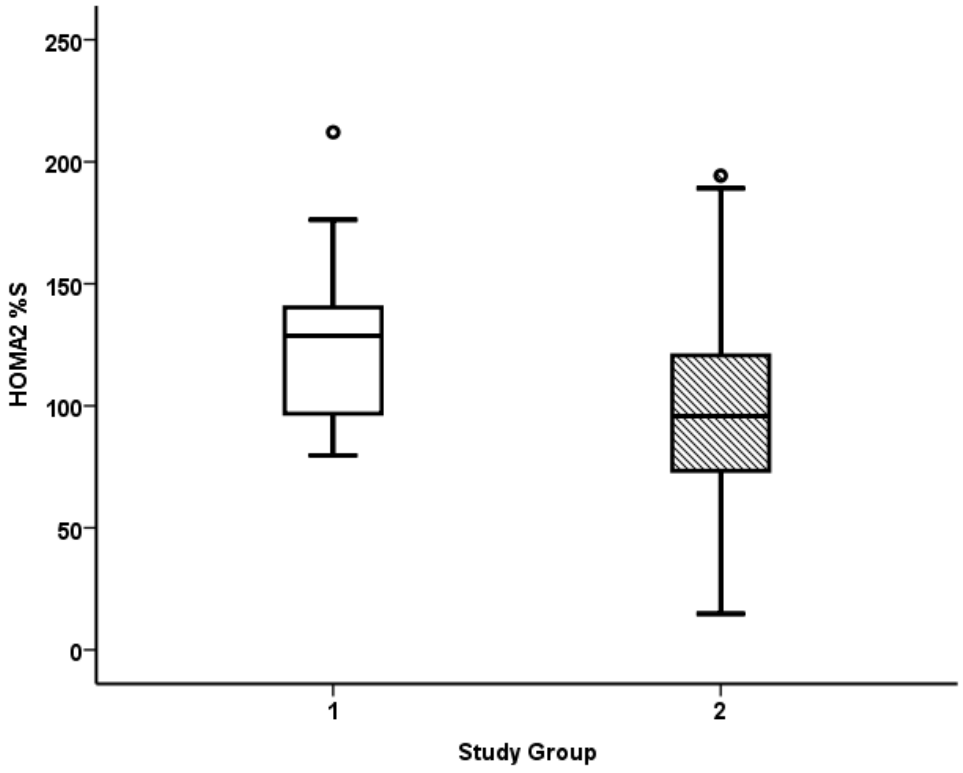


Figure 33: HOMA 2 %S values in group 1 and 2 participants, prospective study (n=37)

An independent samples t-test demonstrated a statistically significant difference between the mean and variance of HOMA2-IR values of group 1 and 2 participants. A difference was also found between the mean %B value for group 1 and 2 participants. No statistically significant differences were found between the mean %S values (Table 45).

		Levene's Test for Equality of Variances		t-test for Equality of Means		
	Equal Variances Assumed	F	Sig.	t	df	Sig. (2-tailed)
HOMA 2-IR	Yes	6.976	0.012*	-1.667	35	0.105
	No			-2.250	24.658	0.034*
%B	Yes	1.313	0.260	-2.037	35	0.049
	No			-2.501	34.215	0.017*
%S	Yes	0.256	0.616	1.954	35	0.059
	No			2.082	29.532	0.046

Table 45: Independent samples t-test of HOMA2, %B and %S, group 1 and 2 participants (prospective study)

* statistically significant p<0.05, ** statistically highly significant p<0.01

HOMA2 values were correlated with various variables as displayed in Table 46.

Variable 1	Variable 2	Pearson Correlation	Sig. (2-tailed)	N
HOMA2 %B	Waist circumference (cm)	0.534**	0.001	35
	ProADM (nmol/L)	-0.335*	0.045	36
HOMA2 %S	BNP (pg/mL)	0.361*	0.033	35

Table 46: Pearson correlations between HOMA2 values and other variables for all prospective study participants (groups 1 and 2 combined) * statistically significant p<0.05, ** statistically highly significant p<0.01

Figure 34 demonstrates that there is no clear association between HOMA2 and RPG in either study group. HOMA2 was also not significantly correlated with LOS.

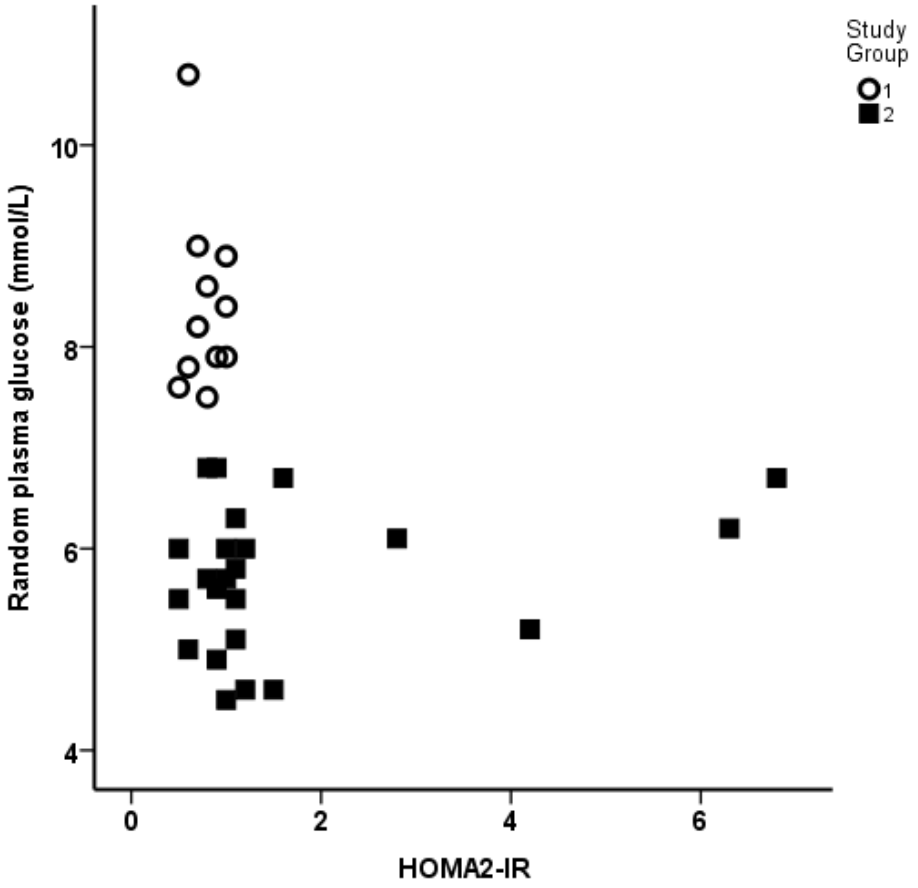


Figure 34: HOMA2 and random plasma glucose values in group 1 and 2 participants, prospective study

4.3 Glycaemic Variability

4.3.1 CGMS Introduction

A total of n=2396 SG values were recorded across all 12 participants: 1051 in group 1 and 1345 in group 2 participants. Table 47 contains a summary of valid and missing sensor readings for all participants in groups 1 and 2 based on the duration of time the CGMS was worn. 'Missing' values refer to time slots recorded on the CGMS without a corresponding SG level. Sensor Glucose (SG) values of participants are profiled in more detail in sections 4.3.2 and 4.3.3.

		SG Values					
		Valid		**Missing**		**Total**	
	Study Group	N	%	N	%	N	%
Sensor Glucose (mmol/L)	Group 1	1051	56%	811	44%	1862	100%
	Group 2	1345	44%	1691	56%	3036	100%

Table 47: Summary of valid and missing sensor readings, group 1 and 2 participants, prospective study

4.3.2 CGMS Profiles for Group 1

Participant 40

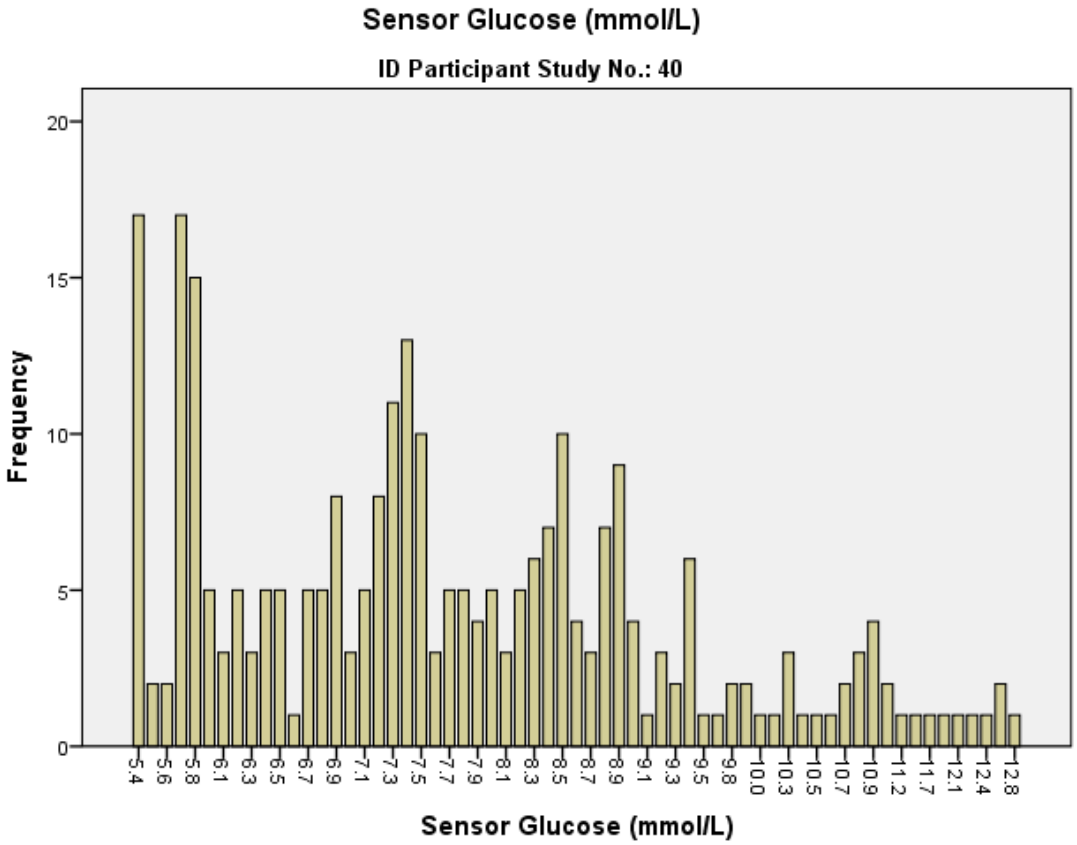


Figure 35: Frequency of each recorded sensor glucose value, participant 40

CGMS readings		Participant Features	
N valid	275	Participant ID	40
N missing	181	Study Group	**1**
CGMS mean	7.7	RPG (mmol/L)	7.6
Std. Error of Mean	0.1	HbA1c (mmol/mol)	33
Median	7.4	HOMA2-IR	0.8
Std. Deviation	1.7	LOS (days)	15
Minimum	5.4		
Maximum	12.8		
% ≥7.1mmol/L*	63.2		
% ≥11.1mmol/L**	3.6		

Table 48: Descriptive statistics of sensor glucose values and selected associated features for participant 40

* % of valid readings ≥ 7.1mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 41

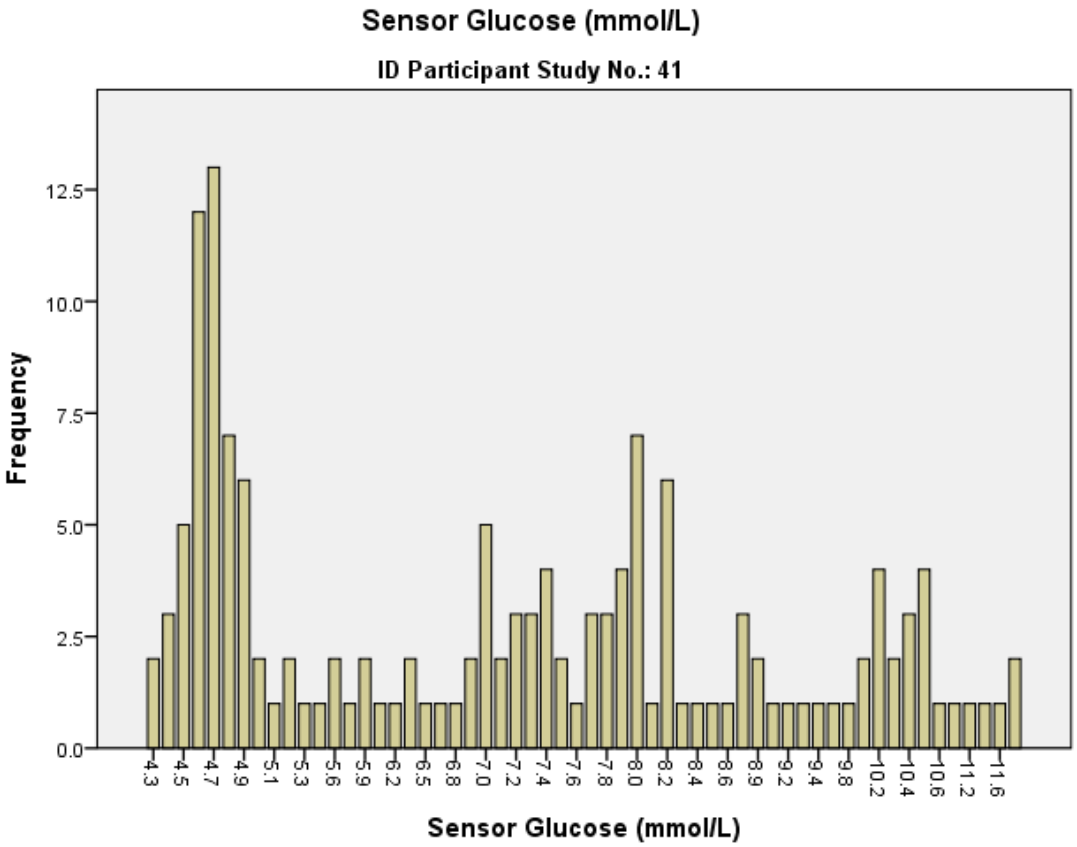


Figure 36: Frequency of each recorded sensor glucose value, participant 41

CGMS readings		**Participant Features**	
N valid	150	Participant ID	41
N missing	87	Study Group	**1**
CGMS mean	7.0	RPG (mmol/L)	7.9
Std. Error of Mean	0.2	HbA1c (mmol/mol)	52
Median	7.1	HOMA2-IR	1.0
Std. Deviation	2.1	LOS (days)	3
Minimum	4.3		
Maximum	11.8		
% ≥7.1mmol/L*	50.7		
% ≥11.1mmol/L**	4.0		

Table 49: Descriptive statistics of sensor glucose values and selected associated features for participant 41

*% of valid readings ≥7.1mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 55

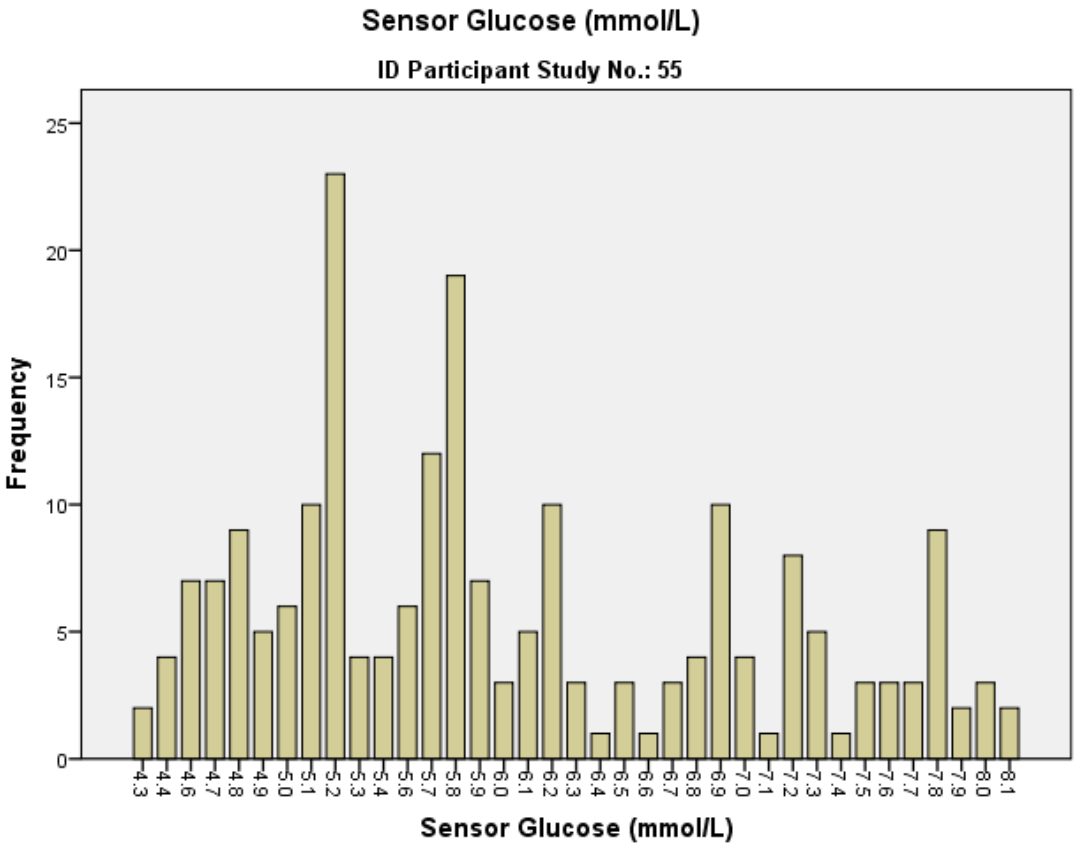


Figure 37: Frequency of each recorded sensor glucose value, participant 55

CGMS readings		Participant Features	
N valid	212	Participant ID	55
N missing	288	Study Group	**1**
CGMS mean	6.0	RPG (mmol/L)	7.6
Std. Error of Mean	0.1	HbA1c (mmol/mol)	36
Median	5.8	HOMA2-IR	0.5
Std. Deviation	1.0	LOS (days)	6
Minimum	4.3		
Maximum	8.1		
% ≥7.1mmol/L*	18.9		
% ≥11.1mmol/L**	0		

Table 50: Descriptive statistics of sensor glucose values and selected associated features for participant 55.

*% of valid readings ≥7.1mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 57

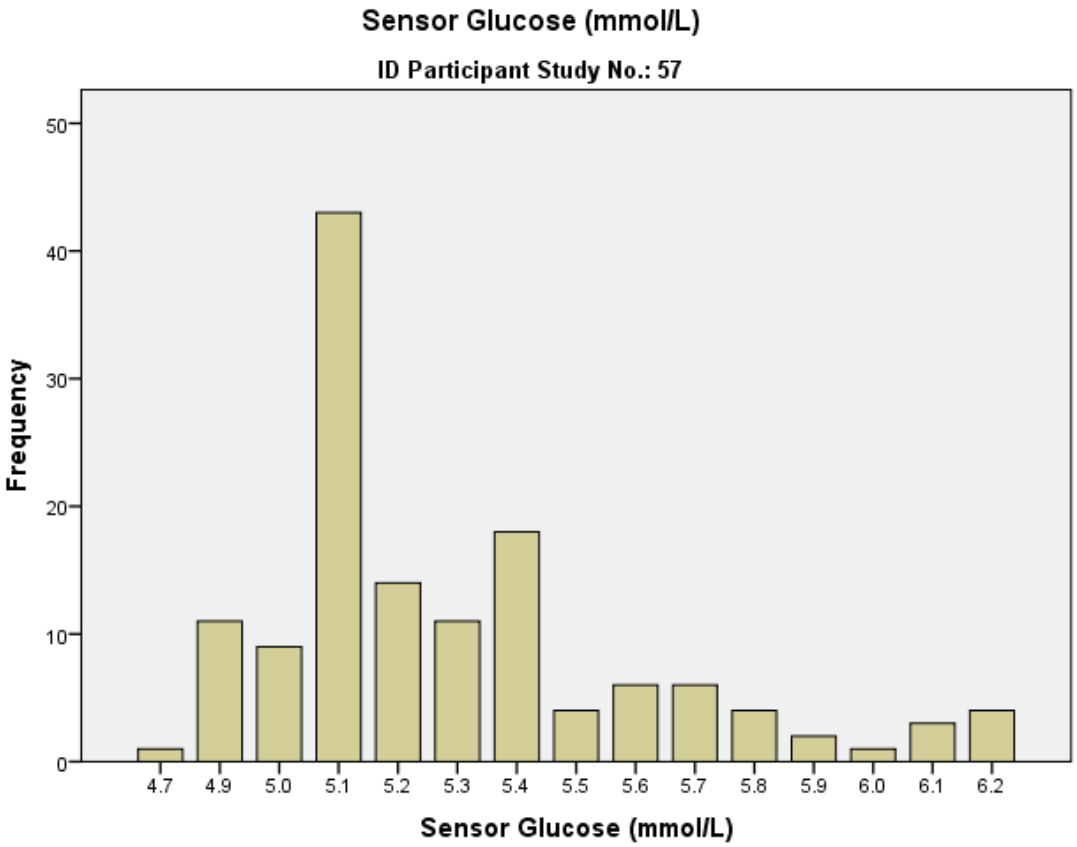


Figure 38: Frequency of each recorded sensor glucose value, participant 57

CGMS readings		Participant Features	
N valid	137	Participant ID	57
N missing	192	Study Group	**1**
CGMS mean	5.3	RPG (mmol/L)	9.5
Std. Error of Mean	0.0	HbA1c (mmol/mol)	42
Median	5.2	HOMA2-IR	Not available
Std. Deviation	0.3	LOS (days)	1
Minimum	4.7		
Maximum	6.2		
% ≥7.1 mmol/L*	0		
% ≥11.1mmol/L**	0		

Table 51: Descriptive statistics of sensor glucose values and selected associated features for participant 57

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 60

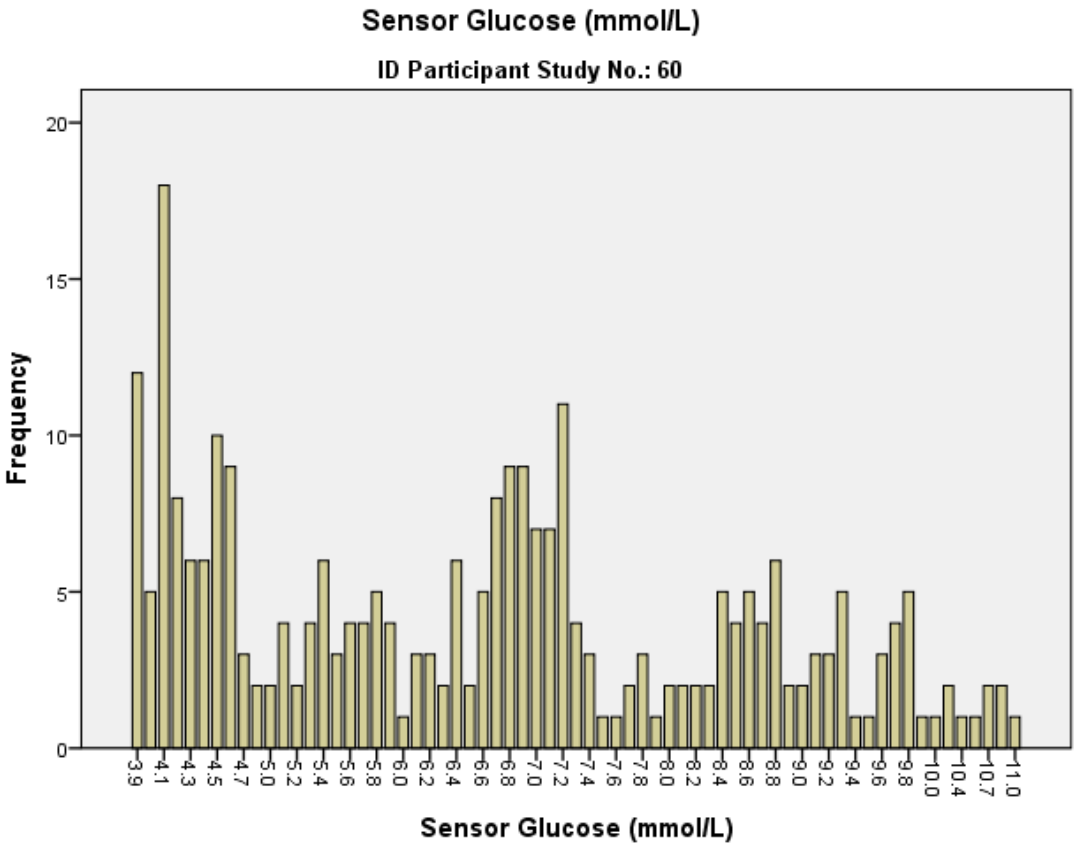


Figure 39: Frequency of each recorded sensor glucose value, participant 60

CGMS readings		Participant Features	
N valid	277	Participant ID	60
N missing	63	Study Group	**1**
CGMS mean	6.5	RPG (mmol/L)	9.5
Std. Error of Mean	0.1	HbA1c (mmol/mol)	36
Median	6.6	HOMA2-IR	Not available
Std. Deviation	1.9	LOS (days)	12
Minimum	3.9		
Maximum	11.0		
% ≥7.1mmol/L*	37.9		
% ≥11.1mmol/L**	0		

Table 52: Descriptive statistics of sensor glucose values and selected associated features for participant 60

