DOSE REDUCTIONS, TOXICITIES AND SURVIVAL IN PATIENTS WITH EXCESS WEIGHT UNDERGOING ADJUVANT CHEMOTHERAPY FOR COLON AND RECTAL CANCERS: INDIVIDUAL PATIENT DATA SECONDARY ANALYSES OF CONSORTIUM TRIALS AND CAUSAL INFERENCE MODELLING

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LIST OF ABBREVIATIONS

5FU 5-Fluorouracil
5FULV 5-Flurouracil with leucovorin
ABW Actual body weight
ACRD Average cumulative relative dose
ACT Adjuvant chemotherapy
AD Aggregate data
AdjBW Adjusted body weight
AIC Akaike's information criterion
AJCC American Joint Committee on Cancer
ARDI Average relative dose intensity
ARDR Average relative dose received
BIC Bayesian information criterion
BIM Boot-Impute (Bootstrapping followed multiple imputation)
BMI Body mass index
BoS Borrowing of strength
BSA Body surface area
C Confounder
CAP Capecitabine
CAPOX Capecitabine + oxaliplatin
CEA Carcinoembryonic antigen
CI Confidence interval
CRD Cumulative relative dose
CRC Colorectal cancer
CSS Cancer specific survival
CTCAE Common Terminology Criteria for Adverse Events
DFS Disease free survival
DPD Dihydropyrimidine dehydrogenase
DXT Radiotherapy
DYPD The gene encoding the dihydropyrimidine dehydrogenase protein
ECOG European Cooperative Oncology Group
EMVI Extramural vascular invasion
HR Hazard Ratio
IBW Ideal body weight
IGF1 Insulin-like growth factor
IPD Individual patient data
IQR Interquartile range
KM Kaplan Meier

KPS	Karnofsky performance status
LNH	Lymph node harvest
LI	Lymphatic invasion
M	Mediator
MA	Meta-analysis
mFOLFOX6	5-fluorouracil + Oxaliplatin (modified De Gramont regimen)
MSR	Mean survival ratio
MST	Mean survival time
MV	Multivariate
NDE	Natural direct effect
NIE	Natural indirect effect
OS	Overall survival
PNI	Perineural invasion
PS	PROCTOR-SCRIPT
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RDR	Relative dose received
RUD	Relative under dosing
TE	Total Effect
TME	Total mesorectal excision
TNM	Tumour, node, metastasis
UV	Univariate
UVFW	Univariate with forced weights
WHO	World health organisation
X	Exposure
Y	Outcome

ABSTRACT

Introduction: Elevated body mass index (BMI) may be associated with reduced survival in non-metastatic colorectal cancer (CRC). Whether this occurs directly, or indirectly through treatment-related mechanisms such as capping of adjuvant chemotherapy (ACT) doses and toxicity, is unclear. This thesis aimed to disentangle the effects of BMI, ACT adherence and toxicity on survival using individual participant data (IPD), causal mediation, and meta-analysis.

Methods: Data from four randomised clinical ACT trials (MOSAIC, SCOT, CHRONICLE and PROCTOR-SCRIPT [five datasets – SCOT arms analysed individually]), with derivable BMI (at trial enrolment) cycle-level dosing and toxicity data were utilised from the OCTOPUS consortium. Dose capping was defined as <95% of the expected (full BSA-based) cycle 1 dose. Two ACT adherence measures were calculated: average cumulative relative dose (ACRD: percentage of actual-to-expected cumulative dose (mg/m^2)) and average relative dose intensity (ARDI: percentage of actual-to-expected dose intensity [DI: cumulative dose/treatment duration (mg/m2/week)]). Directed acyclic graphs pre-defined putative causal pathways/confounders. The primary outcome was overall survival (OS). Trial level chemotherapy and toxicity data were summarised by BMI category (Chapters three and four). Two-stage random effects IPD meta-analyses were performed to assess BMI, adherence, toxicity, and survival relationships (Chapter five). Causal inference mediation analysis methods were explored, followed by meta-analysis of direct, indirect, and total effects from the mediation models (Chapter six).

Results I (Chapter 3): A total of 7269 patients from five datasets demonstrated obesity incidence ranging 5.0%-22.8%. Cycle 1 dose capping rates increased with increasing BMI categories (ranging 29.6% to 62.2% of obese patients), with evidence of attrition of dosing differences across administered cycles (excluding MOSAIC). Subsequent cycle dose reductions and early discontinuation tended not to be associated with BMI. Overall, mean ARDI and ACRD were lowest amongst obese patients.

Results II (Chapter 4): BMI did not appear to be associated with the occurrence of grade 3+ toxicity across the trials. However, there was a tendency for the incidence of neutropenia to reduce with increasing BMI. Additionally, the proportion of first grade 3+ toxicity episode occurring late increased with increasing BMI. However, results were limited by missing data.

Results III (Chapter 5): BMI increments of $5kg/m^2$ were associated with increased dose capping odds (OR (95%CI): 2.70 (2.00, 3.64)) in addition to reduced ARDI (Coef. -1.08% (-1.44, -0.72)) and ACRD (Coef. -1.14% (-1.91, -0.38)), with no demonstrable BMI-grade 3+ toxicity relationship. Increments of 5% ARDI were significantly associated with reduced OS (HR 1.05 (1.01, 1.09)). Conversely, 5% ACRD increments were associated with improved OS (HR 0.94 (0.91, 0.96)), raising the possibility of a small adverse indirect effect of BMI via reduced ACRD. Grade 3+ toxicity was associated with reduced ACRD (-10.37% (-11.77, -8.97)) and reduced OS (HR 1.37 (1.17, 1.61)). The latter effects attenuated on adjusting for ACRD (HR 1.20 (1.02, 1.41)), suggesting partial mediation via ACRD. BMI $5kg/m^2$ increments were not associated with OS.

Results IV (Chapter 6): Meta-mediation demonstrated no significant total effect (TE) of $5kg/m^2$ BMI increments on OS. However, a significant adverse natural indirect effect (NIE) was demonstrated via ACRD (1% reduction in mean survival time (MST)), with no natural direct effect (NDE). Furthermore, a significant TE of $5kg/m^2$ BMI increments on both ARDI and ACRD (1% reduction) was demonstrated, with no NIE mediated via toxicity. Finally, the TE of grade 3+ toxicity on OS was a 19% reduction in MST, partially mediated via ACRD (NIE and NDE demonstrated a 9% and 10% reduction in MST respectively).

Conclusion: Elevated BMI did not influence survival from CRC despite modest under-dosing. However, results support full BSA-based dosing for CRC patients with a high BMI, without significant additional toxicity risks. Toxicity may contribute to poorer overall survival via pathways both including and excluding ACRD, and hence dosing decisions should account for other toxicity risk factors.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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ABOUT THE AUTHOR

Corinna Slawinski is a higher general surgical trainee with an interest in colorectal surgery. Graduating from King's College London Medical School in 2011, she obtained her medical degree with a distinction in student selected components. During her time as a medical student, she undertook an intercalated BSc in Medical Sciences with Surgery and Anaesthesia at Imperial College London, (graduating with a 2:1 in 2009) and achieving a first for her lab-research dissertation project. Corinna was awarded the Colorectal Disease Best Poster Prize at the Association of Coloproctological of Great Britain and Ireland 2021 meeting, for work resulting from this thesis (see appendix **A0.1**).

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PREFACE

There is some evidence that excess adiposity, commonly approximated by elevated body mass index (BMI) is associated with a poorer prognosis in patients with non-metastatic colorectal cancer. This relationship is potentially modifiable, but it is unclear whether it is causal.

This thesis centres on two main questions: firstly, is there an adverse relationship between BMI and colorectal cancer prognosis; and secondly, is any adverse relationship partly explained by mechanisms including sub-optimal adjuvant chemotherapy ([ACT] resulting from dose capping, dose reductions, reduced adherence and toxicity) in obese patients. The aim of this thesis was to answer these questions, by disentangling direct effects of BMI on survival from indirect effects mediated through dosing and adherence (through use of mediation analysis), in a setting of reduced biases (facilitated through use of adjuvant chemotherapy trial data) and with increased power (by utilising meta-analysis approaches).

The thesis is divided into seven Chapters. The first presents evidence relating to the obesity-incident-cancer-risk relationship, including the underlying biological mechanisms, the relationship between obesity and cancer prognosis (in particular colorectal cancer), in addition to the problems with the current evidence base within the context of the obesity paradox. Furthermore, the evidence for obesity and colorectal cancer prognosis in the context of adjuvant chemotherapy trials is explored, discussing dosing of chemotherapy (including dose capping, adherence) and toxicity.

Chapter two serves as an overview of the methods and presents the datasets, data cleaning/harmonisation methods and key definitions utilised throughout the thesis. An overview of the selected methodology is presented: namely the use of trial data, causal inference, directed acyclic graphs (DAGs), mediation analysis and individual participant data (IPD) meta-analysis.

Presented subsequently are four results Chapters, all similarly structured. The methodology for each Chapter develops on from the preceding one, with the results similarly building on the last. Hence, the specific concepts and statistical methods that pertain to the results are discussed within the relevant Chapter, to facilitate context and understanding. Similarly, each concludes with a summary and interpretation of findings, which is not intended to contextualise results, as this is undertaken in the final discussion (Chapter seven) to reduce repetition.

Chapters three (results I) and four (results II) summarise BMI-dosing and BMI-toxicity relationships, respectively at the trial level. These chapters give a detailed understanding of the data, including patient characteristics at the trial and BMI-category-level, before summarising

and characterising the relationships between BMI and adjuvant chemotherapy dosing, and BMI and toxicity.

Chapter five (results III) builds on the preceding two chapters. First, the hypothesised causal relationships between BMI, dosing/adherence, toxicity, and survival, in addition to the relevant confounding assumptions, are introduced through use of DAGs. Second, further causal inference concepts, including traditional mediation analysis, are discussed and implemented. Finally, meta-analysis methods are utilised to formally model the relationships from Chapters three and four, in addition to the hypothesised relationships presented in the DAGs, providing insight into potentially mediated pathways.

Chapter six (results IV) extends the preceding results, to include discussion, exploration and implementation of counterfactual mediation analysis approaches, to formally decompose total effects into direct and indirect effects within the BMI-Adherence-Toxicity-Survival relationships. These methods are further extended to include meta-analysis of direct and indirect effects producing summary meta-mediation estimates.

Finally, Chapter seven discusses the thesis results in relation to the original hypotheses, contextualising the findings in the current literature. Furthermore, the strengths and limitations of the presented work are explored, the clinical implications discussed, and recommendations for future work are presented.

CHAPTER ONE
INTRODUCTION

Literature Review

CHAPTER PREFACE

The following introductory chapter provides a review of the literature and evidence surrounding the thesis. It has previously been submitted as part of the year one PhD literature review and continuation report and assessed as 'passed', and is presented here as Chapter one, with some editing, where some original sections have been moved to later chapters. This literature review subsequently formed the basis for an invited review published in Clinical Oncology.[1] The published paper contained sections lifted from this introduction, and a copy is found in the appendix [**A1**]). The original manuscript draft was written by Corinna Slawinski, was edited by senior authors (A Renehan, J Barriuso and H Guo), and has been through per review processes.

1.1 INTRODUCTION

Overweight and obesity are conditions of excess adiposity, often associated with health problems such as diabetes and cardiovascular disease, and occurring as a result of an imbalance between excess energy (caloric) intake and insufficient energy expenditure (physical activity).[2] Commonly measured by body mass index (BMI; expressed as weight in kilograms divided by height in meters squared) as a proxy for nutritional state, the World Health Organisation (WHO) defines four main categories of adiposity, adopted throughout this thesis: underweight BMI <18.5 kg/m^2; normal BMI 18.5 – 24.9 kg/m^2; overweight BMI 25.0 – 29.9 kg/m^2; obese BMI ≥30 kg/m^2. The latter category can be further subdivided into obese I (BMI 30 - 34.9 kg/m^2), obese II (BMI 35 – 39.9 kg/m^2), obese III (BMI ≥40 kg/m^2).[2]

1.1.1 THE GLOBAL BURDEN OF OBESITY AND COLORECTAL CANCER

World-wide, the overweight and obese epidemic is growing (**Figure 1.1a**). In 2016 there were an estimated 1.9 billion and more than 650 million overweight and obese adults (>18 years), equating to 52% of the world's adult population;[2] figures already starting to exceed the estimates for 2030, made over ten years ago.[3] In the UK, obesity figures for 2018 revealed a rate of 28% for adult obesity, in addition to 20% for primary school final year pupils. Female rates of obesity exceed those in males (29% vs. 26%), and despite increasing world-wide trends, UK obesity rates appear to have remained relatively stable since 2010 (between 25 – 27%, **Figure 1.1b**).[4]

The association between obesity and the risk of cancer incidence is well-established for thirteen cancers.[5] Data from the Renehan research team [5–8] has contributed substantially to this evidence. Consequently, the global burden of obesity-related cancer has been previously evaluated. In 2012, there were an estimated 481,000 (3.6%) new cancers (in ≥30 year olds) attributable to elevated BMI world-wide; specifically, 74,000 new colorectal cancers in males and 36,000 in females.[9]

In the UK, there were more than 375,000 new cancer cases per year in 2016-2018,[10] and obesity is now recognised as the second commonest cause of cancer.[11] With approximately 42,900 cases diagnosed per year, bowel cancer is the 3rd most common cancer in both females and males, and the second leading cause of UK cancer deaths (approximately 16,000 deaths in 2016).[10] Although multifactorial reasons for increasing population trends are likely (including an ageing and expanding population),[12] there is undoubtedly increasing exposure to adiposity as an incident-cancer risk factor. Thus, with upwards global trends of childhood obesity,[13] implying a probable continued rise of adult rates, excess adiposity is an increasingly concerning global public health problem.

Figure 1.1a | Changing world-wide prevalence of obesity with time
Including future projected rates up to 2030, from reference[14]

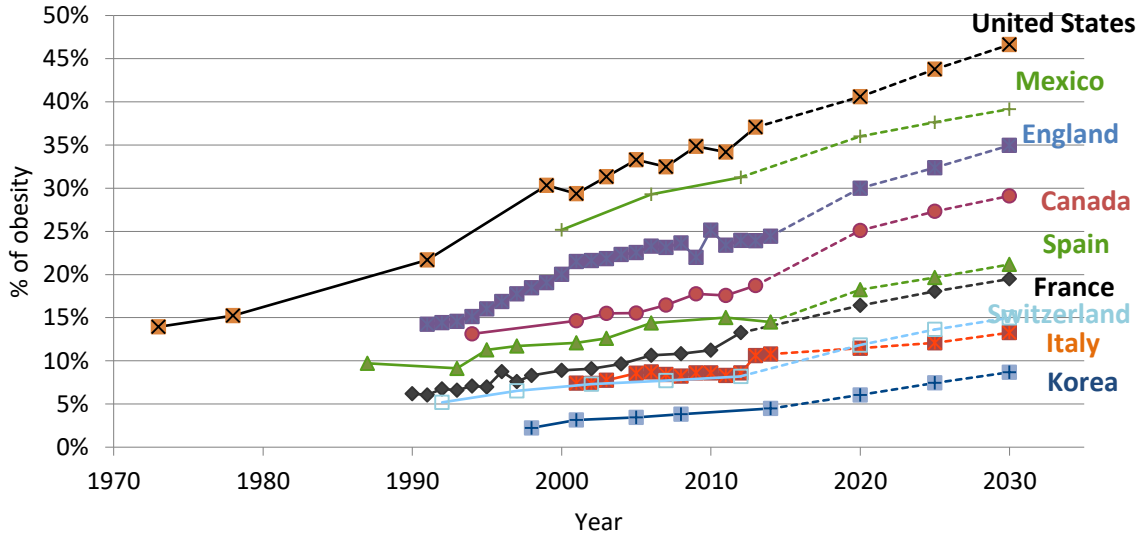
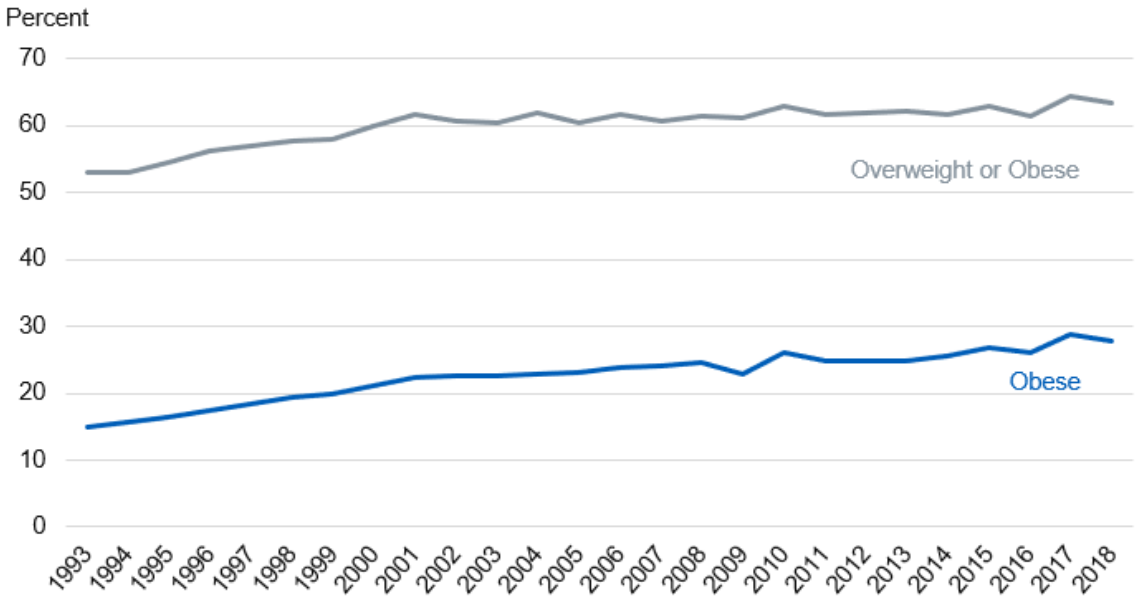


Figure 1.1b | Changing UK prevalence of overweight and obesity over time
From reference[4]



1.1.2 MEASURING ADIPOSITY

Obesity is a challenging epidemiological condition to study as a result of marked heterogeneity in its phenotype, hence, understanding methods for measuring body fatness (**Table 1.1**) is important. For example, obesity in the form of elevated BMI has been associated with increased risk of several metabolic, endocrine, inflammatory, thrombotic, and malignant co-morbidities, at the population level. However, there are obese individuals who do not display such risks, and despite equivalent BMI, are thought to be "metabolically healthy". Equally, there are a group of individuals with BMI-defined "normal" adiposity who may still have higher overall body fat percentage and be at increased risk.[15,16] Hence, though BMI, is the most utilised adiposity measure, it may not accurately represent total body fatness or metabolic function. Indeed, a BMI ≥30kg/m^2 has been demonstrated to have high specificity in men and women (95% and 99%, respectively), but low sensitivity (36% and 49% respectively), for diagnosing obesity, based on WHO obesity criteria using bioelectrical impedance criteria.[17] Furthermore, measures of total body fat such as BMI, do not provide information on adipose tissue distribution.

Simple early measures of central adiposity such as waist circumference (WC) and waist-hip ratio (WHR) have been studied as alternative anthropometric measures, and increased measurements are associated with higher risk of metabolic, cardiovascular[18] and malignant conditions.[19] Their major limitation, however, is in the lack of standardised method for measurement. For WC, at least eight sites for measurement have been described, with the WHO adopting the "mid-point" approach (see **Table 1.1** below). Optimal thresholds to define elevated risk may differ between measurement sites, and thus lack of standardisation may introduce lack of reproducibility, comparability, and measurement error.[16] Moreover, BMI, WC and WHR do not differentiate between subcutaneous adipose tissue (SAT; non-ectopic fat) and visceral adipose tissue (VAT; ectopic fat). However, BMI and WC correlate with SAT and VAT in general, with WC better approximating VAT, and BMI correlating better with SAT.[20]

Hence, imaging methods have been employed to improve identification and quantification of adiposity distributions. Using CT or MRI, it is possible to directly and accurately measure SAT and VAT. Therefore, CT or MRI-derived VAT and SAT measures are currently the gold standard for assessing adipose compartments.[21–24] Imaging derived measures have highlighted differences in disease risks. Whilst excess SAT and VAT both correlate with increased cardiovascular, metabolic[25] and neoplastic risks,[26] increased VAT, in particular, is associated with the highest risks,[25,27] defining the importance of the visceral obesity phenotype in cardiovascular disease.

Other measures of approximating total body adiposity include bioelectrical impedance and DEXA (dual-energy x-ray absorptiometry) scans. DEXA is more sensitive than bioelectrical impedance for estimating the percentage of body fat, in addition to total fat mass and lean body

mass. Both have been demonstrated to be comparable with BMI, yielding similar disease risk estimates for obesity-related or malignant conditions.[28,29]

Ectopic fat deposition has been classified further according to the effects on which it exerts, being systemic or local, with some cross-over for intra-hepatic or intra–pancreatic fat.[15,27] Systemic sites (VAT and intra-muscular fat) have well recognised associations with increased risk of cardiovascular comorbidities. However, local (micro-environment) ectopic fat is thought to contribute to local organ disease, for example, in the development of breast cancer.[30] Hence, other compositions and compartments may be important, such as skeletal muscle mass, lean body mass (or fat-free body mass), bone mass, and intra-muscular, -hepatic or -pancreatic fat, and can be measured from imaging methods such as CT or magnetic resonance imaging (MRI).[16]

Despite its limitations, BMI is inexpensive, non-invasive, and easily derived from height and weight measurements, requiring little additional resources, and thus remains an attractive measure of body fatness in clinical studies.

Table 1.1 | Measures of adiposity[16,31]

Measure	Description	Advantages	Disadvantages
BMI	Weight(kg)/height(m)^2	• Measures total body adiposity • Simple, quick, inexpensive, non-invasive • Minimal equipment • High precision/accuracy • High specificity with BMI ≥30kg/m^2	• Risk of measurement error (especially self-reported measures). • Lack of discrimination for distribution and composition of body mass (especially with BMI ≤30kg/m^2). • Low sensitivity ≥30kg/m^2. • Doesn't account for variations in age, sex, race, ethnicity.
WC / WHR	Measured in cm WC: Multiple sites described: • Mid-point between lowest rib and iliac crest • Point of minimal circumference • Immediately above iliac crest • Umbilicus • At lowest rib • Point of largest circumference around waist WHR: WC divided by Hip circumference.	• Measures body fat distribution. • Simple, quick, inexpensive, non-invasive • Minimal equipment • Correlates with VAT and metabolic risks and adiposity related morbidity/mortality.	• Lack of unified methodology and definitions • Increased inter-observer variability • Measurement error • Lack of discrimination of VAT vs. SAT

CT-VAT / CT-SAT	• Pixels of each image with fat measured according to Hounsfield units (-190 to -30HU).
	• Often measured at a single sliced image L4-L5 intervertebral space.
	• VAT – within abdominal cavity.
	• SAT – outside of abdominal cavity.
		• Measure of body fat distribution/total body fat.
		• Accurate
		• Reproducible
		• Identifies specific adiposity compartments
		• Non-invasive
			• Radiation exposure (however majority of patients with cancer will have CT staging / surveillance).
			• Single site might be less predictive than multiple slices (total body measurements).
			• L4/L5 site may not be optimal site for risk prediction.
			• Resource intensive
			  – Expensive
			  – Time (image acquisition and analysis)
			  – Specialised equipment
			  – Technical skill
			• Limited portability

• DEXA	• Fat mass measured by dual energy X-ray absorptiometry.	• Measure of total body fat. • Abdominal fat measures correlate with CT measures. • Relatively simple, quick • Reproducible • Accurate	• Small radiation exposure • Cost (less than CT) • Specialised equipment. • May underestimate in low body fat percentages • May overestimate in high body fat percentages. • Cannot differentiate between SAT and VAT
• Bioelectric impedance	• Small, alternating, single-frequency current passed through electrodes across the body to measure impedance between.	• Measures of total body fat. • Relatively simple, quick • Non-invasive • Relatively simple • Portable • Can calibrate to different ethnic and racial groups.	• Cost of equipment (less than DEXA/CT/MRI) • Avoided in patients with pacemakers. • Not discriminative of distribution/composition.

1.2 OBESITY AND INCIDENT CANCER RISK

The association between excess adiposity, in the form of elevated BMI, and increased risk of cancer incidence is well established for several common cancers through convincing epidemiological data.[5,6] However, few clinical trials have evaluated the long-term effects of weight gain avoidance and weight loss on the incident cancer risk, hence the majority of evidence for such associations is observational.[32]

In 2002, the International Agency for Research on Cancer (IARC) identified an association between elevated BMI and five cancers: colon, oesophagus (adenocarcinoma), kidney (renal-cell carcinoma), breast (post-menopausal) and endometrium.[7] Following which, the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) produced a series of meta-analyses, determining evidence was "convincing" for the association between body or abdominal fatness and an increased risk of several cancers.[8]

A systematic review and meta-analysis, published by Renehan et al., including 221 datasets from 141 papers with 282,137 incidences of cancer, demonstrated that BMI increments of 5kg/m^2, were strongly associated with several cancers (summarised in **Table 1.2**).[6] Notably, this included colon and rectal cancers examined individually and demonstrating gender- and site-specificity (and histology-specificity in oesophageal cancer). Summary relative risk estimates were strongly predictive in men for colon cancer and less so for rectal cancer, but somewhat attenuated for both in women. Furthermore, there mostly appeared to be geographical consistency across European and Australian, North American, and Asia-Pacific populations. Building on their earlier work, in 2016 IARC confirmed their original findings and identified an additional eight cancers for which there now existed "sufficient evidence" for an adiposity-incident cancer risk,[5] thus totalling thirteen obesity-related cancers (**Table 1.2**).

As evidenced overleaf, the increasing global incidence of overweight and obese has serious implications of increased incident-cancer risk conferred to these thirteen obesity-related cancers; hence, addressing questions of primary and secondary prevention, through improved understanding of effect modification, biological mechanisms, the relationship of obesity with prognosis and consequent treatment implications are globally important.