*% of valid readings ≥7.1mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

4.3.3 CGMS Profiles for Group 2

Participant 54

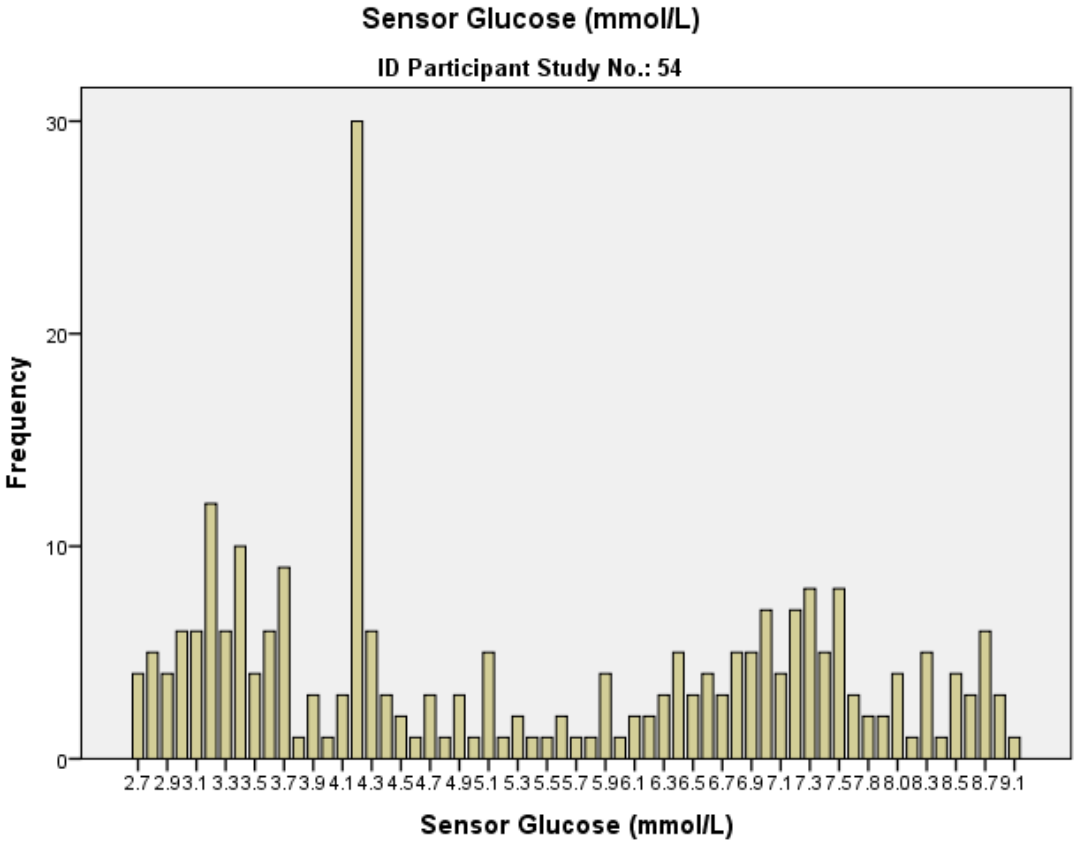


Figure 40: Frequency of each recorded sensor glucose value, participant 54

CGMS readings		Participant Features	
N valid	255	Participant ID	54
N missing	81	Study Group	**2**
CGMS mean	5.4	RPG (mmol/L)	6.0
Std. Error of Mean	0.1	HbA1c (mmol/mol)	38
Median	4.9	HOMA2-IR	0.5
Std. Deviation	1.9	LOS (days)	18
Minimum	2.7		
Maximum	9.1		
% ≥7.1 mmol/L*	26.3		
% ≥11.1mmol/L**	0		

Table 53: Descriptive statistics of sensor glucose values and selected associated features for participant 54

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 56

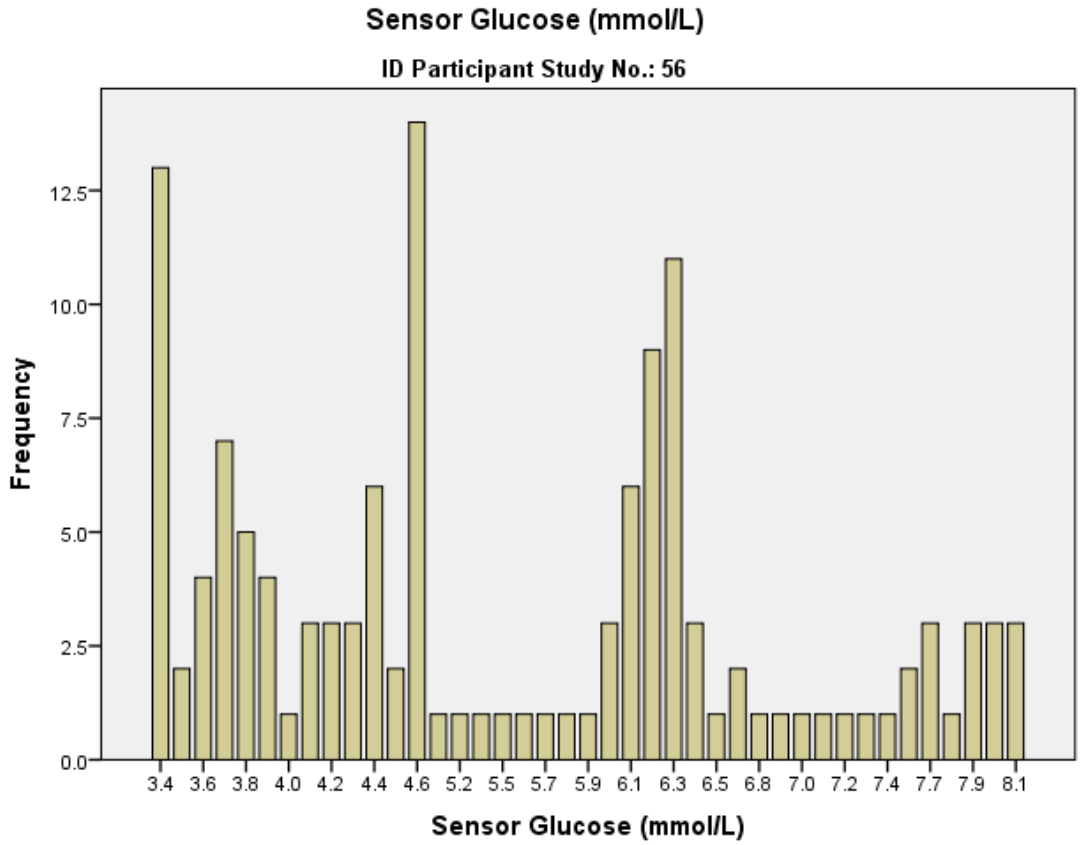


Figure 41: Frequency of each recorded sensor glucose value, participant 56

CGMS readings		**Participant Features**	
N valid	132	Participant ID	56
N missing	278	Study Group	**2**
CGMS mean	5.3	RPG (mmol/L)	6.1
Std. Error of Mean	0.1	HbA1c (mmol/mol)	33
Median	4.6	HOMA2-IR	2.8
Std. Deviation	1.5	LOS (days)	2
Minimum	3.4		
Maximum	8.1		
% ≥7.1 mmol/L*	14.4		
% ≥11.1mmol/L**	0		

Table 54: Descriptive statistics of sensor glucose values and selected associated features for participant 56

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 58

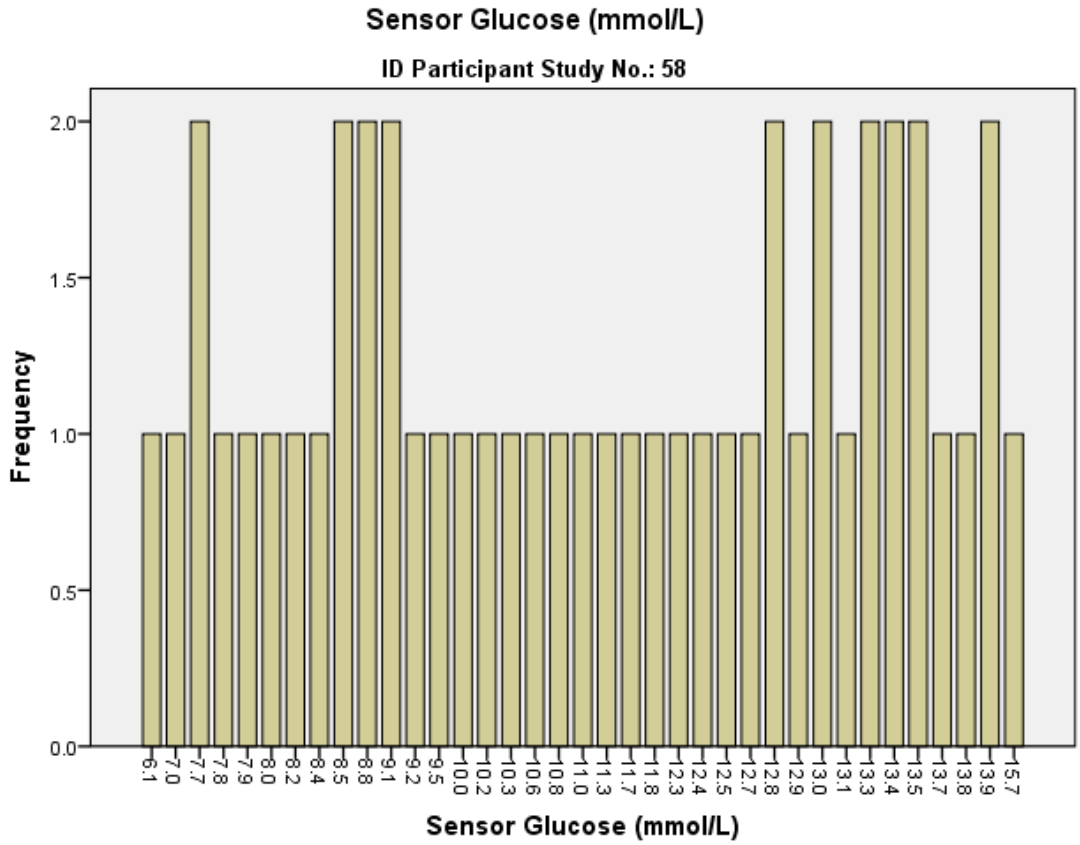


Figure 42: Frequency of each recorded sensor glucose value, participant 58

CGMS readings		Participant Features	
N valid	47	Participant ID	58
N missing	861	Study Group	**2**
CGMS mean	11.0	RPG (mmol/L)	5.6
Std. Error of Mean	0.3	HbA1c (mmol/mol)	41
Median	11.3	HOMA2	0.9
Std. Deviation	2.4	LOS (days)	3
Minimum	6.1		
Maximum	15.7		
% ≥7.1 mmol/L*	95.8		
% ≥11.1mmol/L**	51.1		

Table 55: Descriptive statistics of sensor glucose values and selected associated features for participant 58

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 59

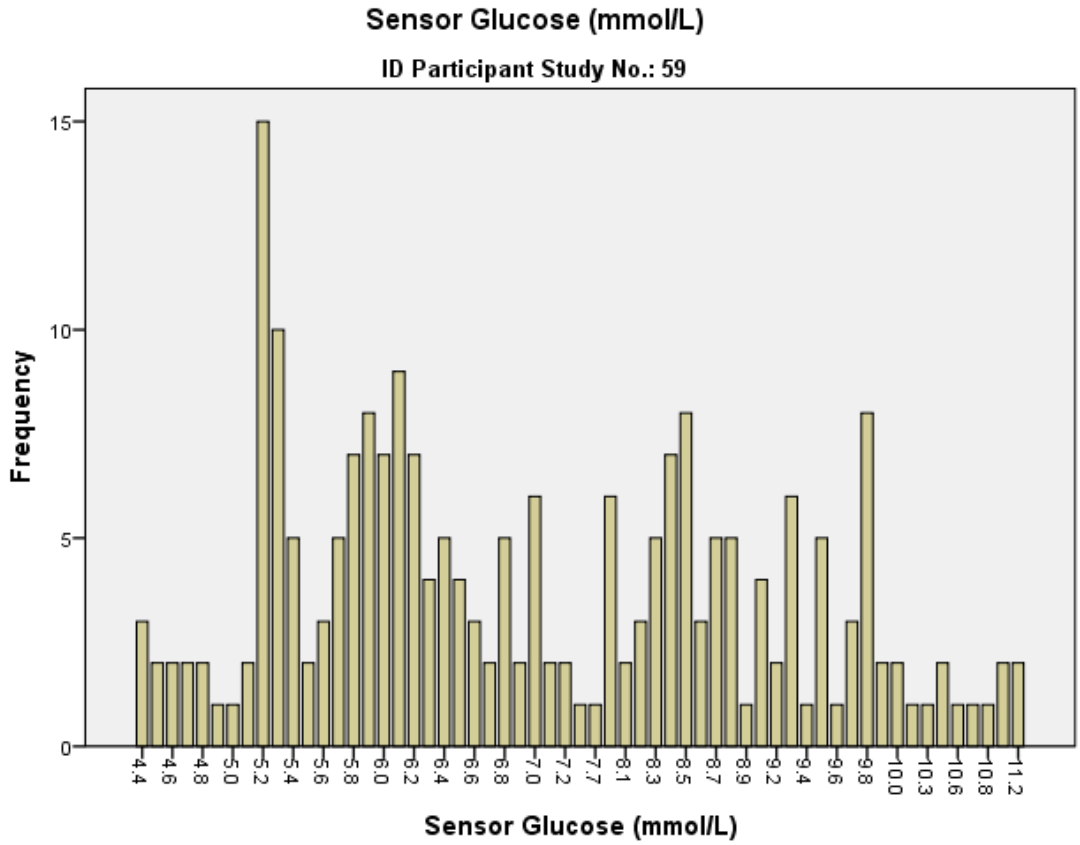


Figure 43: Frequency of each recorded sensor glucose value, participant 59

CGMS readings		**Participant Features**	
N valid	220	Participant ID	59
N missing	187	Study Group	**2**
CGMS mean	7.2	RPG (mmol/L)	6.5
Std. Error of Mean	0.1	HbA1c (mmol/mol)	41
Median	6.7	HOMA2-IR	Not available
Std. Deviation	1.8	LOS (days)	1
Minimum	4.4		
Maximum	11.2		
% ≥7.1 mmol/L*	43.6		
% ≥11.1mmol/L**	0.9		

Table 56: Descriptive statistics of sensor glucose values and selected associated features for participant 59

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 61

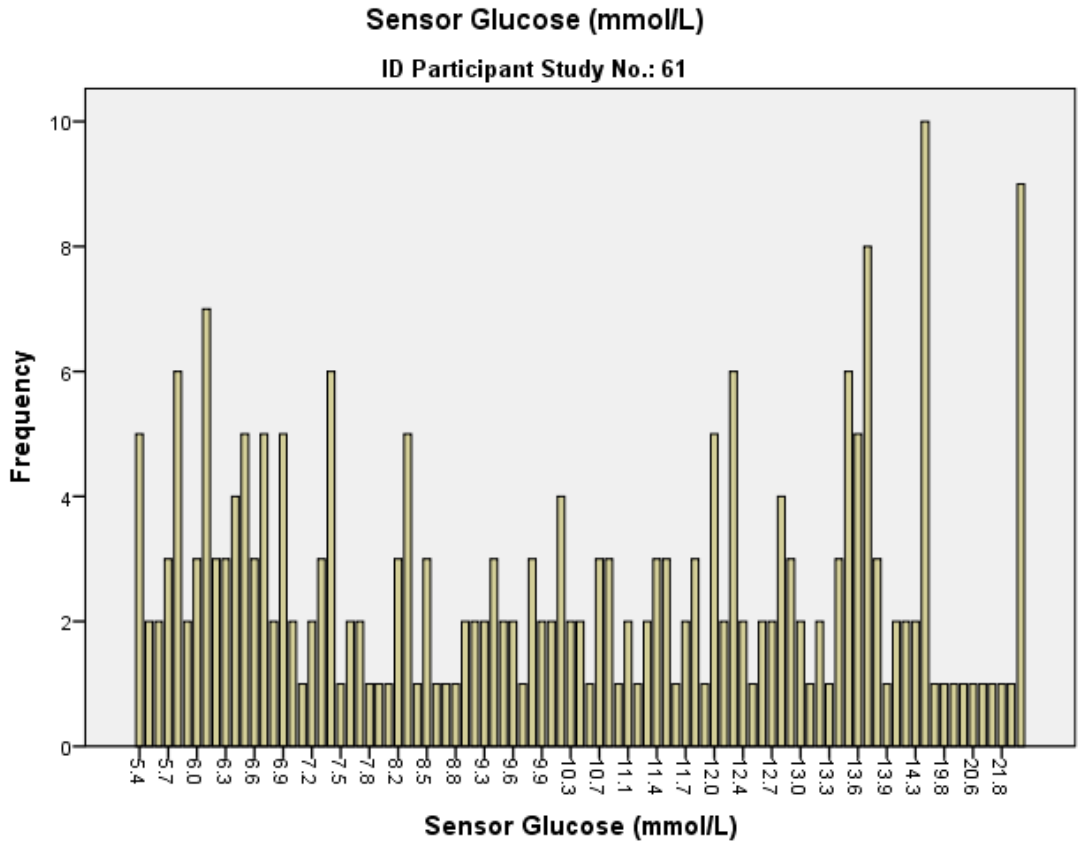


Figure 44: Frequency of each recorded sensor glucose value, participant 61

CGMS readings		**Participant Features**	
N valid	245	Participant ID	61
N missing	80	Study Group	**2**
CGMS mean	10.7	RPG (mmol/L)	6.3
Std. Error of Mean	0.3	HbA1c (mmol/mol)	40
Median	10.3	HOMA2-IR	1.1
Std. Deviation	4.2	LOS (days)	3
Minimum	5.4		
Maximum	22.2		
% ≥7.1 mmol/L*	74.7		
% ≥11.1mmol/L**	45.3		

Table 57: Descriptive statistics of sensor glucose values and selected associated features for participant 61

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 63

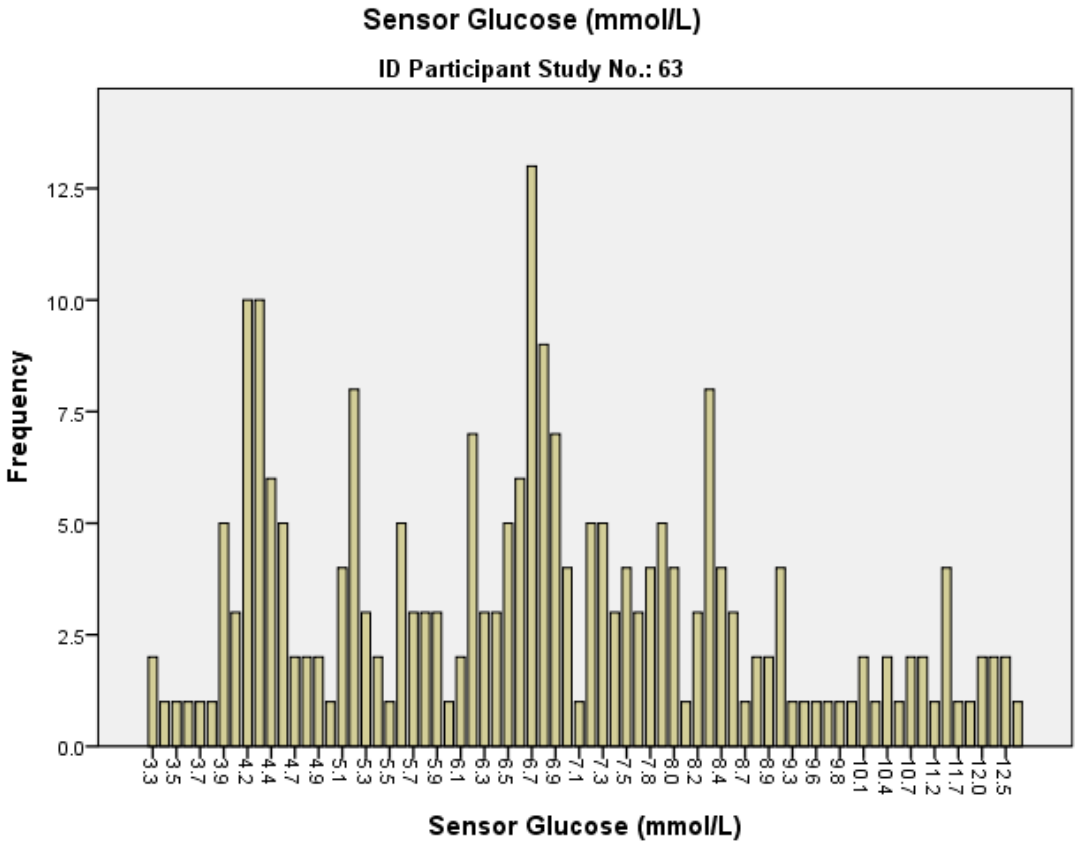


Figure 45: Frequency of each recorded sensor glucose value, participant 63

CGMS readings		**Participant Features**	
N valid	237	Participant ID	63
N missing	81	Study Group	**2**
CGMS mean	6.8	RPG (mmol/L)	4.6
Std. Error of Mean	0.1	HbA1c (mmol/mol)	44
Median	6.7	HOMA2-IR	1.5
Std. Deviation	2.1	LOS (days)	4
Minimum	3.3		
Maximum	12.6		
% ≥7.1 mmol/L*	38.8		
% ≥11.1 mmol/L**	5.9		

Table 58: Descriptive statistics of sensor glucose values and selected associated features for participant 63

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

Participant 64

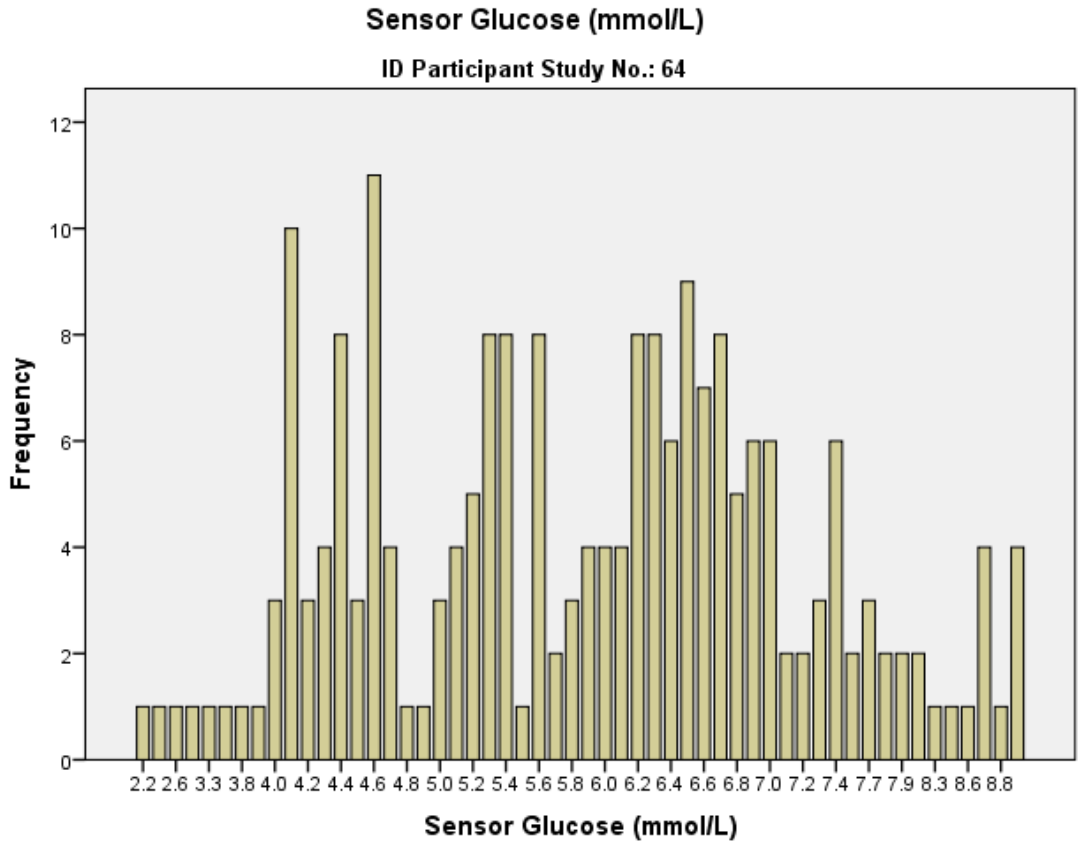


Figure 46: Frequency of each recorded sensor glucose value, participant 64

CGMS readings		**Participant Features**	
N valid	209	Participant ID	64
N missing	123	Study Group	**2**
CGMS mean	5.9	RPG (mmol/L)	6.8
Std. Error of Mean	0.1	HbA1c (mmol/mol)	41
Median	6.0	HOMA2-IR	0.9
Std. Deviation	1.4	LOS (days)	5
Minimum	2.2		
Maximum	8.9		
% ≥7.1mmol/L*	17.2		
% ≥11.1mmol/L**	0		

Table 59: Descriptive statistics of sensor glucose values and selected associated features for participant 64

*% of valid readings ≥7.1 mmol/L (7.1-max inclusive) ** % of valid readings ≥11.1mmol/L (11.1-max inclusive)

4.3.4 Sensor Glucose Values ≥ 7.1 mmol/L in Group 1

Figures 47-50 illustrate the proportion of SG values ≥ 7.1mmol/L for each group 1 participant. Participant 57 recorded 100% of values <7.1mmol/L and is not included in this section.