Table 1.2 | Summary risk estimates by cancer site

Modified from references[5,6]

Site	Combined[5]		Women[6]		Men[6]	
	Evidence	RR† (95%CI)	RR* (95%CI)	P	RR* (95%CI)	P
Breast:						
Premenopausal	**Sufficient**	1.1 (1.1, 1.2)	0.92 (0.88, 0.97)	0.001	-	-
Postmenopausal	**Sufficient**	**1.1 (1.1, 1.2)***	**1.12 (1.08, 1.16)**	**<0.0001**	-	-
Male	Limited	-	-	-	-	-
Colon	-	-	**1.09 (1.05, 1.13)**	**<0.0001**	**1.24 (1.20, 1.28)**	**<0.0001**
Colon & Rectum	**Sufficient**	**1.3 (1.3, 1.4)**	-	-	-	-
Endometrium	**Sufficient**	**7.1 (6.3, 8.1)**	**1.59 (1.50, 1.68)**	**<0.0001**	-	-
Extrahepatic biliary tract	Inadequate	-	-	-	-	-
Gallbladder	**Sufficient**	**1.3 (1.2, 1.4)**	1.59 (1.02, 2.47)	0.04	1.09 (0.99, 1.21)	0.12
Gastric	**Sufficient**	**1.8 (1.3, 2.5)**	1.04 (0.90, 1.20)	0.56	0.97 (0.88, 1.06)	0.49
Glioma: Brain or spinal cord)	Inadequate	-	-	-	-	-
Leukaemia	-	-	1.17 (1.04, 1.32)	0.01	1.08 (1.02, 1.14)	0.009
Lymphoma: Diffuse large B-cell	Limited	-	-	-	-	-
Liver	**Sufficient**	**1.8 (1.6, 2.1)**	1.07 (0.55, 2.08)	NA	1.24 (0.95, 1.62)	0.12
Lung	Inadequate	-	0.80 (0.66, 0.97	0.03	**0.76 (0.70, 0.83)**	**<0.0001**
Malignant Melanoma	Inadequate	-	0.96 (0.92, 1.01)	0.05	1.17 (1.05, 1.30)	0.004
Meningioma	**Sufficient**	**1.5 (1.3, 1.8)**	-	-	-	-
Multiple Myeloma	-	-	**1.11 (10.7, 1.15)**	**<0.0001**	**1.11 (1.05, 1.18)**	**<0.0001**
Non-Hodgkin lymphoma	-	-	1.07 (1.00, 1.14)	0.05	**1.06 (1.03, 1.09)**	**<0.0001**
Oesophageal adenocarcinoma	**Sufficient**	**4.8 (3.0, 7.7)**	**1.51 (1.31, 1.74)**	**<0.0001**	**1.52 (1.33, 1.74)**	**<0.0001**
Oesophageal squamous	Inadequate	-	**0.57 (0.47, 0.69)**	**<0.0001**	**0.71 (0.60, 0.85)**	**<0.0001**
Ovarian	**Sufficient**	**1.1 (1.1, 1.2)**	1.03 (0.99, 1.08)	0.30	-	-
Pancreas	**Sufficient**	**1.5 (1.2, 1.8)**	1.12 (1.02, 1.22)	0.01	1.07 (0.93, 1.23)	0.33
Prostate	Limited	-	-	-	1.03 (1.00, 1.07)	0.11
Rectum	-	-	1.02 (1.00, 1.05)	0.26	**1.09 (1.06, 1.12)**	**<0.0001**
Renal	**Sufficient**	**1.8 (1.7, 1.9)**	**1.34 (1.25, 1.43)**	**<0.0001**	**1.24 (1.15, 1.34)**	**<0.0001**
Testis	Inadequate	-	-	-	-	-
Thyroid	**Sufficient**	**1.5 (1.2, 2.0)***	1.14 (1.06, 1.23)	0.001	1.33 (1.04, 1.70)	0.02
Urinary bladder	Inadequate	-	-	-	-	-

Abbreviations: CI, Confidence Interval; **RR**, Relative risk.

†Relative risk of the highest Body Mass Index category evaluated versus normal BMI, unless otherwise stated.

*Relative risk per 5kg/m^2 increase in Body Mass Index

1.3 BIOLOGICAL MECHANISMS FOR THE OBESITY-CANCER RISK

The underlying mechanisms by which obesity influences cancer development are not fully understood. However, four central mechanisms (interrelated through insulin), summarised in the review by Renehan et al., are thought to exist:[32]

1.3.1 HYPERINSULINAEMIA AND INCREASED IGF1 BIOAVAILABILITY

Hyperinsulinaemia, demonstrated to correlate with increasing BMI and insulin resistance, is hypothesised to mediate carcinogenesis directly via insulin and indirectly through upregulation of free IGF1. The latter, thought to be the principal mechanism, is mediated through reduced production of IGF binding proteins 1 and 2, normally inhibitors of IGF1. Insulin and IGF1 activation of their respective receptors is thus increased, resulting in activation of pro-mitogenic, anti-apoptotic, angiogenic and lymphangiogenic pathways.[32] Epidemiological evidence supports this relationship, demonstrating an increased risk of several cancers, including colorectal, with raised circulating IGF-1.[33,34] Furthermore, type 2 diabetes mellitus, characterised by elevated insulin and insulin resistance, is associated with several cancer types.[35,36]

1.3.2 SEX-HORMONE METABOLISM

Excess adiposity has been associated with increased levels of circulating sex hormones, predominantly associated with sex-hormone-sensitive tumours (breast, endometrium, ovaries, and to some extent prostate).[32] Elevated circulating levels of oestradiol in obese women, resulting from increased peripheral tissue aromatase activity, has been associated with an elevated risk of post-menopausal breast[37] and endometrial cancers; the latter also mediated locally through increased IGF1 production.[38] Raised androgen levels in obese women have additionally been associated with increased risk of breast cancer.[37] Furthermore, progesterone (which inhibits IGF1 and reduces oestrogen effects) may be depleted through obesity-related ovarian suppression and hyperandrogenism.[39] Conversely in men, obesity has been associated with reduced circulating androgen, thought to support development of more aggressive prostate cancer.[40]

1.3.3 ADIPOKINE DYSREGULATION

Adipokines (adipocyte derived polypeptides) leptin (pro-inflammatory) and adiponectin (anti-inflammatory), closely related to the inflammatory system, are also important in obesity-cancer mechanisms.[41]

Insulin-induced leptin gene expression results in appetite suppression, hence leptin production is proportional to body fat. Leptin itself may be mitogenic, anti-apoptotic, pro-angiogenic and

may mediate immune suppression.[42] One leptin receptor, LRb, once activated signals intra-cellular pathways of cell survival, proliferation, and differentiation. Although strong evidence for the leptin mechanism is inconsistent,[32] circulating leptin levels have been associated with increased colorectal adenoma risk, a CRC precursor.[43] Furthermore, leptin stimulates inflammatory cytokine production and may be associated with the inflammatory hypotheses.[41]

Furthermore, reduced circulating adiponectin may be associated with several obesity-related cancers, including CRC.[44] Adiponectin is thought to have anti-carcinogenesis effects through direct (signal transduction) and indirect (insulin-sensitising and anti-inflammatory) pathways. Its secretion from VAT is negatively correlated with BMI (in part through insulin and oestrogen effects), thus reducing its inhibitory effects on carcinogenesis in obesity.[45]

1.3.4 INFLAMMATION AND THE TUMOUR MICROENVIRONMENT

Tumour microenvironment and low-level local, and systemic chronic inflammatory states associated with excess adiposity are increasingly understood to be important mechanisms of obesity-related carcinogenesis.

Chronic gastro-intestinal inflammatory conditions are known to increase cancer incidence, e.g., ulcerative colitis is associated with an increased CRC risk. Within this context, obesity has been associated with several mechanisms contributing to a chronic inflammatory state. Such low-level chronic inflammation may stimulate local environment changes, similar to wound healing, which may be adopted by neoplastic cells to promote further carcinogenesis, local invasion and progression. Specifically, adiposity may result in both systemic and local WAT inflammation.[46]

White adipose tissue (WAT) stores energy in the form of lipid and assists in regulating energy homeostasis.[46] Elevated adiposity is characterised by hypertrophy and/or hyperplasia of adipocytes, outgrowing their blood supply leading to hypoxia, in addition to undergoing mechanical shear stress, and resulting in apoptosis with consequent macrophage infiltration.[46,47] Adipocyte hypertrophy and infiltrating macrophages are associated with increased pro-inflammatory cytokine production: C-reactive protein (CRP), tumour necrosis factor (TNF), interleukins (IL) -1β, -6 and -18, interferon (IFN) gamma, and monocyte chemoattractant protein-1 (MCP-1), which additionally reduce adiponectin production.[46,48] Furthermore, anti-inflammatory cytokines (IL-3, IL-4, IL10, and IL-1 receptor antagonist) production is reduced. MCP-1 production further stimulates macrophage proliferation, which then encircle dead adipocytes forming crown-like structures (CLS). Macrophages then phagocytose the dead adipocytes, releasing free fatty acids (FFA). The latter in turn activate toll-like receptors (TLRs) on macrophages, inducing their pro-inflammatory phenotype and further cytokine production (TNA, IL-1β and cyclooxygenase-2[COX2]) which stimulates lipolysis and FFA release and hence, a self-perpetuating cycle.[46,47,49]

The association between inflammatory markers and cancer is inconsistent, differing across cancer sites. Elevated CRP and IL-6 have been associated with colorectal cancer,[50] and in addition to TNF upregulation, with colorectal adenomas (a precursor to CRC).[51] CLS are found within visceral fat, and have been associated with obesity, metabolic syndromes, breast cancer and adverse breast cancer outcomes.[52,53] Furthermore, WAT inflammation is involved in hormone signalling via CLS and cytokines. For example, TNF, IL-1β and COX-2 derived Prostaglandin E2 increase aromatase expression, the rate-limiting enzyme in the production of oestrogen, and might explain post-menopausal oestrogen-dependent breast cancers.[49] Moreover, there is increasing evidence of the potential contributory role of the gut microbiome in the development of colorectal cancer.[54,55] High fat diets are thought to alter the balance of intestinal microbiota, activating TLR4 (via lipopolysaccharides found in the cell wall of certain bacteria), and downstream cytokine cascades, perpetuating WAT inflammation.[49]

More recently, obesity has been associated with important inhibitory immune checkpoints, which are predominantly associated with T-cells, and can be utilised by tumours to down-regulate T-cell anti-tumour immune responses. Two such inhibitory checkpoints are cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and Programmed Death 1 (PD-1). Wang and colleagues[56] have demonstrated that the chronic inflammatory state associated with obesity suppresses immune responses, whereby increased T-cell exhaustion (ageing) was demonstrated by PD-1 upregulated expression in mouse, primate, and human models. Additionally, obesity related leptin pathways were found at least partly responsible for increased tumour proliferation and infiltration of PD-1-expressing T-cells and PD-1-mediated T-cell dysfunction. These mechanisms are of particular interest due increasing use of immune checkpoint inhibitors for the treatment of a range of (usually metastatic) cancers. It is thought that PD-1 checkpoint inhibitor efficacy might be increased in obese patients resulting from up-regulated PD-1 expression. Murine models suggest increased tumour shrinkage and prevention of metastasis formation, with no observed toxic effects in obese vs. control mice treated with PD-1 inhibitors. Furthermore, there is early evidence that this might translate clinically with prognostic benefits (improved progression-free and overall survival) demonstrated in obese individuals treated with checkpoint blockade.[56–58]

1.4 OBESITY AND CANCER OUTCOMES

1.4.1 THE OBESITY-CANCER SURVIVAL RELATIONSHIP

There is clearly sufficient causal evidence of the BMI-incident cancer risk. Indeed Crosbie et al. have expressed this rather aptly:

"*With plausible biological explanations, consistency of association, and long durations between BMI measurement and cancer occurrence in the meta-analysed cohort studies, these associations are probably causal.*"[59]

It would be intuitive to presume that such a causal relationship would confer a similar causal association to cancer-related survival outcomes. In breast cancer, evidence is reasonably consistent with at least 3 meta-analyses demonstrating an inverse BMI-survival relationship (**Table 1.3**) for both breast-cancer-specific survival and overall survival (OS), implying that increased deaths are not solely the result of obesity-related comorbidities.[60–62] Notably, the dose-response meta-analyses performed by Chan et al., included three BMI measurement timings (pre-, <12 months and ≥12 months of diagnosis) which consistently maintained J-shaped curvilinear relationships for total mortality, and linear relationships for breast-cancer specific mortality.[62]

Conversely, in endometrial cancer, and despite the strength of its BMI-incident-cancer association,[5,6] a large secondary analysis of the MRC ASTEC trial found no association between increased BMI and overall- or endometrial cancer-related survival (in the context of reduced biases from standardised trial protocols).[59] Two large observational cohort studies have previously reported the reverse,[63,64] however, these studies were subject to methodological flaws and significant confounding (from insufficient adjustment), and of increased significant results from elevated incident risk.[65]

Conflicting evidence exists for the majority of obesity-related cancers, indeed, the IARC concluded that outside of breast cancer, "evidence …[of increased peri-diagnosis BMI and reduced survival]... for other cancers was sparse and less consistent".[5] Whilst weight management strategies have been advocated for cancer survivors, this is as part of encouragement to maintain a healthy lifestyle.[66–68] Beyond the incident cancer relationships explored above, the relationship between BMI and prognosis undoubtedly increases in complexity; particularly true in the context of colorectal cancer and evidenced by an increasing body of conflicting evidence.

Table 1.3 | Meta-analyses of BMI-survival relationships in breast cancer

Author (Year) Country	Studies	Timing of adiposity / ER/PR status / menopausal status	BCS mortality HR / RR (95%CI)	Overall mortality HR / RR (95%CI)	Sensitivity analysis	Comments
Chan et al. (2014) UK[62]	82 (213 075 cases)	**Pre-diagnosis BMI**			Sensitivity analyses: Menopausal status ***No difference between pre- and post-menopausal status***	• Random effects model & weighting according to inverse variance. • Large volume study – 41 477 deaths with 213 075 cases. • Risk of confounding: heterogeneous BMI categories, but also performed per 5Kg/m^2 increment linear and non-linear dose response; heterogeneous adjustment for co-morbidities and intentional weight loss; incomplete data on weight change; treatment selection bias. • Cohorts from various populations improving generalisability. • Demonstrated J-shaped association in non-linear dose-response meta-analysis. • Significant heterogeneity demonstrated between studies in analyses. • Detailed sensitivity analyses.
		Underweight	1.02 (0.85, 1.21)*	1.10 (0.92, 1.31)*		
		Normal	1.00 (Ref)	1.00 (Ref)		
		Overweight	**1.11 (0.16, 1.17)***	**1.07 (1.02, 1.12)***		
		Obese	**1.35 (1.24, 1.47)***	**1.41 (1.29, 1.53)***		
		<12 months BMI			Larger no of deaths, Conducted in Europe &height/weight from records ***Weaker association for BMI <12 months diagnosis and overall mortality***	
		Underweight	**1.53 (1.27, 1.83)***	1.25 (0.99, 1.57)*		
		Normal	1.00 (Ref)	1.00 (Ref)		
		Overweight	**1.11 (1.03, 1.20)***	**1.07 (1.02, 1.12)***		
		Obese	**1.25 (1.10, 1.42)***	**1.23 (1.12, 1.33)***		
		≥12 months BMI			Larger no of deaths, Asian study, adjustment for co-morbidities ***Weaker association for <12months BMI & BCS mortality***	
		Underweight	-	**1.29 (1.02, 1.63)***		
		Normal	1.00 (Ref)	1.00 (Ref)		
		Overweight	1.37 (0.96, 1.95)*	0.98 (0.86, 1.11)*		
		Obese	1.68 (0.90, 3.15)*	**1.21 (1.06, 1.38)***		
		Pre-diagnosis Obese vs. Normal			Study designs Disease stage Screening ***No change in RR estimates***	
		Pre-menopausal	NR	1.75 (1.26, 2.41)*		
		Post-menopausal	NR	1.34 (1.18, 1.53)*		
		Per 5Kg/m^2 of BMI[§]				
		Pre-diagnosis	**1.18 (1.12, 12.5)***	**1.17 (1.13, 1.21)***		
		<12 months diagnosis	**1.14 (1.05, 1.24)***	**1.11 (1.06, 1.16)***		
		≥12 months diagnosis	1.29 (0.97, 1.72)*	**1.08 (1.01, 1.15)***		
Niraula et al. (2012) Canada[60]	21 Total	**Peri/post-diagnosis**			Meta-analysis HRs adjusted for: BMI (self or investigator measurement) Follow-up years. Study design. (treatment or observational) ***No difference in HRs***	• Random effects model & weighted according to individual HR. • Dichotomised BMI • Confounding risk: BMI groups heterogeneous, self-reported and directly measured BMI, heterogeneous adjusted variables. • Bias risk – selection bias based on receptor and/or menopausal status • Cohorts from various populations improving generalisability. Subgroups may still lack power.
		ER/PR positive	1.36 (1.20,1.54) †	1.31 (1.17, 1.46) †		
		ER/PgR negative	1.46 (0.98, 2.19) †	1.18 (1.06, 1.31) †		
			P = 0.86‡	*P = 0.31*‡		
		Peri/post-diagnosis				
		Pre-menopausal	1.18 (0.82, 1.70) †	1.23 (1.07, 1.42) †		
		Post-menopausal	1.38 (1.11,1.71) †	1.15 (1.06, 1.26) †		
			P=0.35‡	*P = 0.57*‡		

Table 1.3 | Meta-analyses of BMI-survival relationships in breast cancer

Author (Year) Country	Studies	Timing of adiposity / ER/PR status / menopausal status	BCS mortality HR / RR (95%CI)	Overall mortality HR / RR (95%CI)	Sensitivity analysis	Comments
Protani et al. (2010) Australia[61]	43 Total	**Peri/post-diagnosis** Obese vs. normal	1.33 (1.19, 1.50)†	1.33 (1.21, 1.47)†	Pre-specified: Survival measure (OS or BCSS) Obesity measure (BMI or WHR) Study design (treatment or observational) Period of diagnosis (pre- or post-1995). Menopausal status ***No differences in HR.***	• Random effects model • Dichotomised BMI • Confounding risk: between study heterogeneity (mixture of BMI or WHR, differing BMI groups, mixture of self-reported and measured height and weight, variable methods for survival data collection, inconsistent adjustment for prognostic/ confounding variables) • Several post-hoc sensitivity analyses including differing BMI normal range. Cohorts from various populations improving generalisability.

Abbreviations: BCS, Breast-cancer-specific; **BMI**, Body Mass Index; **HR,** Hazard ratio; **WHR**, Waist Hip Ratio
* RR
‡ Meta-regression test for subgroup analysis
† HR for obese vs. non-obese.
§ Linear model, excluding underweight group.

1.4.2 OBESITY AND COLORECTAL CANCER OUTCOMES

Parkin et al. reported a systematic review and dose-response meta-analyses of survival outcomes in colorectal cancer, stratified according to study characteristics (timing of adiposity measurements and clinical setting), including 35 studies with a total of 41,464 patients (summarised in **Table 1.3**). A number of notable observations were made:[69]

1. Some evidence exists for an association between BMI and survival, which may differ according to timing of anthropometric measurements in relation to diagnosis:
   1.1. The association between pre-diagnosis BMI and cancer-related mortality (time zero at BMI measurement, Group A) demonstrated a significant dose-response relationship in men but not women, however pooled analyses for colon and rectal cancer may have attenuated results in females.[69]
   1.2. There were significantly increased summary risk estimates for OS and cancer-specific survival (CSS) in women but not men, for the association between peri-diagnosis BMI and survival (time zero at diagnosis, Group B). However, risk of confounding from disease and treatment-related weight changes is likely, which may attenuate outcomes and differ between genders.[69]
   1.3. The association between peri/post-diagnosis BMI and survival, in secondary analyses of adjuvant chemotherapy trials (group E) in general demonstrated slight adverse survival (DFS and OS) in men. However, results are not statistically significant and may represent suboptimal treatment rather than a true causal relationship.[69]

2. In general, there was insufficient evidence to confirm a BMI-survival association:
   2.1. There was a lack of consistency in prognostic outcomes related to elevated BMI (including gender-specific differences) for the above groups, and within population-based cohort studies evaluating peri-diagnosis-BMI and survival (Group C).[69]
   2.2. Surgical resection single-institution cohorts evaluating peri-diagnosis-BMI and survival (Group D) were heterogeneous and full of bias and confounding adding “confusion rather than clarity to the literature”.[69]
   2.3. In metastatic colorectal cancer (Group F), dichotomisation of BMI variables and inclusion of underweight patients in reference groups (introducing reverse causality) make results difficult to interpret and represents a rather basic method for exploring what appears more often to be a curvilinear relationship.[69,70]

Table 1.4 | Summary of the Parkin et al. systematic review and meta-analysis

From refernce[69]

Group/ Setting (No. Studies)	Timing of adiposity measures	Survival time zero	Dose-response meta-analysis			Comments
			Studies‡	Male HR / RR (95%CI)*	Female HR / RR (95%CI)	
A Cohort (5)	Pre-diagnosis	At BMI measure	2	**CCM RR: 1.19 (1.14, 1.25)**	CCM RR: 1.06 (0.98, 1.15)	Population-representative & adjusted for risk-factors (RF). Confounding: self-reported/measured BMI; increased CRC incidence. Combined colon/rectal cancer may attenuate female estimates (lower incident risk of rectal cancer in women).
B Registry-based (5)	Pre-diagnosis	Peri-diagnosis	2 (Male) 4 (Female)	OS HR: 1.07 (0.98, 1.17) CSS HR: N/A	**OS HR: 1.16 (1.09, 1.24)** **CSS HR: 1.16 (1.08, 1.25)**	Population-representative & Reasonable RF adjustment. Confounding: self-reported & measured BMI; mixed cancer sites; weight loss; insufficient detail on staging/treatment. Larger number of women might increase significance in women.
C Population & registry-based data. (5)	Peri-diagnosis	Peri-diagnosis	4	OS HR: 0.92 (0.84, 1.00) † CSS HR: 0.94 (0.83, 1.06) †		Population-representative & some adjustment for key RF. Mixed cancer sites and stages. Confounding risk: compliance, ACT dosing, some RF. Immortal time bias risk: self-reported BMI after diagnosis and initial treatment.
D Surgical resection cohorts (10)	Peri-operative/ diagnosis	Peri-diagnosis	NA	***No convincing BMI-survival relationship demonstrated.*** Mixed outcomes – BMI associated with improved/worse/no difference in survival. Significant heterogeneity prevented meta-analysis.		Generally small studies & poor adjustment. Mixed cancer sites and stages. Some CT-derived adiposity measurements. High risk of Bias: selection bias, reverse causality High risk confounding: lacking compliance, ACT dosing;
E Adjuvant chemotherapy (5)	Post-diagnosis	Unclear	NA	***Modest but not statistically significant adverse OS and DFS with increased BMI.***		Large trials >1000 cases - stage II/ III colon and rectal. Less representative of general populations. Reduced risk bias – randomised treatment & protocol-driven. Risk of confounding – adherence, dose capping.
F Metastatic CRC (4)	Peri/post-diagnosis	Unclear	2 chemo-therapy	***No convincing BMI-survival relationship*** *Mixed outcomes (improved and worse survival)*		Risk of confounding: reverse causality; variable BMI categories; inclusion of underweight in referent groups. Possible over-estimation of VAT and SAT due to protocols used.
			2 liver met resection	***No convincing BMI-survival relationship*** *Mixed outcomes (improved and no different survival).*		

Group descriptions: A, Pre-diagnosis adiposity and cancer related mortality (time zero at BMI measurement); **B,** Pre-diagnosis adiposity and survival (time zero at diagnosis); **C,** population-based cohorts; **D,** single institution cohorts; **E,** adjuvant chemotherapy trials. **F,** metastatic disease.

Abbreviations: CCM, Cancer Specific Mortality; **CCS** Cancer Specific Survival; **OS** – Overall survival; **RR**, relative risk; **TTP**, Time to progression.

‡ No studies that were possible to include in the meta-analysis

* RR per 5Kg/m^2 BMI increment.

†Excludes underweight patients due to risk of reverse causality.

In addition to the above, a further three meta-analyses[71–73] examining the BMI-CRC outcome relationship have been published (summarised in **Table 1.5**). In general, these show an increased risk of mortality and recurrence in obesity with pre- and peri-diagnosis BMI but not post-diagnosis BMI.[71–73] However, it is clear that these meta-analyses are significantly limited by several factors, namely significant heterogeneity between included studies. Variation between BMI categories utilised across the included studies (though Doleman et al. did attempt to standardise these [71]) including different ranges for, or dichotomised, BMI as the reference group, may have introduced a degree of reverse causality. Other sources of heterogeneity and confounding include differential adjustment for prognostic/confounding factors and variable BMI measurement timing. Furthermore, no study attempted assessment of dose-response relationships. Although these results should be interpreted with caution, due to likely significant confounding, interestingly, all three studies demonstrated a stronger association for obesity and reduced OS in women compared with men, converse to the BMI-incident cancer risk relationship. Furthermore, results appeared to be influenced by the timing of BMI measurements, suggesting a more complex association than for breast cancer.[72,73]

A large observational cohort study, in particular, is worth exploring in detail; that by Kroenke and colleagues utilising a rich health administrators database of the Kaiser Permanente Northern California population.[70] Their study, comprising 3,408 patients with stage I-III CRC undergoing surgery attempted to explore BMI-prognosis relationships with the assistance of causal diagrams (see **Chapter 2**, **Section 2.5.4** on directed acyclic graphs). Specifically, this allowed the investigators to assess and adjust for potential confounders, selection bias, reverse causality, and collider stratification bias (discussed below). The authors demonstrated that, following adjustment, peri-diagnosis BMI retained a non-linear, J-shaped relationship with all-cause mortality; underweight (BMI <18.5kg/m^2) and obese II/III (BMI ≥35kg/m^2) were associated with increased mortality, compared to low-normal weight (referent group - BMI 18.5 to <23 kg/m^2), whereas high normal (BMI 23 to <25 kg/m^2) low-overweight (BMI 25 to <28 kg/m^2) and high-overweight (BMI 28 to <30 kg/m^2) were associated with lower mortality risk, with no difference for class I obesity (BMI 30 - <35 kg/m^2). With similar associations for CRC-specific mortality and when evaluating post-diagnosis BMI (though class I obese had significantly lower all-cause and cancer-specific mortality). The authors concluded that their study may provide some evidence towards an obesity paradox, representing an additional facet of complexity to the BMI-prognosis relationship.

Finally, it is important to note the relationship between height and cancer outcomes. Height has previously been associated with increased incident CRC risk,[74] hypothesised to be mediated by IGF-1, due to both genetic and environmental factors (early life nutrition, physical and social environments). How BMI-outcome relationships might be affected by height-outcome relationships is unclear, and generally unreported within the BMI-CRC outcome literature. Several large studies, including one mendelian randomisation study,[75] have tended to

demonstrate an increased risk of cancer mortality associated with increased height.[75–80] However, results have been inconsistent, with two studies demonstrating increased risk of overall cancer mortality in women but not men.[77,78] The majority of these studies were limited by examining all-cancer mortality, where multiple tumour sites risk attenuation of overall effect estimates due to potentially opposing effects, and might give rise to inconsistent findings. Few studies have specifically assessed the height-CRC mortality risk, with variable outcomes. Within a large UK male population study (N = 18,403), a small subset of patients (N=283) with colon cancer were not demonstrated to be at increased risk of colon cancer-related mortality with increasing height.[80] A further subset of 603 patients with colon cancer from a larger pooled analysis of seven Austrian, Norwegian and Swedish population cohort studies (N=585,928) similarly did not demonstrate increased colon cancer-related mortality with taller stature.[77] Interestingly, the proportions of obese patients tended to reduce with increasing height in both studies, and results were robust to adjustment for BMI, suggesting that these null relationships were unlikely to be explained by possible BMI-related confounding. Conversely, within the metastatic setting, a secondary analysis of a chemotherapy RCT for metastatic CRC (N = 695) patients, demonstrated a non-linear association with increased mortality associated with both short and tall stature.[81] These studies did not assess the relationships between BMI and height nor were the outcomes for BMI in multi-variate models reported. Hence, how BMI-mortality associations might be influenced by height (and vice-versa) is unclear.

Table 1.5 | Meta-analyses of BMI-survival relationships in colorectal cancer

Author (Year) Country	Studies	Timing of adiposity measures	BMI Category	Meta-analysis OM/OS HR (95%CI)	CSM/CSS HR (95%CI)	DFS HR (95%CI)	Recurrence HR (95%CI)	Sensitivity analysis	Comments
Doleman et al. (2016) US[71]	18	Peri-diagnosis	**Overall**					Standard BMI categories only *Non-significance between obesity and CSM* Prospective data Pre- or peri- diagnosis BMI *No significant change of summary estimates* Removal of largest study *Led to non-significance between obesity and DFS; underweight and RFS* Trim-and-fill method to assess publication bias. *Publication bias for underweight group only*	Included studies that only utilised WHO standard or WHO Asian-specific BMI categories. Attempts to transform data if not within standard BMI categories. Random effects model used Quality assessment Heterogeneity with wide variation in BMI and outcome ascertainment, variable BMI measurement methods. Assessment of publication bias. No meta-regression.
			Underweight	**2.43 (1.26, 2.62)**	**1.50 (1.20, 1.87)**	**1.27 (1.13, 1.43)**	**1.13 (1.05, 1.21)**		
			Normal	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)		
			Overweight	0.99 (0.94, 1.05)	0.98 (0.87, 1.09)	0.96 (0.92, 1.00)	1.00 (0.96, 1.05)		
			Obese	**1.14 (1.07, 1.21)**	**1.14 (1.05, 1.24)**	**1.07 (1.01, 1.13)**	**1.07 (1.02, 1.13)**		
			Men						
			Underweight	**1.40 (1.26, 1.57)**	-	**1.33 (1.17, 1.51)**	1.17 (0.97, 1.41)		
			Normal	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)		
			Overweight	0.96 (0.91, 1.02)	1.04 (0.89, 1.21)	**0.93 (0.88, 0.99)**	0.98 (0.92, 1.04)		
			Obese	**1.11 (1.00, 1.22)**	**1.28 (1.07, 1.54)**	**1.09 (1.01, 1.17)**	**1.09 (1.01, 1.18)**		
			Women						
			Underweight	**1.26 (1.09, 1.46)**	**1.36 (0.99, 1.86)**	1.18 (0.96, 1.46)	1.06 (0.97, 1.16)		
			Normal	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)		
			Overweight	**1.09 (1.00, 1.19)**	1.12 (0.97, 1.29)	1.02 (0.95, 1.10)	1.04 (0.93, 1.17)		
			Obese	**1.21 (1.09, 1.35)**	**1.20 (1.03, 1.38)**	1.04 (0.96, 1.12)	1.04 (0.88, 1.23)		
			Colon						
			Underweight	**1.33 (1.18, 1.49)**	**1.46 (1.14, 1.87)**	**1.31 (1.12, 1.54)**	**1.13 (1.04, 1.21)**		
			Normal	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)		
			Overweight	1.00 (0.96, 1.04)	1.03 (0.91, 1.15)	0.96 (0.92, 1.00)	1.01 (0.96, 1.07)		
			Obese	**1.12 (1.07, 1.18)**	**1.18 (1.08, 1.29)**	**1.07 (1.01, 1.13)**	**1.07 (1.04, 1.21)**		
			Rectum						
			Underweight	**1.43 (1.09, 1.88)**	**1.67 (0.55, 5.03)**	**-**	**1.00 (0.53, 1.89**		
			Normal	1.00 (Ref)	1.00 (Ref)	**-**	1.00 (Ref)		
			Overweight	1.05 (0.89, 1.24)	1.05 (0.83, 1.32)	**-**	0.98 (0.81, 1.19)		
			Obese	**1.31 (1.03, 1.68)**	1.28 (0.94, 1.75)	**-**	1.09 (0.88, 1.35)		
Lee et al. (2015) South Korea [41]	16	Pre-diagnosis	**Overall**					Different peri-diagnosis BMI categories for normal. *Studies with lower range of BMI 20-21 only removed association between overweight and improved OS – Obese group not assessed.*	Prospective studies only. Quality assessment. Heterogeneity with variable BMI categories including underweight patients, variable adjustment, Fixed and random effects models depending on heterogeneity, Publication bias assessed
			Underweight	**1.63 (1.18, 2.23)**	1.54 (0.99, 2.40)				
			Normal	1.00 (Ref)	1.00 (Ref)				
			Overweight	NR	1.05 (0.96, 1.14)				
			Obese	**1.25 (1.14, 1.36)**	**1.22 (1.003, 1.35)**	NA	NA		
		Post-diagnosis	**Overall**						
			Underweight	**1.33 (1.20, 1.47)**	NR				
			Normal	1.00 (Ref)	1.00 (Ref)				
			Overweight	**0.93 (0.86, 0.997)**	**0.84 (0.67, 0.097)**				
			Obese	**1.08 (1.03, 1.13)**	0.95 (0.80, 1.30)	NA	NA		

Table 1.5 | Meta-analyses of BMI-survival relationships in colorectal cancer

Author	Studies	Timing of	BMI	Meta-analysis			Sensitivity analysis	Comments
			Women					Limited sensitivity analysis but suggested that different BMI categories confounded results though reverse causality. Insufficient studies for Rectal cancer analysis
			Underweight	**1.17 (1.08, 1.28)**				
			Normal	1.00 (Ref)				
			Overweight	NR	NA	NA	NA	
			Obese	**1.13 (1.05, 1.21)**				
			Men					
			Underweight	**1.36 (1.02, 1.82)**				
			Normal	1.00 (Ref)				
			Overweight	**0.93 (0.88, 0.98)**	NA	NA	NA	
			Obese	1.05 (0.99, 1.23)				
			Colon					
			Underweight	**1.24 (1.16, 1.32)**				
			Normal	1.00 (Ref)				
			Overweight	1.04 (0.93, 1.18)	NA	NA	NA	
			Obese	**1.09 (1.05, 1.15)**				
Wu et al. (2014), China[73]	29	Peri-diagnosis	**Overall**				Stepwise study exclusion. *No change in HR.* Causes of heterogeneity: Exclusion of post-menopausal women *No change to HR.* Timing of BMI *Significant influence on overweight and obese association with OS.*	Significant heterogeneity with wide variation in BMI categories used, BMI timing and measurement method, site, stage gender, variable adjustment between studies. Fixed or random effect model dependent on heterogeneity. Attempted to deal with variation in BMI categories. Publication bias assessed. Limited sensitivity analysis.
			Normal	1.00 (Ref)				
			Overweight	0.92 (0.86, 1.00)	NA	NA	NA	
			Obese	**1.10 (1.06, 1.15)**				
			Men*					
			Normal	1.00 (Ref)				
			Overweight	0.96 (0.91, 1.02)	NA	NA	NA	
			Obese	**1.09 (1.02, 1.17)**				
			Women*					
			Normal	1.00 (Ref)				
			Overweight	**1.07 (1.00, 1.13**	NA	NA	NA	
			Obese	**1.17 (1.09, 1.25)**				

Abbreviations: BMI, Body mass index; **CI**, Confidence interval; **CSM,** Cancer-specific Mortality; **CSS**, Cancer specific survival **DFS**, Disease-Free Survival; **HR**, Hazard ratio, **NOS**, Newcastle-Ottawa Score; **NR**, Not reported; **OM**, Overall Mortality; **OS**, Overall Survival

*Meta-regression for gender not significant for overweight or obese groups.

1.5 PROBLEMS WITH THE CURRENT EVIDENCE BASE

Contextualised in the nature of the currently available evidence assessing the association between body-fatness and cancer prognosis, the WCRF/AIRC continuous update report "survivors of breast and other cancers" concludes that:

'currently it is not possible to exclude with confidence that any observed association is not due to unidentified confounding or to reverse causation.'[66]

Difficulties in interpreting the current evidence can be summarised through evaluation of the obesity paradox.

1.5.1 THE OBESITY PARADOX

Study findings of a protective effect of BMI on survival where the reverse is expected, termed the "obesity paradox", is a well-recognised paradigm in cardiovascular[17,82] and metabolic research,[83,84] which has extended into the oncological literature. In colorectal cancer, within the inconsistent obesity-related outcomes as demonstrated above, there are instances where the obesity paradox has been observed. **Table 1.6** summarises selected large studies in the colorectal cancer literature where the obesity paradox has been evidenced, in addition to where it has not.

The obesity paradox has prompted critical appraisal of the literature in search of possible explanations for such observations; in particular, methodological problems introducing bias and confounding (and thus consequently spurious results), and more clinical explanations of its true occurrence. These two broad categories go some way towards postulating the reasons for the obesity paradox, but additionally explore the limitations of current evidence, shedding light on the difficulties of drawing concrete conclusions (despite the published meta-analyses). The review by Lennon et al.[85,86] provides a detailed discussion of these issues and is summarised below:

1. Methodological problems resulting in spurious outcomes
    1.1. *BMI:* is unlikely to adequately approximate adiposity and body composition, differing with age, gender and race and resulting in measurement error;[87] thus, other anthropometric measures (e.g. WHC, WHR, CT-quantified VAT, SAT and skeletal muscle mass) may be more accurate.[20,88,89] Second, the method of BMI determination (self-reported vs. measured) may affect estimates of the BMI-incident cancer risk.[6] Finally, BMI may introduce treatment selection bias, including within randomised trial data (from reduced enrolment of obese patients, potentially due to increased comorbidity incidence, but often unclear due to lacking detail in published studies)[90] and

also in the context of chemotherapy dosing (see below). It is important to note that the obesity paradox is almost never reported where the measure of adiposity is, for example waist circumference.

1.2. *Confounding:* occurs where a true effect is obscured by an additional variable. A confounder is associated with both exposure and outcome, but not caused by the exposure and therefore does not lie within the causal pathway.[91] Adjustment for all confounding may not be possible (e.g., data on smoking, outside of lung cancer studies, are often lacking from randomised controlled trials)[85,86] or may not be adequate (due to measurement error), resulting in residual confounding and spurious results.[92,93]

1.3. *Collider stratification bias:* is a specific form of selection bias resulting during statistical analysis. It results in an association between an exposure and a confounder when conditioning on a third "collider" variable (itself caused by both exposure and confounder) which can alter the exposure-outcome association[94,95] (potentially falsely strengthening[96] or reversing it[92]). However, the extent of such bias has also been shown to be small and unlikely to result in such large associations in the opposite direction to entirely explain the obesity paradox.[94]

1.4. *Detection bias:* the phenomenon occurring when diagnosis of one condition (e.g., diabetes) due to an exposure (e.g., obesity) results in further investigations and detection of incidental diseases (here, cancer).[97] This may create an "opportunistic screening", detecting earlier stages of cancer and resulting in better outcomes.[85]

1.5. *Reverse causality:* refers to confounding resulting from an exposure being influenced by the disease in question, which in turn influences the outcome.[98] Cancer-related weight loss (including early stage tumours) correlates with pre-diagnosis BMI, hence migration of peri-diagnosis BMI across categories may result in attenuation of prognosis effects to null or inverse,[99] akin to stage-migration principles and the Will Rogers phenomenon.[100] This may be further exaggerated by, for example, unwise choice of a referent category[86] (e.g., inclusion of underweight through dichotomising BMI). This concept may also be partly responsible for the differences between outcomes observed across differing BMI timings,[72,73,101] which is thought to be increasingly important in understanding BMI-prognosis relationships.[66]

2. Clinical explanations for a true association:

2.1. *Less aggressive tumour biology:* may be associated with obesity e.g., in the case of endometrial cancer where obesity is more commonly associated with type 1 endometrial cancer (over type 2) which in turn has a more favourable prognosis.[59]

2.2. *Better tumour response to treatment:* may be as a result of tumour biology itself, or relate to altered pharmacokinetics (as in the example of increased doxorubicin exposure and toxicity seen with elevated VAT).[102] A further dimension is that the tumour immune response might be altered in the presence of obesity, as recently exemplified

by Wang and colleagues, whereby increased expression of the PD1/PDL1-checkpoint in obese patients may result in improved outcomes when treated with inhibitors of this axis.[56]

2.3. *Loss of chemotherapy-related survival advantage:* may occur through sub-optimal treatment as a result of obesity, particularly at the extreme end of the adiposity spectrum, and thus be responsible for the U-shaped association sometimes observed as part of the obesity paradox.[65] This may occur firstly, through "selecting-out" for chemotherapy or influencing the choice of cytotoxic agents (although this has previously demonstrated not to be the case for breast cancer[103] there is little evidence exploring this possibility in CRC); secondly, through the practice of capping chemotherapy doses for patients with high BMI;[104] and thirdly, though differential adherence to treatment,[105] combining in various extents to produce poor outcomes at the extremes of BMI.

2.4. *Increased energy reserve:* from a degree of adiposity may indeed confer a protective benefit to withstand the physiological stresses secondary to surgery and (neo)-adjuvant treatment. [85,106]

A number of approaches, detailed by Lennon et al., may be implemented to deal with the methodological problems discussed above, in order to draw firmer conclusions from future studies. [85] Thus, contextualised in the limitations of the current evidence base, there remain two particular areas requiring additional careful consideration: firstly, it remains of fundamental importance to establish whether the exposure-incidence link seen for colorectal cancers confers similar exposure-prognosis associations; secondly, it is evident that to do so will require characterisation of the relationship between obesity, chemotherapy and consequent outcome. By answering these questions, not only will the prognostic effects of adiposity be better understood, but the potential role for improving outcomes through weight control interventions and optimising chemotherapy dosing in patients diagnosed with colorectal cancer might also be elucidated.

Table 1.6 | Evidence for and against the "obesity paradox"

Author (Year) Country	Cohort	Timing of BMI	Setting	BMI categories	Cancer-Specific Survival		Overall Survival	
					Male HR or RR* (95%CI)	Female HR or RR* (95%CI)	Male HR or RR* (95%CI)	Female HR or RR* (95%CI)
Studies demonstrating increased overall and/ or cancer-specific mortality in overweight and obese (no obesity paradox)								
Calle et al. (2003) US[64]	Cancer prevention study (n= 2,998)	Pre-diagnosis	Prospective cohort Colon and Rectum cancers	18.5 – 24.9 25 – 29.9 30 – 34.9 35 – 39.9 ≥40	1.00 (Ref)* **1.20 (1.12, 1.30)** **1.47 (1.30, 1.66)** **1.84 (1.39, 2.41)** -	1.00 (Ref)* **1.10 (1.01, 1.19)** **1.33 (1.17, 1.51)** **1.36 (1.06, 1.74)** 1.46 (0.94, 2.24)	NA	NA
Prizment et al. (2010) US[107]	SEER Program (n = 1,096)	Pre-diagnosis	Prospective cohort Colon cancers	<18.5 18.5 – 24.9 25 – 29.9 ≥30	NA	2.13 (0.96, 4.73) 1.00 (Ref) 1.18 (0.87, 1.58) 1.30 (0.95, 1.80)	NA	**2.01 (1.07, 3.80)** 1.00 (Ref) 1.11 (0.88, 1.39) **1.46 (1.15, 1.86)**
Campbell et al. (2012) USA [101]	CPS-II Nutrition cohort (n = 2,303)	Pre-diagnosis	Prospective cohort Colon and Rectum	<18.5 18.5 – 24.9 25 – 29.9 ≥30 per 5 kg/m^2	- 1.00 (Ref) 1.06 (0.77, 1.48) 1.31 (0.88, 1.95) 1.16 (0.96, 1.41)	0.83 (.025, 2.76) 1.00 (Ref) 1.19 (0.96, 2.41) 1.52 (0.94, 1.57) 1.18 (0.98, 1.44)	1.40 (0.55- 3.56) 1.00 (Ref) 0.97 (0.79, 1.19) 1.21 (0.94, 1.57) 1.09 (0.97, 1.24)	1.74 (0.85, 3.58) 1.00 (Ref) 1.22 (0.92, 1.63) **1.42 (1.01, 2.00)** **1.20 (1.04, 1.37)**
Pelser et al. (2014) USA[108]	NIH-AARP Diet and Health Study N= 4213	Pre-diagnosis	Prospective cohort Colon	18.5 – 24.9 25 – 29.9 ≥30	1.00 (Ref)* 0.97 (0.82, 1.15) 1.15 (0.96, 1.39)		RR 1.00 (Ref)* 1.02 (0.88, 1.17) **1.19 (1.02, 1.39)**	
	NIH-AARP Diet and Health Study N=1,514	Pre-diagnosis	Prospective cohort Rectum	18.5 – 24.9 25 – 29.9 ≥30	1.00* 0.92 (0.70, 1.22) 1.04 (0.75, 1.44)		1.00* 0.85 (0.68, 1.07) 1.00 (0.77, 1.30)	
Fedirko et al. (2014) International[109]	EPIC Cohort (n = 3,924)	Pre-diagnosis	Prospective cohort Colon & rectum	<25 25.0 – 29.9 ≥30	1.00 (Ref) 1.07 (0.93, 1.24) **1.21 (1.00, 1.24)**		1.00 (Ref) 1.12 (0.97, 1.30) **1.26 (1.04, 1.52)**	
Campbell et al. (2015) US[110]	Colon-Cancer Family Registry (n= 5,615)	Pre-diagnosis	Prospective cohort Colon & rectum	<18.5 18.5-<25 25-<30 ≥30 30-35 35 -≤40 ≥40	NA	NA	- 1.00 (ref) 1.11 (0.95, 1.29) **1.23 (1.04, 1.46)** 1.16 (0.96, 1.39) **1.59 (1.21, 2.09)** 1.19 (0.81, 1.74)	1.76 (1.18, 2.61) 1.00 (ref) 1.10 (0.93, 1.30) **1.33 (1.12, 1.58)** **1.25 (1.01, 1.54)** **1.31 (1.00, 1.73)** **1.63 (1.21, 2.19)**
					Disease Free Survival		**Overall survival**	
Sinicrope et al. (2013) US[111]	ACCENT 21 RCTs North America and Europe (n = 25, 291)	At study entry/ Peri-treatment	Secondary analysis of trial data Colon	<20 20 – 24.9 25 – 29.9 ≥30 30 – 34.9 ≥35	**1.18 (1.09, 1.28)** 1.00 (Ref) 0.97 (0.92, 1.02 **1.06 (1.00, 1.13)** 1.05 (0.98, 1.12) **1.10 (1.01, 1.21)**	**1.11 (1.01, 1.23)** 1.00 (Ref) 1.03 (0.96, 1.11) 1.04 (0.96, 1.13) 1.03 (0.94, 1.14) 1.06 (0.93, 1.21)	**1.21 (1.11, 1.32)** 1.00 (Ref) 0.99 (0.94, 1.04) **1.10 (1.04, 1.17)** **1.10 (1.02, 1.18)** **1.11 (1.00, 1.23)**	**1.12 (1.00, 1.25)** 1.0 (Ref) 1.05 (0.97, 1.14) 1.09 (1.00, 1.20) 1.10 (0.99, 1.23) 1.07 (0.93, 1.24)

Table 1.6 | *Continued*

Author (Year) Country	Cohort	Timing of BMI	Setting	BMI categories	Cancer-Specific Survival		Overall Survival	
					Male HR or RR* (95%CI)	Female HR or RR* (95%CI)	Male HR or RR* (95%CI)	Female HR or RR* (95%CI)
Studies demonstrating reduced mortality in overweight and/or obese (obesity paradox)								
Reeves et al. (2007) UK[63]	Million Women Study (n = 4,008)	Pre-diagnosis	Prospective cohort Colon and Rectum	<24.9 25 – 27.4 27.5 – 29.9 ≥30	NA	1.0 (0.91, 1.10) 0.98 (0.89, 1.09) **0.86 (0.75, 1.00)** 1.03 (.091, 1.16)	NA	NA
Asghari-Jafarabadi et al. (2009) Iran[112]	Multi-centre (10 hospitals). (n=1,219)	Peri-diagnosis	Retrospective cohort Colon and rectum	<18.5 18.5 – 24.9 25 – 29.9 ≥30	NA		2.74 (1.17, 6.45) 1.00 (Ref) **0.32 (0.14, 0.73)** 0.71 (0.25, 2.03)	
Baade et al. (2011) Australia[113]	Queensland longitudinal study n = 1,219	Peri-diagnosis	Prospective cohort Colon & Rectum	<18.5 18.5 – 24.9 25 – 29.9 ≥30	**1.74 (1.00, 3.04)** 1.00 (Ref) **0.75 (0.59, 0.97)** **0.70 (0.51, 0.97)**		**2.29 (1.47, 3.59)** 1.00 (Ref) **0.75 (0.61, 0.94)** 0.78 (0.59, 1.03)	
Hines et al. (2009) USA[114]	Single Centre (n=496)	BMI at surgery	Surgical resection cohort Colon	<18.5 18.5 - <25 ≥25	NA		1.51 (0.96, 2.45) 1.00 (Ref) **0.77 (0.61, 0.97)**	
Simkens et al. (2011) NL[115]	CAIRO 1	BMI at baseline	Metastatic chemotherapy trial	<18.5 18.5 – 24 25 – 29 ≥30	NA		1.64 (0.93, 3.03) 1.00 (Ref) **0.81 (0.68, 0.96)** **0.73 (0.55, 0.96)**	
	CAIRO 2	BMI at baseline	Metastatic chemotherapy trial	<18.5 18.5 – 24 25 – 29 ≥30	NA		1.09 (0.58, 2.07) 1.00 (Ref) 1.00 (0.82, 1.21) 0.99 (0.74, 1.33)	
Kroenke et al. (2016) US[70]	Kaiser Permanente (n = 3,408)	Peri-diagnosis	Retrospective cohort of prospective data	<18.5 18.5 - <23 23 - <25 25 - <28 28 - <30 30 - <35 35+	3.18 (1.78, 5.69) 1.00 (Ref) 0.89 (0.60, 1.31) 0.81 (0.55, 1.19) **0.45 (0.28, 0.74)** 0.88 (0.58, 1.32) 1.12 (0.61, 2.06)		2.65 (1.63, 4.31) 1.00 (Ref) 0.77 (0.56, 1.06) 0.75 (0.55, 1.04) **0.52 (0.35, 0.77)** 0.81 (0.57, 1.15) 1.33 (0.89, 1.98)	
	Kaiser Permanente (n = 3,157)	Post-diagnosis	Retrospective cohort of prospective data	<18.5 18.5 - <23 23 - <25 25 - <28 28 - <30 30 - <35 35+	**3.25 (2.00, 5.27)** 1.00 (Ref) 0.70 (0.47, 1.04) **0.53 (0.37, 0.76)** **0.53 (0.34, 0.82)** **0.67 (0.47, 0.96)** 0.86 (0.59, 1.27)		**3.38 (2.19, 5.20)** 1.00 (Ref) 0.72 (0.52, 1.02) **0.56 (0.41, 0.77)** **0.39 (0.26, 0.58)** **0.51 (0.35, 0.73)** 0.85 (0.56, 1.30)	

Abbreviations: CCM, Cancer Specific Mortality; **CCS** Cancer Specific Survival; **EPIC**, European Prospective Investigation into Cancer, and Nutrition; **OS**, Overall survival; **SEER**, Surveillance, Epidemiology and end Results **TTP**, Time to progression.
*RR for Cancer Specific Mortality and/or Overall mortality reported
†Not including underweight patients due to risk of reverse causality.
‡ P for trend;

1.6 OBESITY AND COLORECTAL CANCER SURVIVAL WITHIN THE ADJUVANT CHEMOTHERAPY CONTEXT

To explore these concepts in more detail, evidence from secondary (pooled) analyses of ACT trials were examined for a relationship between BMI and colon and rectal cancer prognosis (summarised in T**able 1.7**). Such datasets are likely subject to the least amount of bias[116] through treatment randomisation and protocolled treatment/follow-up. overall, and as demonstrated by Parkin et al.,[69] these demonstrate a modest increased risk of adverse outcomes with increasing BMI, particularly BMI ≥35 kg/m^2 (with the strongest association), [111,117,118] the exception being the 2008 Meyerhardt et al. study, demonstrating a tendency towards an obesity paradox for OS.[119]

Two pooled analyses of adjuvant chemotherapy in colon cancer from Sinicrope et al. merit closer inspection. The first,[118] comprising seven trials and 4,381 patients, demonstrated an increased likelihood of obese patients having higher T/N stages, distal cancers, lower rates of defective mismatch repair (MMR), and being younger and male. In multivariate analysis, BMI ≥35kg/m^2 was associated with a non-significant increase in DFS and OS hazard ratios, whereas overweight displayed a borderline obesity paradox for OS. Subgroup analysis demonstrated gender differences: overweight was associated with an improved OS in men, with no such effect in women; obese I was associated with reduced OS in women, converse to a non-significant risk reduction in men; obese II/III was more strongly associated with reduced OS in men than women.

These results were subsequently updated to include 21 trials from the ACCENT database (25,291 patients) [111] and is likely the largest study of its kind. The authors found significantly worse DFS and OS and a non-significant shorter time to recurrence (TTR) in underweight and obese vs. normal BMI. Subgroup gender analysis revealed stronger adverse associations between BMI and DFS and OS in underweight and obese men, and significant interaction between BMI and gender ($p_{interaction}$ = 0.0340, though mainly due to underweight men). Women generally demonstrated small (non-significant) increases in hazard ratios for DFS, OS and TTR. A curvilinear relationship was demonstrated for continuous BMI for overall OS ($p < 0.025$) and gender-specific OS ($p_{interaction}$ = 0.05), whereas a quadratic relationship was demonstrated for TTR and DFS. Both studies are at risk of the issues discussed above, including for example, confounding related to insufficient adjustment (the latter study not capturing co-morbidities, and not accounting for clustering). In particular, lack of robust data or detailed chemotherapy dosing, adherence and toxicity analysis is a significant limitation, hindering interpretation of the BMI-prognosis relationship.[111,118]

Despite the advantages of utilising trial data for such observational studies, there is growing evidence of sub-optimal chemotherapy dosing in obese patients, the details of which are frequently under-reported, and results are thus not always contextualised. Hence, questions remain regarding the impact this may have on obese patients.