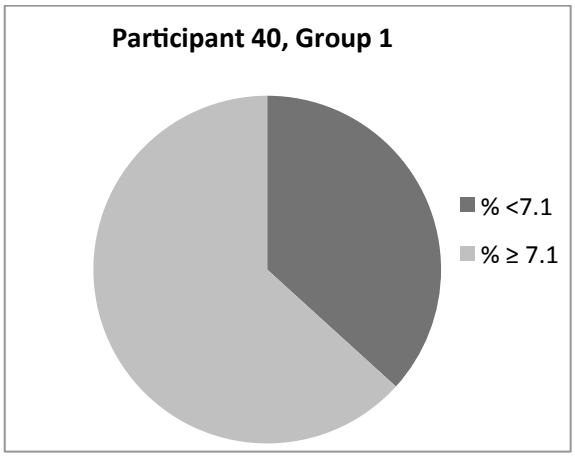


Figure 47: % of SG values ≥ and <7.1mmol/L, participant 40

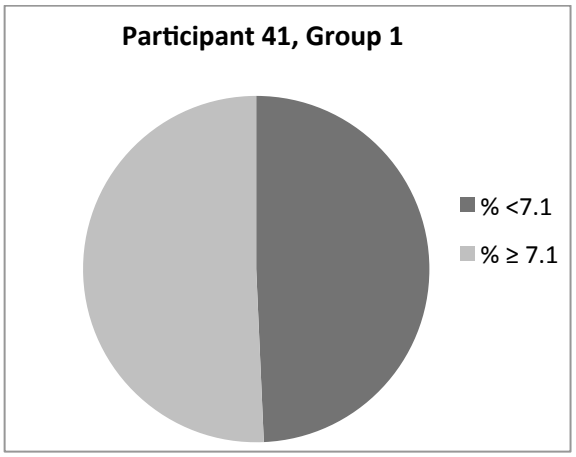


Figure 48: % of SG values ≥ and < 7.1mmol/L, participant 41

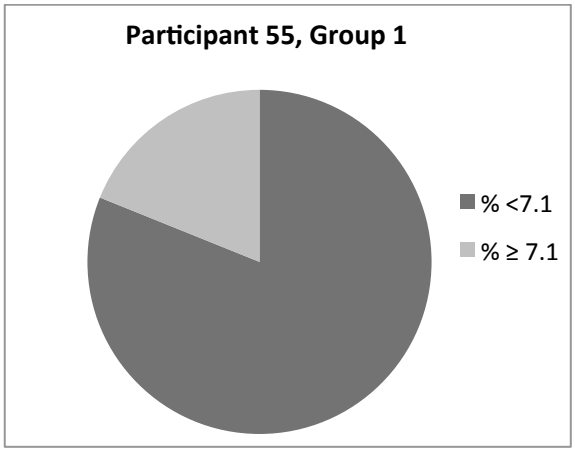


Figure 49: % of SG values ≥ and < 7.1mmol/L, participant 55

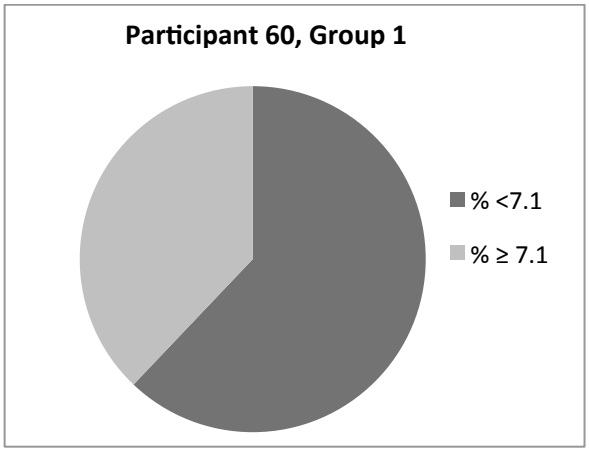


Figure 50: % of SG values ≥ and < 7.1mmol/L, participant 60

4.3.5 Sensor Glucose Values ≥ 7.1 mmol/L in Group 2

Figures 51-57 illustrate the proportion of SG values ≥ 7.1 mmol/L for each group 2 participant.

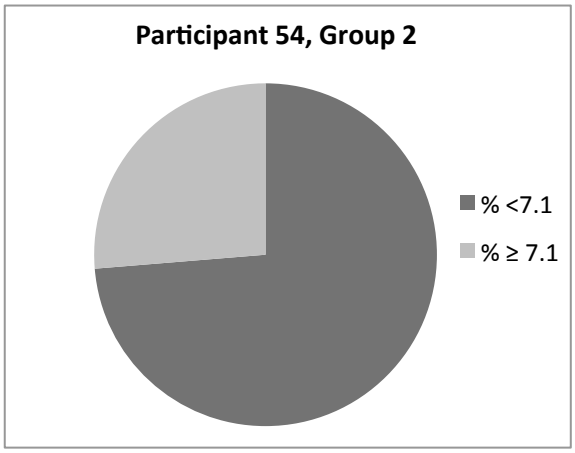


Figure 51: % of SG values ≥ and < 7.1mmol/L , participant 54

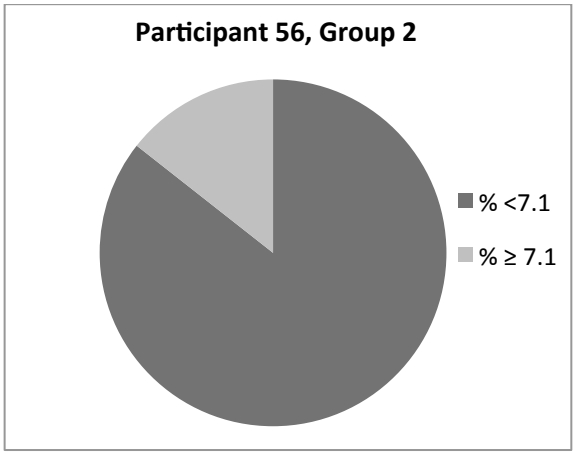


Figure 52: % of SG values ≥ and < 7.1mmol/L, participant 56

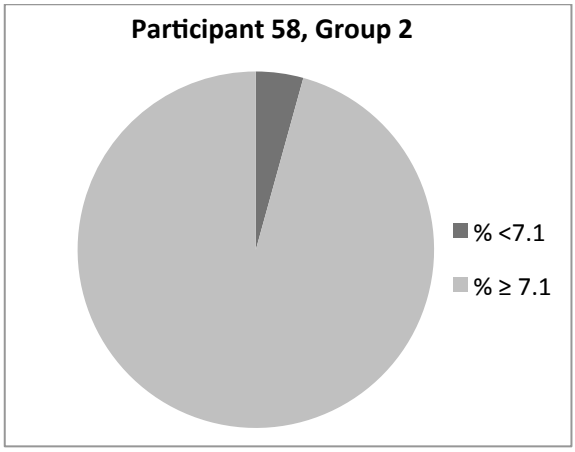


Figure 53: % of SG values ≥ and <7.1mmol/L, participant 58

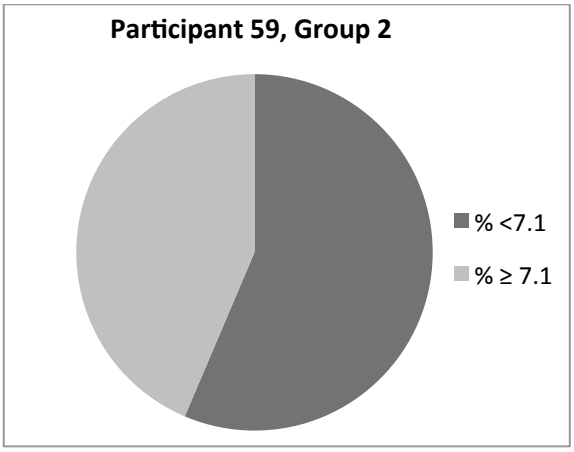


Figure 54: % of SG values ≥ and <7.1mmol/L, participant 59

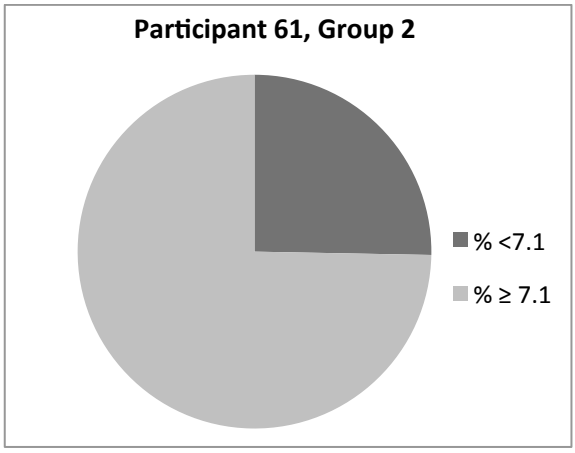


Figure 55: % of SG values ≥ and <7.1mmol/L, participant 61

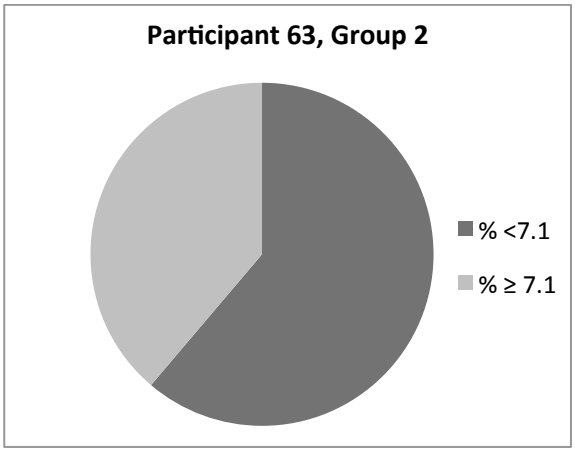


Figure 56: % of SG values ≥ and <7.1mmol/L, participant 63

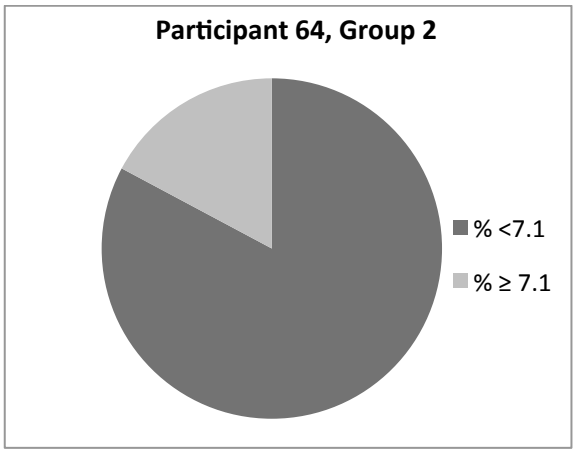


Figure 57: % of SG values ≥ and <7.1mmol/L, participant 64

4.3.6 Sensor Glucose Values ≥ 11.1 mmol/L in Group 1

Figures 58 and 59 illustrate the proportion of SG values ≥ 11.1mmol/L for each group 1 participant. Participants 55, 57, and 60 recorded 0% of values ≥ 11.1mmol/L and are not included in this section.

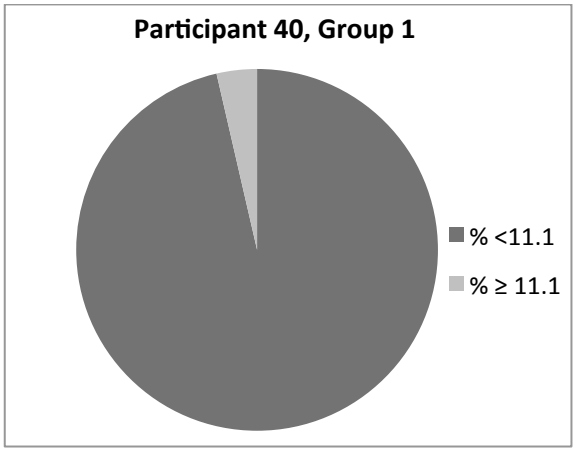


Figure 58: % of SG values ≥ and < 11.1mmol/L, participant 40

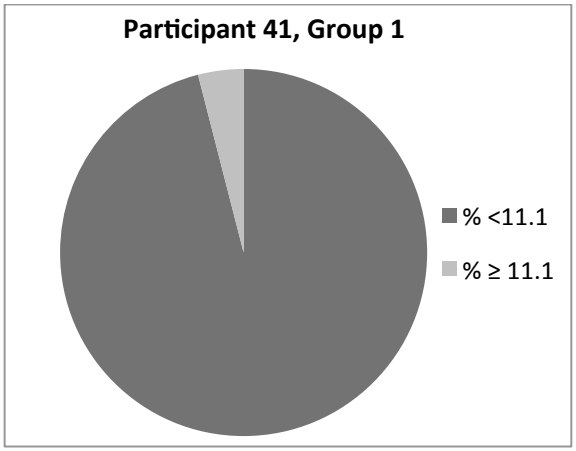


Figure 59: % of SG values ≥ and <11.1mmol/L, participant 41

4.3.7 Sensor Glucose Values ≥ 11.1 mmol/L in Group 2

Figures 60-62 illustrate the proportion of SG values ≥ 11.1 mmol/L for each group 2 participant. Participants 54, 56, 64 recorded 0% of values ≥ 11.1 mmol/L whilst participant 59 recorded 0.9% of values ≥ 11.1 mmol/L. These participants are not included in this section.

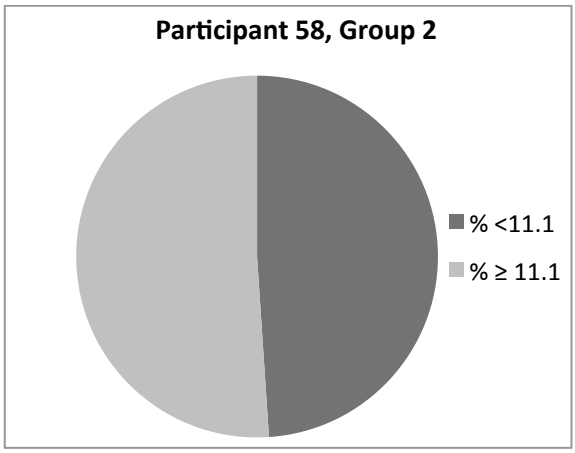


Figure 60: % of SG values ≥ and < 11.1 mmol/L, participant 58

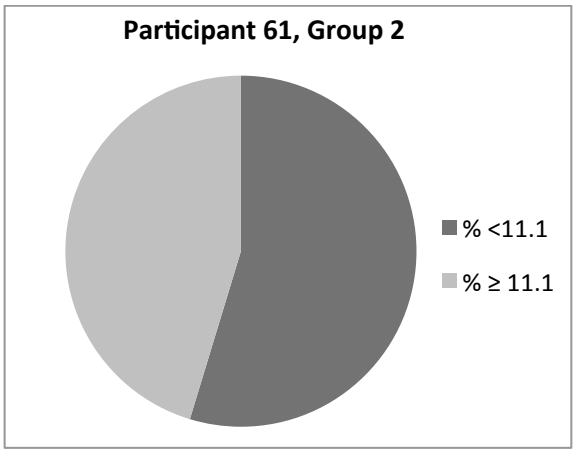


Figure 61: % of SG values ≥ and <11.1 mmol/L, participant 61

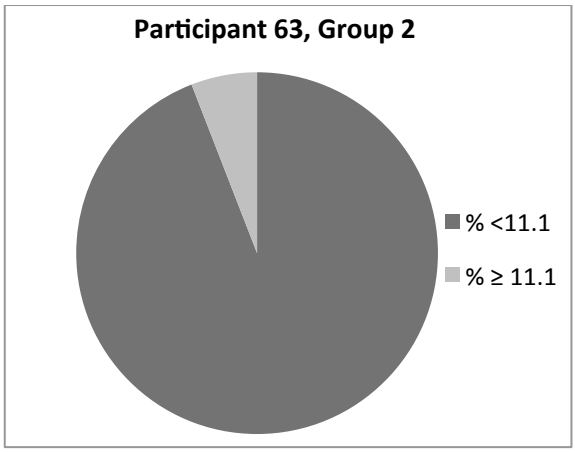


Figure 62: % of SG values ≥ and < 11.1 mmol/L, participant 63

4.3.8 Summary of CGMS Sensor Glucose (SG) Values

Appendix 2 contains descriptive statistics of SG values for each individual CGM participant. Of note, 5 participants (study numbers 054, 056, 060, 063, 064) recorded SG values of <4.0mmol/L. Table 60 describes the SG values within selected ranges (study definition of SH, see section 2.1.8 and WHO biochemical definition of DM using RPG) for all CGMS participants. Table 61 displays this information by study group.

SG Range (mmol/L)	Number of SG values within range	% of SG values within range
< 7.1	1463	61
7.1-11.0	766	32
≥ 11.1	167	7

Table 60: Frequency and Percentage of Sensor Glucose (SG) values within selected ranges, all CGMS participants, prospective study

SG Range (mmol/L)	Study Group	Number of SG values within range	% SG values within range
< 7.1	**1**	656	62
	2	807	60
7.1- 11.0	**1**	379	36
	2	387	29
≥ 11.1	**1**	16	2
	2	151	11

Table 61: Frequency and percentage of Sensor Glucose (SG) values within selected ranges for group 1 and 2 CGMS participants, prospective study

Figure 63 and Figure 64 illustrate the frequency of SG readings at each SG value for each group 1 and 2 participant. Horizontal lines represent SG values of 7.1mmol/L (SH study definition 7.1-11.0mmol/L) and 11.1 mmol/L (WHO/IDF, 2006). Figure 65 plots all group 1 and 2 SG readings together.

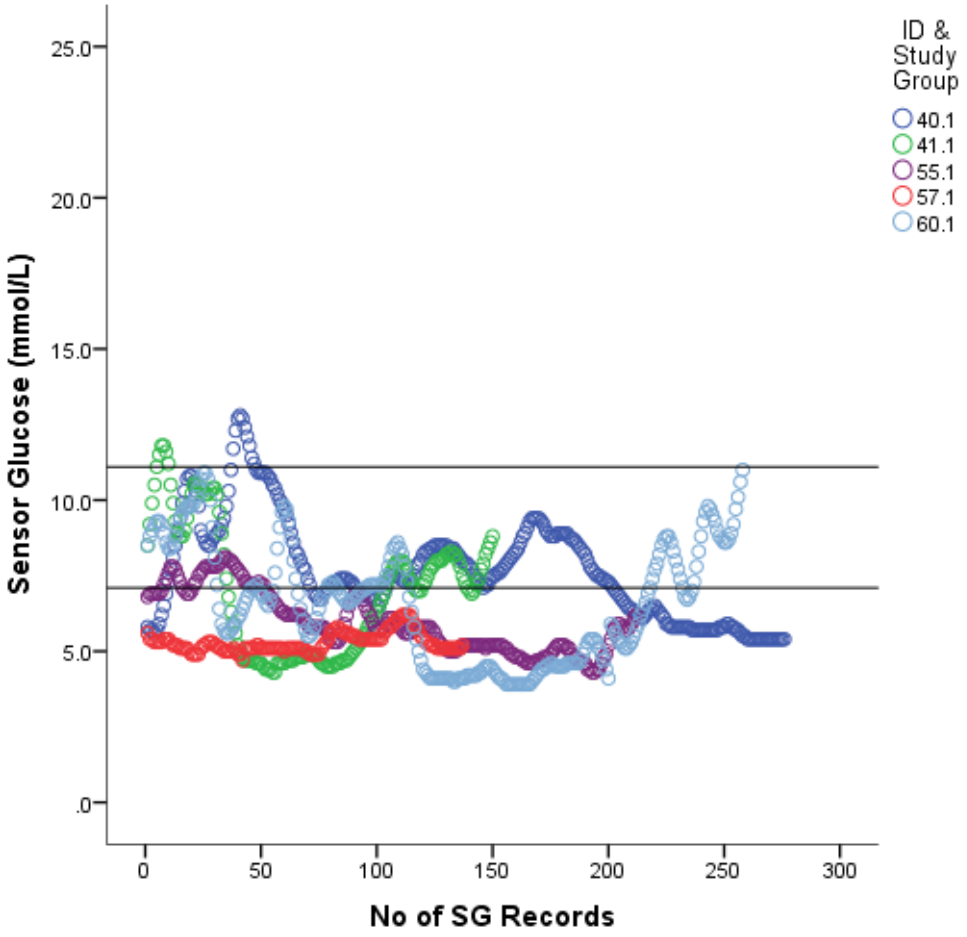


Figure 63: Frequency of SG readings at each SG value for all group 1 CGMS participants (n=5)

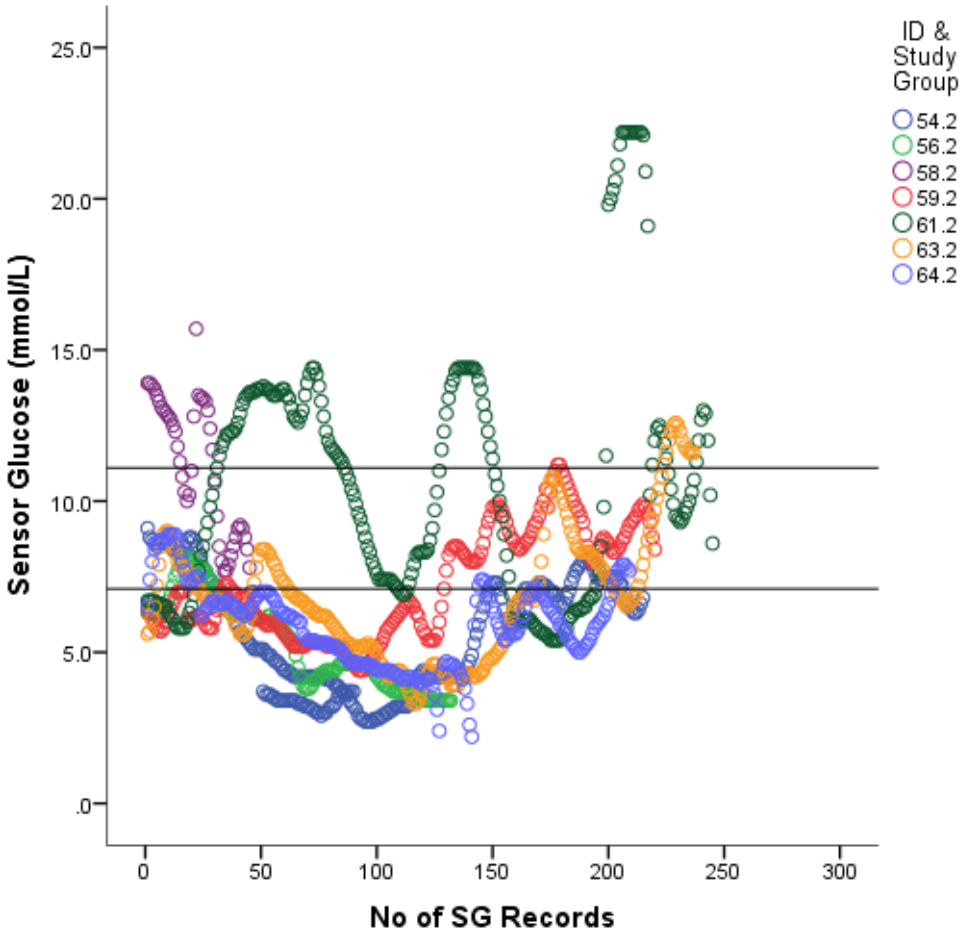


Figure 64: Frequency of SG readings at each SG value for all group 2 CGMS participants (n=7)

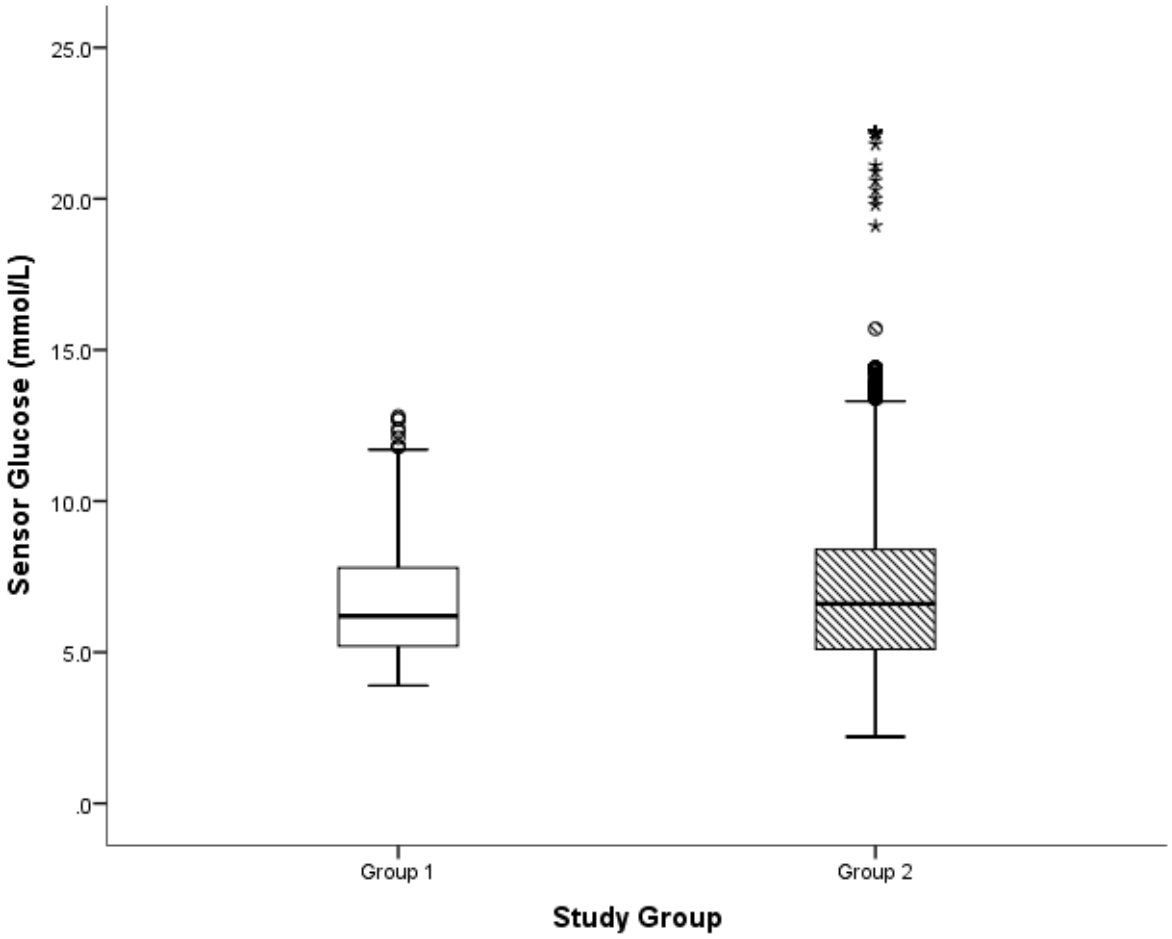


Figure 65: Sensor Glucose values for all group 1 and 2 CGMS participants, prospective study

Table 62 summarises the mean, min/max and standard deviation of SG values for all CGM participants. As suggested in figures 63-65, an independent samples t test confirmed a highly statistically significant difference in the variance and mean of SG values between group 1 and 2 participants (Table 63).

	Study Group	N	Mean	Std. Deviation	Min/Max
Sensor Glucose (mmol/L)	Group 1	1051	6.6	1.80	3.9/12.8
	Group 2	1345	7.2	3.14	2.2/22.2

Table 62: Descriptive statistics of sensor glucose values for group 1 and 2 CGMS participants

		Levene's Test for Equality of Variances		t-test		
	Equal variances assumed	F	Sig.	t	df	Sig. (2-tailed)
SG (mmol/L)	Yes	120.170	0.000**	-4.942	2394	0.000**
	No			-5.258	2211.142	0.000**

Table 63: Independent samples t-test for sensor glucose (SG) values, group 1 and 2 participants.

* statistically significant p<0.05, ** statistically highly significant p<0.01

One-way Analysis of Variance (one-way ANOVA) post-hoc tests were then performed to investigate SG differences between individual participants (from both study groups). Homogenous subsets contained a mix of group 1 and 2 participants. The participants with the highest mean SG values were from group 2 (Appendix 3).

4.3.9 Glycaemic Variability and Associations

As described in section 2.1.21, the Standard Deviation of SG values (SDSG) was used to describe Glycaemic Variability (GV) for each CGMS participant. The SDSG ranged from 0.32 to 4.17 mmol/L for all CGM participants (n=12). Table 64 contains this information by study group.

Group	Min/Max SDSG (mmol/L)	N
1	0.32/2.14	5
2	1.36/4.17	7

Table 64: Descriptive statistics of the SDSG measure for Glycaemic Variability, group 1 and 2 CGMS participants

Using one-way ANOVA (see section 5.7), no statistically significant differences were found between the variances or means of SDSG between group 1 and 2, indicating no difference in glycaemic variability between the study groups.

The SDSG value was then examined in association with other variables. Of note, no correlation was found between SDSG and Length of Stay (Figure 66) or SDSG and HbA1c (Figure 67). SDSG is referred to as 'Std Deviation of CGMS Data' in figures 66 and 67.

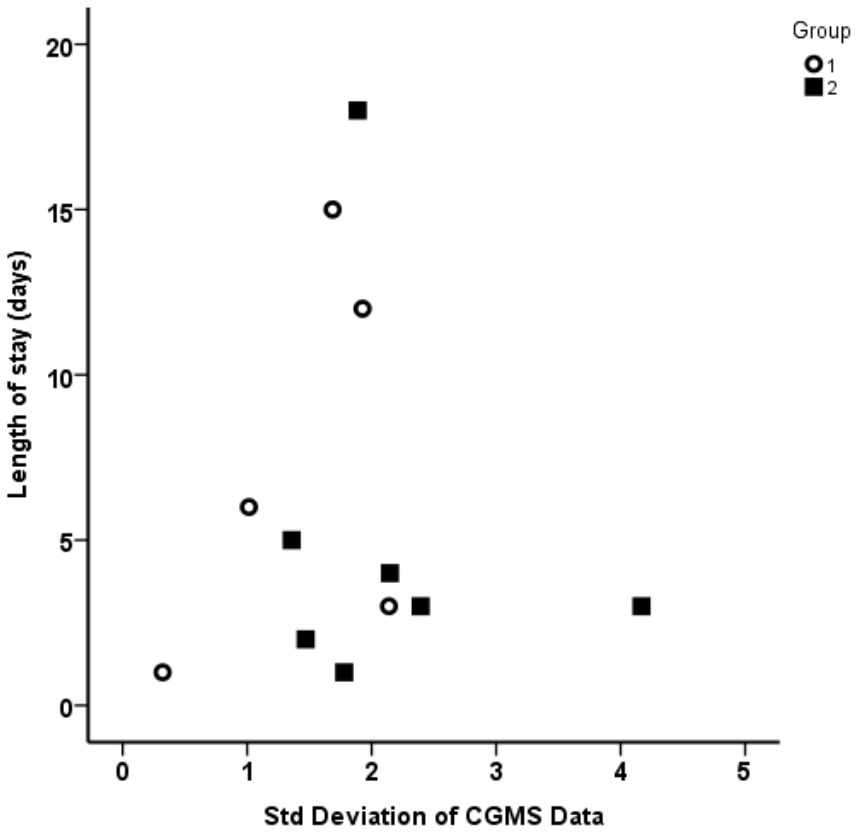


Figure 66: Comparison of Length Stay (days) against Standard Deviation of Sensor Glucose values (SDSG, mmol/L) in n=12 group 1 and 2 CGMS participants

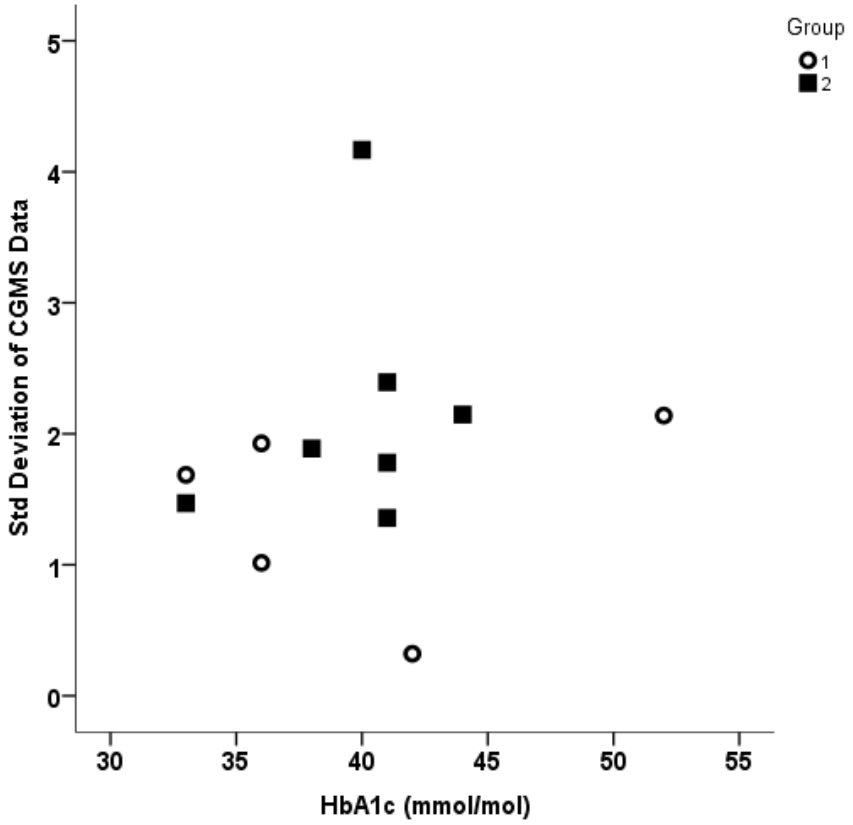


Figure 67: Comparison of HbA1c (mmol/mol) against Std Deviation of Sensor Glucose values (SDSG, mmol/L) in n=12 group 1 and 2 CGMS participants

In group 1, a trend was apparent between SDSG and HOMA2-IR. A 'perfect correlation' was found between these variables in the 3 participants for whom HOMA2 values were available (Figure 68).

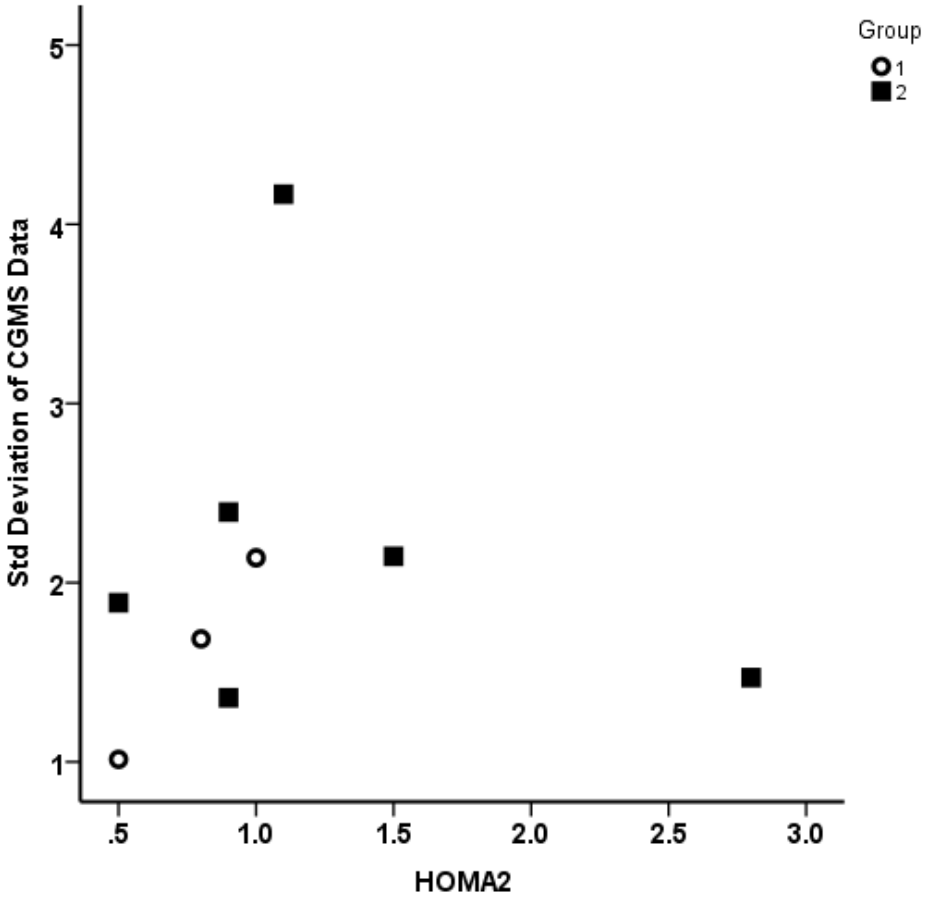


Figure 68: Comparison of HOMA2-IR against Std Deviation of CGMS Data (SDSG, mmol/L) in groups 1 and 2

Std Deviation of Sensor Glucose values (SDSG)		HOMA2-IR
Group 1	Pearson Correlation	1.000
	Sig. (2-tailed)	0.002**
	N	3
Group 2	Pearson Correlation	-0.237
	Sig. (2-tailed)	0.650
	N	6

Table 65: Correlation of SDSG with HOMA2-IR for group 1 and 2 CGMS participants

4.4 Summary of Chapter 4

- Group 1 participants had lower (mean, fasting) insulin values ($p<0.05$) as well as lower variances ($p<0.01$) compared to group 2 participants.
- Group 1 participants were found to have a lower HOMA2 model-derived estimate of steady state B-cell function (%B) compared to group 2 ($p<0.05$). No significant differences were found in mean %S values.
- A statistically significant difference was also found between the mean and variance of HOMA2-IR values of group 1 and 2 participants ($p<0.05$). Despite this, HOMA2-IR was *not found* to be significantly correlated with RPG or length of stay for all participants
- HOMA2 %B was significantly correlated with waist circumference and proADM whilst HOMA2 %S was significantly correlated with BNP (all participants)
- HOMA2-IR *appeared* to be higher in participants diagnosed with a MA compared to those who were not although values were not available for all participants and inferential statistics were not performed
- A small number of participants (n=5 from group 1 and n=7 from group 2) consented to wear a CGMS to measure (frequent) interstitial glucose readings. There were a substantial proportion of 'missing values'
- Uniquely, CGMS profiles were obtained for 3 participants diagnosed with IFG and 2 participants at 'high risk of DM'
- CGMS profiles often demonstrated a discrepancy between RPG and SG values, notably marked episodes of hyperglycaemia (participant 061) and hypoglycaemia (participants 054, 063, 064)

- 11% of SG values from group 2 participants were ≥ 11.1 mmol/L compared to 2% from group 1
- 62% of group 1 SG values were <7.1mmol/L
- Group 1 participants had significantly lower mean SG values and lower SG variance compared to group 2 participants. ($p<0.01$). Despite this, no statistically significant differences were found in the Glycaemic Variability of group 1 and 2 participants
- Glycaemic variability was not correlated with LOS or HbA1c (all participants)
- In group 1, a trend towards a correlation between HOMA2 and SDSG was observed although only 3 participants were studied.

Chapter 5: Stress Hyperglycaemia in COPD (Metformin) Study Results

5.1 Introduction

Respiratory disease was the primary diagnoses for the majority of participants from both group 1 and 2 in the prospective study (section 3.2) and COPD accounted for 31% of all these respiratory cases. (Appendix1). This work looks more closely at the prevalence of stress hyperglycaemia as well as glycaemic variability (GV) and diabetes risk in people with COPD. The effect of metformin on GV was also noted. Full study objectives are listed in section 2.2.1.

As described in section 2.2, this study is a secondary analysis of a multi-centre study entitled, 'A Randomised, Double-Blind, Placebo-Controlled Trial of Metformin in Chronic Obstructive Pulmonary Disease (COPD) Exacerbations: A Pilot Study'. In summary, a total of 52 patients were recruited over 9 sites between 2011 and 2014. Group A were actively treated with metformin and group B were treated with placebo. Primary study methodology and investigator's contributions are described in more detail in section 2.2.

5.2 Metformin Study Participants

Table 66 and Figure 69 display the gender distribution for all metformin study participants.

	Frequency	Percentage
Female	20	38.5
Male	32	61.5
Total	52	100.0

Table 66: Gender distribution (percentage and frequency) for all metformin study participants

Figure 69: Percentage distribution of gender for all metformin study participants

In terms of ethnicity, 1 participant was Mauritian whilst the remaining participants were of white ethnicity. Table 67 contains descriptive data for age, weight, systolic and diastolic blood pressure for all participants.

	N	Mean	Min	Max	Std. Deviation
Age (years)	52	67.4	43	89	9.35
Weight at baseline (kg)	52	72.2	44.5	140.3	19.64
SBP (mmHg)	52	134	85	215	21.36
DBP (mmHg)	52	77	56	104	10.89

Table 67: Descriptive statistics for age, weight, SBP and DBP at baseline visit for all metformin study participants

5.3 Baseline Biochemical Values

Table 68 contains the descriptive statistics for (baseline) plasma glucose, HbA1c and lactate values of all metformin study participants. In comparison, the mean (baseline) plasma

glucose and HbA1c for all prospective study participants was 6.7mmol/L and 40mmol/mol respectively (see sections 3.4 and 3.10.2).

	N	Min	Max	Mean	Std. Deviation
Glucose (mmol/L)	41	4.4	29.5	8.0	4.24
HbA1c (mmol/mol)	32	33	72	43	8.12
Lactate (mmol/L)	42	0.86	3.90	2.0	0.74

Table 68: Descriptive statistics for plasma glucose, HbA1c and lactate at baseline visit for all metformin study participants

Plasma glucose samples were taken at the time of recruitment and values are therefore referred to as 'random' rather than 'fasting' plasma glucose. Figure 70 displays the frequency of (baseline) plasma glucose readings at each glucose value.

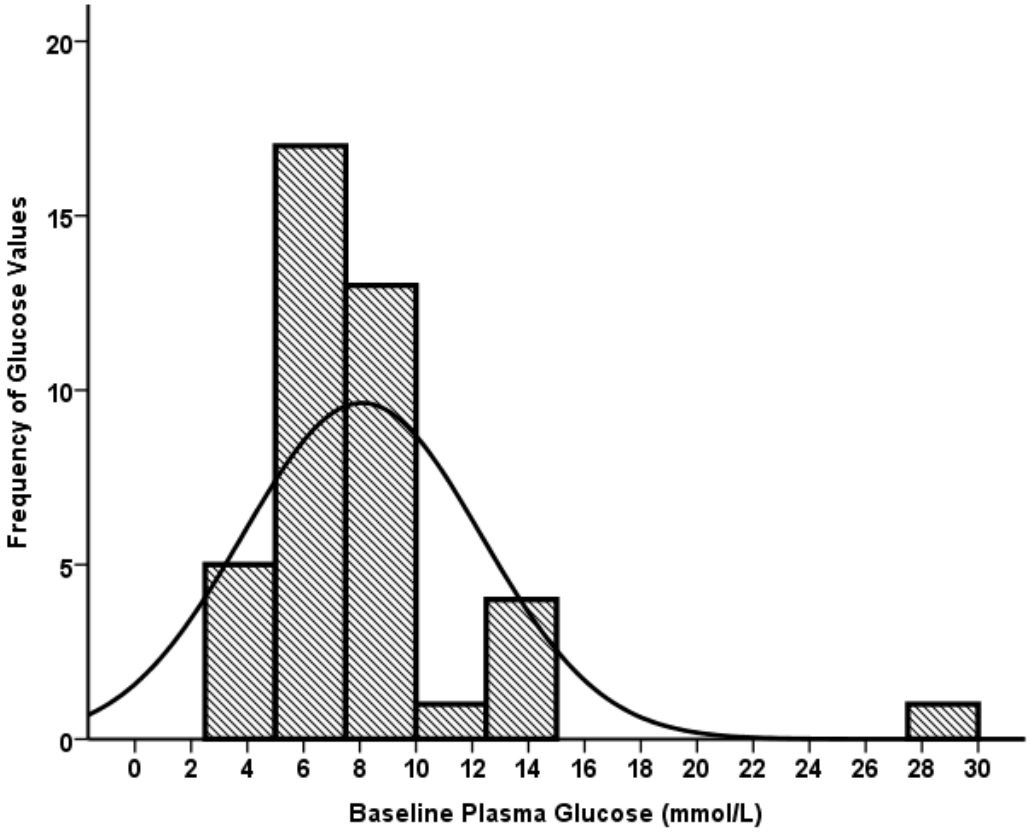


Figure 70: Histogram displaying frequency of glucose values at each 2mmol/L glucose range for all metformin study participants (n=41)

Sixteen participants had a baseline Random Plasma Glucose (RPG) value between 7.1 and 11.0 mmol/L making the prevalence of SH in the recruited COPD study group 39% (using the prospective study definition). Table 69 displays the percentage and frequency of glucose values at ranges <7.1, 7.1-11.1 and ≥ 11.1 mmol/L. Figure 71 illustrates the percentage of values at each of these ranges.

RPG Range	Frequency in range	Percentage in range
< 7.1mmol/L	20	48.8
7.1-11.0 mmol/L	16	39.0
≥ 11.1 mmol/L	5	12.2

Table 69: Baseline random plasma glucose values within selected ranges (n and %) for n=41 metformin study participants

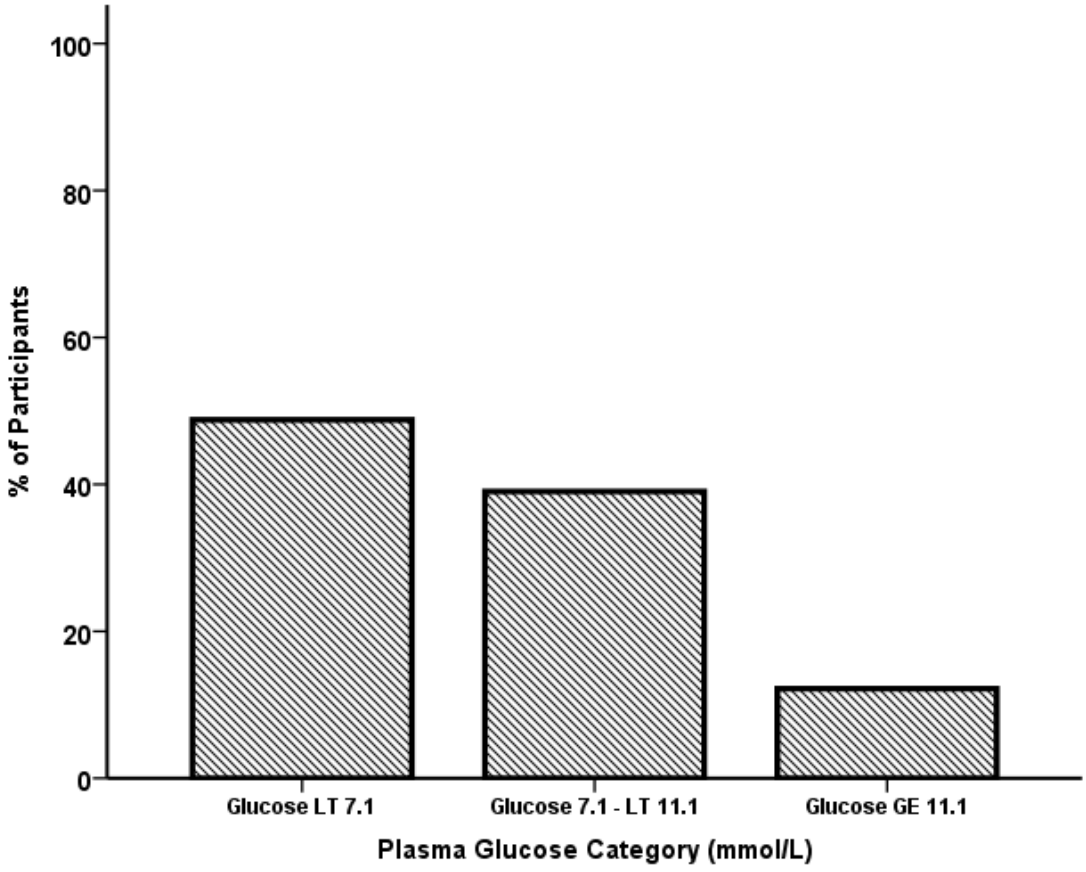


Figure 71: Percentage of metformin study participants with random plasma glucose values less than (LT) 7.1, 7.1 to less than (LT) 11.1 and greater or equal to (GE) 11.1 mmol/L

5.4 Stress Hyperglycaemia and Baseline Variables

Various baseline variables including age, weight, biomarkers and COPD assessment test (CAT) score were examined in relation to the baseline glucose range. Table 70 contains descriptive statistics for these variables at each glucose range described in Table 69. Participants with stress hyperglycaemia (using definition in section 2.1.8) are highlighted in italics in each category.

Baseline Variable		N	Mean	SD	Min	Max
Age (years)	Glucose LT 7.1	20	65.6	10.59	43	81
	Glucose 7.1 - LT 11.1	16	68.6	9.07	58	89
	Glucose GE 11.1	5	73.8	5.22	66	78
Weight (kg)	Glucose LT 7.1	20	67.8	18.92	50.3	133.6
	Glucose 7.1 - LT 11.1	16	70.3	11.60	44.5	87.0
	Glucose GE 11.1	5	78.3	15.95	64.7	101.0
Lactate (mmol/L)	Glucose LT 7.1	19	1.8	0.513	0.86	2.8
	Glucose 7.1 - LT 11.1	16	2.1	0.80	1.00	3.9
	Glucose GE 11.1	5	2.4	1.18	1.00	3.8
eGFR (mL/min)	Glucose LT 7.1	17	73.1	14.70	45	90
	Glucose 7.1 - LT 11.1	13	78.1	13.44	60	90
	Glucose GE 11.1	4	62.3	23.89	32	90
HbA1c (mmol/mol)	Glucose LT 7.1	15	40.2	4.60	33	51
	Glucose 7.1 - LT 11.1	12	42.2	2.89	39	49
	Glucose GE 11.1	4	60.0	10.95	48	72
CAT	Glucose LT 7.1	20	28.0	7.03	8	37
	Glucose 7.1 - LT 11.1	16	27.9	7.19	13	37
	Glucose GE 11.1	5	22.4	6.80	14	31

Table 70: Descriptive statistics for baseline variables within selected random plasma glucose ranges, all metformin study participants

One-way Analysis of Variance (one-way ANOVA) showed a statistically highly significant difference in variance between the RPG groups for HbA1c only ($p<0.01$). Post-hoc tests demonstrated no statistically significant difference between most baseline variables across differing glucose ranges. (LT 7.1, 7.1-11.1 and GE 11.1) The exception being baseline HbA1c which was found to be significantly different ($p<0.05$) in the glucose GE 11.1 participants (Table 71).

	Glucose Levels	N	Subset for alpha = 0.05	
			1	2
Student-Newman-Keuls[a,b]	Glucose LT 7.1	15	40.20	
	Glucose 7.1 - LT 11.1	12	42.17	
	Glucose GE 11.1	4		60.00
	Sig.[c]		0.467	1.000
Tukey HSD[a,b]	Glucose LT 7.1	15	40.20	
	Glucose 7.1 - LT 11.1	12	42.17	
	Glucose GE 11.1	4		60.00
	Sig.[c]		0.744	1.000

Means for groups in homogeneous subsets are displayed. (a) Uses Harmonic Mean Sample Size = 7.500. (b)The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed. (c)This p value refers to all variables within the same column, demonstrating no difference between the values in the homogenous subset

Table 71: Analysis of Variance (one-way ANOVA) with Student-Newman-Keuls (SNK) and Tukey tests demonstrating homogenous subsets for HbA1c values within random plasma glucose ranges, all metformin study participants

5.5 Metabolic Abnormalities & Type 2 Diabetes Risk

As discussed in section 3.10.2, HbA1c values between 42-47mmol/mol are defined as 'high risk for diabetes'(D.M. Nathan et al., 2009; NICE 2012). A total of n=18 (35%) metformin study participants fell within this definition and the mean HbA1c for all participants was also in this high risk range (43mmol/mol).

Additionally, in terms of Type 2 Diabetes (T2DM) risk, the GUARD risk calculator (McAllister et al., 2014) predicted a 4.9% 3 year risk of developing T2DM in the metformin group overall and a 6.8% risk in the metformin SH group (participants with a RPG 7.1-11.0mmol/L). Although a formal diagnosis was not made in the acute setting, 15% of participants were also found to have biochemical features of Diabetes Mellitus (BFD) during the course of the study (Table 28).

5.6 Capillary Glucose Values: All Study Participants

A total of 1250 Capillary Blood Glucose (CBG) values were recorded across all participants - a mean of 24 (min n=3, max n=72) for each participant (n=52) during the in-patient phase of the study. Table 72 displays these values within CBG ranges: 'Less than' (LT) 7.1; 7.1 to LT 11.1 and 'Greater than or equal to' (GE) 11.1 mmol/L.