Table 1.7 | BMI-survival relationships within colorectal cancer adjuvant chemotherapy trials

Author, (Year), Country & Cohort	Setting, Site, N=, Follow-up	Regimen	BMI Category (kg/m^2)	OS HR (95%CI)	*P*	DFS HR (95%CI)	*P*	RFS HR (95%CI)	*P*	LRFS HR (95%CI)	*P*
Meyerhardt et al. (2003) US[120] Intergroup INT-0089	ACT Stage II/III Colon N = 3438 9.4 years	4 arms: combinations of 5-FU + low or high dose LV and/or LEV	**Overall[a]**								
			< 21.0	1.15 (0.98, 1.35)				1.06 (0.88, 1.27)			
			21.0 – 24.9	1.00 (Ref)		-		1.00 (Ref)		-	
			25.0–27.49	1.10 (0.95, 1.26)				1.06 (0.88, 1.27)			
			27.5–29.9	1.05 (0.90, 1.24)				1.12 (0.94, 1.33)			
			30.0	1.11 (0.96, 1.29)	*0.20**			1.11 (0.94, 1.30)	*0.17**		
			Female[a]								
			< 21.0	1.08 (0.87, 1.35)				1.01 (0.79, 1.28)			
			21.0 – 24.9	1.00 (Ref)		-		1.00 (Ref)		-	
			25.0–27.49	1.18 (0.94, 1.49)				1.14 (0.89, 1.47)			
			27.5–29.9	1.23 (0.95, 1.60)				1.20 (0.91, 1.60)			
			30.0	**1.34 (1.07, 1.67)**	*0.007**			1.24 (0.98,1.59)	*0.061**		
			Male[a]								
			< 21.0	**1.33 (1.05, 1.67)**				1.22 (0.93, 1.60)			
			21.0 – 24.9	1.00 (Ref)		-		1.00 (Ref)		-	
			25.0–27.49	1.03 (0.87,1.22)				1.00 (0.82, 1.22)			
			27.5–29.9	0.96 (0.78, 1.17)				1.05 (0.85, 1.32)			
			30.0	0.94 (0.77, 1.15)	*0.39**			0.98 (0.79,1.23)	*0.93**		
Meyerhardt et al. (2004), US[116] Intergroup INT – 0014	ACT & radiotherapy Stage II/III Rectal N = 1688 9.9 years	4 arms – various dosing /combinations of RT + 5FU ± LV	**Overall[b]**								
			<20	1.43 (1.08, 1.89)		1.17 (0.91, 1.52)		1.16 (0.85, 1.58)		1.15 (0.65, 2.02)	
			20 – 24.9	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
			25 – 26.9	0.97 (0.80, 1.17)		0.95 (0.79, 1.14)		1.01(0.81, 1.24)		1.33 (0.93, 1.90)	
			27 – 29.9	0.95 (0.78, 1.15)		0.90 (0.76, 1.06)		0.88 (0.71, 1.09)		1.10 (0.76, 1.59)	
			≥30	1.09 (0.90, 1.33)	*0.50*‡	1.10 (0.91, 1.32)	*0.50*‡	1.08 (0.87, 1.33)	*0.80*‡	1.31 (0.91, 1.88)	*0.17*‡
			Female[b]								
			<20	1.29 (0.87, 1.91)				0.84 (0.54, 1.31)		0.99 (0.48, 2.04)	
			20 – 24.9	1.00 (ref)		-		1.00 (Ref)		1.00 (Ref)	
			25 – 26.9	0.75 (0.49, 1.16)				0.79 (0.52, 1.22)		0.91 (0.45, 1.81)	
			27 – 29.9	0.89 (0.61, 1.33)				0.72 (0.48, 1.08)		0.66 (0.33, 1.32)	
			≥30	0.94 (0.66, 1.33)	*0.70*‡			0.89 (0.62, 1.27)	*0.30*‡	1.01 (0.57, 1.81)	*0.80*‡
			Male[b]								
			<20	**1.62 (1.08, 2.43)**				1.53 (0.98, 2.39)		1.32 (0.52, 3.36)	
			20 – 24.9	1.00 (Ref)		-		1.0 (Ref)		1.0 (Ref)	
			25 – 26.9	1.07 (0.86, 1.33)				1.14 (0.89, 1.46)		1.66 (1.07, 2.56)	
			27 – 29.9	0.99 (0.79, 1.25)				0.98 (0.76, 1.27)	*0.20*‡	1.41 (0.89, 2.22)	
			≥30	1.19 (0.94, 1.52)	*0.50*‡			1.23 (0.93, 1.61)		**1.61 (1.00, 2.59)**	*0.06*‡

Table 1.7 | *Continued*

Author, (Year), Country & Cohort	Setting, Site, N=, Follow-up	Regimen	BMI Category (kg/m^2)	OS HR (95%CI)	*P*[#]	DFS HR (95%CI)	*P*[#]	CSS HR (95%CI)	*P*[#]	
Dignam et al. (2006), US[117] NSABP C-04 & C-05	ACT, Dukes B & C Colon N = 4288 11.2 years	**NSABP C-04:** 5FU + LV 5FU + LEV 5FU + LV + LEV **NSABP C-05:** 5FU/LV ± IFN-α	**Overall**[c] <18.5 18.5-24.9 25.0-29.9 30-34.9 ≥35	**1.49 (1.17, 1.91)** 1.00 (Ref) 1.02 (0.91, 1.14) 1.11 (0.96, 1.28) **1.28 (1.04, 1.57)**	 0.003[#]	**1.42(1.14, 1.78)** 1.00 (Ref) 0.96 (0.87,1.06) 1.06 (0.93,1.21) **1.27 (1.05, 1.53)**	 <0.001[#]	1.22 (0.89, 1.67) 1.00 (Ref) 1.12 (0.98, 1.28) 1.08 (0.90, 1.30) **1.36 (1.06,1.73)**	 0.02[#]	-
				OS (HR 95%CI)	***P***	**DFS (HR 95%CI)**	***P***	**RFS (HR 95%CI)**	***P***	
Meyerhardt et al. (2008), US[119] CALBG 89803	ACT Colon stage III N = 1264 5.3 years	5-FU/LV Irinotecan	**Overall**[d] <21 21-24.9 25 – 29.9 30 – 34.9 ≥35	 1.07 (0.61 – 1.87) 1.00 (Ref) 0.72 (0.50 – 1.03) 0.90 (0.61 – 1.34) 0.87 (0.54 – 1.42)	 *0.65*[†]	 1.35 (0.86 – 2.13) 1.00 (Ref) 0.81 (0.59 – 1.11) 1.00 (0.72 – 1.40) 1.24 (0.84 – 1.83)	 *0.63*[†]	 1.22 (0.75 – 1.98) 1.00 (Ref) 0.75 (0.54 – 1.03) 0.97 (0.69 – 1.37) 1.27 (0.85 – 1.89)	 *0.86*[†]	-
Sinicrope et al. (2010), US[118] ACCENT 7 Trials: SWOG 9495; INT-0035; NCCTG 784852, 794604, 874651, 894651, 914653	ACT Colon stage II/III N = 4,381 8.0 years	5-FU based chemotherapy.	**Overall**[e] <20 20 – 24.9 25 – 29.9 30 – 34.9 ≥35	 **1.24 (1.03-1.50)** 1.00 (Ref) 0.90 (0.80-1.00) 1.07 (0.93-1.23) 1.19 (0.98-1.45)	**0.0017**[¶] **0.0258** - 0.0500 0.3717 0.0805	 **NR**[§] 1.00 (Ref)[§] 1.06 (0.88-1.27)[§] 1.12 (0.94 – 1.33)[§] 1.11 (0.94 – 1.30)[§]	**0.0297**[¶] **NR** **NR** **NR** **NR** **NR**	-	-	-
			Women[e] <20 20 – 24.9 25 – 29.9 30 – 34.9 ≥35	NR **1.32 (1.05-1.67)** 1.00 (Ref) 1.01 (0.85-1.19) **1.24 (1.01-1.53)** 1.11 (0.84-1.45)	0.0674[¶] **0.0194** - 0.9366 **0.0447** 0.4651	**NR**		-		-
			Men[e] <20 20 – 24.9 25 – 29.9 30 – 34.9 ≥35	NR 1.14 (0.81-1.61) 1.00 (Ref) **0.82 (0.71-0.95)** 0.94 (0.78-1.15) **1.35 (1.02-1.79)**	**0.0021**[¶] 0.4474 . **0.0063** 0.5599 **0.0391**	**NR**		-		-

Table 1.7 | *Continued*

Author, (Year), Country & Cohort	Setting, Site, N=, Follow-up	Regimen	BMI Category (kg/m^2)	OFS HR (95%CI)	*P*¶	DFS HR (95%CI)	*P*¶	TTR HR (95%CI)	*P*¶	
Sinicrope et al. (2013), US ACCENT 21 RCTs North America and Europe	ACT Colon N = 25, 291 7.8 years	5-FU-based chemotherapy	**Overall**[f]		**<0.0001**		**<0.0001**	TtR	**0.0073**	
			<20	**1.21 (1.11 – 1.32)**	**<0.0001**	**1.10 (1.09 – 1.28)**	**<0.0001**	**1.13 (1.04 – 1.24)**	**0.0044**	
			20 – 24.9	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-	
			25 – 29.9	0.99 (0.94 – 1.04)	0.6074	0.97 (0.92 – 1.02)	0.1912	0.99 (0.94 – 1.04)	0.7258	-
			≥30	**1.10 (1.04 – 1.17)**	**0.0023**	**1.06 (1.00 – 1.13)**	**0.0337**	1.06 (1.00 – 1.13)	0.0707	
			30 – 34.9	**1.10(1.02 – 1.18)**	**0.0084**	1.05 (0.98 – 1.12)	0.1526	1.05 (0.98 – 1.12)	0.1797	
			≥35	**1.11 (1.00 – 1.23)**	**0.0450**	**1.10 (1.01 – 1.21)**	**0.0362**	1.08 (0.98 – 1.20)	0.1194	
			Women[f]		0.1070		0.1070		0.4597	
			<20	**1.12 (1.00 – 1.25)**	**0.0455**	**1.11 (1.01 – 1.23)**	**0.0362**	1.09 (0.98 – 1.21)	0.1255	
			20 – 24.9	1.0 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-	
			25 – 29.9	1.05 (0.97 – 1.14)	0.1970	1.03 (0.96- 1.11)	0.4506	1.04 (0.96 – 1.12)	0.3776	-
			≥30	1.09 (1.00 – 1.20)	0.0553	1.04 (0.96 – 1.13)	0.3268	1.01 (0.93 – 1.11)	0.7637	
			30 – 34.9	1.10 (0.99 – 1.23)	0.0655	1.03 (0.94 – 1.14)	0.5091	1.00 (0.90 – 1.11)	0.9828	
			≥35	1.07 (0.93 – 1.24)	0.3258	1.06 (0.93 – 1.21)	0.3548	1.04 (0.91 – 1.19)	0.5827	
			Men[f]		**<0.0001**		**<0.0001**		**0.007**	
			<20	**1.21 (1.11 – 1.32)**	**<0.0001**	**1.18 (1.09 – 1.28)**	**<0.0001**	**1.13 (1.04 – 1.24)**	**0.0044**	
			20 – 24.9	1.00 (Ref)	-	1.00 (Ref)	-	1.00 (Ref)	-	
			25 – 29.9	0.99 (0.94 – 1.04)	0.6074	0.97 (0.92 – 1.02	0.1912	0.99 (0.94 – 1.04)	0.7258	
			≥30	**1.10 (1.04 – 1.17)**	**0.0023**	**1.06 (1.00 – 1.13)**	**0.0337**	1.06 (1.00 – 1.13)	0.0707	
			30 – 34.9	**1.10 (1.02 – 1.18)**	**0.0084**	1.05 (0.98 – 1.12)	0.1526	1.05 (0.98 – 1.12)	0.1797	
			≥35	**1.11 (1.00 – 1.23)**	**0.0450**	**1.10 (1.01 – 1.21)**	**0.0362**	1.08 (0.98 – 1.20)	0.1194	

Abbreviations: BMI, Body Mass Index; **CI**, Confidence Interval; **CSS**, Cancer-Specific Survival; **DFS,** Disease-Free Survival; **5-FU**, 5-fluorouracil; **HR,** Hazard Ratio; **IFN-α**, Interferon-alpha, **LEV**, Levamisole; **LRFS,** Local-Recurrence-Free Survival; **LV**, Leucovorin; **NR,** Not Reported**; OS,** Overall Survival; **RFS,** Recurrence-Free Survival; **RT**, Radiotherapy,
*P trend for BMI classes greater than reference group with median BMI in each class.
‡ P for trend for median BMI in BMI classes ≥20kg/m^2.
# - Likelihood-ratio test (two-sided) for BMI term(s) for continuous functional form: BMI + BMI^2 for endpoints
† Likelihood ratio test (2 sided) for BMI term for continual functional form of BMI + BMI^2
§ From Parkin et al.,[69] detail not reported in original paper.
¶ Wald X^2 P value

[a] Adjusted for age, gender, race, baseline PS, bowel obstruction/perforation, Dukes' stage, peritoneal implants, predominant macroscopic feature, chemotherapy completion.
[b] Adjusted for age, sex, race, performance status, bowel obstruction, bowel wall invasion, number of positive lymph nodes, operation type.
[c] Adjusted for treatment group, age (continuous), sex, race, performance status, number of positive lymph nodes, bowel obstruction.
[d] Adjusted for sex, age, T & N stages, perforation, bowel obstruction, performance status, treatment arm, weight change, smoking status, physical activity.
[e] Adjusted for age, stage, treatment arm and gender.
[f] Adjusted for age, stage, treatment, gender.

1.7 OBESITY AND ADJUVANT CHEMOTHERAPY

1.7.1 DOSING OF CHEMOTHERAPY

Current dosing practices of chemotherapeutic agents are based on historical animal and human studies, extrapolating doses from the former to the latter over a wide range of weights, in attempt to reduce potential toxicity.[121] Originally advocated by Pinkel,[122] dosing of chemotherapy agents is routinely undertaken according to body surface area (BSA). With a number of proposed equations existing based on an individual's height and weight (**Table 1.8**), but not substantially varying in their products, current guidance does not advocate use of any one particular formula over another. [117] However, BSA does not distinguish well between tall and lean, and obese patients. Other methods for dosing chemotherapy including flat-fixed[121] dosing and dose-banding have been proposed.[123] However, BSA-dosing continues to be the most widely accepted method, advocated by current guidance. [117]

1.7.2 DOSE CAPPING, DOSE REDUCTIONS, ADHERENCE AND TOXICITY

Concerns over toxicity in obese patients have resulted in the practice of dose capping or empiric dose adjustments. For patients with a calculated body surface area (often) greater than 2.2m^2 a number of methods for dose capping may be employed, rather than dosing according to their actual body weight (ABW). Furthermore, in routine clinical practice several potential sources exist for reduction in dose and/or intensity of chemotherapy across cycles:

1. *Treatment selection*: may differ according to BMI, whereby patients are selected out from receiving aggressive/optimum chemotherapy.
2. *Dose capping:* may be considered for patients with a BSA of greater than 2.0 or 2.2m^2. Dosing may be capped at the dose corresponding to a BSA of 2.2m^2, or alternatively calculated using ideal body weight (IBW), lean body mass or adjusted body weight (AdjBW; ideal body weight plus 25% or 40% of obese weight). In addition, dosing based on creatinine clearance (e.g., carboplatin) may be capped at 125mL/min or calculated using the Cockroft-Gault formula with AdjBW40 or IBW.[124]
3. *Empirical dose reduction*: may additionally be considered for patients with significant comorbidities, (e.g., pre-existing hepatic impairment or deranged liver function tests and renal impairment, where those with a creatinine clearance of <50mL/min are often ineligible for clinical trials) increased performance status, age, palliative intent, and type of chemotherapy.[124]
4. *Reduced adherence:* from sequential dose reductions or delays between cycles as a result of toxicities or exacerbation of patient co-morbidities (e.g., ACT-related cholestasis and/or steatohepatitis resulting in new/worsening liver impairment).[125] Adherence may also be a problem with oral chemotherapy agents (potentially unrelated to BMI).[126]
5. *Discontinuation:* may occur as a result of toxicity/intolerance or from patient choice.

Table 1.8 | BSA equations
Modified from Lyman et al.[121]

Name	Equation
Moseteller method	BSA (m^2) = sqrt [(height (cm) * wt (kg)) / 3600]
du Bois:	BSA (m^2) = [(weight)$^{0.425}$ * (height)$^{0.725}$ * 71.84] / 10, 000
DuBois & DuBois	BSA (m^2) = 0.20247 * Ht (m)$^{0.725}$ * Wt (kg)$^{0.425}$
Boyd	BSA (m^2) = 0.0003207 * Ht (cm)$^{0.3}$ * Wt (g)$^{0.7285 - (0.0188 \times \log(Wt))}$
Gehan & George	BSA (m^2) = 0.0235 * Ht (cm)$^{0.42246}$ * Wt (kg)$^{0.51456}$
Haycock	BSA(m^2) = 0.024265 * Ht (cm)$^{0.3964}$ * Wt (kg)$^{0.5378}$

1.7.3 How are dose reductions assessed?

Broadly, there are two measurements of assessing dosing differences in the literature:

1. *Relative dose:* the ratio of dose delivered to the standard dose (the latter based on ABW-derived BSA and the protocol dosing regimen). In general, thresholds of 85%,[127,128] 90%[129] or, more commonly, 95%[116,120,130,131] of the standard dose have been used. This is usually evaluated for the first cycle[116,120,129–131] (though some have assessed subsequent cycles [127,128]), therefore, dose reductions and delays remain unaccounted for.
2. *Relative dose intensity (RDI):* the ratio between delivered dose intensity and standard dose intensity (where dose intensity is the dose/m^2 divided by the duration of delivery, usually in weeks). Here, the examined threshold has commonly been <85%.[127,128,132–136] This is usually calculated for the entire course of chemotherapy and therefore takes into account both dosing and dose delays, reflecting adherence to the regimen.

Adherence to oral anti-neoplastic agents is difficult to quantify beyond dose reductions and omitting doses or delays led by the clinician. The impact of patient-related non-adherence to oral chemotherapy agents is unclear. Reduced adherence to oral chemotherapy agents in clinical studies will potentially confound outcomes and hence may be an important problem. Several methods utilised to assess adherence are limited by bias and methodologic weaknesses. Direct observation, self-reporting (often criticised for subjectivity), pill counts (also potentially unreliable due to patients' ability to alter them), and drug serum or urine levels (wide variations may exist for pharmacokinetic reasons), are just some of the methods employed. Few published studies have focused on adherence to oral chemotherapy, and those that do have often utilised pill counts or self-reporting methods. However, where reported, adherence in clinical trials ranges from less than 20% to 100%.[105] One small UK observational study (43 patients) demonstrated non-compliance in 23% patients taking capecitabine for colorectal and breast cancers in an oncology outpatient clinic setting.[137] A further small study assessing compliance in rectal cancer found discrepancies between self-reported adherence (83.2%) and pill count adherence (66.9%).[126]

Equally, concerns of over-adherence to oral anti-neoplastic agents have also been raised, particularly within the metastatic setting. Here, patients might continue to take oral cytotoxics following toxicity, despite advice to the contrary, take them for extra days beyond planned cycles, take additional doses each day, or skip doses and then "overcompensate" by taking additional subsequent doses.[138] One small study of 40 patients with locally advanced/metastatic breast or colorectal cancer, receiving oral cytotoxic therapy, assessed adherence using a variety of approaches including pill count, metabolite measurements and an electronic medication event monitoring system. The authors found that 17.5% experienced at least one over-adherence event, in addition to 10% displaying consistent over-adherence across cycles. Furthermore, over-adherence was associated with increased serious toxicity risk.[138] However, a

larger study of 242 patients treated with capecitabine and oxaliplatin reported a much smaller over-adherence rate of 1.5%, though adherence was purely self-reported, and may have been under-reported.[139] Such behaviours are difficult to quantify, and rarely acknowledged or described in the literature.[138] Consequently, the overall influence of over-adherence on dosing-outcome relationships is not known.

1.7.4 DOSE CAPPING IS COMMON IN HIGH BMI

There is mounting evidence of potentially sub-optimal dosing in overweight and obese patients with cancer; including those of the colon,[104,116,117,120] rectum,[104,116] breast[129,132,140–142] and ovaries,[133–135] however the implications of this are not fully understood. The practices of dose capping or dose reductions are relatively common (demonstrated in **Tables 1.9a, b,** and **c** for colon, breast, and ovarian cancers respectively), including within ACT clinical trials. In colon and rectal cancer, at least four large studies demonstrate a proportional relationship between rates of first cycle dose reduction or dose capping, and increasing BMI.[104,116,117,120] Furthermore, in both breast[129,132] and ovarian cancer,[134,135] increasing BMI has been found to be predictive of a reduced relative dose or relative dose intensity (RDI).

Table 1.9a | Selected studies reporting BMI-dosing relationships for colorectal cancer

Author (year) country	Cancer Type & Setting	Study name/ type	N	Setting	Chemotherapy regimen	Dose reduction	BMI Category(mg/m^2)	Proportion in receipt of dose reduction (%)	*p*
Chambers et al. (2012), UK [104]	Colorectal cancer	FOCUS FOCUS 2 COIN	2057	Metastatic	FOCUS – 5 arm trial: 5FU ± IR or OX	< 95% standard dose[a]	<25 25 – 29 30+	4% 9% 32%	**<0.001***
			380	Metastatic	FOCUS 2 – 2x2 factorial trial: 5FU or CAP ± OX	< 95% standard dose[a]	<25 25 – 29 30+	12% 21% 60%	**<0.001***
			2344	Metastatic	COIN - 3 arm trial: intermittent vs. continuous 5-FU + Ox ± cetuximab	< 95% standard dose[a]	<25 25 – 29 30+	3% 20% 70%	**<0.001***
			4781	Metastatic	Above three combined.	< 95% standard dose[a]	<25 25 – 29 30+	4% 16% 54%	**<0.001***
Dignam et al. (2006), US[117]	Colon Dukes B & C	NSABP C04 & C05	4288	Adjuvant	**NSABP C-04:** 5FU + LV and/or LEV **NSABP C-05:** 5FU/LV ± IFN-α	Dose capping	<18.5 18.5-24.9 25.0-29.9 30-34.9 >35	NR 7% NR 55% 73%	NR
Meyerhardt et al. (2004), US[116]	Rectum Stage II/III	Intergroup Trial 0014	1688	Adjuvant chemotherapy + radiotherapy	4 arms – various dosing /combinations of RT + 5FU ± LV	<95% standard dose[a]	< 20.0 20.0 – 24.9 25.0–26.9 27.0–29.9 ≥30.0	0.0% 2.0% 1.9% 2.0% 2.3%	0.66†
Meyerhardt et al. (2003), US[120]	Colon Stage II/III	Intergroup Trial 089	3438‡	Adjuvant	LDLV + 5FU HDLV + 5FU LEV + 5FU LEV+ 5FU + LDLV	<95% standard dose[a]	< 21.0 21.0 – 24.9 25.0–27.49 27.5–29.9 ≥30.0	2.9%‡ 2.1%‡ 1.6%‡ 2.9%‡ 4.9%‡	0.18†

Abbreviations:
5-FU, 5-Fluorouracil; **BMI**, Body Mass Index; **CAP**, Capecitabine; **IR**, Irinotecan; **OX**, Oxaliplatin; LEV**,** levamisole; **IFN- α**, Interferon alfa 2a; **LDLV**, Low dose Leucovorin; **HDLV**, high dose Leucovorin; **NR**, Not reported; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated; **RT,** Radiotherapy

[a] Dose at 1st cycle
* Test for trend across BMI groups.
‡ Number of patients in entire study, however, only dose capping proportions for female patients were presented.
† - Chi-squared test.

Table 1.9b | Selected studies reporting BMI-dosing relationships for breast cancer

Author (year) country	Cancer Type & Setting	Study name/ type	N	Setting	Chemotherapy regimen	Dose reduction	BMI Category (kg/m^2)	Proportion in receipt of dose reduction (%)	*P*
Lote et al. (2016) UK[140]	Breast Stage I-III	Tertiary centre Retrospective cohort	325	(Neo-)adjuvant chemotherapy	FEC FEC-T (+GSF) ECaP	Dose capping	<25 ≥25- <30 ≥30	0 0 4.9%	NR
Carroll et al. (2014) Australia[132]	Breast Stage I-III	Two tertiary hospitals	374	Adjuvant	Mainly FEC-T or ACTH, Others including TC or TCH	Dose capping	<30 ≥30	0% 15.8%	**<0.001**
								OR (95%CI)	***P***
						ARDI <85%	< 30 ≥ 30	1.00 (Ref) 1.08 (0.56, 2.06)	
Colleoni et al. (2005) International[141]	Pre-menopausal Node positive Breast cancer	International Breast Cancer Study Group (4 Trials)	2140	Adjuvant	CMF	<85% standard dose[a]	<30 ≥30	16% 39%	**<0.0001**
								Proportion (%) OR (95%CI)*	***P****
Griggs et al. (2005) US[129]	Breast Stage I-III	Retrospective cohort Multi-centre	9672	Adjuvant	Doxorubicin + cyclophosphamide	<90% standard dose[a] (averaged for the two drugs)	<25 25.0-29.9 30-34.9 ≥35	9% - 1 (Ref) **11% - 1.21 (1.02, 2.42)** **20% - 2.34 (1.92, 2.85)** **37% - 5.97 (4.90, 7.27)**	**0.03** **<0.001** **<0.001**
								Change in RDI proportion	***P*** †
						RDI	18.5-25 25.0-29.9 30-34.9 ≥35	1.00 (Ref) **0.017** **-0.034** **-0.071**	 **<0.001** **<0.001** **<0.001**
								Proportion (%)	***P***
Rosner et al. (1996) US[142]	Breast cancer Stage II	CALGB 8541	1435	Adjuvant	CAF 300/30/3000	<95% standard dose[a]	<27.3 ≥27.3	5.1% 24.7%	**<0.001**
					CAF 400/40/400	<95% standard dose[a]	<27.3 ≥27.3	4.7% 24.4%	**<0.001**
					CAF 600/60/6000	<95% standard dose[a]	<27.3 ≥27.3	7.0% 35.7%	**<0.001**

Abbreviations:
5-FU, 5-Fluorouracil; **ACTH**, Doxorubicin + cyclophosphamide then docetaxel + trastuzumab; **BMI**, Body Mass Index **CAF**, Cyclophosphamide, Doxorubicin, fluorouracil; **CMF**, cyclophosphamide, methotrexate and 5-FU; **ECaP**, Epirubicin, cyclophosphamide then paclitaxel; **FEC**, Fluorouracil + Cyclophosphamide; **FEC-T**, Fluorouracil + cyclophosphamide + docetaxel; IR, Irinotecan; **OR**, Odds ratio; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated); **TC**, Docetaxel + cyclophosphamide, **TCH**, Docetaxel and carboplatin

[a] Dose at 1st cycle
* Logistic regression
† Multivariate logistic regression: age, chemotherapy regimen, RDI, smoking status, co-morbidity score, GCSF, stage, dose capping.