Capillary Blood Glucose Category	Capillary Blood Glucose Values (mmol/L)				
	N	**Min**	**Max**	**Mean**	**SD**
LT 7.1	721	2.2	7.0	5.50	0.91
7.1-LT 11.1	460	7.1	11.0	8.49	1.09
GE 11.1	69	11.1	27.2	15.21	4.57

Table 72: Descriptive statistics for capillary blood values within ranges 'Less than (LT) 7.1', 7.1 to Less Than (LT) 11.1' and 'Greater than or equal to (GE) 11.1mmol/L', all metformin study participants

The CBG values were then examined in relation to baseline RPG categories. CBG values reached a maximum of 23.2mmol/L within the lowest RPG category (RPG LE 7.0).[Table 73]

RPG Category (mmol/L)	N	Min	Max	Mean	SD
LT 7.1	383	3.7	23.2	7.059	2.34
7.1 – LT 11.1	519	2.2	16.3	6.775	2.03
GE 11.1	90	4.1	27.2	10.128	6.15

Table 73: Descriptive statistics for capillary blood glucose values in relation to baseline Random Plasma Glucose (RPG) categories, all metformin study participants

As with the prospective observational study, the standard deviation was used to express glycaemic variability. Figure 72 plots SD of CBG for all participants within the RPG categories described in Table 69.

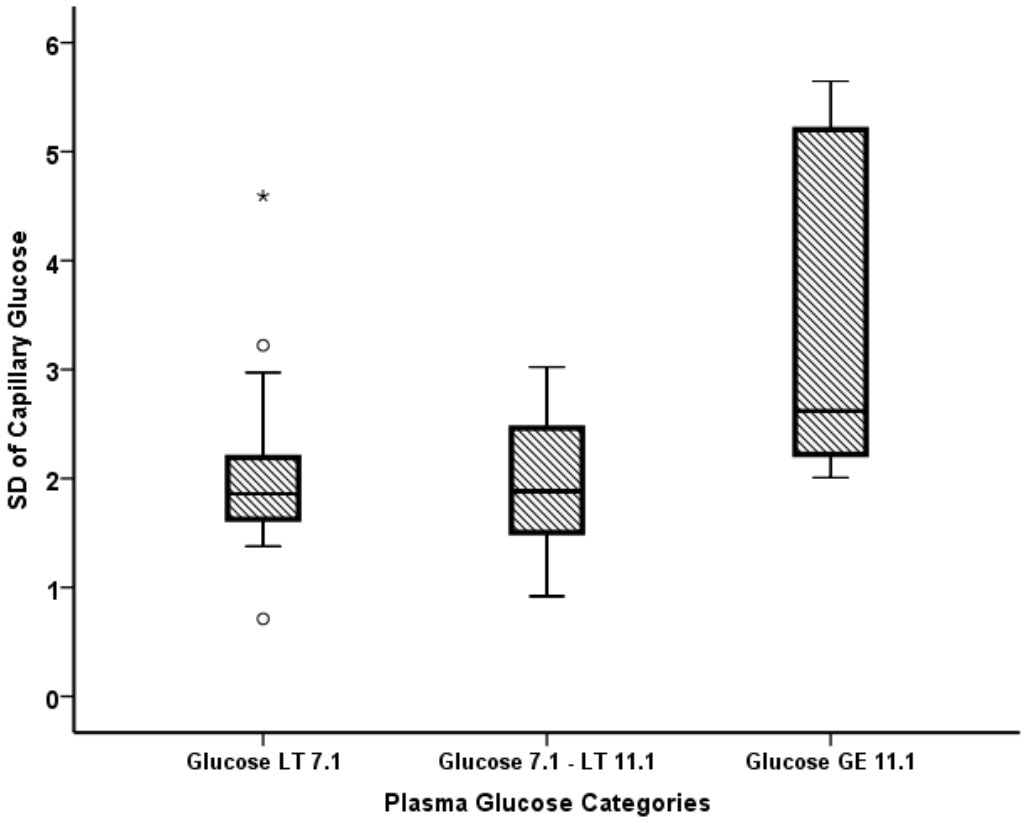


Figure 72: Standard deviation of CBG values for RPG ranges LT 7.1, 7.1-11.1 and GE 11.1, all metformin study participants

5.7 Capillary Glucose Values: Group A and B Participants

12 participants had recorded episodes of hypoglycaemia (defined as CBG<4.0mmol/L, NHS Diabetes, 2010) during the in-patient phase of the study. Six participants were from the metformin group (group A) and 6 from the placebo-treated group (group B). In total, there were 33 individual episodes of hypoglycaemia: n=25 were recorded in group A participants; and n=8 in group B participants.

Figure 73 illustrates the mean CBG by study day for group A and B participants during the in-patient phase of the study.

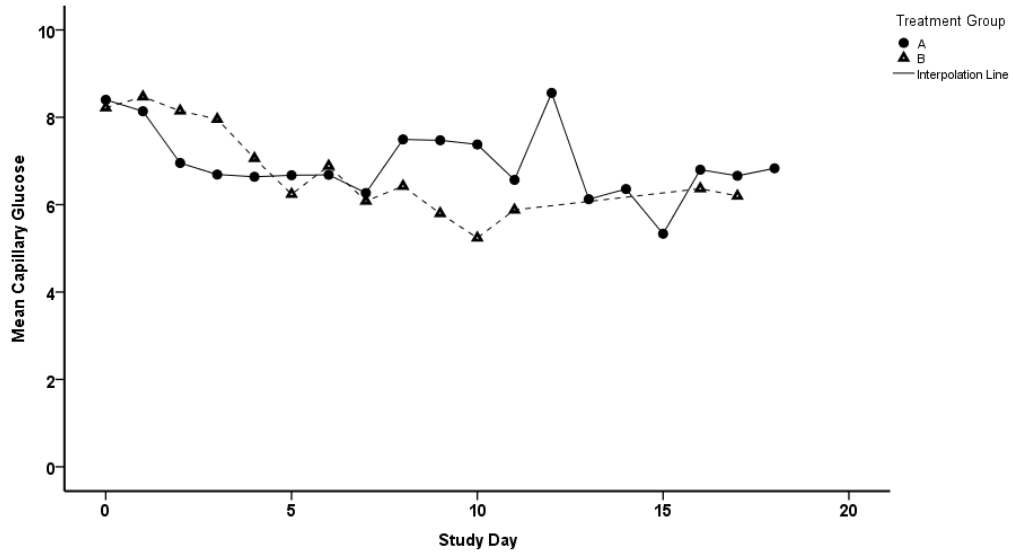


Figure 73: Mean capillary blood glucose by study day for group A and B metformin study participants

Figure 74 illustrates the overall CBG values for group A (metformin) and group B (placebo) participants. Descriptive statistics are contained within Table 74.

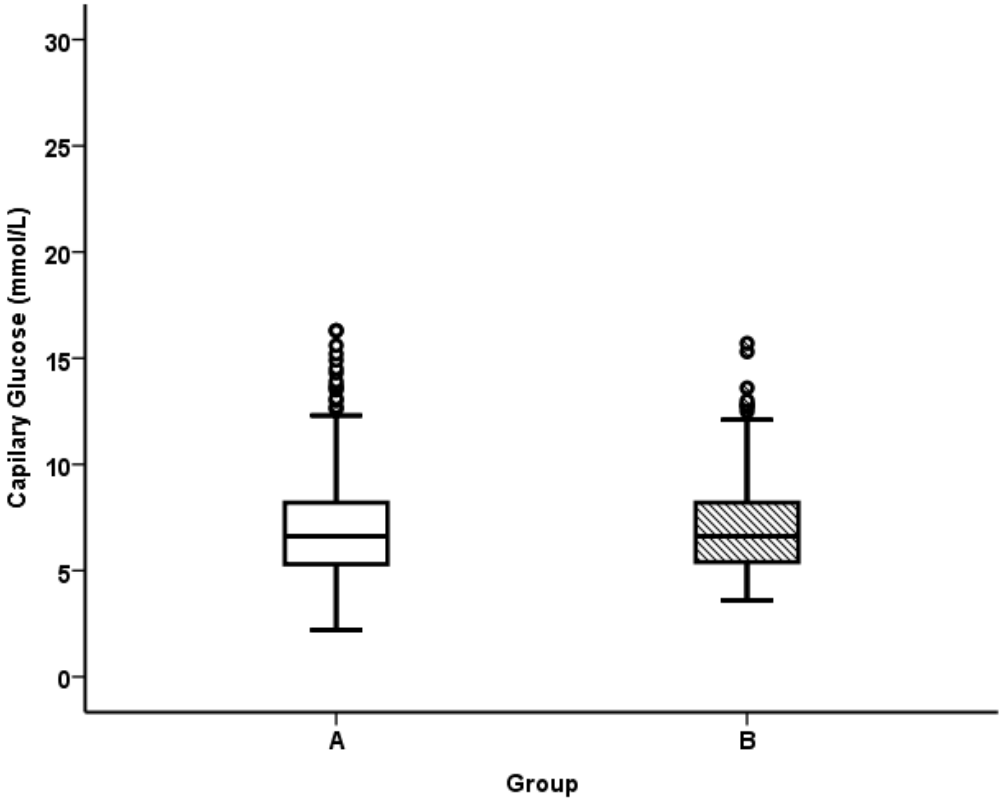
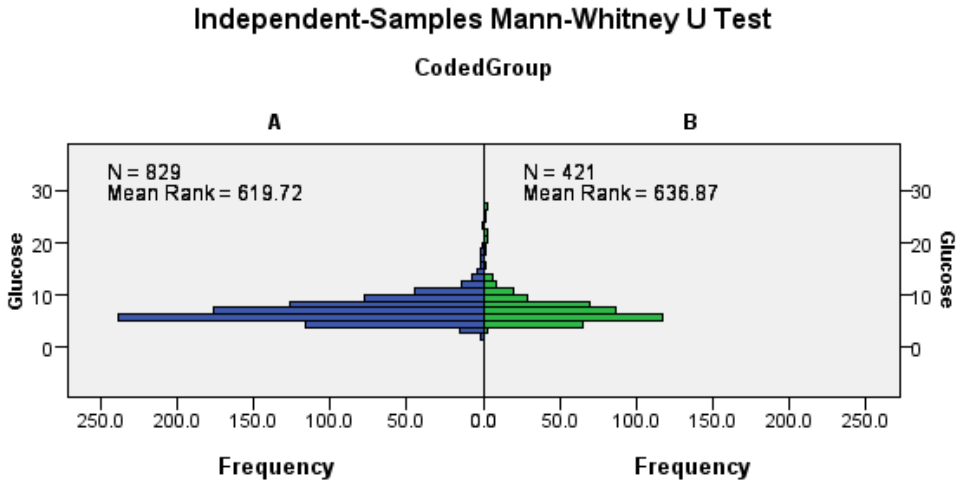


Figure 74: Capillary Blood Glucose values for group A and B metformin study participants

Study Group	Capillary Blood Glucose (mmol/L)		
	N	**Mean**	**SD**
A	829	6.971	2.32
B	421	7.456	3.56

Table 74: Descriptive statistics for capillary blood glucose values, group A and B metformin participants

An independent samples t-test demonstrated a highly statistically significant difference between the CBG variances ($p<0.01$). Therefore the Mann-Whitney U non-parametric test was performed to check whether the distribution of glucose was the same across group A and B (rather than comparison of means using an independent samples t-test). The asymptotic significance (equivalent to significance in parametric statistical tests) was >0.05 (0.43) confirming that there was no statistically significant difference in the distribution of glucose across group A and B (Figure 75).



Total N	1,250
Mann-Whitney U	179,292.500
Wilcoxon W	268,123.500
Test Statistic	179,292.500
Standard Error	6,030.978
Standardized Test Statistic	.794
Asymptotic Sig. (2-sided test)	.427

Figure 75: Mann-Whitney U test to test null hypothesis, 'there is no difference between groups A and B with regard capillary glucose values' (metformin study participants)

Glycaemic variability was then examined in group A and B participants. Firstly, using the independent samples t-test, equal variances not assumed, the mean capillary glucose SDs for Groups A and B were compared. There was no statistically significant difference between the means for the two groups, significance levels > 0.05 (Table 75).

	Levene's Test for Equality of Variances		t-test for Equality of Means		
Equal variances assumed	F	Sig.	t	df	Sig. (2-tailed)
Yes	2.033	0.160	-0.289	50	0.774
No			-0.246	23.043	0.808

Table 75: Independent samples t-test of mean capillary blood glucose standard deviation (measure of glycaemic variability), group A and B metformin study participants. *p<0.05 –statistically significant, **p<0.01 statistically highly significant

Secondly, the distribution of the capillary glucose SD was compared for Groups A and B using the Mann-Whitney U Test; there was no statistically significant difference between the distributions of the data for the two groups (asymptotic significance 0.45).

Finally, the mean GV (CBG SD) of 4 study groups: metformin study groups A and B (n=1250 glucose values) and mean GV (SG SD) of prospective study group 1 and 2 (n=2396 glucose values) were compared using the One-Way Analysis of Variance (One-Way ANOVA) with the Student-Newman-Keuls Test (SNK Test) and the Tukey's Honestly Significant Difference Test (Tukey's HSD) for homogeneity of subsets. No statistically significant differences were found between the variances or means of the four groups indicating no difference in glycaemic variability between the 4 groups. As the distribution was slightly different from a normal curve, the nonparametric Kruskal-Wallis test was run for extra reassurance. This agreed with the ANOVA.

5.8 Follow-up Variables

As described in methodology section 2.2.3, a follow-up visit was organised at days 28-35 where possible. Table 76 contains descriptive statistics of baseline and follow-up glucose and HbA1c for all participants (where available).

	N	Min	Max	Mean	SD
Baseline glucose (mmol/L)	41	4.4	29.5	8.1	4.24
Follow-up glucose (mmol/L)	33	2.8	17.4	6.6	3.16
Baseline HbA1c (mmol/mol)	32	33	72	43.4	8.12
Follow-up HbA1c (mmol/mol)	33	32.0	78.0	41.7	8.35

Table 76: Descriptive statistics of baseline and follow-up glucose (mmol/L) and HbA1c (mmol/mol) for all metformin study participants

A paired samples t-test demonstrated a statistically significant difference between baseline and follow-up glucose (follow-up glucose lower than baseline) but no statistically significant difference between baseline and follow-up HbA1c for all participants.[Table 77]

		Paired Differences		t	df	Sig. (2-tailed)
		Mean	Std. Deviation			
Pair 1	Baseline glucose Follow Up glucose	1.63	3.43	2.472	26	0.020*
Pair 2	Baseline HbA1c Follow Up HbA1c	-0.33	3.43	-0.446	20	0.660

Table 77: Paired samples t-test for baseline and follow-up glucose and baseline and follow-up HbA1c, all metformin study participants. * Statistically significant p<0.05, ** statistically highly significant p<0.01

Table 78 contains descriptive statistics of baseline and follow-up glucose and HbA1c for group A (metformin) and B (placebo) participants separately.

	Group	N	Mean	SD
Baseline glucose	A	28	7.3	2.54
	B	13	9.6	6.45
Baseline HbA1c	A	19	42.2	5.36
	B	13	45.1	11.03
Follow Up glucose	A	21	5.8	2.05
	B	12	7.8	4.32
Follow Up HbA1c	A	22	40.7	5.62
	B	11	43.7	12.26

Table 78: Descriptive statistics of baseline and follow-up glucose (mmol/L) and HbA1c (mmol/mol) for groups A and B metformin study participants

An independent samples t-test did not show a statistically significant difference between the mean values for baseline glucose, follow-up glucose, baseline HbA1c and follow-up HbA1c between group A and B participants (Table 79).

		Levene's Test for Equality of Variances		t-test for Equality of Means		
	Equal variances Assumed	F	Sig.	t	df	Sig. (2-tailed)
Baseline glucose	Yes	3.302	0.077	-1.643	39	0.108
	No			-1.237	13.762	0.237
Baseline HbA1c	Yes	2.883	0.100	-0.981	30	0.335
	No			-0.869	15.912	0.398
Glucose Follow Up	Yes	7.181	0.012	-1.790	31	0.083
	No			-1.493	13.876	0.158
HbA1c Follow Up	Yes	2.145	0.153	-0.972	31	0.339
	No			-0.772	12.153	0.455

Table 79: Independent samples t-test of baseline and follow-up glucose and HbA1c between group A and B metformin study participants

Length of stay for all participants is presented in Table 80 and for group A and B participants separated in Table 81. An independent samples t-test did not demonstrate a statistically significant difference for length of stay between group A and B participants.

	N	Min	Max	Mean	SD
Length of Stay (Days)	50	3	50	10.52	8.63

Table 80: Descriptive statistics for length of stay, all metformin study participants

Group		N	Min	Max	Mean	SD
A	Length of Stay (Days)	32	3	50	11.00	9.847
B	Length of Stay (Days)	18	5	27	9.67	6.068

Table 81: Descriptive statistics for length of stay, group A and B metformin study participants

5.9 Correlations

Table 82 describes significant and highly significant correlations noted in all metformin study participants (group A and B combined). Notably, SD of CBG was *not* correlated with length of stay (all participants and group A and B separated.)

Variable 1	Variable 2	Pearson Correlation	Sig. (2-tailed)	N
Baseline HbA1c (mmol/mol)	Age (years)	0.393*	0.026	32
	Discharge CAT score	-0.631**	0.000	28
	SD of CBG (GV)	0.691**	0.000	32
Discharge CAT score	Baseline glucose (mmol/L)	-0.469**	0.006	33
SD of CBG (GV)	Baseline glucose (mmol/L)	0.578**	0.000	41
	Discharge CAT score	-0.575**	0.000	40

Table 82: Pearson correlations between variables for all metformin study participants (groups A and B combined) * statistically significant p<0.05, ** statistically highly significant p<0.01

5.10 Summary of Chapter 5

NB: Group A –metformin treated, Group B- placebo treated

- The prevalence of SH was 39% in the recruited COPD population
- The majority (61.5%) of participants were men. All apart from n=1 were of white ethnicity. The mean age was 67.4 years. There were some similarities with the prospective study population where the mean age was 68yrs and 60% of participants were men.
- At baseline, mean RPG was 8.0mmol/L, mean HbA1c was 43 mmol/mol (classified as 'high risk for DM'). In comparison, mean RPG and HbA1c for prospective study participants was 6.7mmol/L and 40mmol/mol respectively.
- 15% of participants met the biochemical criteria for a diagnosis of T2DM
- There were no statistically significant differences in age, weight, lactate, eGFR, and CAT values between participants with and without stress hyperglycaemia. However, baseline HbA1c was found to be significantly higher in participants with a baseline RPG ≥ 11.1mmol/L (n=4) compared to those with lower baseline RPG values (n=27).
- Mean CBG was highest in GE11.1 RPG group but CBG values reached a maximum of 23.2mmol/L within the lowest RPG category (glucose LE 7.0).
- Equal numbers of participants from group A and group B had episodes of hypoglycaemia during the in-patient phase of the study but total number of episodes were greater in group A
- Glycaemic variability (SD of CBG) appeared to be highest in participants with a RPG ≥ 11.1mmol/L

- The distribution of CBG values and glycaemic variability (expressed as SD) were not different between group A and B participants. There were also no statistically significant differences in GV between metformin and prospective study groups
- There were also no differences between group A and B participants with regards: baseline RPG, follow-up RPG, baseline HbA1c, follow-up HbA1c and length of stay
- Follow-up glucose was significantly lower than baseline glucose for all participants
- Glycaemic Variability (SD of CBG) was not correlated with length of stay (all participants and group A and B separated.) A positive correlation was found between Glycaemic Variability and baseline RPG ($p<0.01$) for all participants
- Overall (for all participants) follow-up glucose was significantly lower than baseline glucose ($p<0.05$)

Chapter 6: Discussion

6.1 Summary of Study Hypotheses and Research Objectives

To recap, the main research objective, addressed through a prospective observational study (see section 1.5), investigated the metabolic profile of people with and without Stress Hyperglycaemia through five separate null hypotheses:

NULL HYPOTHESIS 1: There is no statistically significant difference between the mean Body Mass Index (BMI) values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 2: There is no statistically significant difference between the mean waist circumference values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 3: There is no statistically significant difference between the mean (systolic and diastolic) blood pressure values of people with and without stress hyperglycaemia

NULL HYPOTHESIS 4: There is no statistically significant difference between the mean Epworth score of people with and without stress hyperglycaemia

NULL HYPOTHESIS 5: There is no statistically significant difference between the mean Copeptin values of people with and without stress hyperglycaemia

Independent samples t-tests displayed in table 12 did not reveal statistically significant differences in the mean (or variance) of hypothesis 1-4 variables between group 1 and 2 participants (Table 13). There was also no statistically significant difference in the mean copeptin values between group 1 and 2 participants (Table 15). **Therefore, there was insufficient evidence to reject any of the null hypotheses.**

In addition to the central hypotheses, several research questions were also considered throughout this work:

- Question 3: Do people with Stress Hyperglycaemia actually have underlying glucose intolerance, unmasked during acute illness, rather than a genuinely transient disorder?
- Question 5: What is the best management for stress hyperglycaemia in the acute care setting?

Study results as well as implications of findings will be discussed in the forthcoming sections. Results pertaining to hypotheses 1-4 are discussed in section 6.2, hypothesis 5 is discussed in more detail in section 6.10.10.

6.2 Metabolic Profiling

The heterogeneous mix of patients with SH in the AMU setting has not been well described. Previous studies have examined intensive care settings, (G van den Berghe et al., 2001) isolated diagnoses associated with SH (Lepper et al., 2012; Malmberg et al., 2005) or large population outcomes using registries and retrospective methodology. (McAllister et al., 2014) To our knowledge, this is the first prospective study to offer a detailed profile of a broad group of patients admitted to the acute care setting with SH. The overarching aim of this work is to improve understanding of the condition, potentially supporting clinical decision making.

A number of studies have reported that people with SH may be at a greater risk of Diabetes Mellitus. (Carmen Wong et al., 2010; Gornik, Vujaklija, Lukić, Madžarac, & Gašparović, 2010; Greci et al., 2003; Sewdarsen et al., 1987; Wahid et al., 2002) In a recent, large (n= 86 634 patients) Scottish study, a ‘national database of hospital admissions was linked with a

national register of diabetes to describe the association between admission glucose and the risk of subsequently developing type 2 diabetes' (McAllister et al., 2014). Plasma glucose levels measured during an emergency hospital admission were found to predict subsequent risk of developing type 2 diabetes. The 3 year risk of DM was <1% for a RPG of ≤5mmol/L and increased to 15% at 15 mmol/L. Unfortunately, the study could not confirm whether these were fasting or random plasma glucose levels. Of interest, 90% of those with admission glucose of 11.1mmol/L were not diagnosed with diabetes within 3 years of discharge from hospital. An earlier study also demonstrated that the level of RPG did not predict the future development of DM (Wahid et al., 2002). The nature and frequency of patient follow-up should be considered in interpreting this information.

Aside from glucose levels, a number of other factors including BMI (Looker et al., 2001), waist circumference (Diabetes Prevention Program Research Group, 2006), blood pressure (Conen et al., 2007), OSA (Idris et al., 2009) and ethnicity (Shai et al., 2006) have been linked to the development of Type 2 diabetes. Given the retrospective nature of the Scottish study, the full phenotype of people with SH who developed DM was not available or therefore incorporated within the derived predictive model.

Treatment of diabetes is guided by phenotype and NICE recommends that individualised goals are set for management (NICE, 2009). If treatment is to be considered for SH in the acute setting, a similar approach should be adopted. Blanket use of insulin for modest levels of hyperglycaemia seem likely to be harmful (Finfer et al., 2009) and also impractical. In this context, the metabolic profile of patients with SH is of interest, particularly given the association with DM. Previous studies on the treatment of SH, in condition specific contexts, have generally used insulin treatment (Finfer et al., 2009). Metabolic profiling could guide

therapy towards alternative treatments such as metformin. The metabolic profile is also of interest as a potential tool for the prediction of metabolic abnormalities (section 3.10.2).

The results of the prospective study showed no difference in the metabolic profile (as defined in section 1.5) of people with and without stress hyperglycaemia (tables 12-14). Similar (estimated) proportions of participants from group 1 and 2 also met the IDF diagnostic criteria for metabolic syndrome.

As described above, links between the metabolic profile and T2DM have been well established, with measures such as BMI, waist circumference and BP frequently incorporated into risk assessment tools for primary care (L. J. Gray et al., 2010; Griffin, Little, Hales, Kinmonth, & Wareham, 2000; Lindström & Tuomilehto, 2003). Studies have also shown associations between copeptin and DM (Enhörning et al., 2010).

People with SH are thought to be at greater risk of T2DM as well as abnormal glucose tolerance with figures ranging from 16% (Gornik et al., 2010) to 75% (Sewdarsen et al., 1987). These data are consistent with those studies in suggesting a higher 3-year risk for T2DM (section 3.10.2), as well as a possible higher proportion of metabolic abnormalities (Table 36) in participants with SH. It is therefore a surprise that the metabolic profile of people with SH did not significantly differ from that of people without SH.

Additionally, the metabolic profile of participants with a GUARD score < and ≥ 5% (Table 38) appeared to be largely similar. BMI and waist circumference, however, was significantly different in those who did and didn't develop MA (section 3.10.2).

Although numbers involved in these calculations were relatively small, they imply that metabolic profiling has limited utility in risk prediction of MA in the acute setting (Table 28). Therefore, it is possible that the metabolic profile of people with SH does not differ from that

of people without the condition whilst they still remain a group at high-risk of DM. Other explanations for these findings include:

- The metabolic profile is a useful predictive tool but SH is mostly a 'transient hyperglycaemia' (Dungan et al., 2009) and only a small percentage are actually at risk of DM. This is not, however, consistent with existing literature (see chapter 1)
- Aspects of the metabolic profile, whilst helpful in primary care, are not appropriate for risk prediction in the acute care setting
- The GUARD tool and MA proportions (no inferential statistics performed) are insufficient to classify people with SH as having a higher DM risk compared to people without the condition. The GUARD tool in particular, whilst developed for unselected admissions, only required information on 'age', 'sex' and 'admission glucose' in order to produce a score. Notably, fasting insulin and systolic BP values appeared lower in the higher risk GUARD group (table 38).

In conclusion, people with SH do not appear to have a distinct metabolic profile as defined by this study. Perhaps these findings, along with the practical challenges of metabolic profiling in a fast-moving in-patient population with other care priorities suggest that this approach may be unproductive.

6.3 The Diagnosis of Impaired Glucose Regulation (IGR) in the Acute Care Setting

An unexpectedly high prevalence of Metabolic Abnormalities (MA), were seen in both the prospective and metformin studies (see sections 3.10.2 and 5.5). Whilst MA is used as a summary term for the purposes of this study, it is also important to consider the conventional definitions.

Both IFG and IGT are known to be risk factors for future diabetes (David M Nathan et al.,

2007) and are collectively termed 'Impaired Glucose Regulation' (IGR, see Table 28). Patients with a HbA1c of 42-47mmol/mol have also been proposed as a high risk group, equivalent to IGR by an International Expert Committee (D.M. Nathan et al., 2009). The committee comments that 'risk for diabetes based on levels of glycemia is a continuum; therefore, there is no lower glycemic threshold at which risk clearly begins.' There is no consensus on this issue -the ADA recommends a lower HbA1c of 39-46mmol/mol as a cut-off for IGR whilst the WHO does not recommend the use of HbA1c to diagnose IGR at all. (WHO, 2011) For this study, UK NICE guidance (HbA1c 42-47mmol/mol) has been used to define 'high risk for DM'/IGR (NICE 2012).

Given the biochemical definitions (requiring fasting plasma glucose and an OGTT), IGR is not routinely diagnosed in the acute setting and is also under-diagnosed in primary care (Gillett et al., 2012). The prospective study noted a diagnosis of IGR in 34% of all participants (section 3.10.2) and uniquely, obtained CGM profiles on n=5 (participants 054, 056, 057, 059 and 063, see sections 4.3.2 and 4.3.3).

The figures of 34% is higher than previous national estimates for IGR (Gillett et al., 2012) although a similarly high/or higher prevalence has been reported in research studies describing patients with ACS (Attia, Ragy, Enany, & Elgamal, 2013; Bartnik et al., 2004; Norhammar et al., 2002; Okosieme et al., 2008; Ambady Ramachandran et al., 2005) and stroke. (Fonville, den Hertog, Zandbergen, Koudstaal, & Lingsma, 2014; C. S. Gray et al., 2004; Jia et al., 2012). This figure could also be an underestimation as FPG is not as sensitive as OGTT in the diagnosis of IGR (Mostafa et al., 2010). The latter was only performed in a

handful of group 1 participants who attended follow-up (n=10, 16% of overall prospective population).

IGR is of interest in this context as it is an analogous condition to SH:

- Both IGR and SH are linked to T2DM. (David M Nathan et al., 2007; Sewdarsen et al., 1987)
- Both IGR and SH may revert to normal glucose tolerance (Dungan et al., 2009; Lu et al., 2008)
- Both IGR and SH may be under-recognised in the acute care setting.
- Evidence exists linking IGR and SH to poor outcomes from associated, underlying conditions (Baker et al., 2006; Meier et al., 2002)
- As with SH, the metabolic profile is not always striking. A national study of 9096 people with IGT/IFG observed 30% with a 'healthy/low' BMI of <25 kg/m^2. (Gillett et al., 2012) In the prospective study, a similar pattern was observed with 31% of participants in group 1 and 41% in group 2 found to have a BMI <25 kg/m^2

Given the similarities noted above, it is of interest to examine the standard approach to IGR. Studies have shown that preventative measures may prevent progression of IGT to frank DM (Knowler et al., 2002; Tuomilehto et al., 2001). Implementation of these evidence-based interventions does not, however, always occur (Karve & Hayward, 2010).

UK guidelines (NICE 2012) recommend intensive lifestyle programmes and annual monitoring for people considered to be at high risk for DM (Figure 76). Despite the similarities between IGR and SH, and the fact that SH could also be considered a high-risk

group for future DM, there are currently no UK guidelines on follow-on care or monitoring. Further work in this direction would benefit patients and clinicians.

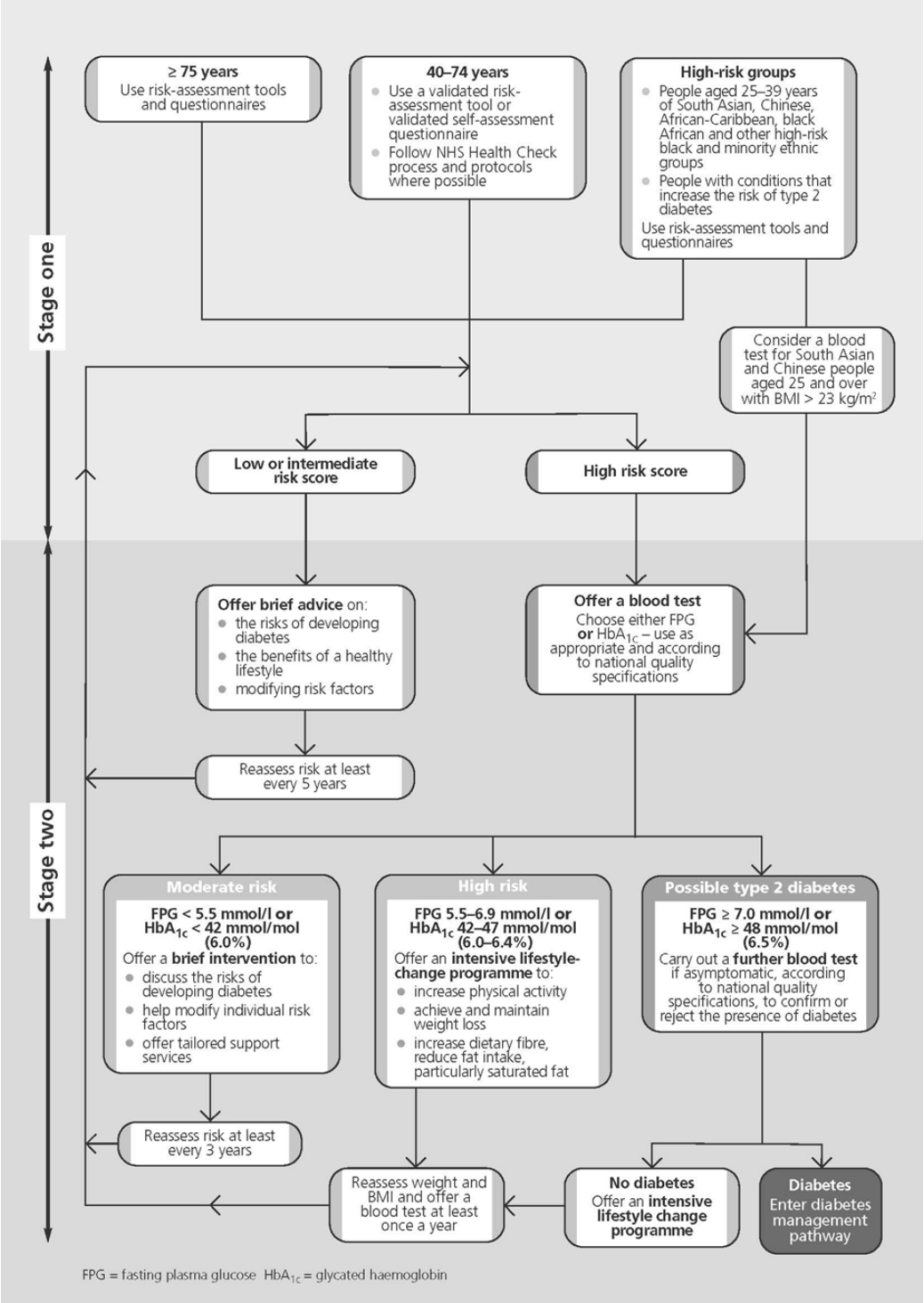


Figure 76: Identifying and Managing Risk of Type 2 Diabetes. National Institute for Health and Clinical Excellence (2012) *PH 38 Preventing type 2 diabetes: risk identification and interventions for individuals at high risk*. Manchester: NICE. Available from www.nice.org.uk/PH38 Reproduced with permission.

6.4 The Diagnosis of Diabetes in the Acute Care Setting

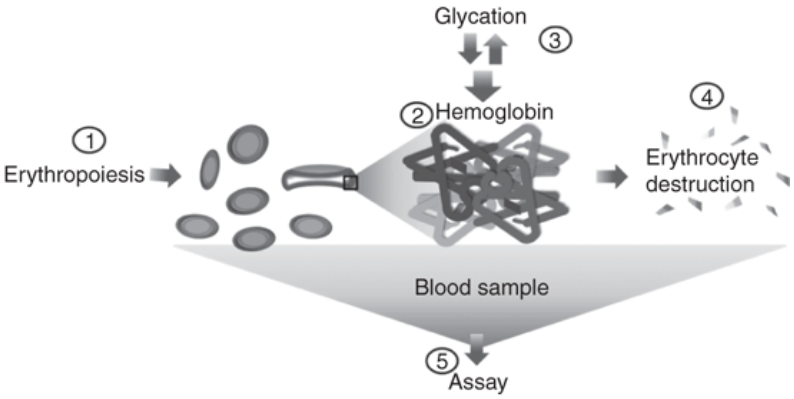
There are currently 3.2 million people with DM in the UK and it is estimated that a further 850 000 people with Type 2 DM remain undiagnosed (Diabetes UK). People with undiagnosed T2DM are often asymptomatic. Studies have demonstrated the presence of microvascular complications at the point of diagnosis, suggesting a lag of between 4-7 years between onset of the condition and a formal diagnosis of T2DM (M. I. Harris, Klein, Welborn, & Knuiman, 1992). Clearly there is a significant benefit in early diagnosis.

An acute presentation may generate an opportunistic diagnosis of DM in people for whom diagnostic criteria are clearly met. A high index of suspicion may prompt a RPG check although, anecdotally, this practice often varies between clinicians. In 2012 the Endocrine society (USA) published guidelines recommending that 'all patients, independent of a prior diagnosis of diabetes, have laboratory blood glucose testing on admission' (Umpierrez et al., 2012). There are currently no equivalent UK guidelines and although in some UK hospitals, mechanisms exist to ensure that a CBG must be entered into a discharge summary in order for the discharge to proceed, it is unclear how widespread this practice is. Additionally, the yield of DM pick-up using this approach has not been well studied.

With the advent of new WHO advice (WHO, 2011) recommending that a HbA1c ≥ 48mmol/mol may be used for the diagnosis of diabetes, the diagnosis of DM becomes potentially easier in the acute care setting - HbA1c testing does not require the patient to be fasting and can be taken at any time of day.

One study, preceding the WHO advice, used FPG and a 2hr OGTT to identify HbA1c cut-offs appropriate for the acute setting. An HbA1c value of > 42mmol/mol (6.0% DCCT) was found to be 100% specific and 57% sensitive for the diagnosis of diabetes (Greci et al., 2003). HbA1c may, however, be affected by a number of factors (Figure 77) and an expert

group recommend that it is not used as a sole test to diagnose DM in this context, stating that, 'as HbA1c reflects glycaemia over the preceding 2-3 months, it may *not* be raised in patients at high risk of DM who are acutely ill' (Expert Group, 2012).



Factor influencing A_{1c}	Increased A_{1c}	Decreased A_{1c}	Variable change in A_{1c}
1. Erythropoiesis	Iron deficiency, vitamin B_{12} deficiency, decreased erythropoiesis	Administration of erythropoietin, iron or vitamin B_{12}; reticulocytosis, chronic liver disease	
2. Altered hemoglobin			Fetal hemoglobin, hemoglobinopathies, methemoglobin
3. Glycation	Alcoholism, chronic renal failure, decreased erythrocyte pH	Ingestion of aspirin, vitamin C, vitamin E; certain hemoglobinopathies, increased erythrocyte pH	Genetic determinants
4. Erythrocyte destruction	Increased erythrocyte lifespan: splenectomy	Decreased erythrocyte lifespan: hemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs such as antiretrovirals, ribavirin, and dapsone	
5. Assays	Hyperbilirubinemia, carbamylated hemoglobin, alcoholism, large doses of aspirin, chronic opiate use	Hypertriglyceridemia	Hemoglobinopathies

Figure 77: Factors influencing HbA1c. Reprinted from the Journal of Diabetes, volume 1, issue 1, Gallagher EJ, Le Roith D, Bloomgarden Z. 'Review of Hemoglobin A1c In the Management of Diabetes', Figure 1, p10. Copyright © 1999-2015 John Wiley & Sons, Inc., reproduced with permission from Rightslink (Appendix 7)

For a number of people presenting in the acute care setting, there will be little ambiguity over the diagnosis. For example, the prospective study identified one patient (participant 006) with an HbA1c above the WHO diagnostic criteria for DM (51mmol/L). This individual was excluded from the study and diagnosed with DM based on a RPG of 11.2mmol/L and symptoms suggestive of DM (see section 3.6.2). In addition, 4 participants had 'Biochemical Features of Diabetes' (see Table 28 for definition and tables 32-35 and section 4.3 for detailed/CGM profiling).

Patients with newly diagnosed DM may present to the acute setting anywhere on a spectrum from asymptomatic to severe metabolic decompensation. Greater clinical awareness and a high index of suspicion would increase the pick-up of Type 2 DM in the acute care setting. A public health conversation is required to assess the impact and sustainability of this approach. Further work into the extent to which SH is a risk factor for DM might facilitate more appropriate intervention/investigation.

6.5 The Prevalence of Occult Hyperglycaemia in the Acute Care Setting

CGMS were first approved by the US Food and Drug Administration (FDA) in 1999 (Tavris & Shoaibi, 2004) and discussed by NICE in 2004 (NICE, 2004). Traditionally, they have been used to provide insights in people with type 1 DM. (Hoeks, Greven, & de Valk, 2011; Maia & Araújo, 2007; Tavris & Shoaibi, 2004). Increasingly, researchers have employed the technology for a variety of uses including diagnosis of DM in high risk groups (A. Soliman, DeSanctis, Yassin, Elalaily, & Eldarsy, 2014), assessment of GV (Gohbara et al., 2015; Ma et al., 2011), detection of hyperglycaemia during pregnancy (Bühling et al., 2004), and the optimisation of glycaemic control in the critical care setting (Brunner et al., 2011; Goldberg et al., 2004). As described in section 2.1.9, the device has many advantages: frequency of

glucose readings (up to 288 values in 24 hours); only minimal patient training required and few attendant risks.

One study, conducted in an Australian stroke unit, reported novel insights with the utilisation of CGM, demonstrating frequent episodes of hyperglycaemia in people without DM. In a cohort of n=59 patients with ischaemic stroke, 50% of people without DM and 100% of people with DM had a sensor glucose value ≥ 7.0 mmol/L (defined as 'hyperglycaemia') 8 hours post-stroke. This was followed by decrease in glucose and a later hyperglycaemic phase 48-88 hours post-stroke. Overall, 34% of people without DM and 86% of people with DM were hyperglycaemic for at least 25% of the monitoring period. (Allport et al., 2006)

In this work, continuous glucose monitoring (prospective study) and capillary blood glucose readings (metformin study) revealed multiple episodes of otherwise clinically occult hyperglycaemia and unpredictable glycaemic patterns. Notably:

- CBG 23.2mmol/L in a COPD patient despite a RPG of <7.1mmol/L (Table 73)
- Marked episodes of (CGM recorded) hyperglycaemia (participant 061) and hypoglycaemia (participants 054, 063, 064) with values ranging from 2.2-21.8mmol/L (see section 6.9 for further discussion on in-patient hypoglycaemia)
- 11% of Sensor Glucose (SG) values from group 2 participants ≥ 11.1 mmol/L compared to 2% from group 1 (prospective study, Table 61).
- Mean SG lower for group 1 compared to group 2 participants ($p<0.01$, section 4.3.8).

Without the additional monitoring employed for research purposes, these readings would have been missed in a clinical setting. As observed in other studies (Xu et al., 2012; Yu et al., 2004), it suggests even those with supposed 'normoglycaemia', have a marked glycaemic variability and episodes of otherwise clinically occult hyperglycaemia. This demonstrates the

limitations of a single RPG in the diagnosis of SH as is already recognised in the diagnosis of DM (see section 6.4).

To our knowledge, CGM has only rarely been utilised for people without DM in the acute care setting (Burt, Roberts, Aguilar-Loza, Frith, & Stranks, 2011) and there are few studies examining the accuracy of the technique and optimal wearing time. A number of the prospective study in-patient readings were classified as 'missing' (Table 47). There were also a number of practical challenges to managing the technology in this setting as well a substantial expense over CBG monitoring. Therefore, whilst the technology provided some interesting findings, particularly the glycaemic excursions of supposed 'normoglycaemic' individuals, it is unlikely to be implemented in the AMU setting as part of standard care.

6.6 Glycaemic Variability in Stress Hyperglycaemia

As outlined in section 4.3.1 Glycaemic Variability (GV), defined as glucose fluctuations around the mean, was studied in a small number of participants who consented to wear a CGM (n=12 from prospective study) as well as participants with CBG readings in the metformin study (sections 5.6 and 5.7). The Standard Deviation of Sensor Glucose (SDSG) was used as a measure of GV (section 2.1.21).

Although a previous study used CBG readings to calculate GV in COPD patients (Archer et al., 2011), to our knowledge, this is one of the first times continuous glucose monitoring has been used to examine glycaemic variability in an undifferentiated patient cohort with stress hyperglycaemia. This was considered useful for a number of reasons (see also sections 1.4 and 4.1.1):

- Studies have shown the importance of GV in predicting mortality/adverse outcomes in hospitalised patients (Ali et al., 2008; Dungan, Binkley, Nagaraja, Schuster, & Osei, 2011; M Egi et al., 2006)
- Given the rapid onset and short-term nature of hyperglycaemia in some patients with SH (Dungan et al., 2009), glycaemic variability may be a more appropriate measure than HbA1c for predicting short-term outcomes and guiding treatment

The results of this work did not show a statistically significant difference in GV between the 4 study groups (prospective groups 1 and 2 and metformin groups A and B, see section 5.7). The groups were not, however, case matched and serial glucose assessment was with CBG in metformin study versus SBG in prospective study.

Unfortunately, this is a consistent problem within this field of study as a variety of glucose measurements and GV indices have been used including standard deviation, glucose variability index and MAGE. This lack of uniformity has led to difficulties in drawing robust conclusions from existing studies (Eslami, Taherzadeh, Schultz, & Abu-Hanna, 2011).

Although GV was not different across the 4 study groups, it is useful to compare our findings to existing literature. Interestingly, the lowest (mean) GV recorded in our study was in the SH group (1.42mmol/L). This is lower than the median value reported from n=4 ICU studies (Eslami, de Keizer, de Jonge, Schultz, & Abu-Hanna, 2008). The highest GV was in the metformin study, placebo group (2.23 mmol/L). In comparison, a study of insulin-treated COPD patients (Archer et al., 2011) reported a median GV (SD) of 2.9mmol/L using CBG monitoring. Metformin study participants with a higher RPG were also found to have a higher GV (Table 73, Figure 72). This is discussed in more detail in section 6.9.

Factors linked to increased GV include exogenous insulin treatment (Archer et al., 2011) as well as endogenous insulin reserve (Kohnert et al., 2010). GV was seen to increase with HOMA2-IR in group 1 participants only (Figure 68). Although only small numbers were examined, (n=12), this is a novel finding meriting further work. As described in section 4.1.1, a body of literature links both glycaemic variability and insulin resistance to adverse outcomes. If a causative link is established, this could have implications for the treatment of SH.

In terms of outcomes there was no (statistically significant) correlation between GV and length of stay in either the prospective (Figure 66) or metformin studies (section 5.9). Additionally, GV was not significantly different between CGM participants with and without MA (Appendix 5). Further work to examine correlations between GVs and metabolic and longer-term outcomes would be of benefit and could guide management for patients with SH in the acute care setting.

6.7 Fasting Insulin Values in Stress Hyperglycaemia

Although C-peptide is generally preferred over fasting insulin for assessment of insulin secretion (A. G. Jones & Hattersley, 2013), insulin values may be used in the description of the metabolic syndrome (Alberti et al., 2006) or, as in this case, to provide HOMA2 values. One of the striking results of the prospective study was a significantly lower mean fasting insulin value in group 1 compared with group 2 participants ($p<0.05$, section 4.2.1) as well as other populations (Table 83).

Population	Fasting Insulin (Original study units)	Fasting Insulin (Prospective study units)
Melanesian island of Kitava (Lindeberg, Eliasson, Lindahl, & Ahrén, 1999) (60-74 yr. old males and females)	3.5 uIU/mL	**3.5 mIU/L**
Prospective study, group 1	5.76 mIU/L	**5.8 mIU/L**
Whitehall II study (Tabák et al., 2009) (baseline visit, group without DM)	47 pmol/L	**6.8 mIU/L**
Swedish population (Lindeberg et al., 1999) (60-74 years)	7.3 uIU/ml	**7.3 mIU/L**
NHANES III (Maureen I Harris et al., 2002) (US males)	8.8 uIU/ml	**8.8 mIU/L**
NHANES III (Maureen I Harris et al., 2002) (US females)	8.4 uIU/ml	**8.4 mIU/L**
Whitehall II study (Tabák et al., 2009) (baseline visit, group with DM)	73 pmol/L	**10.5 mIU/L**
Prospective study, group 2	15.33 mIU/L	**15.33 mIU/L**

Table 83: Mean fasting insulin levels in the prospective study compared to other populations (group 1 in grey). Unit conversion performed using: http://www.endmemo.com/medical/unitconvert/Insulin.php

It is firstly worth considering the timing of the insulin sample. A rise in BG to >5mmol/L should lead to a release in insulin and c-peptide. Insulin is cleared in the liver and has a half-life of approximately 5 minutes. Given that FPG for group 1 and 2 were similar the morning after recruitment (FPG 5.4 mmol/L group 1 and 5.5mmol/L group 2, section 3.4), and CGM demonstrated lower mean sensor glucose in group 1 compared to group 2 participants (6.6 mmol/L v 7.2mmol/L respectively, Table 62), it seems likely that SH was short-lived. In this context, it is possible that insulin levels peaked at the time of recruitment but fell the next morning when measured. Even considering this, and the pulsatile nature of insulin secretion, lower levels compared to group 2 suggests suppression of insulin.

This concept is supported by existing literature. It is well recognised that counter-regulatory hormones released during SH (glucagon, cortisol, epinephrine) oppose insulin activity (Halter, Beard, & Porte, 1984) and a number of studies have demonstrated that insulin levels are normal or reduced in this context (Clowes et al., 1978; Dahn et al., 1985; Marik & Raghavan, 2004; Mizock, 2001; Opie, 1971; Schalch, 1967). Other factors linked to a suppression in insulin release during stress hyperglycaemia include IL-1 and TNF-α (V. K. Mehta, Hao, Brooks-Worrell, & Palmer, 1994).

Finally, as recognised in IGT (Kahn, 2003; David M Nathan et al., 2007), it is worth considering that low insulin levels may be linked to beta cell exhaustion (Cerf, 2013). The GUARD Type 2 Diabetes risk calculator predicted a 5.4% three year risk of developing Type 2 Diabetes compared to 1.7% for participants without SH (section 3.10.2). If this is accurate, then it is possible that reduced insulin secretory capacity is an indicator of incipient diabetes mellitus in certain participants with SH. This was predicted in the HOMA2 model (lower estimate of steady state B-cell function (%B) in group 1 compared to group 2 participants ($p<0.01$).

6.8 Insulin Resistance in Stress Hyperglycaemia

Although HOMA modelling has been reported in over 500 publications (T. Wallace et al., 2004), this is the first study to use HOMA2 in a non-critically unwell population with SH. It is an attractive method of IR assessment given its relative ease of use and low cost.

The results of this study show significantly lower HOMA2-IR and %B (beta cell function) values in group 1 compared to group 2 participants ($p<0.05$). Building on section 6.7, the HOMA2 model also suggests a higher insulin sensitivity in group 1 participants which, although not statistically significant, may justify the lower beta-cell function and insulin levels seen (T. Wallace et al., 2004).

Other studies using the HOMA2 model are presented in tables Table 84 and Table 85. HOMA2-IR (as well as %B) in the SH group appear to be the lowest across all the populations. This is particularly interesting given that waist circumference, a good predictor of insulin resistance (Wahrenberg et al., 2005), was not statistically different between group 1 and 2 participants (table 12).

Population	**Fasting glucose** (mmol/L)	**HOMA2** (%B/%S)
Prospective study, group 1	5.4	70.6 / 127.8
Whitehall II cohort (Ikehara et al., 2015) (baseline visit, white participants without DM)	**5.2**	80.2 / 113.2
Prospective study, group 2	5.5	96.4 / 97.3

Table 84: Fasting glucose and HOMA2 %B and %S values for all prospective study participants and (British White) participants without Diabetes Mellitus in Whitehall II cohort.

Population	**HOMA2-IR**
Prospective study, group 1	0.85 (0.24)
BRAMS population (Geloneze et al., 2009) (healthy group n=297)	0.87 (0.66-1.30)
**Tehran lipid and glucose study (Ghasemi et al., 2015) (optimal cut-off for T2DM prediction)	1.41
*BRAMS population (Geloneze et al., 2009) (whole group n=1203 aged 18-78 years	1.5 (0.9-2.6)
Prospective study, group 2	1.65 (1.70)
**BRAMS population (Geloneze et al., 2009) (defined cut-off value for IR)	>1.8
GREAT2DO study cohort (Mavros et al., 2013) (resistance training group, baseline)	2.73 (0.95)
GREAT2DO study cohort (Mavros et al., 2013) (sham group, baseline)	3.09 (1.26)

Table 85: HOMA2-IR values from prospective study groups and other populations. All values are mean (±SD) except *median (interquartile range) and **cut-off values

Insulin resistance in SH has been described as having central and peripheral components. Centrally, an inability to suppress hepatic glucose production has been described (Dungan et al., 2009). Peripherally, a number of factors lead to reduced insulin-mediated glucose uptake (Fan, Li, Wojnar, & Lang, 1996; Lang et al., 1989). Whilst the updated HOMA2 model is said to take into account 'variations in hepatic and peripheral glucose resistance' (Levy et al., 1998), it is ultimately estimating insulin sensitivity from plasma insulin and glucose concentrations and assumptions about normal homeostasis. In SH, where a multitude of factors including counter-regulatory hormones and excessive gluconeogenesis contribute to glucose metabolism and insulin levels, it may be that HOMA2 is not the best model to assess insulin resistance. Alternatively, it could be considered that the model incorporates these factors in its expression of insulin resistance. In this case, group 2 participants with higher HOMA-IR and %B values may, in fact, have trained beta cells from pre-existing insulin resistance which are therefore more capable of mounting an insulin response to the IR associated with acute illness and thereby protecting against SH.