Table 1.9c | Selected studies reporting BMI-dosing relationships for ovarian cancer

Author (year) country	Cancer Type & Setting	Study name/ type	N	Setting	Chemotherapy regimen	Dose reduction	BMI Category(mg/m^2)	Proportion in receipt of dose reduction (%) / OR (95%CI)	*p*
								OR (95%CI)	***P***
Bandera et al. (2015) US[135]	Epithelial Ovarian Cancer FIGO I-IV	KP-ROCS	806	Adjuvant	Carboplatin + Paclitaxel	ARDI <85%	<18.50 18.5-24.9 25-29.9 30-34.9 35-39.9 ≥40	1.08 (0.38, 3.04) 1.00 (Ref) **1.60 (1.09, 2.35)** **2.85 (1.79, 4.55)** **5.65 (3.01, 10.62)** **19.85 (7.21, 54.65)**	-
Au-Yeung et al. (2014) Australia[133]	Serous Ovarian Cancer FIGO Stage III/IV	AOCS Prospective population-based	333	Stage III/IV	Carboplatin-based chemotherapy	RDI <85%	**Carboplatin** <25 25 – 29.9 >30 **Paclitaxel** <25 25 – 29.9 >30 **Combined** Obese vs. non-obese	 39% 39% 67% 50% 54% 48% NR	 **<0.001** 0.76 **0.002**
						Dose delay > 1 week	<25 25 – 29.9 >30	30% 26% 29%	0.74
								OR (95%CI) *	***P* ***
Hanna et al. (2013) US[134]	Epithelial ovarian cancer FIGO Stage III/IV	Retrospective Multi-centre	325	Stage III/IV	Combination of: Carboplatin + Paclitaxel and/or doxorubicin, gemcitabine, topotecan, Docetaxel, OX	Planned RDI < 85%[a]	BSA > 2m^2	6.14 (2.32, 16.20)	**<0.001**
						Delivered RDI <85%[a]	BMI >30 vs. <30	2.35 (1.25, 4.41)	**0.008**

Abbreviations:
ARDI, Average Relative Dose Intensity across all drugs in regimen; **BMI**, Body Mass Index, **NR**, Not reported; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated); **OR**, Odds ratio; **TC**, Docetaxel + cyclophosphamide, **TCH**, Docetaxel and carboplatin

[a] RDI across 4 cycles of chemotherapy only.
* - Multivariate logistic regression

1.7.5 DO DOSE REDUCTIONS AFFECT OUTCOME?

Chemotherapy drug concentrations and dose intensity, particularly in the setting of chemo-sensitive malignancies (e.g., lymphoma and leukaemia) have historically been demonstrated to directly correlate with efficacy and toxicity, with steep dose-response relationships.[143,144] Furthermore, in animal models, a reduction of dosing results in reduced complete remission and cure rates. [121]

The most convincing evidence for maintenance of chemotherapy dose intensity as a prognostic factor comes from randomised controlled trials in the adjuvant breast cancer setting, whereby higher dosing has been demonstrated to result in improved OS.[145,146] Other malignancies, such as haematological[147] and germ cell tumours[148] have additionally demonstrated a prognostic benefit from higher dose intensity. Furthermore, dose-dense chemotherapy regimens (involving reduction of dosing intervals) have been associated with improved survival compared with standard dosing.[149–151] Finally, a systematic review and meta-analysis demonstrated primary use of granulocyte colony stimulating factor (G-CSF), to maintain either a higher chemotherapy dose intensity or dose density compared to standard chemotherapy, was associated with increased overall survival for solid and haematological malignancies (namely breast, lymphoma and lung cancer). However, this was in addition to an increased risk of developing secondary malignancies (including haematological).[152]

The evidence for prognostic outcomes in relation to dose reductions and BMI in colorectal, breast and ovarian cancers are summarised in **Tables 1.10 a, b,** and **c**. For colorectal cancer, several studies have demonstrated (in both metastatic and adjuvant settings) evidence for a possible relationship between reduced first cycle relative dose or RDI and adverse prognostic outcomes. [104,131,153,154] In a pooled analysis from Chambers et al., including 4781 patients with metastatic colorectal cancer, obese patients in receipt of full dosing (compared with <95% of the standard ABW-based BSA first cycle dose) resulted in improved progression free survival. This study was limited, however, by "lumping" together of data without performing an individual participant data (IPD) meta-analysis retaining trial clustering. [104] Conversely, in a large study of NSABP C04 and C05 trials including 4288 patients, by Dignam et al.,[117] addition of dose capping as an indicator variable in Cox proportional hazards model did not change the overall association of BMI and increased risk of overall mortality. Additionally, no significant association was demonstrated between the dose-capping indicator and colon-cancer related mortality or recurrence. However, dose-capping as a dichotomous variable may not have been sensitive enough to assess the impact of dose reduction despite the large proportions of dose capping (73% in BMI ≥35kg/m^2 group), and detailed dosing analyses were not undertaken to explore this relationship further, particularly in the context of overall adherence. Finally, two large studies by Meyerhardt et al., one in the rectal cancer setting [116] and the other in the colon cancer setting[120] also failed to demonstrate a significant association of first cycle relative dose reduction with

overall and disease-free survival (DFS). However, numbers of patients under-dosed are likely to have resulted in underpowered results (only 2.3% and 4.9% of the obese groups in each study respectively).

Studies of breast[141,142] and ovarian cancer[133–135] have more consistently investigated the effects of relative dose intensity as opposed to first cycle relative dose. In general, results suggest a survival advantage for patients receiving an RDI ≥70-85%, though mostly non-statistically significant. However, the majority of studies are small and thus likely underpowered, in addition to mainly being a mixture of retrospective observational cohorts and secondary trial analyses. Finally, worth considering is the study by Bonadonna et al. reporting 20-year follow-up from a randomised controlled trial of no treatment vs. chemotherapy in node positive breast cancer after radical mastectomy. The Kaplan Meier survival curve for those receiving <85% cumulative dose was similar to the control, in comparison to those optimally dosed, suggesting that the survival advantage from chemotherapy is lost as a result of sub-optimal dosing, however no statistical comparative analysis (e.g., log-rank test) was presented.[130]

Table 1.10a | Selected studies reporting survival outcomes in relation to chemotherapy dosing in colorectal cancer

Author (year) country	Cancer Type	Cohort	N	Treatment type	Chemotherapy regimen	Mean/ Median Follow-up	Dose-Reduction measurement ± BMI Categories	OUTCOME			
								OS HR (95%CI)	***P*[§]**	**RFS HR (95%CI)**	***P*[§]**
Stocker et al. (2018), Germany[131]	Colon cancer Stage III	PETACC 3 Trial	280	Adjuvant	Irinotecan & 5FU	66.3 months	BMI ≥30 FD BMI ≥30 RD[a] BMI ≥30 +BSA ≥2 FD BMI ≥30 +BSA ≥2 RD	0.71 (0.42, 1.18) 1.00 (Ref) 0.53 (0.28, 1.01) 1.00 (Ref)	0.19 0.092	0.69 (0.43, 1.09) 1.00 (Ref) 0.48 (0.27, 0.85) 1.00 (Ref)	0.11 **0.018**
								2-year OS % [HR (95%CI)]	***P***	**1-year PFS % [HR (95%CI)]**	***P***
Chambers et al. (2012) UK [104]	Colorectal cancer	FOCUS FOCUS 2 COIN	2057	Metastatic	FOCUS – 5 arm trial: 5FU ± IR or Ox	NR	BMI ≥30 FD BMI ≥30 RD[a]	38.0 [1.00 (Ref)] 29.6 [1.02 (0.79, 1.32)]	0.19	-	-
			380	Metastatic	FOCUS 2 – 2x2 factorial trial: 5FU or Cap ± Ox	NR	BMI ≥30 FD BMI ≥30 RD[a]	20.0 [1.00 (Ref)] 14.4 [1.18 (0.70, 2.00)]	0.53	-	-
			2344	Metastatic	COIN - 3 arm trial: intermittent vs. continuous 5-FU + Ox (or OxCAP) ± cetuximab	NR	BMI ≥30 FD BMI ≥30 RD[a]	32.3% [1.00 (Ref)] 31.4% [1.01 (0.80,1.28)]	0.90	-	-
			4781	Metastatic	Above three combined.	NR	BMI ≥30 FD BMI ≥30 RD[a]	35% [1.00 (Ref)] 29.5% [1.12 (0.96, 1.30)]	0.152	21.2% [1.00 (Ref)] 14.8% [1.21 (1.06, 1.39)]	**0.006**
Dignam et al. (2006), US[117]	Colon Dukes B & C	NSABP C04 & C05	4288	Adjuvant	**NSABP C-04:** 5FU + LV 5FU + LEV 5FU + LV + LEV **NSABP C-05:** 5FU/LV ± IFN-α	11.2 years	Dose capping as an indicator variable in Cox Proportional Hazards model	No change in association between BMI and OS (BMI remained associated with increased risk of overall mortality in the very obese group)			
								5-year OS %, [HR (95%CI)]	***P***	**3-year DFS%, [HR (95%CI)]**	***P***
Aspinall et al. (2005) US[153]	Colon	Retrospective cohort	367	Adjuvant Stage III	5FU + LV ± Ox Cap ± Ox	NR	RDI >70%[b] RDI ≤70%	66.3% [1.00 (Ref)] 50.5% [NA[c]]	**<0.001***	66.1% [1.00 (Referent)] 52.7% [0.75 (0.50, 1.11]	**0.009***
Meyerhardt et al. (2004), US[116]	Rectum Stage II/III	Intergroup Trial 0014	1688	Adjuvant chemotherapy + radiotherapy	4 arms – various dosing /combinations of RT + 5FU ± LV	9.9 years	<95% dose reduction in proportional hazards models	No change in association between obesity and overall survival after adjustment for dose-reduction. Furthermore, numbers of patients under-dosed are too small to stratify analysis.			

Table 1.10a | *Continued*

Author (year) country	Cancer Type	Cohort	N	Treatment type	Chemotherapy regimen	Mean/ Median Follow-up	Dose-Reduction measurement ± BMI Categories	OUTCOME
Meyerhardt et al. (2003) US[120]	Colon Stage II/III	Intergroup Trial 089	3438	Adjuvant	LDLV + 5FU HDLV + 5FU LEV + 5FU LEV+ 5FU + LDLV	9.4 years	<95% standard dose in multivariate model	Not predictive of overall or recurrence-free survival (HR, 95%CI and P values not reported).

Abbreviations:
5-FU, 5-Fluorouracil; **BMI**, Body Mass Index; **CAP**, Capecitabine; **DFS**, Disease Free Survival; **FD,** Full Dose; **IR**, Irinotecan; **HDLV**, high dose Leucovorin; **IFN-** α, Interferon alfa 2a; **LDLV**, Low dose Leucovorin; **NR**, Not reported; **LEV,** levamisole; **OS**, Overall Survival; **OX**, Oxaliplatin; **PFS**, Progression-Free Survival; **RD**, Reduced dose; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated; **RFS**, Recurrence-Free-Survival

[a] Dose at 1st cycle <95% standard.
[b] Calculated as the proportion of the standard regimen dose intensity for each drug averaged across each drug used within a given regimen, irrespective of BMI.
[c] Proportional Hazards assumption violated for RDI in OS model.
* - Log rank tests for Kaplan-Meier survival curves
§ - Cox proportional hazards multivariate analysis

Table 1.10b | Selected studies reporting survival outcomes in relation to chemotherapy dosing in breast cancer

Author (year) country (ref)	Cancer Type	Cohort	N	Treatment type	Chemotherapy regimen	Mean/ Median Follow-up	Dose-Reduction measurement ± BMI Categories	OUTCOME			
								DFS HR (95%CI)	*P*	OS HR (95%CI)	*P*
Colleoni et al. (2005) International[141]	Pre-menopausal Node positive Breast cancer	International Breast Cancer Study Group (4 Trials)	739	Adjuvant	CMF	22 years 22 years 18 years 12 years	**ER-negative** **BMI<25** RDI≥85% RDI<85% **BMI 25 – 29.9** RDI ≥85% RDI <85% **BMI ≥30** RDI ≥85% RDI <85%	0.75 (0.54, 1.05) 1.00 (Ref) 0.67 (0.43, 1.03) 1.00 (Ref) **0.55 (0.33, 0.93)** 1.00 (Ref)	0.0966 0.0676 **0.0261**	0.84 (0.57, 1.24) 1.00 (Ref) 0.75 (0.46, 1.22) 1.00 (Ref) **0.50 (0.28, 0.88)** 1.00 (Ref)	0.3702 0.2440 **0.0158**
			1401				**ER-positive** **BMI<25** RDI≥85% RDI<85% **BMI 25 – 29.9** RDI ≥85% RDI <85% **BMI ≥30** RDI ≥85% RDI <85%	1.21 (0.94, 1.55) 1.00 (Ref) 1.04 (0.73, 1.49) 1.00 (Ref) 1.20 (0.80, 1.81) 1.00 (Ref)	0.1318 0.8360 0.3687	1.22 (0.91, 1.62) 1.00 (Ref) 0.99 (0.65, 1.49) 1.00 (Ref) 1.26 (0.78, 2.06) 1.00 (Ref)	0.1880 0.9418 0.3492
								Failures (death / relapse) HR (95%CI)			
Rosner et al. (1996) US[142]	Breast cancer Stage II	CALGB 8541	1435	Adjuvant	CAF 300/30/3000	-	**BMI ≥30** RDI ≥95 vs. <95% dose[a]	**0.54 (0.31, 0.96)**	NR	-	-
					CAF 400/40/400	-	**BMI ≥30** RDI ≥95 vs. <95% dose[a]	0.91 (0.51, 1.61)	NR	-	-
					CAF 600/60/6000	-	**BMI ≥30** RDI ≥95 vs. <95% dose[a]	0.67 (0.38, 1.20)	NR	-	-

Abbreviations:
5-FU, 5-Fluorouracil; **BMI**, Body Mass Index; **CAF**, Cyclophosphamide, Doxorubicin, fluorouracil; **CMF**, cyclophosphamide, methotrexate and 5-FU; **DFS**, Disease Free Survival; **ER**, Oestrogen Receptor; **NR**, not reported; **OS**, Overall Survival; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated);

[a] Dose at 1st cycle <95% standard.

Table 1.10c | Selected studies reporting survival outcomes in relation to chemotherapy dosing in ovarian cancer

Author (year) Country	Cancer Type	Cohort	N	Treatment type	Chemotherapy regimen	Mean/ Median Follow-up	Dose-Reduction measurement ± BMI Categories	OUTCOME			
								OS HR (95%CI)	***P***	**CSS HR (95%CI)**	***P***
Bandera et al. (2015) US [135]	Epithelial Ovarian Cancer FIGO I-IV	KP-ROCS	806	Adjuvant	Carboplatin + Paclitaxel	52.5 months	**Normal**				
							RDI ≥85%	1 (Ref)		1 (Ref)*	
							RDI <85%	1.50 (1.02, 2.21)		**1.62 (1.07, 2.45)**	
							Overweight				
							RDI ≥85%	0.98 (0.69, 1.39)	0.36*	1.02 (0.70, 1.50)	0.37*
							RDI <85%	1.10 (0.75, 1.61)		1.18 (0.79, 1.78)	
							Obese				
							RDI ≥85%	0.79 (0.51, 1.21)		0.73 (0.45, 1/17)	
							RDI <85%	0.93 (0.65, 1.33)		0.95 (0.64, 1.40)	
							Overall				
							RDI >100%	0.84 (0.57, 1.25)		0.78 (0.51, 1.20)	
							RDI 100 – 85%	1.00 (Ref)	**0.05**†	1.00 (Ref)	**0.03**†
							RDI <85-70%	1.16 (0.88, 1.52)		1.21 (0.90, 1.62)	
							RDI<70%	**1.62 (1.10, 2.37)**		**1.69 (1.12, 2.55)**	
								Median PFS (months); [HR (95%CI)]	***P***	**Median OS (months) [HR (95%CI)]**	***P***
Au-Yeung et al. (2014) Australia[133]	Serous Ovarian Cancer FIGO Stage III/IV	AOCS Retrospective population-based	333	FIGO Stage III/IV	Carboplatin-based chemotherapy	NR	**Carboplatin**				
							RDI <85%	11 [1.29 (1.02, 1.63)]	**0.004‡**	40 [1.17 (0.90, 1.51)]	0.25‡
							RDI >85%	15 [1.00 (Ref)]		46; 1.00 (Ref)	
							Paclitaxel				
							RDI <85%	14 [1.02 (0.80, 1.30)]	0.87‡	40 [1.16 (0.89, 1.52)]	0.28‡
							RDI >85%	14 [1.00 (Ref)]		46 [1.00 (Ref)]	
							Combined				
							RDI <85%	12 [1.15 (0.90, 1.46)]	0.28‡	39 [1.18 (0.90, 1.54)]	0.24‡
							RDI >85%	15 [1.00 (Ref)]		47 [1.00 (Ref)]	
								PFS HR (95%CI)	***P***	**OS HR (95%CI)**	***P***
Hanna et al. (2013) US[134]	Epithelial ovarian cancer FIGO Stage III/IV	Retrospective Multi-centre	325	FIGO Stage III/IV	Combination of: Carboplatin + Paclitaxel and/or doxorubicin, gemcitabine, topotecan, Docetaxel, OX	34 months	Delivered RDI <85%	1.15 (0.64, 2.06)	0.650§	**1.71 (1.19-2.45)**	**0.003**§

Abbreviations:
BMI, Body Mass Index; **CSS**, Cancer-Specific Survival; **DFS**, Disease Free Survival; **NR**, Not reported; **OS**, Overall Survival; **OX**, Oxaliplatin; **PFS**, Progression-Free Survival; **RD**, Reduced dose; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated;

* P interaction; Multivariable Cox models adjusted for age, race, BMI, stage, grade, histologic type, toxicity, GCSF use, diabetes mellitus, hypertension, cardiovascular disease, renal disease, post-treatment Ca125
† P for trend; Cox proportional hazards adjusted for age, race, BMI, stage, grade, histologic type, toxicity, GCSF use, diabetes mellitus, hypertension, cardiovascular disease, renal disease, post-treatment Ca125
‡ - Unadjusted Cox models. After adjustment, there was no longer a significant difference for PFS in the carboplatin subgroup (p = 0.06). Adjusted models not presented.
§ - Multivariable Cox proportional hazards Adjusted for stage, race, elevated Ca125, age, suboptimal debulking, histology

1.7.6 Is there pharmacokinetic evidence to justify dose reductions?

Drug clearance (hepatic and renal) is an important consideration in chemotherapy dosing regimens. It is thought that obesity may alter drug metabolism through alterations in hepatic blood flow as a result of hepatic steatosis, furthermore effects of obesity on renal drug clearance are unknown. Three hypothesised observations have been described by Han et al.:

> "Observation 1: Absolute clearance is greater in obese individuals.
> Observation 2: Clearance increases non-linearly with total body weight.
> Observation 3: Clearance correlates linearly with lean body weight."[155]

However, according to current guidelines, there is a general lack of evidence for the influence of pharmacokinetics in obese patients, and in particular from randomised studies, to justify dose reduction.[117]

Saif et al. undertook a comprehensive review of optimising chemotherapy dosing from a pharmacokinetics perspective in the context of 5-FU (which forms the basis of chemotherapy treatment in colorectal cancer). They evidence the significant pharmacokinetic variability that occurs from BSA-based dosing of 5-FU (where up to 60% of patients may be under-dosed), and the significant improvements that can be made to dosing through pharmacokinetically-guided dose adjustments, (using dose-adjustment algorithms), demonstrated to reduce toxicity and improve outcomes. Until recently, 5-FU serum testing has been limited by expense, time, and complexity. New advances in this field, however, may make this an attractive option for optimising dosing in clinical practice.[156]

1.7.7 Is toxicity increased in obese patients?

The major driving influence of dose reductions is the concern of chemotherapy-related toxicity. Thus, the question remains, are obese patients truly at an increased risk of toxicity, and is the practice of dose capping therefore substantiated? In fact, there is mounting evidence to the contrary, whereby increasing BMI is associated with similar or reducing levels of toxicity amongst obese patients who are fully dosed, in comparison to patients with normal BMI. [104,131] **Tables 1.11 a**, **b**, and **c** summarise the evidence for the occurrence of toxicity according to BMI category. Notably, the majority of evidence comes from small observational studies, although some secondary analyses of large, randomised trials also concur. In non-small-cell lung cancer[157] and epithelial ovarian cancer,[134] there is some data to suggest that those who experience chemotherapy-related myelosuppressive toxicity have improved outcomes, implying that toxicity might be a surrogate of more optimal dosing.[121,157]

Table 1.11a | Selected studies reporting BMI-toxicity relationships in colorectal cancer

Author (year) country	Cancer Type	Study name/ type	N	Adjuvant/ Neoadjuvant/ Palliative	Chemotherapy regimen	Dose reduction	BMI Category (mg/m^2)	Proportion grade 3 or 4 toxicity (%)		*p*
								Fully Dosed	Dose reduced	
Stocker et al. (2018) Germany[131]	Colon cancer Stage III	Secondary analysis of trial data	280	Adjuvant	Irinotecan & 5FU	<95% standard dose[a]	BMI ≥30	No difference in grade 3 and 4 toxicities except neutropenia, which was increased in patients receiving full dose (15.7% vs. 6.7%)		NR
Chambers et al. (2012) UK[104]	Colorectal cancer	FOCUS FOCUS 2 COIN	2057	Metastatic	FOCUS – 5 arm trial: 5FU ± IR or Ox	< 95% standard dose[a]	<25 25 – 29 30+	17% 17% 15% *p 0.11**	11% 19% 15%	0.94
			380	Metastatic	FOCUS 2 – 2x2 factorial trial: 5FU or Cap ± Ox	< 95% standard dose[a]	<25 25 – 29 30+	12% 9% 4% *p 0.22**	10) 18 13	0.15
			2344	Metastatic	COIN - 3 arm trial: intermittent vs. continuous 5-FU + Ox (or OxCAP) ± CET	< 95% standard dose[a]	<25 25 – 29 30+	257 (27%) 176 (25%) 30 (22%) *p 0.16**	5 (17%) 45 (25%) 51 (16%)	0.15
			4781	Metastatic	Above three combined.	< 95% standard dose[a]	<25 25 – 29 30+	441 (21%) 295 (20%) 67 (17%) ***p 0.035****	11 (13%) 62 (23%) 73 (16%)	0.71
Simkens et al. (2011) Neterlands[115]	Colorectal cancer	CAIRO	820	Metastatic colorectal cancer	Sequential vs. combined CAP, IR, OX	NA	<18.50 18.50-24.9 25-29.9 ≥30	29% 52% 53% 52%		0.363
						Dose capping	NA – Sequential arm NA – Combination arm	30% 66%	25% 60%	0.708 0.793
		CAIRO 2	755	Metastatic colorectal cancer	CAP + OX + BEV ± CET	NA	<18.50 18.50-24.9 25-29.9 ≥30	83% 80% 79% 78%		0.924
Dignam et al. (2006) US[117]	Colon Dukes B&C	NSABP C04 & C05	4288	Adjuvant	**NSABP C-04:** 5FU + LV 5FU + LEV 5FU + LV + LEV **NSABP C-05:** 5FU/LV ± IFN-α	NA	<18.5 18.5-24.9 25.0-29.9 30-34.9 >35	45.0 50.0 49.1 49.3 36.6		0.90‡
Meyerhardt et al. (2004) US[116]	Rectum Stage II/III	INT - 0014	1688	Adjuvant chemotherapy + radiotherapy	4 arms – various dosing /combinations of RT + 5FU ± LV	NA	< 20.0 20.0 – 24.9 25.0–26.9 27.0–29.9 ≥30.0	81.7 75.7 78.9 71.7 70.0		**0.05***

Table 1.11a | *Continued*

Author (year) country	Cancer Type	Study name/ type	N	Adjuvant/ Neoadjuvant/ Palliative	Chemotherapy regimen	Dose reduction	BMI Category (mg/m^2)	Proportion grade 3 or 4 toxicity (%)	P
Meyerhardt et al. (2003) US [120]	Colon	INT-0089	3438	Adjuvant Stage II/III Colon	LDLV + 5FU HDLV + 5FU LEV + 5FU LEV+ 5FU + LDLV	NA[†]	< 21.0 21.0 – 24.9 25.0–27.49 27.5–29.9 30.0	53.4 53.2 51.3 51.8 45.8	**0.020***

Abbreviations:
5-FU, 5-Fluorouracil; **BMI**, Body Mass Index; **CAP**, Capecitabine; **CET,** Cetuximab; **IR**, Irinotecan; **OX**, Oxaliplatin; LEV**,** levamisole; **IFN-** α, Interferon alfa 2a;); **LDLV**, Low dose Leucovorin; **HDLV**, high dose Leucovorin; **NA,** Not applicable; **NR**, Not reported; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated;

[a]Dose at 1st cycle

* - Test for trend across BMI groups excluding underweight group.
† - No significant change in toxicity rates according to BMI when analyses limited to ≥95% of standard dose based on actual body weight.
‡ - Chi squared test

Table 1.11b | Selected studies reporting BMI-toxicity relationships in breast cancer

Author (year), country	Cancer Type	Study name/ type	N	Adjuvant/ Neoadjuvant/ Palliative	Chemotherapy regimen	Dose reduction	BMI Category(mg/m^2)	Proportion grade 3 or 4 toxicity (%)		*p*
								Fully Dosed	**Dose reduced**	
Lote et al. (2016) UK[140]	Breast Stage I-III	Tertiary centre Retrospective cohort	325	(Neo-)adjuvant chemotherapy	FEC FEC-T (+GSF) ECaP	Dose capping	**Full Dose** <25 25-29.9 ≥30	17.5% 20.0% 20.5%	-	0.8467†`
									OR (95%CI)	***P***
Carroll et al. (2014) Australia[132]	Breast cancer ≤Stage III	Two tertiary hospitals	374	Adjuvant	Mainly FEC-T or ACTH, Others including TC or TCH	No significant difference in ARDI <85%	**Febrile Neutropenia** BMI <30 BMI ≥30	1.00 (Ref) 0.63 (0.30-1.29)		NR
									Proportion grade 3 or 4 toxicity (%)	***P***
Jenkins et al. (2007) UK[136]	Breast	Retrospective	662	(Neo)-adjuvant	5-FU + Epirubicin + cyclophosphamide	Mean RDI higher in overweight p=0.03	**Febrile Neutropenia** BMI <25 BMI ≥25	6% 11%		**0.02**
Colleoni et al. (2005) International[141]	Pre-menopausal Node positive	International Breast Cancer Study Group	2140 (4 Trials)	Adjuvant	CMF	<85% standard dose[a]	BMI≥30	14%	12%	0.62
									Hospitalisation – feb neutropenia OR (95%CI)*	***P****
Griggs et al. (2005) US[129]	Breast Stage I, II, III	Retrospective cohort Multi-centre	8022	Adjuvant	Doxorubicin + cyclophosphamide	No first cycle dose reduction	<18.5 + 18.5-24.9 25.0-29.9 30-34.9 ≥35	1 (Ref) 0.91 (0.71 – 1.16) 0.83 (0.61 – 1.13) 0.61 (0.38 – 0.97)		- >0.05 >0.05 **0.04**
									Proportion grade ≥3 toxicity cycle 1	***P***
Rosner et al. (1996), US[142]	Breast cancer Stage II	CALGB 8541	1435	Adjuvant	CAF 300/30/3000	<95% standard dose[a]	**Haematologic** BMI <27.3vs. ≥27.3 **Non-haematologic** BMI <27.3vs. ≥27.3	1% vs. 2% 23% vs. 23%	- -	0.40 1.00
					CAF 400/40/400	<95% standard dose[a]	**Haematologic** BMI <27.3vs. ≥27.3 **Non-haematologic** BMI <27.3vs. ≥27.3	5% vs. 4% 39% vs. 39%	- -	0.81 1.00
					CAF 600/60/6000	<95% standard dose[a]	**Haematologic** BMI <27.3vs. ≥27.3 **Non-haematologic** BMI <27.3vs. ≥27.3	51% vs. 47% 59% vs. 57%	- -	0.51 0.82

Abbreviations: 5-FU, 5-Fluorouracil; **ACTH**, Doxorubicin + cyclophosphamide then docetaxel + trastuzumab; **BMI**, Body Mass Index **CAF**, Cyclophosphamide, Doxorubicin, fluorouracil; **CMF**, cyclophosphamide, methotrexate and 5-FU; **ECaP**, Epirubicin, cyclophosphamide then paclitaxel; **FEC**, Fluorouracil + Cyclophosphamide; **FEC-T**, Fluorouracil + cyclophosphamide + docetaxel; **NR**, Not reported; **RDI**, relative dose intensity (calculated across all cycles unless otherwise stated); **TC**, Docetaxel + cyclophosphamide, **TCH**, Docetaxel and carboplatin.

[a] Dose at 1st cycle

†- ANOVA with Bartlett's test for three-way comparisons.

* - Logistic regression

Table 1.11c | Selected studies reporting BMI-toxicity relationships in ovarian cancer

Author (year), country	Cancer Type	Study name/ type	N	Adjuvant/ Neoadjuvant/ Palliative	Chemotherapy regimen	Dose reduction	BMI Category(mg/m^2)	Proportion grade 3 or 4 toxicity (%)
Bandera (2015) US [135]	Epithelial Ovarian Cancer FIGO I-IV	KP-ROCS	806	Adjuvant	Carboplatin + Paclitaxel	ARDI <85%	NA	Toxicity was more common among lower RDI for all BMI categories (data not shown). Likely reverse causality, i.e., toxicity resulting in dose reduction.

ACTH Doxorubicin + cyclophosphamide then docetaxel + trastuzumab; **ARDI,** Average Relative Dose Reduction for both drugs in regimen (across all cycles unless otherwise stated); **BMI**, Body Mass Index; **FEC-T**, 5-FU + Epirubicin + cyclophosphamide; **TC** – Docetaxel + cyclophosphamide, **TCH,** Docetaxel + carboplatin + trastuzumab.

In answer to the above question, and in attempt to improve and standardise care for obese patients receiving chemotherapy, ASCO have previously undertaken a comprehensive evaluation of the implications of full or reduced dosing in obese patients on toxicity and outcomes. They concluded:

"There is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight-based chemotherapy doses." [117]

Thus, the key dosing recommendations were as follows: [117]

1. Full weight-based chemotherapy doses should be used in obese patients, especially where cure is the primary aim.
2. Toxicities should be managed in the same way regardless of BMI.
3. Consideration of resuming full weight-based-dosing should be made in subsequent treatment cycles following a toxicity-related dose reduction (particularly where possible contributory factors have resolved).
4. Evidence does not support increased dose reductions in obese vs. non-obese patients.
5. Fixed dosing of chemotherapy is only justified for a select few agents.

The main limitation of this guidance is the lack of randomised trials available exploring ABW-based and capped dosing in obese patients, on which to base recommendations. [117] However, a number of issues are likely to preclude future RCTs, as discussed by Lyman and Sparreboom[121]: firstly, a likely requirement of large sample sizes to provide sufficient power for effect estimates with small reductions in dose intensity, and secondly ethical approval in the context of current guidance advocating the opposite is questionable.

1.7.8 LIMITATIONS TO THE EVIDENCE

In general, there are a number of limitations to the current evidence base regarding potential suboptimal dosing and consequent prognostic outcomes in patients with colorectal cancer (in addition to breast and ovarian cancers). There is a lack of standardised reporting of dosing both in relation to occurrence of sub-optimal dosing compared with standard, and to assessment of this effect on outcome. This is particularly seen within the RCT setting.[158] Furthermore, reporting of toxicity in relation to chemotherapy dosing is variable, making the rates of toxicity according to BMI difficult to compare. In the colorectal cancer setting, where several studies have not accounted for dose-capping in their toxicity rates, it is unclear whether equivalent/improved toxicity is the result of a capped or reduced first doses. Finally, the majority of current studies are subject to the same methodological issues already discussed above, that is they remain plagued with bias and confounding.

1.8 COLORECTAL CANCER OUTCOMES: ADDITIONAL CONSIDERATIONS

Surgical resection remains the mainstay of treatment for non-metastatic colorectal cancer. However, continued improvements in outcomes are likely to come through various routes, including better understanding of patient factors (such as obesity) that might modify prognosis, and optimisation of chemotherapy.

There is strong evidence for the benefit of adjuvant chemotherapy in stage III colon cancer, which has become standard practice. Risks of recurrence and death are reduced by up to 30% with fluoropyrimidine-based chemotherapy (5-fluorouracil (5FU) or capecitabine),[159–161] and further improvements have been convincingly demonstrated for disease free survival with the addition of oxaliplatin in colon cancer.[162–164] The role of adjuvant chemotherapy in stage II colon cancer remains an area of controversy despite multiple clinical trials and meta-analyses, though it is widely accepted that some benefits are retained in high-risk stage II disease (i.e. stage II plus one or more high risk feature of T4 stage, <12 lymph nodes, lymphatic invasion, vascular invasion, perineural invasion, obstruction or perforation, poorly differentiated histology).[165]

Tumour mismatch repair status (MMR) is also an important consideration, particularly in stage II disease. MMR gene mutations (either hereditary or spontaneous) result in tumours that are MMR deficient (d-MMR) and/or that have microsatellite instability (MSI-H). Whilst patients with d-MMR or MSI-H tumours display a better prognosis, they are conversely less responsive to 5FU ACT. Hence, those with stage II disease and d-MMR/MSI-H, represent a small population of patients with a low risk of recurrence and no demonstrated to benefit from 5FU chemotherapy, and therefore should not receive adjuvant chemotherapy according to current guidance.[166]

1.8.1 RECTAL CANCER AND THE EVIDENCE FOR ADJUVANT THERAPY

Evidence for adjuvant treatment in rectal cancer is, however, more conflicting. A detailed review by Carvalho and Glynn-Jones discussed the evidence for adjuvant (5-FU based) chemotherapy in rectal cancer.[167] The authors noted that although a 2011 Cochrane review and meta-analysis[168] demonstrated a significant improvement in disease free- and overall- survival, most included trials were undertaken prior to the widespread adoption of total mesorectal excision (TME), with some trials including post-operative radiotherapy or chemoradiotherapy without separate analyses. They cite three further phase III RCTs in the interim,[169–171] of pre-operative radiotherapy or chemoradiotherapy followed by adjuvant post-operative chemotherapy vs. control, in addition to updated results from the EORTC 2291 trial,[172] which all failed to demonstrate a benefit for ACT over observation alone. Furthermore, the authors discuss study limitations which may have attenuated rectal cancer ACT trial results in detail. For example, problems with inaccurate baseline clinical staging may have resulted in recruitment of patients

with lower-stage tumours, requiring additional power to detect differences, in addition to unbalancing treatment groups. Furthermore, down-staging through neo-adjuvant treatment alters surgical histopathology and might result in stage-migration, with variable response rates potentially confounding results. However, of particular relevance, are issues with significant variation in chemotherapy adherence across trials, as low as 48% in CHRONICLE (data from which is included in the thesis).[169]

More recently, the management rectal cancer has moved towards total neo-adjuvant therapy (TNT), with the aim of improving distant metastatic disease rates. TNT has altered the traditional sequence of treatments for rectal cancer, altering the timing of systemic adjuvant chemotherapy, and moving it to between neoadjuvant (chemo)radiotherapy and TME surgery. The rational for this is threefold: firstly, to improve adherence, where neoadjuvant chemotherapy has been associated with reduced toxicity and better tolerability compared with adjuvant chemotherapy in rectal cancer;[173] secondly due to the uncertainty surrounding the benefits of adjuvant chemotherapy (as discussed above); thirdly, the longer delay created between (chemo)radiotherapy and surgery has been demonstrated to result in a higher chance of achieving a complete response,[174,175] which may enable watch and wait and organ preservation strategies. A number of key trials (RAPIDO,[176] CAO/ARO/AIO-12[177] and PRODIGE23[178]) have reported significant improvements in disease-free survival[178] or disease-related treatment failure,[176] at 3-years, in addition to improved complete response,[176–178] and distant metastasis, rates.[176,178] Longer-term overall survival results are still awaited.

1.9 HYPOTHESIS

For colorectal cancer, despite strong evidence for the obesity-incident-cancer relationship and some evidence of a possible obesity-adverse prognosis association, the literature is firstly, not able to confirm this association with certainty, and secondly, not able to establish causation. Thus, the question remains: does a causal relationship exist, and are observed adverse relationships the effect of sub-optimal chemotherapy dosing?

Hence, the hypotheses for this thesis were four-fold. That elevated BMI:

1. Increases the likelihood of sub-optimal dosing in chemotherapy (through dose capping, dose reductions, and reduced adherence).
2. Does not increase the risk of toxicity from adjuvant chemotherapy.
3. Adversely influences survival outcomes in colorectal cancer.
4. Effects on survival are mediated (at least in part) through sub-optimal adjuvant chemotherapy.

1.9.1 AIMS

The aims of this thesis were to answer the above hypotheses using three core methodological concepts to underpin the work. First, to use data from adjuvant chemotherapy randomised clinical trials (from the OCTOPUS consortium, detailed in Chapter two),[179] to reduce biases. Second, to develop a causal inference mediation model that assesses the direct effects of peri-randomisation excess BMI on survival, accounting for the indirect effect of BMI through suboptimal chemotherapy treatment. And third, to implement individual participant data (IPD) meta-analysis approaches to meta-analyse the mediation models, as relatively new methodology.

1.9.2 PICOS

The above questions were examined within the PICOS framework:

- ***Population*** – Patients with non-metastatic colon or rectal cancer undergoing adjuvant chemotherapy following curative resection.
- ***Interventions & Comparisons*** – Elevated BMI in comparison with normal BMI
- ***Outcomes (& mediators)*** – Survival; adjuvant chemotherapy dosing; adherence; toxicity
- ***Study design*** – randomised controlled trials

CHAPTER TWO
METHODS

CHAPTER TWO PREFACE

Chapter two presents an overview of the methodology undertaken for the thesis. The focus within this Chapter is threefold. First, the data sources and the process taken for data harmonisation and cleaning are described. Second, important definitions are provided for exposures, mediators and outcomes utilised throughout the thesis, including the calculation of key measures of chemotherapy adherence required for analysis. Third, a general overview of the statistical principles for the thesis are outlined including missing data, causal inference, mediation modelling, and individual participant data meta-analysis approaches. Further specific methodology relating to each Chapter is then presented with the relevant results Chapter.

2.1 INTRODUCTION

The aims of this thesis, as described in Chapter one, were to improve mechanistic understanding of the relationship between BMI, adjuvant chemotherapy dosing, toxicity, and survival. Three underpinning methodological concepts for this thesis were i) the use of adjuvant chemotherapy trial (ACT) data in the setting of non-metastatic colorectal cancer (CRC), ii) causal inference methods for mediation analysis, and iii) individual participant data (IPD) meta-analysis (MA).

The concept of utilising trial data for an observational study, through secondary analysis of that data, has been previously discussed as the ideal setting in which to study the effects of obesity on survival in colorectal and endometrial cancers. [85] The advantages and disadvantages of using trial data in this way are discussed in **Table 2.1**. The principal advantages are the ability to undertake an observational study within the context of reduced biases (e.g., selection and recall bias, and residual confounding),[116] the detailed data collection of intermediate chemotherapy and toxicity outcomes, and the ability to combine trial data to undertake IPD-meta analyses, enabling (*a priori*) subgroup analysis with increased power.[180]

2.2 DATA SOURCES AND POPULATION

2.2.1 SEARCH STRATEGY

The presented work formed part of the "Obesity and Cancer TOgether impact Upon Survival" (OCTOPUS) project, funded by the World Cancer Research Fund (WCRF). The project was established to examine the relationship between obesity and survival in non-metastatic colon, rectal and endometrial cancers. The aims were therefore to undertake an observational study to explore these relationships in the context of curative randomised controlled trials (RCTs), where biases are reduced compared with 'real world' data and utilise IPD-meta-analysis approaches to aggregate results.

RCTs within the curative setting (ACT, follow-up strategy or surgical resection trials) with derivable BMI data were therefore sought. (PROSPERO registration CRD42017073699).[179] Given the hypotheses in question were not dealing with treatment comparisons of specific chemotherapy regimens or surgical approaches, and there were no obvious MESH terms to capture the required trials, a degree of pragmatism was employed through the data acquisition process. However, IPD-MA principles were adopted as far as possible through implementation of Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) guidance.[181]

Data for the OCTOPUS project were identified through a search of eligible and available trials for non-metastatic colorectal cancer through Project Data Sphere® (a not-for-profit data sharing platform for historical, patient level data from phase III clinical trials in oncology from both academic and industry sources),[182] in addition to literature review and expert knowledge by the wider research team, to identify ACT and surgical trials for colorectal and endometrial cancers, that might contain BMI data at trial entry. This process was undertaken by the OCTOPUS project research team, who then contacted the relevant trial authors and institutions. Trial data were then obtained either through specific data transfer agreements with the individual trial institutions, or directly from Project Data Sphere®, to establish the OCTOPUS consortium, most of which occurred prior to the start of the PhD in 2018.

Thereafter, an additional systematic review to identify published studies containing relevant aggregate data results for BMI-adherence-toxicity-survival outcomes was not undertaken for several reasons. First, the detailed literature review undertaken in Chapter one established the lack of published data within the colorectal cancer setting. Second, exposures and outcome measures within published reports tended to be heterogenous precluding meta-analysis. Finally, the use of IPD data specifically allowed causal inference approaches and mediation analysis that were not possible with aggregate data.

2.2.2 DATA SOURCES: TRIALS WITH ADJUVANT CHEMOTHERAPY DATA

The OCTOPUS consortium contained five ACT trials from a total of nine trials: MOSAIC, SCOT, CHRONICLE, PROCTOR-SCRIPT (PS) and NCCTG N0174. A brief summary of each trial is as follows, with more detailed summaries in the appendix (**Table A2.1**).

Multicentre International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC)

The MOSAIC trial was a phase III, open label (industry funded) randomised control trial (RCT) comparing outcomes for the addition of oxaliplatin to standard 5FU/LV adjuvant therapy in stage III and high-risk stage II colon cancer following curative resection. Accrual occurred between 1998 and 2001, enrolling 2246 patients from 146 centres across 20 countries. The trial was one of the first to demonstrate improved 5-year disease-free survival (DFS) (from 67.4% to 73.3%; HR: 0.80; 95% confidence interval (CI): 0.68, 0.93; P =0.003) and 6-year overall survival (OS) (from 76.0% to 78.5%; HR: 0.84; 95%CI: 0.71, 1.00; P =0.046) with the addition of Oxaliplatin.[163,183] Data for the control arm (5FU/LV) only were available via Project Data Sphere®.[182] The lack of treatment arm data is likely the result of MOSAIC being an industry sponsored trial, with data collection, management and analysis performed by the sponsor Sanofi-Synthelabo.[183] It is conceivable that concerns over protecting intellectual property and experimental-arm data meant that complete data were not shared with the Project Data Sphere platform.[184]

Table 2.1 | Advantages and disadvantages of using trial data

From references[116,119,120,180]

Advantages	Disadvantages
1. Less treatment bias due to randomisation and standardised treatment/follow-up according to protocol 2. Subgroup analysis with increased power possible, through IPD meta-analysis. 3. Data capture often detailed and well thought-out to control for baseline prognostic and other confounding factors. 4. Improved adjustment for prognostic/confounding factors due to detailed data-collection. 5. BMI measures are more likely to be accurate as prospectively collected and not relying on recall or self-measurement. 6. Survival/disease progression is prospectively collected and therefore at reduced risk of bias. 7. Obtain a clearer understanding of cancer specific survival, as patients are generally fitter with fewer co-morbidities and follow-up is protocol-driven.	1. Remains susceptible to treatment alterations – however, this is the main research question for thesis. 2. Remains a retrospective observational analysis. 3. BMI usually measured at trial entry/randomisation and may not account for preceding BMI changes resulting from surgery and/or chemoradiotherapy. 4. There may be an element of trial recruitment bias. 5. Possible under-representation of patients with obesity-related metabolic factors and/or co-morbidities which may alter overall survival and reduce applicability to wider populations. 6. Like most studies, there may remain unknown confounders due to data not being collected (e.g., smoking).

Short Course Oncology Therapy (SCOT)

The SCOT trial was a recent international (UK-lead) phase III non-inferiority RCT comparing duration of adjuvant chemotherapy (3 months vs. the standard 6 months) with either modified FOLFOX-6 (mFOLFOX6) or CAPOX in high-risk stage II and stage III colorectal cancer,[185] and was part of the recently published IDEA collaboration (a collaboration of six international trials evaluating the ideal duration of chemotherapy). Trial accrual occurred between 2008 and 2013 with 6088 patients undergoing randomisation but was stopped early due to slow recruitment. Although the trial was underpowered to confirm non-inferiority, the results of the study demonstrated that 3 months vs. 6 months treatment with oxaliplatin-based adjuvant did not result in a significant difference in 3-year DFS (HR 1.006 (95%CI 0.909-1.114, $p_{(non\text{-}inferiority)}$ = 0.012). Data from both arms of the trial were shared from the Cancer Research UK Clinical Trials Unit, Glasgow through a data transfer agreement. Each arm was treated as a separate population due to the differences in chemotherapy duration. This was appropriate given that selection to treatment arm was randomised and therefore the two arms represent two randomised sub-populations. Furthermore, this was appropriate from a statistical modelling perspective. Firstly, the two arms resulted in different mean values of treatment adherence (see **Table 3.4**) and a bimodal distribution when analysed together. Secondly, these differences are important when considering exposure or treatment effects in the context of IPD meta-analysis, where assumption of random effects is usually the most appropriate and robust method (see **Section 5.2.8**). In this context, the true exposure or treatment effect was likely to vary due to differences in adherence and toxicity between the two arms.

CHRONICLE

CHRONICLE was a multi-centre, phase III RCT comparing the addition of adjuvant chemotherapy (CAPOX) to observation in patients with locally advanced rectal adenocarcinoma treated with pre-operative (chemo)-radiotherapy.[169] The trial randomised only 113 patients between 2004 and 2008, closing early due to poor accrual. A benefit from the addition of adjuvant chemotherapy on 3-year DFS was not demonstrated; 3-year DFS rate with CAPOX 78% vs 71% with observation (HR: 0.80; 95%CI: 0.38, 1.69; P = 0.56. Data for the whole trial were shared with a data transfer agreement with Cancer Research UK and University College London (UCL) Clinical Trials Centre, London.

PROCTOR-SCRIPT

PROCTOR-SCRIPT (PS) was a Dutch Colorectal Cancer Group phase III RCT comparing adjuvant chemotherapy vs. observation in patients with rectal cancer following neoadjuvant (chemo)-radiotherapy and TME resection. Trial recruitment was between 2000 and 2013 but was closed early due to poor accrual. 470 patients (437 eligible) were enrolled, and no significant benefit was demonstrated in the primary outcome of 5-year OS for adjuvant chemotherapy compared with observation group (80.4% vs. 79.2%; HR: 0.93; 95%CI 0.62,

1.39; P = 0.73).[171] Data from the whole trial were shared through a data transfer agreement with Leiden University Medical Centre, the Netherlands.

The North Central Cancer Treatment Group (NCCTG): N0147

The NCCTG N0147 trial was a randomised phase III ACT trial for stage III colon cancer. Initially designed to randomise patients to one of three arms: mFOLFOX6, FOLFIRI or a hybrid cross-over of mFOFLOX6 then FOLFIRI,[186] it opened to recruitment in 2004. Several modifications occurred: randomisation of additional cetuximab to the above (totalling 6 arms); discontinuation of FOLFIRI arms (mFOLFOX6 continued for patients on hybrid arms not yet receiving FOLFIRI); randomisation of only patients with tumours expressing wild-type KRAS (plus additional observational arm for mutant KRAS). Recruitment closed early as a result of interim analysis suggesting no DFS benefit compared with the control. Hence, the final analysis assessed mFOLFOX6 with and without cetuximab, and found no significant difference in the primary outcome of 3-year DFS (71.5% vs. 74.6% respectively; HR: 1.21; 95%CI: 0.98, 1.49; P=0.08).[187] Data from the trial were available through Project Data Sphere®. However, during the data cleaning and harmonising process, it became clear that neither cycle-level nor cumulative chemotherapy dosing data were available. Furthermore, neutropenia data were missing from toxicity, which was the most commonly reported toxicity in the NCCTG N0147 trial, [187] unfortunately rendering the data unusable within the context of this thesis.

The MOSAIC, SCOT, CHRONICLE and PS trials have complete chemotherapy and toxicity dosing data and are therefore the trials on which the of the work of this thesis are based.

2.2.3 ETHICS & DATA-SHARING

Ethical approval for each respective trial had been gained by the relevant trial study groups prior to patient recruitment, without the requirement for additional ethical approval for this thesis. Data were shared through data-transfer agreements, with all data anonymised and no patient-identifiable data.

2.2.4 DATA CHECKING AND HARMONISATION

A substantial data checking, cleaning and harmonisation process was undertaken. This was planned to involve four key steps: first assessment for the presence of key variables required for a minimum dataset; second, assessment for potential data errors and inconsistencies; third, harmonisation of variables across the datasets; finally, creation of additional variables required for analyses. This detailed piece of work served several vital purposes including identification of missing data, facilitation of a robust and standardised assessment of the data and later standardised analyses across the trials and combination into a single dataset for IPD meta-analysis.

All datasets were examined and assessed for the presence or absence of key variables required for a minimum dataset (**Appendix A2.2**). Additional requests were made to the clinical trials units for missing data, where possible and/or where data were available.

Assessment for potential errors or inconsistencies included, for example, extreme values of height/weight/BMI/age/chemotherapy doses, duplicate observations, date inconsistencies etc. Of note, the SCOT chemotherapy dataset was complicated in its organisation, and required some discussion with the trial statistician in order to extract cycle-level data (e.g., dosing, repeated weight measurements and cycle dates) with corresponding cycle numbers. Problems with cycle numbering and/or missing cycle dates occurred in 48 patients. Following personal correspondence with the trial statistician, it was possible to clarify issues such as truly missing data, duplicate cycle data, and cycle-number mislabelling etc., and institute minor common-sense cycle number corrections (where appropriate) to allow extraction of cycle-level information. For example, a cycle number labelled as “43” had dates corresponding to cycle number 4 and was corrected accordingly. Records were kept of all corrections and potential errors identified (including within Stata do files for reproducibility), and indicator variables were generated for such observations/corrections to facilitate later sensitivity analyses, planned to exclude such patients to assess the potential influence of minor edits, or potential errors.

Variable harmonisation was performed, including standardisation of naming and definitions e.g., units of measure, setting time zero for time-to-event variables, ensuring categorical variable numbering matched, and converting Karnofsky performance status to European Cooperative Oncology Group (ECOG) performance status. Finally, additional variables required for analyses were generated e.g., dose capping indicator and adherence measures (defined below).

Key aspects of the data-cleaning, harmonisation and variable generation process are presented where appropriate throughout the methods in relation to specific variables in question e.g., BMI, BSA, chemotherapy dosing, toxicity, and survival variables.

2.2.5 INCLUSION/EXCLUSION CRITERIA

Study Eligibility

IPD from RCTs within the OCTOPUS consortium were eligible for inclusion if the trials included patients with colon or rectal cancers who had undergone curative resection, prior to trial randomisation, and had BMI, adjuvant chemotherapy and toxicity data. RCT arms were excluded if patients did not receive chemotherapy, similarly patients not randomised were also excluded.

Patient Eligibility

A single 'Main' dataset was generated from the eligible trials. Participants were required to have height and weight data (to derive BMI), and have received at least one dose of chemotherapy, with cycle-level dosing and toxicity data available. Hence, patients were excluded if they had had missing or extreme BMI values of < 15.0 kg/m^2 and ≥60.0kg/m^2 at trial entry (to reduce the risk of bias of the exposure from data entry errors), metastatic disease (M1 stage or AJCC stage IV), non-calculable adherence measures (e.g., due to missing first or last cycle dates) or extreme values of adherence measures (see **Section 2.4.3**). Missing data were generally low, and hence patients were excluded if they lacked complete covariate data (excluding the SCOT trial toxicity data, see **Section 2.4.4**). From 7479 eligible patients, a total of 165 patients (2.2%) were excluded for missing data (see **Chapter 3, Figure 3.1**).

Two additional toxicity complete case datasets were generated as a result of substantial missing toxicity data from the SCOT trial. The missing toxicity data was due to the trial protocolled requirement for toxicity data collection to be undertaken only for the first 700 patients (with an administrative delay in notifying trial sites resulting in data being collected for 868 patients). Hence, the TOX1 dataset excluded all patients who were not defined as being within the trial safety population (i.e., it excluded those from the SCOT trial that did not have trial-mandated toxicity data collected) and five patients from PS with completely missing toxicity data. Furthermore, the TOX2 dataset excluded patients with any incomplete toxicity, and therefore included an additional subset of patients in the SCOT trial with some toxicity data recorded for patients who were not within the protocol-mandated safety population (**Chapter 3, Figure 3.1**).

Risk of bias

Assessment of risk of bias of the included studies and data was undertaken using version 2 of the Cochrane risk-of-bias (RoB2) assessment tool for randomised trials.[188] Due to the nature of this study, not all domains were applicable. Furthermore, assessment of certain domains was extended to include exposure, mediator, and confounders, in addition to outcomes. Risk of bias from the included studies was deemed to be low overall, and a summary of the judgement made across the trials, for each domain is provided in the appendix (**Table A2.3**). Of note, however, there was a moderate risk of bias due to missing data, pertaining mainly to the SCOT trial and the protocolised collection of toxicity data for only the first 848 patients. Use of the TOX2 dataset to evaluate toxicity relationships may have increased the risk of bias resulting from the contribution of data collected "ad-hoc" compared with the protocolised data collection for the TOX1 dataset. These issues are discussed further in the context of data harmonisation (**Section 2.4.4)**, missing data mechanisms (**Section 2.5.2**), initial toxicity data characterisation (**Section 4.4.1**), multiple imputation methods (**Section 5.2.8**), results (**Sections 5.4.1 and 6.4.1**) and study limitations (**Section 7.2.2**).