This finding requires further consideration and exploration.

6.9 Metformin in Stress Hyperglycaemia

Only a few studies have reported on hyperglycaemia in non-diabetic patients hospitalised with COPD. Although it should be noted that there is substantial heterogeneity in terms of population type studied and measurements of glycaemia obtained, a high prevalence of hyperglycaemia has been described (Table 86).

Study	Description of Hyperglycaemia
(Islam, Limsuwat, Nantsupawat, Berdine, & Nugent, 2015)	'The first database included 30 patients admitted to non-intensive care unit (ICU) hospital beds. Six of 20 non-diabetic patients had peak glucoses above 200 mg/dl.' (>11.1mmol/L)
(McAllister et al., 2014)	Retrospective study. Glucose available in n=3003 patients hospitalised with COPD: glucose 7.0-11.0mmol/L in n=814 (27%) and ≥ 11.1mmol/L in n=100 patients (3%). Investigators unclear as to whether fasting/non-fasting glucose was measured
(Koskela, Salonen, & Niskanen, 2013)	Of 130 patients without a previous diagnosis of diabetes, 79% showed hyperglycaemia, defined as a FPG>6.9mmol/L or post-prandial glucose>11.1mmol/L
(Chakrabarti, Angus, Agarwal, Lane, & Calverley, 2009)	Hyperglycaemia (defined as RPG>7.0mmol/L) was present in 50% (44/88) of patients whilst 28 (32%) did not have a pre-existing diagnosis of diabetes mellitus.

Table 86: Studies reporting hyperglycaemia in non-diabetic patients hospitalised with COPD exacerbations

A number of factors associated with increased peripheral insulin resistance, including hypoxia, acidosis, inflammation and corticosteroid treatment have been linked to the development of hyperglycaemia in COPD. (Adrogué et al., 1988; Blackburn, Hux, & Mamdani, 2002; Gläser, Krüger, Merkel, Bramlage, & Herth, 2015; Louis & Punjabi, 2009; Slatore, Bryson, & Au, 2009; Van Cromphaut, 2009)

Metformin is known to improve insulin sensitivity (Bailey & Turner, 1996) and has additional anti-inflammatory (Huang et al., 2009; Isoda et al., 2006) and anti-oxidant effects (Faure et al., 1999). As a treatment, it is easy to administer and is rarely associated with hypoglycaemia when used as monotherapy. (Wright, Cull, Macleod, & Holman, 2006). Additionally, it has been used in the COPD population without leading to lactic acidosis (Hitchings, Archer, Srivastava, & Baker, 2014).

The Metformin study therefore provided a safe opportunity to examine the practical aspects of treating IR (and SH) in the acute care setting. Whilst there are many studies reporting on insulin treatment in SH, only a few have used metformin to treat SH (Gore, Wolf, Herndon, & Wolfe, 2003; Gore, Wolf, Sanford, Herndon, & Wolfe, 2005; Panahi et al., 2011) and none of these have been in an acute medical population, making this novel work. This study also provided the opportunity to comment on the metabolic characteristics of patients hospitalised with COPD as well as their circadian CBG patterns -to our knowledge, the first time that this has been done.

It is also of interest to compare relevant metformin study findings with that of the prospective study - there were some similarities between the populations in terms of demographic data (see section 4.10) and so it was considered reasonable to provide descriptive statistics for interest. However, the populations were not case matched and so inferential statistics (section 4.7) should be interpreted with caution.

Several interesting observations were made. Firstly, consistent with existing literature, (Table 86) the prevalence of hyperglycaemia was relatively high in the COPD group. Mean RPG in the metformin study was 8.0mmol/L (Table 68) compared to 6.7mmol/L in the prospective group (section 3.4) and 39% of participants had stress hyperglycaemia by the prospective study definition (Table 69). As observed in the prospective study, there was evidence of otherwise clinically occult hyperglycaemia (Table 73). There were no differences in baseline variables (including age, weight, CAT score) between people with and without SH (Table 70).

In terms of metabolic abnormalities (section 3.10.2), the mean HbA1c for all metformin study participants was in the 'high risk' category at baseline (Table 68). Higher proportions of participants had an HbA1c in the high-risk category (35%, total n=18) compared to 19% in the prospective study (Table 36). A relatively high proportion of participants (15%) were

found to have biochemical features of DM (see section 3.10.2) in comparison to 6.4% of participants in the prospective study. These differences may, in part, be related to preceding steroid therapy in the COPD population (Panthakalam, Bhatnagar, & Klimiuk, 2004). It was not possible to compare proportions of participants with IGR (including IFG, IGT and high risk HbA1c -see section 5.3) as an OGTT and FPG were not included in the protocol of the metformin study.

Results from published studies are conflicting. A high prevalence of metabolic syndrome has been reported in COPD (ranging from 43-57%), observed more frequently in overweight or obese COPD patients than in BMI matched healthy subjects (Breyer et al., 2014; Díez-Manglano et al., 2013). Meanwhile, a large, (n=16 088) longitudinal study which corrected for confounding factors, reported a higher risk of T2DM in COPD patients compared to those without COPD (C. T. Lee, Mao, Lin, Lin, & Hsieh, 2013).

When looking at the risk of T2DM in our COPD group (section 4.5), the GUARD risk calculator (http://www.cphs.mvm.ed.ac.uk/diabetes-risk/) predicted a 4.9% 3 year risk of developing DM in the metformin group overall (3.1% in prospective group overall) and 6.8% in the metformin SH group compared to 5.4% in the prospective SH group (baseline RPG only). A value of 5% corresponds to 'high risk' as defined by NICE (McAllister et al., 2014; NICE 2012).

The GUARD calculator does not require information on diagnosis (only age, gender and admission glucose) but data from the original study (McAllister et al., 2014) predicted the 3-year risk of T2DM in people with COPD (Figure 78). Further work is needed to establish these findings as well as to develop appropriate interventions for this group of patients following their discharge from the acute setting.

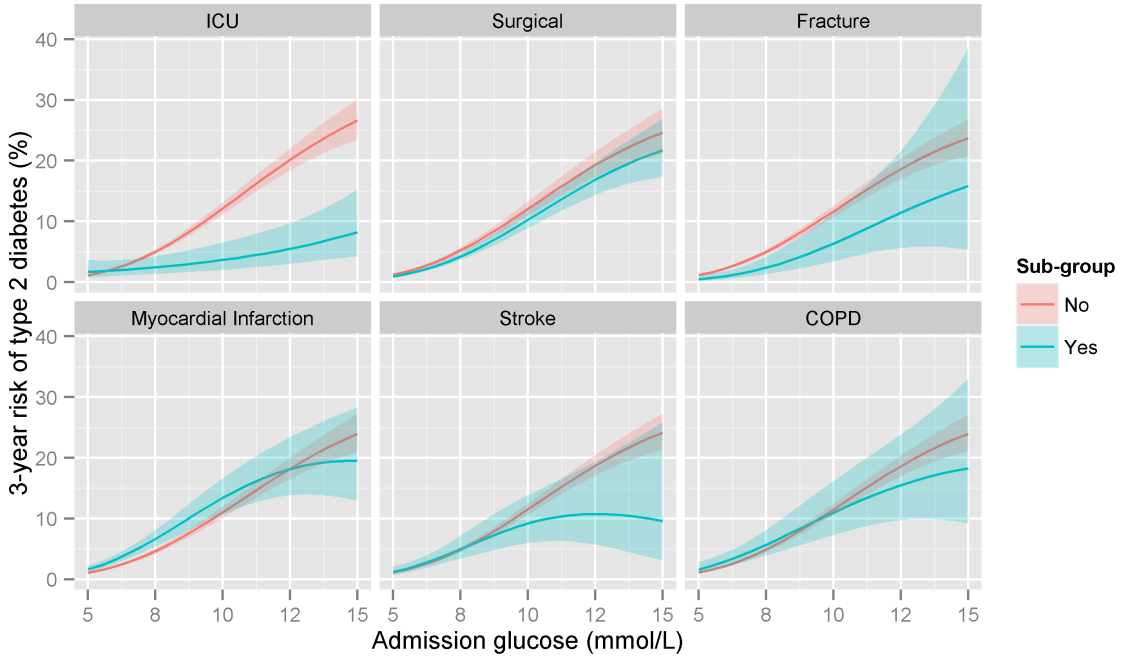


Figure 78: Three year risk of Type 2 Diabetes by glucose for patients in subgroups (including COPD) predicted by glucose level obtained from logistic regression models. *'All models adjust for age, sex and a main term and interaction term with glucose for the relevant grouping variable (eg admission to ICU). Lines represent estimates and ribbons indicate 95% CIs with blue used to indicate membership of the relevant sub-group and red used to describe the remainder of the population'.*

Figure and description reprinted from PLOS Medicine, August 2014;11(8). McAlister DA et al. 'Stress hyperglycaemia in hospitalised patients and their 3-year risk of diabetes: a Scottish retrospective cohort study' Figure 4, page 9. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4138030/) Open access article, reprinted under Creative Commons Attribution License. Material not modified.

With regards the management of SH in the acute setting (question 5, section 1.4), metformin appeared to be largely well tolerated at the local centre. Treatment did not, however, appear to have a statistically significant lowering effect on in-patient CBG (Figure 75), follow-up RPG and HbA1c values (Table 79) or length of stay (Table 81).

It is of interest that there was a discrepancy in RPG and CBG values (Table 73). This is perhaps not surprising given the fact that the COPD participants were all steroid-treated (Figure 10). It is well recognised that blood glucose levels may peak later in the day in individuals prescribed morning corticosteroids (Burt et al., 2011) and, as such, a single RPG may not be the best measure to assess hyperglycaemia. Scheduled CBG measurements,

whilst labour intensive, undoubtedly provide a rounder view. This is illustrated by the earlier example of a participant with marked hyperglycaemia identified through CBG measurement (CBG of 23.2mmol/L) who based on a RPG of <7.1mmol/L, may otherwise have been passed as 'normoglycaemic' (Table 73). Only a handful of studies have reported frequent (capillary or continuous) glucose values in people hospitalised with COPD (Archer et al., 2011; Burt et al., 2011). Further work to establish the feasibility of such measurements in the AMU setting would be beneficial.

It is also recognised that 2 individuals may have a similar mean glucose level but markedly different glycaemic variability (Moritoki Egi & Bellomo, 2009) (Figure 79). The importance of GV has been highlighted in a number of studies which report that the measure is a better predictor of adverse outcomes than mean glucose level (Ali et al., 2008; Donati et al., 2014; Dungan et al., 2011; M Egi et al., 2006; Wintergerst et al., 2006). Pathological mechanisms linking increased GV to adverse outcomes are outlined in 4.1.1.

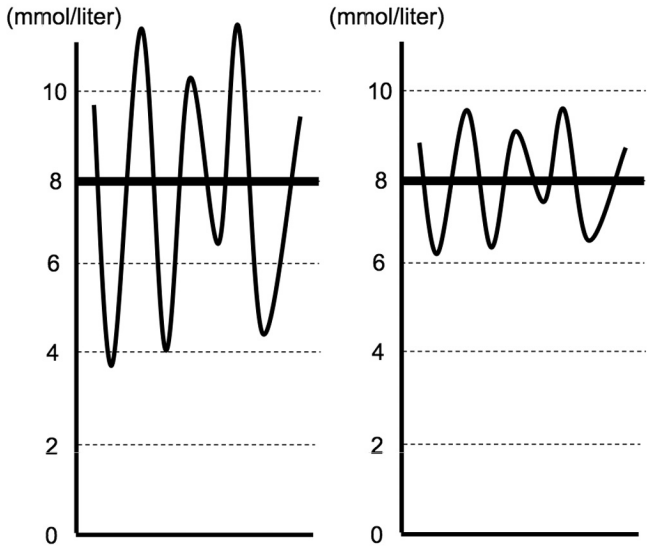


Figure 79: Graphic representation of glycaemic control with a high mean glucose level and high variability (left) and a high mean glucose level and low variability (right).

Figure and description reprinted from the Journal of Diabetes, Science and Technology 2009;3:6. Egi M and Bellomo R. 'Reducing glycaemic variability in intensive care unit patients: a new therapeutic target?' Figure 1, p1304. Reprinted with permission from Rightslink® and UMI's 'Books on Demand' program.

Notably, GV was positively correlated with RPG and HbA1c in the metformin study (Table 82) and appeared to be highest in the group with the highest baseline RPG (Table 73). There is a scarcity of similar work available to draw comparison with as the measure has only rarely been studied in COPD patients outside of the ITU setting. One study of GV in T2DM (n=63) found that in participants with similar HbA1c levels <7.5% (<59 mmol/mol), almost all glycaemic markers and GV parameters were significantly correlated. These correlations were not observed in those with HbA1c levels ≥ 7.5% (≥ 59 mmol/mol). (Suh et al., 2014). Authors of a similar study conclude that, 'ambient hyperglycaemia and glycaemic variability coexist…although it is difficult to know whether glycaemic variability is the chicken or the egg' (L Monnier & Colette, 2014).

In any case, given the adverse outcomes described with increased GV, careful consideration should be given to the most appropriate tools for assessment/management of glycaemic variability in COPD. Tight glycaemic control with insulin has been shown to be feasible and acceptable to patients with COPD in a general ward setting (Archer et al., 2011) but was associated with 'considerable glycaemic variability'.

Metformin shows promise in this context. Although participants treated with metformin did not have a lower GV compared to those treated with placebo, they were noted to have lower GV (2.15 mmol/L) when compared to a separate COPD population treated with insulin (2.9mmol/L). (Archer et al., 2011). Once again, given the novelty of this work, there were very little further data to consider. A comparison is therefore made with a study in people with T2DM. In n=75 drug-naïve patients with early T2DM and good glycaemic control (HbA1c 6.5-8.0%), metformin 1g bd was associated with a lower GV when compared to

insulin glargine after 36 weeks of treatment (SD of interstitial glucose 1.3 versus 1.6 respectively p=0.001) (Pistrosch et al., 2013).

Of note, the standard deviation of CBG was used to express GV in the metformin study. This measure is widely recognised and simple to use but it is accepted that it has some limitations (Kohnert et al., 2010).

Another important aspect in the treatment of SH and one which has plagued a number of insulin-treated studies is hypoglycaemia (Finfer et al., 2012). Despite the fact that metformin monotherapy is not normally associated with hypoglycaemia, a greater number of episodes were recorded in group A compared to group B participants. (section 5.7)

When examined in more detail, the majority of episodes in group A (19/25 or 76%) actually occurred in 2 patients. This secondary analysis did not investigate the multifactorial causes of hypoglycaemia but, notably, both of these participants were over the age of 60 years. Following a number of high profile cases, (Panorama, 2011, *A Jury in the Dark,* BBC), it is increasingly recognised that spontaneous hypoglycaemia may occur in a relatively high proportion of elderly, hospitalised patients (Mannucci et al., 2006) . With this in mind, it is difficult to draw any robust conclusions as to the link between metformin therapy and hypoglycaemia.

To conclude, this novel work presents a number of findings which merit further investigation. Adding to the body of existing literature, a relatively high prevalence of SH was found in people hospitalised with an exacerbation of COPD. Although the study was not specifically designed to investigate metabolic disorders, a strikingly high proportion of people with COPD were also found to be at 'high risk' of DM. Steroid prescription was equivalent in the active and placebo metformin groups but may of course have varied before admission. Further work could investigate this in more detail.

CBG readings illustrated (otherwise clinically occult) episodes of hypo- and hyperglycaemia as well as glycaemic variability and demonstrated that a random plasma glucose measurement is often inadequate to provide the full picture. Whether more detailed glycaemic profiles are practical in the AMU setting is a matter for further consideration.

Finally, this is the first randomised controlled trial to bear on metformin as a treatment option for SH in the acute care setting. Metformin is a highly attractive therapy in this context for a number of reasons. In contrast to insulin therapy, which is costly, cumbersome and may be associated with increased mortality (Finfer et al., 2009), metformin is cheap and well-tolerated. Furthermore, metformin has also been shown to reduce the risk of progression to T2DM in certain high-risk populations of which COPD may be considered one (Aroda et al., 2015; A. Ramachandran et al., 2006).

6.10 Biomarkers in Stress Hyperglycaemia

Selected biomarkers were examined to see whether they may offer prognostic utility in SH and aid management. (see section 3.1.1) Study findings are discussed in the context of existing literature in the sections below (6.10.1-6.10.11).

6.10.1 Cortisol in Stress Hyperglycaemia

All prospective study participants were found to have an objectively low illness severity (CEWS score was '0' in all but 3 group 1 participants who had a score of '1', section 3.8). Therefore, it was not possible to examine whether lower cortisol levels were associated with lower illness severity scores and persistent glucose intolerance as previously reported (Carmen Wong et al., 2010). In contrast to earlier data, (Lehrke et al., 2008) cortisol was not associated with IR in the prospective study.

Notably, despite a commonly held view that cortisol levels are elevated during acute illness, there are very little data in favour of this. There was no significant difference in cortisol values between group 1 'stressed' participants and group 2 participants with 'normal glucose tolerance'. Additionally, the mean cortisol value, (taken between 07:30 and 09:00 on the morning after study entry) for prospective study participants) was modest at 406 nmol/L (see section 3.9).

6.10.2 Troponin I in Stress Hyperglycaemia

Cardiac troponin I is a sensitive marker of acute cardiac damage but also has a role in predicting mortality in many other contexts. For example, a high incidental rise in troponin I in older patients carries a higher mortality risk than a rise associated with a diagnosis of acute coronary syndrome (Myint et al., 2008). Similarly, a mildly elevated Troponin measured in patients with COPD during an acute exacerbation is a strong independent predictor of mortality following discharge (Martins et al., 2009). The association between elevated troponin levels and mortality has also been demonstrated in patients with sepsis (John et al., 2010), pulmonary emboli (Becattini, Vedovati, & Agnelli, 2007) and a variety of other conditions. Troponin I levels have not yet been studied in patients with SH.

In all participants apart from 3, the Troponin I value was <0.05 ng/mL. Therefore, no further analyses were performed. Despite the wide number of presenting diagnoses in the prospective study and the fact that Troponin I is known to be elevated in a variety of non-ischaemic causes of myocardial injury as well as non-cardiac pathologies including renal failure, COPD and sepsis (Tanindi & Cemri, 2011), this novel work only found elevated Troponin I levels in three patients in the acute care setting. This implies a limited utility for Troponin I as a prognostic marker in SH.

6.10.3 BNP in Stress Hyperglycaemia

In view of established associations between heart failure, DM and IGT (Turfan et al., 2012), links between BNP and glucose values were explored. Although the mean BNP value appeared higher in those with metabolic abnormalities (176, n=21), compared to those without (97.7, n=34), this difference was not statistically significant (section 3.10.2). No statistical difference was found in BNP values between group 1 and 2 participants.

B-type natriuretic peptide (BNP) is secreted from the left and right ventricle in response to ventricular stretch and is elevated in both systolic and diastolic dysfunction (Epshteyn et al., 2003). Many studies have found elevated BNP levels in patients with asymptomatic left ventricular dysfunction (Macabasco-O'Connell, Meymandi, & Bryg, 2010) and coronary artery disease. (Rana et al., 2006) This has led to its proposal as a screening tool to exclude LVD in high-risk patients, such as those with diabetes (Romano et al., 2010). Combined analysis of BNP and glucose have also been shown to be helpful in the risk stratification of patients with ACS (Wei, Wang, Fu, Bai, & Zhu, 2014).

Although a small study exploring the effect of BNP on glucose metabolism found no diabetogenic properties (Heinisch et al., 2012), other work suggests a close relationship between glucose metabolism and the natriuretic peptide axis. An increase in BNP values has been seen with poor glycaemic control in DM (Dal et al., 2014) and dual angiotensin-II suppression therapy has been shown to decrease blood glucose levels (White et al., 2007).

There are also conflicting data on the relationship between BNP and insulin resistance with some studies showing an association (Hamasaki, Yanai, Kakei, Noda, & Ezaki, 2015; Mizuno et al., 2013; Tassone et al., 2009) and some not. The prospective study showed that BNP levels were correlated with HOMA2 %S ($p<0.05$).

6.10.4 CRP in Stress Hyperglycaemia

Inflammation is known to play a pathogenic role in the development of T2DM and a number of studies have linked higher levels of the acute-phase protein CRP to IGT, the metabolic syndrome and T2DM. (Choi et al., 2004; Knudsen et al., 2010; Luna et al., 2012; Yuan et al., 2006). Our findings were not in keeping with this as CRP levels were not significantly higher in those with metabolic abnormalities (section 3.10.2). Of course, numbers analysed in the prospective study were relatively small and CRP levels will have been affected by differences in presenting diagnoses. It is also worth considering that the relatively short duration of study follow-up, in contrast to other studies (Doi et al., 2005) did not capture all MAs which may have been associated with a higher CRP.

Of interest, CRP was positively correlated with fasting insulin ($p<0.05$) for all participants in the prospective study (Table 26). This has been observed previously and linked to the development of insulin resistance. (Yuan et al., 2006).

6.10.5 Lactate in Stress Hyperglycaemia

A number of studies have linked elevated lactate levels to the development of T2DM. (Crawford et al., 2010; Juraschek, Selvin, Miller, Brancati, & Young, 2013; Juraschek, Shantha, et al., 2013) Both an insufficient oxidative capacity (Juraschek, Selvin, et al., 2013) and increased insulin resistance (Juraschek, Shantha, et al., 2013) have been proposed as potential mechanisms. Lactate values in the prospective study were not significantly different between participants with and without metabolic abnormalities (section 3.10.2). Again, this may have been related to the relatively short follow-up.

Lactate has also been shown to have value in predicting mortality (Husain, Martin, Mullenix, Steele, & Elliott, 2003; Kruse, Grunnet, & Barfod, 2011; McNelis et al., 2001; Mikkelsen et al., 2009) and length of ICU stay (H. M. Soliman & Vincent, 2010) in critically ill patients.

There is a paucity of evidence examining lactate values in the AMU setting. Notably, the mean (baseline) lactate value appeared higher in COPD compared to prospective study participants (1.96 mmol/L and 1.34 mmol/L respectively), an expected finding given that blood lactate is a sensitive marker of anaerobic metabolism, reflecting oxygenation. There was no association between lactate and length of stay in the prospective study.

6.10.6 Vitamin D in Stress Hyperglycaemia

An independent samples t-test demonstrated a statistically significant difference ($p < 0.05$) between the 25-OH-Vitamin D values of group 1 and 2 participants (means 23.4 and 52.8 nmol/L respectively, section 3.9). Results were only available for a few participants (n=13) so no further analyses were performed. In view of work linking 25-hydroxyvitamin D levels to insulin sensitivity and beta cell dysfunction (Gao et al., 2015; Kayaniyil et al., 2010), further research in this context would be of benefit.

6.10.7 Blood Ketone Levels in Stress Hyperglycaemia

Blood ketones were predominantly checked as a safety measure to ensure that ketosis in newly hyperglycaemic patients was identified and appropriately managed. Before the advent of blood ketone testing, urine dispticks were used for this purpose. Urine testing did not, however, capture the predominant ketone body responsible for acidosis in Diabetic Ketoacidosis (DKA) -beta-hydroxybutyrate (β-OHB).

Blood ketone testing is now part of standard clinical care for DKA, providing rapid, accurate results (Byrne, Tieszen, Hollis, Dornan, & New, 2000) and endorsed by the American Diabetes Association (T. M. Wallace & Matthews, 2004), and the Joint British Diabetes Societies. (Savage et al., 2011).

DKA and SH share some similarities - increased levels of stress hormones, a catabolic state with lipolysis and increased gluconeogenesis are features of both conditions. (Dungan et al., 2009; T. M. Wallace & Matthews, 2004) In this context, it is interesting to note that group 1 participants had lower mean ketone values ($p \leq 0.05$) as well as lower variance in ketone values ($p \leq 0.01$) compared to group 2 (n=58 overall). This adds to the body of work which suggests that insulin may not be the best treatment for SH (Finfer et al., 2009). It is also interesting to note that a higher proportion of participants within group 2 had a cachectic body type (table 20). This may explain the higher ketone values in group 2. Further work could explore whether this may, in fact, be protective for the development of SH.

The mean ketone value for all prospective study participants was 0.3mmol/L**.** Ketonaemia of ≥3mmol/L forms part of the diagnosis criteria for DKA whilst levels <0.6mmol/L are considered normal (Wiggam et al., 1997). There are no studies examining ketone values in the acute medical population or in people with SH. This novel work adds to knowledge on the pathophysiology of SH - further work in this area may help to guide treatment decisions in the future.

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6.10.8 eGFR in Stress Hyperglycaemia

Links between a reduced estimated glomerular filtration rate (eGFR) and features of the metabolic syndrome have been proposed. (Miyatake, Shikata, Makino, & Numata, 2010). In addition, a large study including 99 140 people of varying ages (Okada et al., 2012) found that glomerular hyper-filtration (increased eGFR), a well-recognised and reversible feature of early renal dysfunction in DM (S. L. Jones, Wiseman, & Viberti, 1991; Neuringer & Brenner, 1992), was also a feature of pre-diabetes (defined as FPG 5.6-6.9mmol/L). This was corroborated by a separate smaller study (Melsom et al., 2011).