2.3 PRIMARY EXPOSURE: BMI

2.3.1 DERIVATION OF BMI

BMI measurements were derived from available height and weight data according to the standard equation:

$$BMI\ (kg/m^2) = \frac{weight\ (kg)}{height\ (m)^2}$$

Height and weight data at trial entry were used to generate "baseline" BMI, and where required, BMI was categorised according to the WHO definitions of underweight (<18.5kg/ m^2), normal weight (18.5 – 24.9kg/m^2), overweight (25.0 – 29.99 kg/m^2) and obese (≥30.0kg/m^2). Further sub-categorisation of the obese group according to WHO extended categories into obese I (30.0 – 34.9 kg/m^2) obese II (35.0 – 39.9kg/m^2) obese III (≥40.0kg/m^2) was not undertaken due to small sample sizes that resulted within these sub-groups.

Timing of baseline BMI was available for all trials, and for the majority were taken within +/- 14 days of randomisation (MOSAIC 95.72%, SCOT_3M 93.56%; SCOT_6M 92.85%; CHRONICLE 81.63%; PS 94.4%).

2.3.2 BASELINE HEIGHT DATA

For all but one dataset, a single height measurement was provided. The SCOT trial, however, provided repeated height measurements (up to four measurements per patient) recorded in the dataset corresponding with up to four chemotherapy treatment case report forms (CRF) forms (each representing 6 weeks of treatment). These were assumed to represent individual measurements, though they may have been simply carried forward. For 253 (4.14%) of the 6118 patients within the SCOT chemotherapy dataset provided, these measurements differed and were assumed to represent a small degree of measurement error. Following correspondence with the SCOT trial statistician the following was adopted as a reasonable approach to dealing with these discrepancies:

1. In patients with three or more values, the most frequently occurring value was used
2. In patients with only two or all differing values (n = 124), the first recorded height was used.
3. Sensitivity analyses were planned to exclude this patient group.

Whilst an alternative option would have been to simply take the first recorded height for all cases, in patients where there was a most frequently occurring value, it seemed reasonable to use the value on which most dose calculations were likely based on, in attempt to reduce further measurement error.

2.3.3 BASELINE AND REPEATED WEIGHT DATA

Weight data at trial entry was used to calculate baseline BMI. Repeated weight data were available for SCOT, MOSAIC and PS trials, related to each chemotherapy cycle received. Weight measurements were assessed longitudinally for changes in weight compared to baseline and compared to the preceding value that were likely to represent unrealistic changes and hence measurement or data-entry error; a threshold of 20% increase or decrease in weight was used. Within the individual full trial datasets, these represented 2.67 % of MOSAIC, 0.53% of SCOT_3M, 2.01% of SCOT_6M, and 0.64% of PS trials. Again, a sensitivity analysis was planned to assess the influence of potential data or measurement errors on results.

2.3.4 OVERALL BMI DATA QUALITY

Overall BMI data quality was good. BMI was derivable for 99.64% of MOSAIC; 98.19% of SCOT; 46.90% of CHRONICLE and 80.64% of PROCTOR-SCRIPT. The majority of missing height and weight data were for the observation arms in CHRONICLE (completely missing for patients in observation arm) and PS (derivable for 29.3% patients in observation arm). Overall, only 3.4% of the full datasets combined (all patients, pre-exclusions) had non-derivable BMI data.

Of those eligible for inclusion into the study, BMI was derivable for 99.64% of MOSAIC; 98.09% of SCOT_3M; 98.38% of SCOT_6M; 98.15% of CHRONICLE; and 90.34% of PROCTOR-SCRIPT patients. Overall, only 1.81% of eligible patients from all datasets had non-derivable BMI data.

2.4 OUTCOME MEASURES

2.4.1 PRIMARY OUTCOME MEASURE: OVERALL SURVIVAL

The primary outcome measure, explored in Chapters five and six, was overall survival, defined as time to death resulting from any cause, and according to Punt et al.'s survival outcome definitions for colorectal cancer.[189]

Time zero

For all time-to-event analyses, time zero was defined as the day of randomisation. Randomisation as time zero is standard practice in clinical trial data, including all trials within the OCTOPUS consortium, and was hence the most appropriate entry point, allowing standardisation.[189] Only minor harmonisation was required, where data were provided in different time formats.

2.4.2 SECONDARY SURVIVAL OUTCOME MEASURES

Additional secondary survival outcome measures were explored in Chapters five and six. Disease-free survival was defined as time to any recurrence (loco-regional or distant, as defined by the individual studies), a new primary colorectal cancer or death from any cause. Data on non-colorectal cancer primary tumours were not provided by all trials and was therefore not included as a DFS event (hence a modification of Punt et al. definitions) [189] to allow standardisation across trials. However, the utilised definitions were those of both MOSAIC and SCOT trials. Cancer specific survival (CSS) was defined as time to death resulting from colorectal cancer, thus, censoring any other causes of death e.g., treatment related.

2.4.3 INTERMEDIATE OUTCOME MEASURES: CHEMOTHERAPY

Chapter three explores the effects of BMI on a number of chemotherapy dosing outcomes, including overall measures of adherence, which are hypothesised mediators of the BMI survival relationship and further explored throughout the thesis.

BSA

Dosing of adjuvant chemotherapy agents in colon and rectal cancers is undertaken according to body surface area (BSA). Available trial protocols and published papers did not specify the equation used to calculate BSA (though it should be noted that late correspondence with one of the SCOT trialists identified that the du Bois du Bois formula had been utilised), and it is possible that this may have varied between trials and also between trial centres within the same trial. Given that no preference has been given to any one particular formula over another (as recommended in ASCO guidance due to their products not varying substantially),[190] the most

frequently adopted method in published studies assessing BMI-chemotherapy-dosing relationships, the Mosteller equation, was therefore used to calculate BSA:[116,120,129,132,142]

$$BSA(m^2) = \sqrt{\frac{height\ (cm) * \ weight\ (kg)}{3600}}$$

For trials with repeated weight data, actual body weight for each cycle was used to calculate cycle-level BSA measurements, thus accounting for weight changes, as per clinical practice. Where cycle-level weight data were missing, the preceding BSA measurement was utilised to calculate chemotherapy dosing for that cycle.

Actual cycle dose (ACD) of chemotherapy received

Total cycle-level doses of chemotherapy were converted to the per m^2 dose to allow for comparison across trials and individuals.

$$ACD\ (mg/m^2) = \frac{total\ dose\ recieved\ for\ cycle}{BSA\ (m^2)}$$

Where possible, the actual administered or received doses were used, rather than prescribed doses, to take into account effects of toxicity on adherence and compliance. For capecitabine, only PS provided cycle-level data for the number of tablets actually taken by patients, and therefore captured patient-related adherence in addition to BSA-based dosing adherence.

Cycle-level doses were checked for unlikely dosing where the dose was less than that for a BSA of $1m^2$ or 20% greater than the dose expected for the patient's BSA. Most low doses were the effect of dose reductions and therefore assumed correct, however, common-sense corrections were instituted only for obvious errors. For example, very low capecitabine doses commonly appeared to be due to being recorded as the single dose (requiring multiplication by 28) or the daily dose (requiring multiplication by 14) to obtain the full cycle dose. Corrections to such doses were cross checked with toxicity, dose delays and any documented free text to ensure that these were simple data-entry errors rather than true dose reductions. Sensitivity analyses were planned to assess the effects of potential measurement or data entry errors in such patients.

Expected cycle dose

Expected cycle doses of adjuvant chemotherapy were calculated for each cycle according to the individual trials' protocols (**Table 2.2**). The SCOT trial protocol required capecitabine to be dose banded to the nearest 500mg and allowed individual recruitment sites to utilise their own dose banding tables to extend dose banding above a BSA of $1.87m^2$ to a maximum of $2.2m^2$. Oxaliplatin dose banding was also allowed according to local sites' own protocols, which were not individually reported. It was not clear whether dose banding was utilised for the other trials.

Hence, expected cycle doses were calculated from the protocoled doses (see **Table 2.2**) for all trials.

Relative dose received

The relative dose received (RDR) for each cycle of chemotherapy was calculated as the percentage of the expected cycle dose that was actually received for that cycle:

$$RDR = \frac{Actual\ cycle\ dose\ (mg/m^2)}{Expected\ \text{cycle dose}\ (mg/m^2)} * 100$$

Dose capping

Dose capping was undertaken in the SCOT protocol at a BSA of 2.2m^2, however the MOSAIC protocol did not specify either dose capping or a maximum dose (**Table 2.2**). Dose capping for a cycle of chemotherapy was defined as an actual cycle dose of <95% of the expected dose (i.e., an RDR of <95%). This threshold is previously adopted in the literature,[104,142,191] and represents a more sensitive measure of dose capping compared with other less frequently used levels ranging 85% – 90%.[104,127–129,142,191] First cycle capping and subsequent cycle relative under dosing (RUD) were both defined in the same way.

Dose Reduction

A dose reduction for a given cycle of chemotherapy was defined as an actual cycle dose of <95% of the preceding cycle dose received, for consistency with dose capping, and was thus, calculated from the second cycle onwards. This differed from the RUD in that it was calculated from the preceding dose rather than the standard dose.

Dose Delay

Dose delays were defined as a delay in the start date of any given cycle by > 7 days from the expected start date. **Table 2.2** describes expected durations of ACT cycles according to the trial and regimen, from which dose delays were calculated. In routine clinical practice, it is widely accepted that dosing delays may occur up to +/- 3 days due to weekends and national holidays. The majority of studies assessing the effects of chemotherapy dose capping, reductions, delays or toxicity on outcomes define a dose delay as greater than 1 week or 7 days from the expected start date of the next cycle. Most chemotherapy-related toxicity will result in a dose delay and re-assessment the following week. Thus, utilising a threshold of 7 days for definition of a dose delay is clinically relevant, and supported by the literature.[127,128,133,135,136,192,193]

Early discontinuation of chemotherapy

Early discontinuation (ED) was defined as receiving fewer than the expected number of ACT cycles, where receipt of a cycle was defined as administration of at least one cytotoxic agent.

Expected number of chemotherapy cycles

The expected number of cycles varied (between four and twelve cycles) according to the trial, regimen and study arm and can be found in **Table 2.2.**[169,171,183,185]

Table 2.2 | Summary of the chemotherapy regimens of the included trials

Trial	Regimen	Drug	Dose/m^2	Dosing/Duration	Expected cycle dose/m^2	No. Cycles	Dosing interval	Expected cumulative dose/m^2	Expected duration (weeks)	Expected Dose intensity (mg/ m^2/week)
MOSAIC	5FU/LV2	5FU-B	400mg	Day 1 & 2 (bolus)	2000mg	12	14 days	24,000mg	24	1000
		5FU-I	600mg	Day 1 & 2 (22hrs)		12				
SCOT	mFOLFOX6	5FU-B	400mg	Day 1 (bolus)	2800mg	6 or 12*	14 days	16,800mg 33,600mg*	12 or 24*	1400
		5FU-I	2400mg	Day 1 – 2 (46hrs)						
		OX	85mg	Day 1 (2hrs)	85mg		14 days	510mg or 1020mg*		42.5
	CAPOX	CAP	1000mg	Days 1-14 (BD)	28,000mg	4 or 8*	21 days	112,000 or 224,000	12 or 24*	9,333
		OX	135mg	Day 1 (2hrs)	135mg		21 days	540mg or 1,080mg		45
CHRONICLE	CAPOX	CAP	1000mg	Days 1-14 (BD)	28,000mg	6	21 days	168,000mg	18	9,333
		OX	135mg	Day 1 (2hrs)	135mg	6	21 days	810mg		45
PROCTOR	MAYO	5FU	435mg	Days 1-5 (bolus)	2,175mg	6	4-5 weeks	13,050mg	25.7†	507.5
	NORDIC	5FU:	500mg	Days 1-2 (bolus)	1,000mg	12	14 days	12,000mg	24	500
SCRIPT	CAP	CAP	1250mg	Days 1-14 (BD)	35,000mg	8	21 days	280,000mg	24	11,667

Abbreviations: **5FU**, 5 Fluorouracil; **5FU-B**, 5FU bolus; **5FU-I**, 5FU infusion; **BD**, twice daily; **CAP**, Capecitabine; **OX**, oxaliplatin.
*3 months vs. 6 months arms arm.
† Dosing interval of 30 days assumed (4-5 weeks) for 6 cycles to calculate total expected duration

Average cumulative relative dose

Cumulative relative dose (CRD) is an overall measure of actual compared with expected dosing of chemotherapy over the entire course. It provides a single value which describes dosing and captures both dose capping and subsequent cycle dose reductions, in addition to early discontinuation of chemotherapy.

$$CRD = \frac{Actual\ cumulative\ dose\ (mg/m^2)}{Expected\ cumulative\ dose\ (mg/m^2)} * 100$$

CRD is calculated for each chemotherapy drug, then averaged across the drugs to produce an average cumulative relative dose (ACRD) for the regimen.

A small proportion of patients from the SCOT trial (194 total; equating to 3.23%) changed chemotherapy arms at least once, from mFOLFOX6 to CAPOX or vice-versa. As ACRD is the percentage of the total expected dose received, the CRD was first calculated for each fluorouracil and oxaliplatin component of each regimen and simply summed to obtain the overall CRD for fluorouracil and oxaliplatin, then averaged across the two drugs to obtain the ACRD.

Average relative Dose Intensity

Relative dose intensity (RDI) is another single measure of adherence which additionally captures treatment duration and has been used to explore dosing in relation to BMI: [135,194]

$$RDI = \frac{Actual\ dose\ intensity\ (mg/m^2/week)}{Expected\ dose\ intensity\ (mg/m^2/week)} * 100$$

Where dose intensity is the total cumulative dose of the drug per m^2 divided by the duration of chemotherapy in weeks. Again, RDI can be averaged across the drugs of a regimen to produce an average RDI (ARDI) for the regimen.[135] RDI therefore accounts for dose capping, subsequent dose reductions and dosing delays, and is commonly used in clinical trials to explore dosing, where expected doses are often based on cycle one dosing. Here, however, a key difference is that both actual and expected doses are calculated based on actual-body-weight based BSA doses. For those patients switching regimen within the SCOT trial, after calculating the RDI for each fluorouracil and oxaliplatin component of each regimen, an average for each component was taken (weighted according to the proportion of cycles received for each regimen), and finally the averaged fluorouracil and oxaliplatin components were averaged to obtain the ARDI.

The main limitation of ARDI is its lack of ability to adequately differentiate between fully dosed patients receiving all cycles and those discontinuing chemotherapy early (**Table 2.3**). Due to the nature of ARDI as a percentage of expected dose intensity, patients receiving less than the expected number of cycles could still have an ARDI of 100% if the dose is maintained for all cycles.

Table 2.3 | Relative Dose Intensity (RDI) and Cumulative Relative Dose (CRD)

Differences in cumulative dose, total duration, ARDI and ACRD are demonstrated for four example patients who are enrolled in a hypothetical chemotherapy trial with expected protocol doses of 2000mg/m^2 of a single drug per cycle for 6 cycles of 14 days duration. **Green** cycles demonstrate full doses with no dose delays. **Orange** cycles are dose delayed and/or dose reduced. **Red** cycles are not given after discontinuation of chemotherapy. Patient A receives full doses for all cycles, with no delays. Patient B receives full doses with no delays for three cycles but subsequently develops severe toxicity and chemotherapy is stopped, their RDI is the same as patient A, but their CRD is half that patient A. Patient C develops mild-to-moderate toxicity warranting dose delays but is able to maintain the full dose until severe toxicity after cycle 3 and chemotherapy stops, RDI is reduced compared with patient B but CRD is equivalent. Patient D develops moderate toxicity warranting both dose delay and dose reduction, but despite dose reductions toxicity continues and chemotherapy is stopped, reducing both their RDI and CRD compared with Patient B.

Patient	Time (weeks)						Cumulative Dose (mg/m2)	Total Duration (weeks)	RDI	CRD
	1-2	3-4	5-6	7-8	9-10	11-12				
A	C1 – 100%	C2 – 100%	C3 – 100%	C4 – 100%	C5 – 100%	C6 – 100%	12000	12	100%	100%
B	C1 – 100%	C2 – 100%	C3 – 100%				6000	6	100%	50%
C	C1 – 100%		C2 – 100%		C3 – 100%		6000	10	60%	50%
D	C1 – 100%		C2 – 75%		C3 – 50%		4500	10	45%	37.5%

Abbreviations:
C, cycle; **CRD**, Cumulative Relative Dose; **RDI**, Relative Dose Intensity;

2.4.4 INTERMEDIATE OUTCOME MEASURES: TOXICITY

Chapter four describes and characterises the BMI-toxicity relationships. Toxicity is then later explored a putative mediator within Chapters five and six. All trials assessed toxicity according to the CTCAE definitions and grading,[183,185] commonly used for safety monitoring in clinical trials (**Table A2.1**), though there were differences in the versions used. Grade 3 and 4 toxicities are considered to be severe and life-threatening respectively, with treatment-related death defined as grade 5. Grade 3+ toxicities are commonly dose-limiting, resulting in dose reductions or potentially early discontinuation of chemotherapy, and are often used as a threshold to report toxicity in clinical trials.[195]

Peripheral neuropathy is a common and quality of life lowering toxicity related to Oxaliplatin therapy, whereas gastrointestinal toxicities (in particular diarrhoea) are more frequently associated with fluorouracil-based chemotherapy agents (higher incidence with 5FU than capecitabine) and dermatological toxicities (e.g., hand-foot syndrome), more common with capecitabine. Furthermore, differences in mFOLFOX6 and CAPOX regimens are observed with neutropenia more commonly associated with the former, and diarrhoea and hand-foot-syndrome with the latter.[196]

Data harmonisation

Substantial data-harmonisation was required for toxicity, as data from each trial were provided in different formats. It was planned *a priori* to examine the occurrence of any toxicity, in addition to individual types of toxicities. Hence data were harmonised to nine toxicity categories, including eight specific toxicities which were selected as the most commonly reported toxicities within the included trials' published results, with a ninth "other" category to include all other toxicities. These were:

1. Neuropathy (including sensory and motor neuropathy)
2. Diarrhoea
3. Nausea
4. Vomiting
5. Neutropenia
6. Stomatitis and/or mucositis
7. Fatigue
8. Skin (including hand-foot syndrome (HFS) & other dermatological toxicities)
9. "Other".

Where trials provided cycle level data (all except CHRONICLE), these were cleaned and harmonised first to produce variables containing the highest known reported grade of the nine categories above for each cycle. Cycle-level data were not available for CHRONICLE, where only overall grade 3+ toxicity data was provided, though this did include individual toxicities.

Cycle-level data then enabled creation of summary toxicity variables in line with the definitions below. These summary variables consisted of the highest known grades of toxicity, and data were therefore missing if there was no toxicity data for the individual toxicity or for the patient:

1. Overall indicator variable for any grade 3+ toxicity.
2. Overall highest grade of any toxicity (graded 0 [none] to 5 [protocol-related death]).
3. Nine overall grade 3+ indicator variables for the individual toxicity variables.
4. Indicator variable describing whether the first episode grade 3+ toxicity occurred during early cycles or late cycles.

Generally, cycle-level data were provided as a set of variables named with specific toxicities and a set of additional "other" toxicity variables, usually containing free text specifying toxicity type, and including corresponding grades. All data was used to generate the summary variables, with care not to miss any pre-specified toxicities that were documented in the "other" variables (**Table A2.4**, **Appendix**). Where dates were provided with toxicity data these were cross-checked with cycle dates for accuracy.

Where data did not include grade 0 (i.e., no toxicity), and it appeared that only toxicities that actually occurred were present in the dataset, data were assumed complete (MOSAIC and CHRONICLE). This was mainly the case for MOSAIC, with cycle-level data graded 1-4 (i.e., no data for no toxicity, grade 0), where it appeared that only toxicities occurring were included in the dataset. Hence only named toxicities (of which there were 305 individual toxicities) with missing grade were assumed to be truly missing (i.e., "unknown"). Given the high overall quality of the MOSAIC dataset, with minimal missing data in other variables and total percentages for grade 3+ toxicities closely matching those published, this was considered a reasonable assumption. CHRONICLE data was provided as overall regimen-level variables, only for toxicities of grade 3 and above, and only for those patients with a toxicity. These matched the published data, which contained no suggestion of missing data and was assumed complete. However, only overall grade 3+ indicator variables could be generated for CHRONICLE.

Where data did include grade 0, and missing data were evident, or cycle toxicity data were missing but chemotherapy doses were received for that cycle (SCOT and PS), data were assumed missing. For SCOT, there were 18 pre-specified toxicities graded 0-5, in addition to a number of other defined toxicities. For the first 868 patients who were included in the "safety" population, there was relatively low cycle-level missingness. However, some "ad hoc" toxicity data were available for an additional 921 patients, which tended to have higher and more variable cycle-level missingness. Consequently, and as discussed above, two toxicity datasets were generated to explore the potential issues with complete case analysis: TOX1 containing the protocoled "safety" population and TOX2 which additionally included the "ad hoc" toxicity data. The concern with utilising such data is that missing mechanisms might differ between populations and may be related to the grade of toxicity itself, i.e., severe toxicity increasing the

likelihood of reporting, and hence an increased risk of bias from MNAR mechanisms. However, missing data patterns did not appear to be related to grade of toxicity, with the proportion of toxicity grades reported for the 921 “ad hoc” patients following a similar distribution to the 868 “safety” patients. Indeed, toxicity appeared more likely to be under-estimated rather than over-estimated. Furthermore, there was a clear trend for missingness to increase with the date of randomisation, both in the number of patients with overall missing data, and in the number of cycles/individual toxicities with missing data per patient. This was hypothesised to result from toxicity data collection being initiated prior to centres being informed that it could cease (indeed a delay was noted in this notification), and therefore being initiated but then halted. Finally, it is possible that there may have been variation between sites, with some centres or trialists collecting toxicity routinely data regardless of this cessation, however data on trial site was not available and these assumption/associations could not be explored. Further discussion on missing data mechanisms and methods employed to reduce risk of bias are found below (**Section 2.5.2**) and in Chapters five (**Section 5.2.8**) and six (**Section 6.2.7**).

Data from PS were provided separately for PROCTOR and SCRIPT. PROCTOR pre-specified six toxicities in addition to a set of “other” toxicities variables which included free text to specify type and grade. Whereas SCRIPT pre-specified 23, plus additional “other” toxicities variables describing type and grade. SCRIPT, furthermore, provided a variable describing the likelihood of toxicity being related to chemotherapy, hence those marked as unrelated or unlikely to be related were excluded.

Toxicity outcome measures

Overall grade 3+ toxicity

Defined as the occurrence of any grade 3, 4 or 5 toxicity, regardless of type occurring across all cycles of chemotherapy. Grading was defined by the trials according to the relevant CTCAE version definitions in use.

Individual grade 3+ toxicities

Individual grade 3+ toxicity was defined as the occurrence of the named toxicity with a severity of grade 3, 4 or 5, at any time across all cycles of chemotherapy. Again, grading was defined by the trials according to CTCAE definitions.

Highest overall grade of toxicity

The highest known grade of toxicity occurring throughout the chemotherapy regimen, graded 0 (meaning no toxicity) to 5 (meaning treatment related death), defined according to CTCAE definitions used in the trials.

Early vs. late grade 3+ toxicity

For patients experiencing grade 3+ toxicity, the timing of first episode was categorised as occurring during early cycles (defined as during cycles expected to be administered within the first three months of treatment) and late cycles (defined as those cycles expected to be administered after the first three months of ACT). For the majority of trials, this three-month threshold was the mid-point of the chemotherapy regimen, and with varying cycle durations and numbers of cycles, this was a feasible threshold for all trials. However, this excluded CHRONICLE (as cycle-level toxicity data were not available) and SCOT_3M (as chemotherapy regimens were only 3 months duration).

2.5 STATISTICAL PRINCIPLES

2.5.1 OVERVIEW

Statistical methods are presented with the relevant results chapters to facilitate interpretation of results. Specifically, methods for descriptive statistics and testing of differences between groups are presented in Chapters three and four. Whereas methods for statistical modelling are presented throughout Chapters five and six, including: path analysis regression and survival modelling (Chapters five and six), multiple imputation (Chapters five and six), multiple imputation combined with bootstrapping (Chapter six), mediation-analysis (Chapters five and six) and meta-analysis (Chapters five and six). Hence, introduced here are a number of statistical principles that are employed through subsequent chapters: the problem of missing data (relevant to toxicity data); causal inference and IPD meta-analysis principles.

2.5.2 MISSING DATA

The problem of missing data is widely inevitable, including in the robust data-collection setting of a clinical trial (though often minimised) and may be a potential source of bias. Missing data can be classified as belonging to one of three categories:[197]

1. Missing completely at random (MCAR) – There is no relationship between the causes(s) of missing values and the missing values themselves, nor with the observed values.
2. Missing at random (MAR) – there is a relationship between the cause(s) of the missing values and the observed data (but not the missing values).
3. Missing not at random (MNAR) – there is a relationship between the cause(s) of the missing values and the missing values themselves (which remains after consideration of the observed data).

Distinguishing between the latter two categories is not possible within observational data and may only be assessed through sensitivity analysis.[198] A number of statistical methods for dealing with missing data exist, and may be appropriate dependent on the assumed mechanisms. In general, there are three principles: [169,170]

1. Ignoring missing data (i.e., complete case analysis, which is simple but may produce biased and non-valid estimates where data is MAR).
2. Single imputation using replacement values (e.g., single mean imputation, also simple to implement and retains power, but does not account for uncertainty and again, will produce biased estimates under the MAR assumption).
3. Imputation accounting for uncertainty (e.g., multiple imputation, widely accepted and advantageous due to the ability to produce valid results in the context of data that is MAR).

Multiple imputation, involves the creation of multiple datasets with plausible imputed values based on predicted distributions of the observed data, which are then used to model the relationships of interest, followed by an averaging of estimated effects; a process through which there is inherently a degree of variation introduced, reflecting the uncertainty resulting from the multiple imputed datasets.[199,200] Though a single imputation approach has been used (backfilling as described above) for deriving missing cycle-level BSA and thus relative doses of chemotherapy, it is possible that this may introduce a small degree of bias at the cycle-level. However, less so than if cycle-level BMI were not available and baseline BMI were used for all cycle-level calculations. Multiple imputation was instituted for missing SCOT toxicity data during definitive statistical modelling, in order to assess the potential for bias as a result of complete case analyses. Within the context of the SCOT trial toxicity data missingness (see above), missing data were assumed to be missing at random, with a probable relationship between the cause of the missing data (date of randomisation) and the observed data. The relevant multiple imputation methodologies employed are described in in Chapters five and six.

2.5.3 CAUSAL INFERENCE: GENERAL PRINCIPLES

Causal inference is the concept of determining that an exposure-outcome relationship is causal, and as such, is central to principles of public health, whereby identification of a causal relationship creates possibilities of prevention, targeted screening and intervention.[201,202] Historically, causal inference is based on expert judgement utilising guidance and criteria originally developed in the 1950s-60s (**Table 2.4**), a process which has formed the basis of public health systematic reviews, including those of the International Association for Research on Cancer.[202] The causal inference framework encompasses a range of statistical concepts, approaches, and methodology which aim to reduce bias and provide deeper understanding of associations, and the assumptions required to make causal inferences from observational data, some of which are explored below.