To our knowledge, glomerular filtration rates have not previously been described in stress hyperglycaemia. No differences were observed in the prospective study and proportions of participants with an eGFR <60 ml/min/1.73 m^2 were similar in the group with and without metabolic abnormalities (13% and 10% respectively). When the prospective study participants were divided into group 1 (stress hyperglycaemia) and group 2 (normal glucose tolerance), no statistical difference was found in eGFR values and there were equal proportions of participants with an eGFR <60 ml/min/1.73 m^2 (14%).

6.10.9 Pro-Adrenomedullin in Stress Hyperglycaemia

Mid-regional pro-adrenomedullin (MR-proADM) is a stable, surrogate marker of adrenomedullin, a potent vasoactive peptide linked to endothelial cell function and glucose metabolism. (Tesauro & Cardillo, 2011). Elevated levels of MR-proADM have been demonstrated in the metabolic syndrome and T2DM (Lim et al., 2007; Seissler et al., 2012; Vila et al., 2009) and shown to fall with bariatric surgery and weight loss. (Vila et al., 2009).

MR-proADM offers prognostic utility in a range of acute diagnoses, particularly cardiovascular disease (Nishida et al., 2008; Peacock et al., 2011; Potocki et al., 2009; Stolz et al., 2008) as well as stress hyperglycaemia (Schuetz et al., 2014).

Although the prospective study did not offer the opportunity to study the association between MR-proADM and outcomes in any great detail, there was no statistical difference between MR-proADM values of group 1 and 2 participants, adding support to the premise that people with SH are not metabolically different to people with normal glucose tolerance.

Interestingly, our study did demonstrate a highly significant correlation between MR-proADM and Copeptin for all participants (Table 26). This is a novel finding worthy of further investigation.

6.10.10 Copeptin in Stress Hyperglycaemia

Copeptin is the stable C-terminal fragment of AVP prohormone with links to DM, (Enhörning et al., 2010), metabolic syndrome (Enhörning et al., 2011) and stress (Katan & Christ-Crain, 2010). A central hypothesis of this study (hypothesis 5) investigated whether people with SH would have significantly different copeptin values compared to people without Stress Hyperglycaemia.

In fact, no statistically significant difference was observed between mean copeptin values for group 1 and 2 participants and there was insufficient evidence to reject the null hypothesis (see section 6.1). Group 1 participants were, however, noted to have a lower variance in copeptin values compared to group 2 participants ($p \leq 0.01$). Copeptin values were also not significantly different in participants with metabolic abnormalities compared to those without (see section 3.10.2).

In all participants (group 1 and 2 combined) a statistically significant correlation was noted between fasting insulin and Copeptin ($p<0.05$). This is consistent with the findings of (Enhörning et al., 2010) who demonstrated that copeptin levels are independently associated with hyperinsulinaemia and future development of diabetes mellitus. A longer follow-up would be of benefit for future work of this nature.

With regards the pro-ADM correlation mentioned in section 3.9, both markers have been shown to be independently elevated in IGT and previously unknown DM (S. et al., 2012) but to our knowledge, a strong correlation between them both has not been described before. This novel finding could shed further light on the early pathogenesis of metabolic syndrome.

Copeptin was also noted to be correlated with length of stay in group 1 but not group 2 participants ($p<0.05$). This is another interesting finding which could be of practical use in the future if supported by further work.

6.10.11 Biomarkers in Stress Hyperglycaemia-Conclusion

In view of budget and time constraints, biomarker values were not available for all participants and it was not possible to examine associations between biomarkers and long-term outcomes. Nonetheless, the data presented is novel, fleshes out the profile of people with SH, and highlights some interesting trends which merit further study.

A number of biomarkers linked to the metabolic syndrome and IGR were not significantly different between group 1 and 2 participants (e.g. CRP, eGFR, MR-proADM), supporting the theory that people with SH are not as a group, metabolically different and destined to develop MA. There were also no significant differences in these biomarker values between participants with and without MA (section 3.10.2), although, notably, numbers were small.

A number of other interesting findings including low ketone levels in SH, and links between copeptin and proADM emerged through this work and may be worthy of further exploration. It should of course be considered that there are challenges to translating biomarker evidence into clinical practice (Tang, 2010) with they may offer little in the way of support for the practising physician unless a number of criteria are fulfilled (D. S. Lee & Tu, 2009; University of Leicester and UK National Screening Committee, 2012). With this in mind, perhaps the best role for biomarkers is not at the front door but rather behind the scenes further to address research questions 3 and 5 (section 1.4) through greater knowledge on the pathophysiology of SH.

6.11 Stress Hyperglycaemia –The Phenotype

As described in section 1.5, the main research objective relates to the metabolic profile of people with stress hyperglycaemia and differences between individuals with and without the condition. The results are presented in section 3.3 and discussed in sections 6.2 and 6.10.10. In addition to the central hypotheses, a number of measures were carefully selected for their novelty, potential ability to flesh out the profile of the individual with stress hyperglycaemia and relevance to research questions 3 and 5 (see section 1.4).

Some of these measures including biomarkers, glycaemic variability and insulin resistance are discussed in separate sections (see 6.10, 6.6 and 6.7 respectively). This section focuses on the remaining measures, namely those presented in result sections 3.2, 3.4-3.8 and 3.10. It is hoped that these descriptions as well as comparisons between people with and without SH will provide the basis for future work in this field. Because of the novelty of the data, there is little comparative work.

Firstly, people with SH did not appear to fall within a particular age or gender demographic. (section 3.2). Effects of ethnicity could not be well studied as there was limited variation within the study population. A similar study used a retrospective methodology to examine the records of n=2030 all-comers admitted to a US hospital. The investigators also found no difference in mean age, gender and racial distribution between n=223 people with new hyperglycaemia but no history of DM and other groups (Umpierrez et al., 2002).

Metabolic profiling is discussed in section 6.2. BIVA was selected to compliment this and provide more detailed characterisation. In support of the results displayed in section 3.3, no statistically significant differences were found in the BIVA-derived nutrition scores of group 1 and 2 participants (section 3.6). Reassuringly, stress hyperglycaemia was not associated

with marked dehydration as supported by clinical assessment and BIVA-derived hydration scores.

In terms of diagnosis associated with SH, a large body of work (see Chapter 1) focuses on selected, single disease groups rather than an undifferentiated patient cohort. The US study of all-comers described above (Umpierrez et al., 2002) did not report on individual diagnoses but rather admitting specialities. The prospective study showed that the most frequent primary diagnosis category within both study groups was respiratory disease, with COPD accounting for 31% of cases (Appendix 1).

Although mean RPG values were not statistically significantly different across different diagnostic categories of group 1 participants (Table 17), the metformin study (Chapter 5) demonstrated a high prevalence of metabolic abnormalities and stress hyperglycaemia within the COPD group. This is discussed in more detail in section 6.9 and merits further work. For example, the feasibility of RPG inclusion into COPD assessment tools could be investigated. This would be particularly pertinent in view of frequent corticosteroid therapy in this group of patients. This approach would, of course, only be helpful if clear evidence-based management goals were established.

All participants in the metformin study were steroid-treated. In the prospective study, similar proportions of participants in group 1 and 2 as well as similar proportions of participants who did/didn't develop metabolic abnormalities were steroid-treated (Figure 21, section 3.10.2). Elucidating the contribution of steroid therapy to stress hyperglycaemia and metabolic abnormalities (Clore & Thurby-Hay, 2009) is a substantial body of work which follows on from this thesis.

There were a number of other notable similarities between groups 1 and 2, namely illness severity, anxiety scores and family history of DM (sections 3.3, 3.7 and 3.8). Perhaps the

most interesting similarities, however, relate to HbA1c and fasting plasma glucose levels (Table 24 and Table 18). The latter suggests that SH is short-lived in this cohort. CGM provided another illustration as to the importance of more than one glucose reading in this context: SG values were often incongruous with the relatively modest RPG values recorded and marked glycaemic excursions were seen in both study groups (section 4.3). Ideally, this study would have had a more substantial follow-up to examine the effect of this variability in more detail across both study groups.

In terms of outcomes, a surprisingly high proportion of all study participants (40%) were found to have metabolic abnormalities during the course of this study.. Other studies incorporating a return visit have reported similar figures of up to 42% for IGT and 46% for DM (Vancheri et al., 2005; Wallander, Malmberg, Norhammar, Rydén, & Tenerz, 2008). Post discharge follow-up incorporating people with *and without* SH would be of interest to take this work forward.

Variables including HbA1c were not significantly different from baseline in group 1 participants attending study follow-up. Although fasting insulin and HOMA2-IR values appeared higher at study follow-up, these findings were not statistically significant (Table 39 and Table 40). These measures are discussed in more detail in sections 6.7 and 6.8.

Length of stay was the other outcome of interest. Again, there was no statistically significant difference between group 1 and 2 participants (section 3.10.1). This is not in keeping with existing literature (Campbell, 2007) and could, perhaps, be explained by the AAU recruitment environment which supports early discharge.

In conclusion, detailed profiling of people with stress hyperglycaemia did not reveal any significant differences in the measures discussed (see section 6.7 and 6.8 for discussion of

fasting insulin). The similarities are, however, of significant interest and will be discussed in the final study conclusions (section 6.13).

6.12 Stress Hyperglycaemia in the Acute Care Setting, The Practical Aspects

6.12.1 The Acute Care Setting

Participants for the prospective and metformin study were recruited from the acute care setting. The research challenges and questions posed -particularly question 5 ('what is the best management for stress hyperglycaemia in the acute care setting?) -require consideration of context.

Substantial evidence demonstrates that early recognition and management of acutely unwell patients contributes towards optimal clinical outcomes. This evidence, along with an increasing number of medical admissions as well as other drivers led to the development of acute medicine. As a speciality, it has been pivotal in improving care (National Patient Safety Agency, 2007; B. Williams et al., 2007) and Acute Medical Units (AMUs) are now integral to the vast majority of acute hospitals in the UK (Jayawarna, Atkinson, Ahmed, & Leong, 2010).

The workforce within the acute setting faces unique challenges in caring for a diverse and often clinically complex population at the point of admission to hospital. Timely communication with a broad range of stakeholders is required in order to ensure rapid, effective treatment and safe discharge/transfer of care. A broad range of guidelines and care pathways have been developed to support and enhance clinical decision-making in this dynamic environment (National Institute for Health and Care Excellence, 2007).

Acute medicine is one of the fastest growing specialties in the UK with an 81.4% expansion in acute medicine consultants between 2010 and 2011 (n=295) (Federation of the Royal Colleges of Physicians of the UK, 2013). Whilst dedicated consultant cover seven days a week has been shown to be associated with reductions in readmissions and mortality, junior doctors, nurses, allied health professionals and pharmacists also play an essential role in delivering high quality acute care in the AMU setting (Royal College of Physicians, 2012).

6.12.2 Challenges of Conducting Research in the Acute Care Setting

Whilst patients were very accommodating towards research and willing to give their time, there were a number of challenges encountered in conducting research in this setting:

- Rapid turnover of patients and staff
- Difficulty with labour-intensive research procedures especially CGM
- Buy-in to research from busy staff
- Difficulty in obtaining fasting blood samples
- Poor attendance at study-follow, perhaps due to the absence of an on-going condition
- Difficulty in effectively monitoring new treatments and devices

A number of these challenges could be overcome through greater engagement of all relevant stakeholders. It is of interest to consider other models of research which have worked well in the acute care setting. The Investigator was also involved in the design and distribution of a

Society of Acute Medicine survey which was sent out electronically and received rapid responses from units across the United Kingdom (Soong, Balasanthiran, MacLeod, & Bell, 2013).

A questionnaire survey was also conducted in the acute care setting examining doctors' views towards SH and its management. This obtained a good response rate and was easy to conduct. It illustrated that doctors vary considerably in their perceptions of and approaches to stress hyperglycaemia (Appendix 6).

6.13 Final Study Conclusions

Stress Hyperglycaemia is a field which has gradually gained more interest over the years as researchers and clinicians have established the association with poor outcomes. There are still a number of barriers to conducting research in this field including a lack of a consensus definition for SH.

This novel work profiled people with SH in a setting and to a level not reported previously. The headline findings may be summarised as:

1. Similar metabolic profiles, HbA1c, cortisol values and phenotype in people with and without stress hyperglycaemia
2. Lower fasting insulin values in people with stress hyperglycaemia compared to those without
3. Lower HOMA2 reported insulin resistance in people with stress hyperglycaemia compared to those without
4. Normal FPG in people with stress hyperglycaemia the morning after recruitment (and similar FPG in people with and without SH the morning after recruitment)

5. High prevalence of occult and stress hyperglycaemia in the acute care setting
6. High prevalence of metabolic abnormalities in the acute care setting: 52% in participants with stress hyperglycaemia
7. 35% of participants in the metformin study presenting with an HbA1c value in the 'high risk for DM' category
8. High predicted 3 year risk of DM in metformin (6.8%) and prospective SH (5.4%) groups
9. Associations between copeptin, proADM and insulin
10. Association between GV and IR
11. No difference in glycaemic variability between people with/without stress hyperglycaemia or any obvious effect of metformin on GV

The similarities between people with and without stress hyperglycaemia are of significant interest. Whilst a number of studies have shown that SH is often a precursor to glucose intolerance, few have compared the SH population to a normoglycaemic group. Despite a relatively short follow-up period, this work has shown that occult hyperglycaemia, as illustrated by CGM, and metabolic abnormalities occur frequently in both SH and (seemingly) normoglycaemic populations. An important conclusion from this is that, as already recognised in the diagnosis of DM, a single RPG is insufficient to provide a relevant insight into an individual's glycaemic excursions during hospitalisation.

Along the same lines, it could also be argued that a single RPG is insufficient to classify an individual as having SH or not. The difference in insulin levels between the study groups, however, seems to suggest a distinction between the groups.

Despite this, people with SH do not appear to be phenotypically different from people without the condition and marked hyper and hypoglycaemia were common in both groups of patients despite modest RPG levels.

The phenotypic similarities between people with and without SH also supports the argument made by some researchers that SH is, in fact, an 'evolutionarily conserved adaptive response' which allows a higher blood 'glucose diffusion gradient' and thus maximises cellular glucose uptake during times of stress. This is supported by a lack of data demonstrating causation of harm by SH (as opposed to *association* with harm) as well as the studies showing a lack of benefit to intensive insulin therapy (Marik & Bellomo, 2013). This hypothesis ideally requires more detailed consideration by future investigators.

In conclusion of this thesis, the acute care setting provides an excellent opportunity for the opportunistic pick-up of metabolic abnormalities. Significant morbidity could then be prevented with timely and appropriate intervention. The practicalities of this approach are subjects for further research and debate.

6.14 Study Limitations & Future Work

- Given time constraints, only approximately half of the patients that were found to be eligible for study could be approached by a solo investigator for inclusion (n=93 out of a possible n=196). Attempts were made to make the approach process as random as possible although it is recognised that this step may have introduced an element of selection bias.

- Episodes of marked hypo and hyperglycaemia were only evident to the investigator following removal of the CGM and sometimes after the participant had been discharged from the acute setting. It is therefore not possible to fully comment on the causes and implications of glycaemic variability in the prospective study. Future work could address this in more detail and, in particular, why participants from group 2 had more hyperglycaemic readings on CGM.

- Notably, only 32 out of 52 metformin study participants had an HbA1c value available for analysis. As this data was received for secondary analysis from the main investigators and included data from 9 UK study centres, the reasons for missing data were not always clear to the investigator.

- 50% of group 1 subjects were lost to follow-up and this is clearly not optimal. Table 6 in section 3.1.2 lists the various reasons that participants were lost to follow-up

despite the best efforts of the investigator. A number of these reasons are discussed in section 6.12.2 and include the absence of an ongoing condition/relationship with the clinical team in the AMU environment.

- In addition, there was a variation in visit 1 follow-up time period ranging from 94-190 days (see section 3.10.3). It is recognised that this may have had an impact on visit 1 findings. This variation occurred for a number of reasons, mostly practical (see section 2.1.2). Notably, the follow up aspect is, however, only a small part of the study and does not form part of the central study hypothesis. Future work could look at less complex follow-up arrangements (perhaps using relevant databases/telephone appointments) to increase timely uptake. Future work with more resource could also incorporate a visit 1 assessment for group 2 in order to provide a comparison (deemed too challenging within the available timescale of this project)

- Future work could look at correlation of RPG overall with other indices (rather than a cut-off value)

- Future work could also examine whether higher ketone values may be protective for the development of SH

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Appendix

Appendix 1:Primary Diagnosis Categories for all Prospective Study Participants

ICD-10 code	Number of Participants
Bacterial, viral and unspecified respiratory disease	11
COPD	9
Asthma	4
Bronchiectasis	2
Pleural Effusion	1
Pulmonary Embolism	2
TOTAL	**29**

Table 87: Conditions included in category 'Respiratory disease',prospective study

ICD-10 code	Number of Participants
Unstable angina/AMI/IHD	4
AF and Flutter	1
Cardiovascular disease unspecified	1
TOTAL	**6**

Table 88: Conditions included in category 'Cardiovascular Disease', prospective study

ICD-10 code	Number of Participants
Anaemia	1
Disorders of mineral metabolism	1
TOTAL	**2**

Table 89: Conditions included in category 'Metabolic/Haematological', prospective study

ICD-10 code	Number of Participants
Cellulitis	6
Polyneuropathy	1
Monoarthritis	1
Back pain	1
Other muscle disorder	1
Injury of Achilles tendon	1
TOTAL	**11**

Table 90: Conditions included in category 'Skin/Rheum', prospective study

(Additional diagnoses not included above: Falls/syncope n=9, chronic pain n=1, unclear n=1, Reflux, constipation, abdominal pain, acute nephritis, other urinary disorders all n=1 each)

Appendix 2: Descriptive statistics for all CGMS participants

	Particpant ID	Sensor Glucose Values (mmol/L)				
		N	Min	Max	Mean	SD
(1)	40	275	5.4	12.8	7.7	1.69
	41	150	4.3	11.8	7.0	2.14
	55	212	4.3	8.1	6.0	1.01
	57	137	4.7	6.2	5.3	0.32
	60	277	3.9	11.0	6.5	1.93
(2)	54	255	2.7	9.1	5.4	1.89
	56	132	3.4	8.1	5.3	1.47
	58	47	6.1	15.7	11.0	2.39
	59	220	4.4	11.2	7.2	1.78
	61	245	5.4	22.2	10.7	4.17
	63	237	3.3	12.6	6.8	2.15
	64	209	2.2	8.9	5.9	1.36

Appendix 3: ANOVA for CGM Participants

Sensor Glucose (mmol/L)

ID & Study Group		N	Subset for alpha = 0.05					
			1	2	3	4	5	6
Student-Newman-Keuls[a,b]	56.2	132	5.289					
	57.1	137	5.293					
	54.2	255	5.384					
	64.2	209	5.898	5.898				
	55.1	212		5.968				
	60.1	277			6.545			
	63.2	237			6.840	6.840		
	41.1	150			7.013	7.013		
	59.2	220				7.199		
	40.1	275					7.700	
	61.2	245						10.690
	58.2	47						10.998
	Sig.		0.051	0.766	0.120	0.286	1.000	0.195
Tukey HSD[a,b]	56.2	132	5.289					
	57.1	137	5.293					
	54.2	255	5.384					
	64.2	209	5.898	5.898				
	55.1	212	5.968	5.968				
	60.1	277		6.545	6.545			
	63.2	237			6.840			
	41.1	150			7.013	7.013		
	59.2	220			7.199	7.199		
	40.1	275				7.700		
	61.2	245					10.690	
	58.2	47					10.998	
	Sig[c].		0.155	0.213	0.202	0.145	0.980	

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 157.203.

b. The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed.

c. This p value refers to all variables within the same column, demonstrating no difference between the values in the homogenous subset

Table 91: One-way Analysis of Variance (one-way ANOVA) post-hoc tests to examine differences in mean SG values between individual (group 1 and 2) CGM participants.

Appendix 4: Group 1 Follow-Up Variables, Prospective Study

Participant ID	Baseline weight (kg)	F/up Weight (kg)
002R	74.1	70.6
041	74.3	73.3
065	73.0	91.5
011	84.9	94.7
018	82.5	77.3
019	112.5	116.5
057	89.5	86.3
028	98.0	98.5
055	86.0	80.9
060	70.9	71.7

Table 92: Baseline and follow-up (visit 1) weight for n=10 group 1 prospective study participants

Participant ID	Baseline FPG (mmol/L)	F/up FPG (mmol/L	Baseline Insulin (mIU/L)	F/up Insulin (mIU/L)
002R	5.9	10.2	9.3	10.1
041	8.0	6.1	7.2	6.9
065	5.2	6.1	5.9	10.8
011	4.9	5.4	8.0	34.9
018	5.5	5.2	8.8	6.8
019	5.6	5.1	6.9	10.9
028	5.5	4.6	5.4	3.2
055	5.0	4.3	3.6	4.0

Table 93: Baseline and follow-up (visit 1) fasting plasma glucose and insulin for n=8 group 1 participants

Participant ID	Baseline HbA1c (mmol/mol)	F/up HbA1c (mmol/mol)
002R	44	42
041	52	36
065	38	36
011	40	39
018	43	43
019	37	37
057	42	38
028	42	41
055	36	33
060	36	34

Table 94: Baseline and follow-up (visit 1) HbA1c for n=10 group 1 participants

Participant ID	Baseline HOMA2-IR	F/up HOMA2-IR
002R	1.3	1.50
041	1.0	0.90
011	1.0	4.40
018	1.2	0.90
019	0.9	1.40
028	0.7	0.40
055	0.5	0.50

Table 95: Baseline and follow-up (visit 1) HOMA2 for n=7 group 1 participants

Participant ID	Baseline Copeptin (pmol/L)	F/up Copeptin (pmol/L)
002R	3.4	1.8
041	8.7	10.5
065	2.3	6.09
011	24.5	15.8
018	11.5	6.3
019	13.0	15.5
057	3.4	4.9
028	5.2	4.5
055	14.7	4.8
060	6.1	5.4

Table 96: Baseline and follow-up (visit 1) Copeptin for n=10 group 1 participants

Participant ID	Baseline proADM (nmol/L)	F/up proADM (nmol/L)
002R	0.75	0.27
041	0.69	0.84
065	0.63	0.58
011	1.44	0.91
018	1.55	1.40
019	1.52	0.99
057	0.48	0.47
028	0.80	0.64
055	1.81	0.75
060	0.86	1.07

Table 97: Baseline and follow-up (visit 1) proADM for n=10 group 1 participants

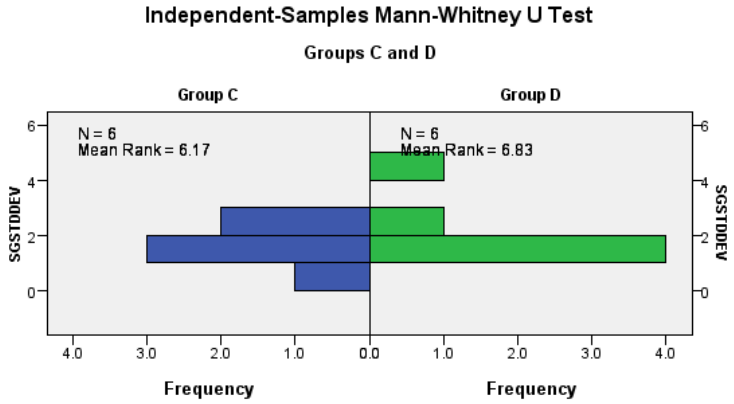
Appendix 5: Mann-Whitney Test for GV in Metabolic Abnormalities

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of SGSTDDEV is the same across categories of Groups C and D.	Independent-Samples Mann-Whitney U Test	.818[1]	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

[1]Exact significance is displayed for this test.



Total N	12
Mann-Whitney U	20.000
Wilcoxon W	41.000
Test Statistic	20.000
Standard Error	6.245
Standardized Test Statistic	.320
Asymptotic Sig. (2-sided test)	.749
Exact Sig. (2-sided test)	.818

Figure 80: Mann-Whitney test to examine Glycaemic Variability in CGM participants with and without metabolic abnormalities

Appendix 6: AAU Questionnaire Study

NIHR CLAHRC for Northwest London

sam

NHS National Institute for Health Research

Understanding of Stress Hyperglycaemia in Acute Care

Laura Kemp, Cameron Bell, Anjali Balasanthiran, Derek Bell

Aim: Stress hyperglycaemia (SH) is an insulin resistant and acute hyperglycaemic state commonly seen during acute illness. Despite being associated with poor outcomes, including prolonged length of stay and increased mortality in a range of medical conditions, it remains under-recognised. We examined perceptions of SH using a short survey.

Method: A brief, ten question survey was handed out to doctors on wards at Chelsea and Westminster hospital, NHS Foundation trust. The survey was pre-publicised at hospital meetings.

Results/outcomes: 40 doctors completed the survey (FY 57.5%, CT 7.5%, ST 20% and Consultants 15%) over two weeks. Random plasma glucose definitions for SH ranged from 6.1-20mmol/L (median 10mmmol/L).

For initial management responses to SH see Table 1.

Table 1

Initial Responses to SH	Yes (%)	No (%)	Not Known (%)
Review medication chart/nutrition	90.0	2.5	7.5
Monitor BMs	90.0	5.0	5.0
Repeat blood glucose	90.0	2.5	7.5
Dietetic review	30.0	50.0	20.0
Inform diabetes team	27.5	52.5	20.0
Start treatment for hyperglycaemia	7.5	70.0	22.5

- 50% of respondents would alter their initial actions based on the level of random blood glucose.
- Suggested treatments for SH included: insulin (45%), metformin (20%) and gliclazide (12.5%). 7.5% required confirmation of diabetes or specialist advice prior to prescribing treatment (22.5% NK).
- The majority (77.5%) would arrange follow-up with 35% specifying diabetes specialist and 35% GP.
- HbA1c (45%), fasting glucose (37.5%), Oral glucose tolerance test (22.5%) and urinary and blood ketones (10%) were suggested to further investigate patients.

Conclusions: Doctors vary considerably in their perceptions and responses to SH. Further work to improve understanding and develop a national consensus for the large numbers of acute patients presenting with SH would be of significant benefit.

Imperial College London — in partnership with Northwest London — Chelsea and Westminster Hospital NHS Foundation Trust

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