2.5.4 DIRECTED ACYCLIC GRAPHS

Within the causal inference literature, the use of directed acyclic graphs (DAGs) has become commonplace to demonstrate putative associations between variables, including hypothesised causal relationships, interactions of covariates (moderators), confounders and unknown confounders etc. (**Figure 2.1**).[95,203] A DAG has two main components: nodal points describing each variable; and arrows (termed edges), describing the presence and direction of the relationship. They are termed ‘acyclic’ because no cycle is allowed in the graph[95,203,204] (that is, there is no directed path starting from a variable and ending with that same variable).

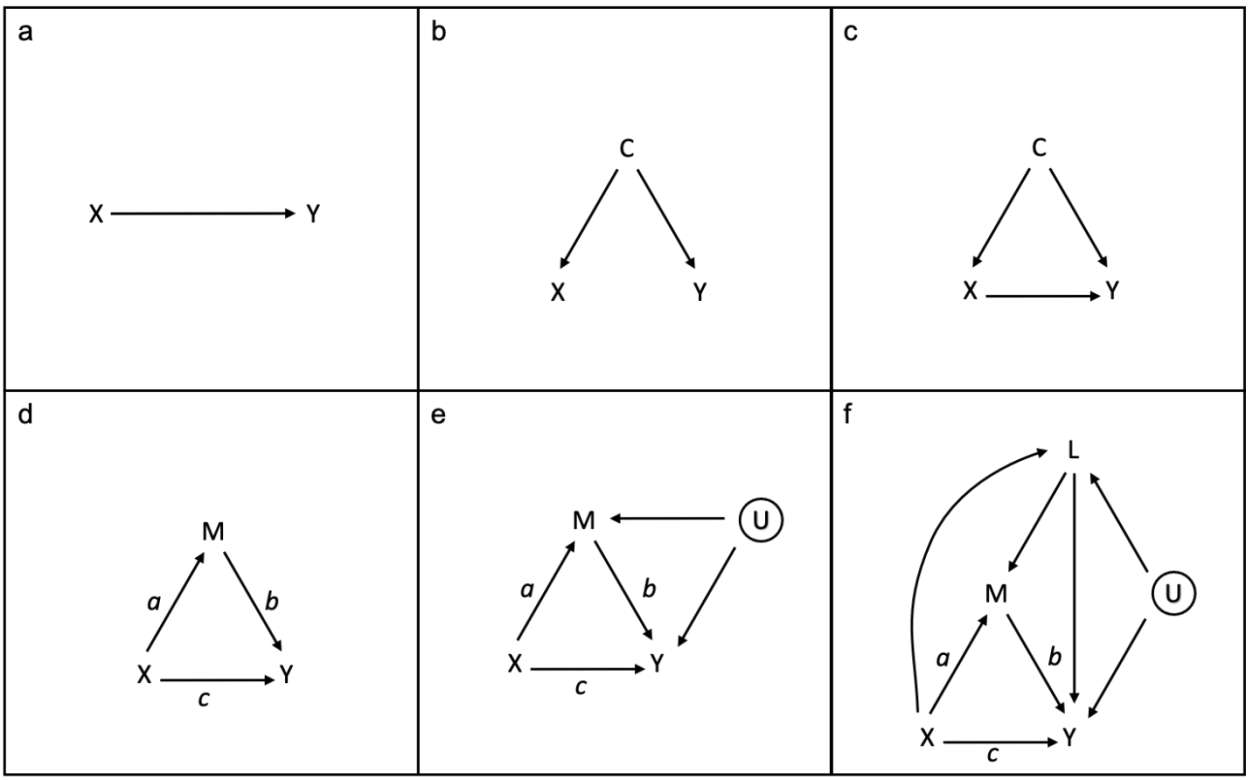
Table 2.4 | Criteria for causal inference

From Glass et al.[202] based on the work by US Department of health Education and Welfare and Bradford-Hill.

US Surgeon General Report's Criteria	Bradford-Hill Criteria
Consistency of association	Strength
Strength of association	Consistency
Specificity of association	Specificity
Temporal relationship of association	Temporality
Coherence of association	Biological gradient
	Coherence
	Experiment

Figure 2.1 | Direct acyclic graphs (DAG)

DAGs a-f demonstrating statistical and causal relationships between variables, where X is an exposure, Y is an outcome, C is a common cause (or confounder), M is a mediator, U is an unmeasured confounder and L is a time-varying confounder. **a).** Statistical association between X and Y may be found if there is a true causal effect of X on Y; **b).** Common effect of C on X and Y may generate a statistical association despite no true causal effect, here adjusting for C would remove the statistical association, revealing no causal association; **c).** Causal relationship between X and Y, both of which are also caused by covariate C, thus adjusting for C appropriately will retain and demonstrate the strength of the X-Y causal association, but only if there is no measurement error of C. If measurement error exists for C, adjustment will result in a biased X-Y estimate of association. **d).** The causal association between X and Y may also be mediated by M, this forms the basis of the mediation model whereby a direct effect exerted by X on Y (path *c)* and an indirect effect exerted by X through M on Y (path *ab*) combine to form a total effect (*ab* + *c*). **e).** The direct effect of X on Y can be estimated by adjusting for M, however this may introduce collider-stratification bias. M is a collider variable (a common effect (where two variables (arrows) collide on it)), hence adjustment for M will open up a backdoor pathway via U (which cannot be adjusted for because it is unmeasured). **f).** Adjustment for confounders for the association between mediator and outcome can remove collider stratification bias assuming all confounders have been measured. However, given that the confounders L may themselves be affected by the exposure, adjustment for L can continue to introduce bias. Inverse probability weighting and G-estimation are two methods that can deal with intermediate confounding. Modified from Renehan et al. supplemental information S3[32,205] and Vansteelandt et al.[206]



2.5.5 MEDIATION ANALYSIS

The relationship between obesity and survival in the adjuvant setting is likely complicated, as evidenced within Chapter one. A causal relationship is hypothesised but cannot be inferred with confidence due to the limitations of current evidence (in particular the issue of variable ACT dosing).[32] Consequently, to understand the relative effects of obesity and sub-optimal chemotherapy on survival, statistical methodology is required that is able to decompose and quantify these effects, whilst appropriately dealing with confounding and bias.

Mediation analysis is one such strategy allowing researchers to answer, "*how* does a relationship occur?" and not simply "*does* it occur?". The early seminal work by Baron and Kenney in 1986[207] laid the foundations for regression-type mediation modelling, later followed by structural equation modelling (SEM)[208] and counterfactual approaches.[202,209] Mediation analysis is a valuable tool in observational and randomised controlled studies, permitting disentangling of the total effect of an exposure on an outcome into its direct effect and indirect effect through a mediator.[208,210,211]

These relationships are illustrated and expanded on by the DAG in **Figure 2.1d**, demonstrating the total effect (paths *ab* + *c*) of an exposure (X) on an outcome (Y) is made up of its direct (X → Y; path *c*) and indirect (X → M → Y; path *ab*) effects. Thus, through mediation approaches one can infer, not only whether X is associated with Y, but how this relationship occurs (whether entirely directly, indirectly or by combination of the two pathways).[212] Furthermore, it is possible to understand how confounding and unmeasured confounding might influence these relationships.[95]

2.5.6 CONFOUNDING

Definitions of and methods to deal with potential confounding have been well defined within the casual inference literature. A confounder is defined as a variable associated with (a common cause of) both the exposure and outcome (**Figure 2.1b** and **2.1c)**.[213] The presence of confounders, if not adequately adjusted for can bias or obscure the true effect of an exposure-outcome relationship. Selection of confounders for adjustment may be facilitated through use of causal inference theory and DAGs.

2.5.7 EFFECT MODIFICATION

Effect modification (sometimes termed moderation or interaction) occurs where a variable interacts on the relationship between an exposure and outcome, thus altering the magnitude of the effect rather than masking it. It can be considered as "what works for whom?",[214] e.g., the effect of a treatment on outcome may differ with age, the latter being an effect modifier. Both

confounding and effect modification are important in causal inference and are explored in Chapters five and six.

2.5.8 Individual Participant Meta-Analysis: General Principles

Meta-analyses of randomised controlled trials are well established as the highest level of evidence,[215] and their wide-spread adoption have addressed many important clinical questions. Two forms of meta-analysis exist, aggregate (or study-level) data (AD-MA) and individual participant data meta-analyses (IPD-MA). The majority of meta-analyses published are based on the former approach, however, IPD-MA has become the gold-standard offering numerous advantages.[181]

The Cochrane Collaboration, in their review of IPD-MA compared with AD-MA recommended the following:

"IPD offers the potential to explore additional, more thorough, and potentially more appropriate analyses compared to those possible with AD. But in many cases, similar results and conclusions can be drawn from IPD-MA and AD-MA. Therefore, … researchers should carefully consider the potential added benefits of IPD."[216]

In general, meta-analyses produce summary outcome estimates (e.g. hazard ratio, relative risk or odds ratio) and their associated uncertainty estimate (e.g. 95% confidence interval) in answer to a specific question, by combining outcomes across several studies, each attempting to answer the same question.[217] IPD-MA, however, sources and utilises raw individual participant data from each study to generate summary effect estimates in contrast to AD-MA, which combines the averaged or estimated outcomes previously defined by each included study.[180]

IPD meta-analysis can be undertaken utilising two- or one-stage approaches. In the first approach data is analysed at the individual trial level, producing aggregate summary outcomes or effects, which are then combined in a second stage utilising an appropriate meta-analysis model. The latter approach models the individual data from all studies simultaneously, and relies on models and assumptions specific to the outcome being generated.[218] The one-stage approach, despite requiring only a single model, may in actual fact be more complex, whereas although more onerous, the two- stage approach allows use of conventional meta-analysis techniques in the second stage.[180,219] The two approaches often generate similar results, however, where differences arise, these are often the result of adopting differing assumptions.[220,221] Both IPD-MA approaches allow clustering to be retained within and between trials (improving heterogeneity and reducing introduction of bias),[222] in addition to permitting either fixed- or random-effects analysis (the latter taking into account population differences by assuming heterogeneity of the estimated treatment effects between studies).[218,223]

Advantages and disadvantages of IPD meta-analysis

The advantages and disadvantages of IPD and AD meta-analysis are summarised in **Table 2.5**.[180,220,223–225] It is clear that the advantages of IPD-MA are numerous, and as such are not only used to synthesise summary effect estimates, but increasingly influence trial design (e.g. similar trial design across studies to permit a prospectively designed meta-analyses of their results, as in AlaCart & American College of Surgeons Oncology Group protocol Z6051 study),[226] conduct and analysis.[225]

In the context of this thesis, the use of IPD-meta-analysis is supported by its advantages, in particular the ability to facilitate:

1. Analyses which have not been reported in the literature (in this case to assess the effects of varying chemotherapy exposure (the reporting of which is not sufficiently detailed or standardised across studies), with greater power.
2. Reduction of heterogeneity, confounding and bias and thus improve reliability, by retaining clustering, use of random effects models and standardisation of factors to be adjusted for.
3. Management of missing data at the individual participant level.
4. Use of standardised outcome definitions across trials.
5. Complex modelling, thus allowing meta-analysis of mediation model effect estimates.

These key methodological concepts will allow for improved understanding of the association between obesity and colorectal cancer outcomes, including the BMI-ACT relationships, how this association occurs (through mediation analysis), with reduced confounding and bias (through use of trial data and careful *a priori* identification of confounding though causal inference approaches) and increased precision and power (through IPD-MA).

Table 2.5 | Advantages and disadvantages of individual participant data and aggregate data meta-analyses

From references [180,220,223–225]

	Advantages	Disadvantages
Aggregate data (AD) Meta-analysis	• Less resource intense (time and cost). • Less complicated statistical methods. • Summarises outcome estimates with increased power. • Allows weighting of studies (e.g., by inverse of the variance) • Pooled analyses are conceptually the same as IPD meta-analyses, including estimating of study-specific treatment effects, assessment of heterogeneity, and estimation of summary effect size.	• Aggregate data may not be available/reported/standardised across studies (e.g., analysis and reporting of outcomes) • Limited ability to explore the influence of characteristics at the individual participant level. • Publication bias may be a problem, where statistically significant results are more likely to be reported. • Quality of the IPD will depend on quality of the included studies, but also on the variability of reported outcomes. • Exploration of effect modifiers lack power and may be prone to ecological bias.
Individual participant data (IPD) Meta-analysis	• Consistent definitions (inclusion/exclusion criteria, outcomes etc.) • Analysis of missing or poorly reported outcomes • Data checking and updating (including follow-up, duplication etc.) • Analysis checking • Assessment of randomisation adequacy. • Inclusion of unpublished studies (reducing publication bias). • Exploration of heterogeneity at the patient level • Sub-group/additional analyses (hypothesis generating) with greater power. • Management of missing data at the individual level. • Standardisation of statistical analysis (inc. adjustment for confounding/prognostic factors). • More powerful/reliable examination of effect modification and confounding. • Modelling of complex relationships (e.g., non-linear data). • Generation and validation of prognostic models. • Impact on trial design, conduct and analysis. • Potentially more reliable for all of the above reasons.	• Resource intensive: time & costs required to contact study authors & obtain, clean/harmonise, and analyse data. • Relies on extensive cooperation of original investigators, institutions, review boards, pharmaceutical companies etc. • May require advanced statistical expertise (especially one-stage approach or modelling complex relationships). • Possible ethical or confidentiality concerns regarding patient level data (though with anonymised data this is not usually a problem) • Some data may not be available for all studies despite having IPD, which may introduce some bias. • Overall, the quality remains reliant on adequacy and quality of randomisation and data-collection of the original studies.

Abbreviations: AD, Aggregate data; **IPD**, Individual participant data; **MA,** Meta-analysis

CHAPTER THREE

RESULTS PART I

Characterising BMI-chemotherapy dosing relationships

CHAPTER THREE PREFACE

Chapter three characterises the relationship between body mass index (BMI) and adjuvant chemotherapy (ACT) dosing. Chemotherapy dosing is richly phenotyped within the data available from each trial, and hence the different aspects of adherence to a regimen of chemotherapy are examined to provide an understanding of the underlying datasets, their differences, and potential underlying relationships with BMI prior to the formal statistical modelling undertaken in Chapters five and six.

3.1 INTRODUCTION

A regimen of chemotherapy comprises the administration of a number of cycles, where a dose of chemotherapy is administered, with each cycle separated by a specific time period (cycle length). The doses, cycle lengths and numbers of cycles are pre-defined according to a standard dosing protocol. Thus, adherence to such a protocol, involves receipt of the standard dose, over the standard time frame for a pre-defined number of cycles. Body mass index (BMI) has the potential to influence all of aspects of chemotherapy administration from the selection of a starting dose, to subsequent cycle dose reductions, dose delays and early discontinuation of chemotherapy (usually the result of toxicity).

3.2 METHODS

3.2.1 AIMS

The aims of Chapter three were to describe the rich adjuvant chemotherapy (ACT) datasets and characterise the relationship between BMI and chemotherapy dosing. In particular, to understand how BMI might influence the components of adherence to chemotherapy regimens, thus, providing insight into potential mechanisms of BMI-chemotherapy adherence pathways.

3.2.2 DATA SOURCE & POPULATION

The main dataset, as previously described in Chapter two was utilised, containing cycle-level chemotherapy data, including doses for each drug administered and dates of administration.

2.2.3 EXPOSURE

The primary exposure throughout this Chapter was BMI, categorised according to WHO definitions as previously defined (Chapters one and two). The expanded categorisation, including obese I, II and III, was not used due the small number of patients included in the higher obese categories.

3.2.4 OUTCOMES

Intermediate chemotherapy outcomes, consisting of the various components of adherence, were explored (see Chapter two for definitions), and analyses are summarised in **Table 3.1.** Due to the complexity in the nature of chemotherapy regimens, which differed according to trial, dose-related metrics were calculated relative to BSA and also to the relevant expected protocol-defined dosing schedules, allowing comparison across the range of BMI in addition to the different drugs, regimens and trials.

Table 3.1 | BMI-chemotherapy analysis outcomes

The chemotherapy outcomes explored in relation to BMI, the levels of stratification explored, and the statistical tests performed if applicable.

	Outcome	Drug	Regimen	Trial
Cycle 1	Median cycle 1 relative dose	✓	✓[a]	✓[a]
	Dose capping rate	✓	✓[b]	✓[b]
Cycle-level	Median cycle relative dose*	✓	✓	×
	Relative under-dosing rate*	✓	✓	×
	Subsequent cycle dose-reduction rate*	✓	✓	×
	Early discontinuation rate (overall)*	✓	✓[b]	✓[b]
	Cycle-level early discontinuation (attrition)*	✓	✓	×
	Dose delay rate (overall)	×	✓	✓
	Cycle level percentage of patients dose delayed*	×	✓	×
Overall adherence measures	Median (A)RDI	✓	✓[a]	✓[a]
	Median (A)CRD	✓	✓[a]	✓[a]

Abbreviations: ACRD, Average cumulative relative dose; **ARDI,** average relative dose received.

[a] Cuzick's test for trend

[b] Cochran Armitage test for trend

*Excludes patients changing regimen

3.2.5 STATISTICAL ANALYSIS

Baseline demographics were summarised by trial. Selected variables were additionally stratified by BMI categories per trial and included: age, sex, performance status, T-stage, N-stage, American Joint Committee on Cancer (AJCC) stage, race, differentiation category (poorly-/un-differentiated vs. well-/moderately- differentiated), obstruction and/or perforation, perineural invasion (PNI), lymphovascular invasion (LVI), lymph node harvest and lymph node adequacy (≥10 nodes) and post-operative carcinoembryonic antigen (CEA). Distributions of continuous variables were graphically assessed, with central tendency measures chosen based on data distributions. Where data appeared normally distributed, means and standard deviation (SD) are presented, and conversely where data appeared non-normally distributed, medians and interquartile ranges (IQR) are presented, with proportions reported as n (%).

Outcomes were stratified at the regimen and drug-level and, where appropriate, at the trial level (**Table 3.1**). Where trial-level results are presented, regimen-level results are only presented for multi-regimen trials (SCOT and PROCTOR-SCRIPT [PS]) to reduce repetition. Trial-level analyses were not performed for longitudinal cycle-level outcomes (median relative dose received (RDR), relative under dosing (RUD), dose reductions, attrition, and dose-delays) due to the regimen-dependent differences in the numbers of cycles received and lengths of cycles, which would not be appropriate to combine within SCOT and PS trials. Furthermore, drug-level stratification would not provide additional information for dose-delays as cycle start days would be the same for all drugs given. Finally, the small number of SCOT patients who changed regimen, were excluded from longitudinal cycle-level analyses, as it was not possible to calculate e.g., expected numbers of cycles, nor was it appropriate to assess and plot cycle-level data where patients were switching in and out of regimens with different cycle timings. However, cycle 1 and overall adherence measures could be stratified at each level and hence included all patients.

Differences across ordered BMI categories were tested using Cuzick's[227] (for continuous outcomes) and Cochran Armitage[228] (for binary outcomes) tests for trend. These test for an association between an ordinal predictor and outcome and are therefore often more powerful than Wilcoxon rank sum or Chi squared tests. However, their main limitation is the lack of ability to demonstrate non-linear relationships (e.g., U-shaped). Where categorical outcomes had three or more categories, the chi-squared (χ^2) test was used, the limitation being lack of ability to identify which comparisons are statistically significant, limiting their interpretation, unless post-estimation tests are performed. Statistical testing was only performed on certain key analyses (**Table 3.1**) to reduce the number of tests performed in attempt to reduce the problem of significance in the context of multiple testing. Definitive statistical modelling of BMI-chemotherapy relationships was undertaken in Chapters five and six. Statistical significance

was attributed a p value threshold of 5%. All statistical analyses presented within this Chapter were performed in Stata® version 17 (StataCorp LLC, 2021, College Station, TX, USA).

3.3 RESULTS

3.3.1 PATIENT INCLUSION

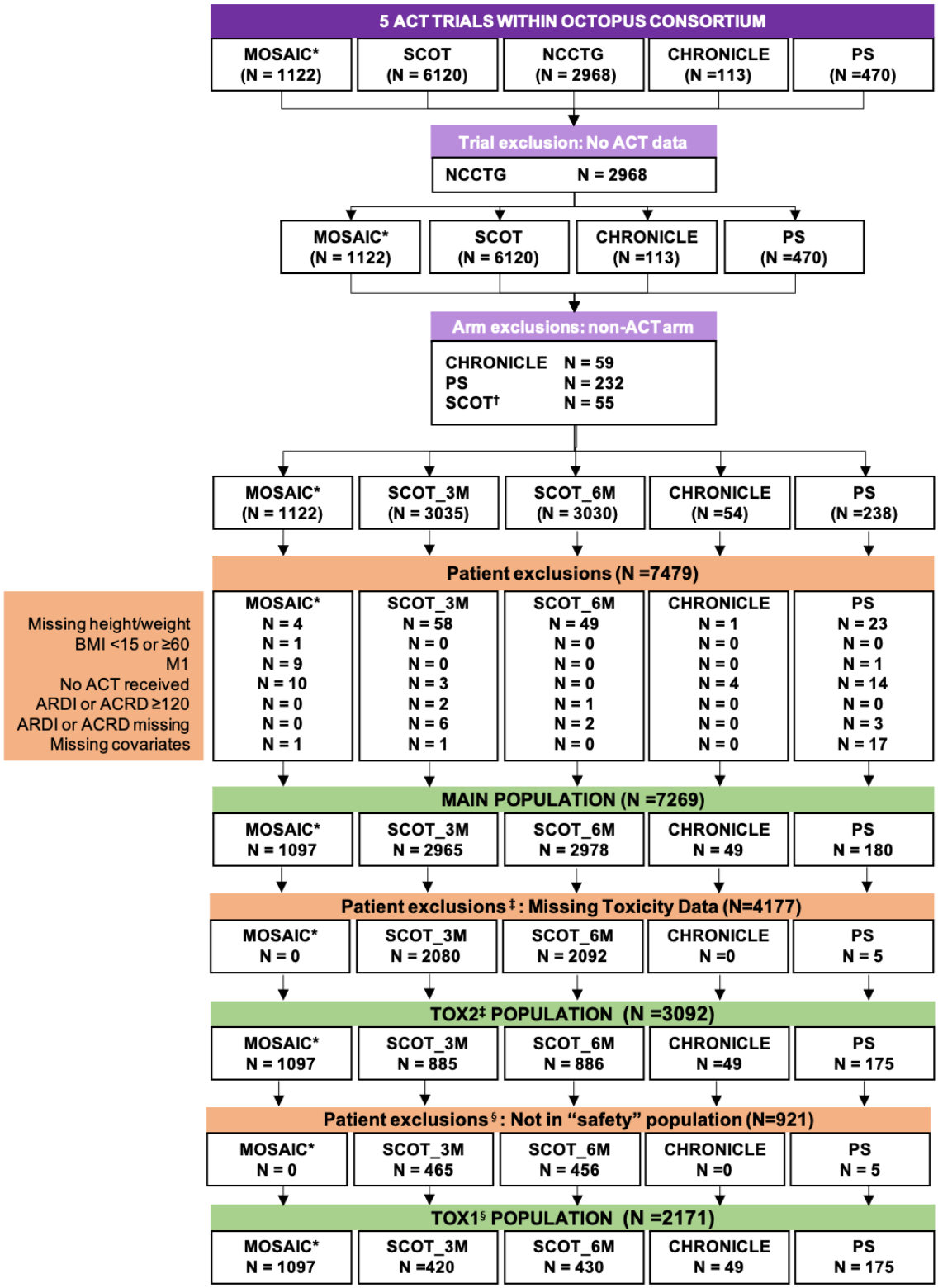
The OCTOPUS consortium contained five adjuvant chemotherapy trials. Of these, four had available BMI, adjuvant chemotherapy and toxicity data (MOSAIC, SCOT, CHRONICLE and PS). One trial (NCCTG N0147) was excluded due to lacking cycle-level chemotherapy data, and missing neutropenia data (see Chapter two). Data were available and included for the control arm only of the MOSAIC trial (5-FU/LV arm) and both arms of the SCOT trial (3months and 6 months). Though both arms of CHRONICLE and PS trials were available, the control arms were observation-only and therefore only the treatment arms were included. Furthermore 55 patients from the SCOT trial were not randomised and therefore had no ACT data, leaving 7479 patients eligible from four trials (**Figure 3.1**).

Following patient-level exclusions, a total of 7269 patients (97.2% of the 7479 eligible for inclusion) constituted the Main population for analysis, with the majority of exclusions the result of missing height and/or weight at trial entry. Two additional toxicity populations were created due to missing toxicity data as described in Chapter 2. The TOX1 population, consisting of a complete case dataset of all patients with toxicity data collected as mandated by trial protocols (i.e., “safety” populations), with 2171 patients. The TOX2 population, consisting of a complete case dataset of patients with any recorded toxicity data, which included 3092 patients (**Figure 3.1**). Both of these were utilised in Chapters four, five and six.

3.3.2 TRIAL-LEVEL BASELINE CHARACTERISTICS

Trial baseline demographics are presented in **Table 3.2**. A number of baseline differences across the trials were noted. Both arms of the SCOT trial had a higher mean BMI with a higher proportion of obese patients, more representative of current UK proportions of obese patients, with patients also tending to be older. WHO performance status tended to be higher in the MOSAIC trial. There were also differences in the proportions of female patients, (y)pT stage, (y)pN stage and AJCC disease stages across the trials.

Figure 3.1 | Flow chart of participant inclusion



* Control arm only available from project DataSphere
† 55 patients withdrew, therefore no randomisation or chemotherapy data
‡ TOX2 population excludes any patient with missing toxicity data
§ TOX1 population excludes any patients who had did not have protocol-mandated toxicity data collected i.e. were in the trial "safety" populations (exclusions apply to the SCOT trial only)

Table 3.2 | Trial baseline characteristics

			MOSAIC N = 1097	SCOT_3M N = 2965	SCOT_6M N = 2978	CHRONICLE N = 49	PS N = 180	Total N = 7269
Mean BMI (SD), kg/m^2			25.22 (4.21)	26.88 (4.79)	26.98 (4.82)	25.19 (3.28)	24.61 (3.28)	26.60 (4.73)
Baseline BMI WHO category	**Underweight**		36 (3.28%)	42 (1.42%)	36 (1.21%)	0 (0.00%)	1 (0.56%)	115 (1.58%)
	Normal		542 (49.41%)	1,069 (36.05%)	1,071 (35.96%)	27 (55.10%)	98 (54.44%)	2,807 (38.62%)
	Overweight		384 (35.00%)	1,211 (40.84%)	1,191 (39.99%)	17 (34.69%)	72 (40.00%)	2,875 (39.55%)
	Obese		135 (12.31%)	643 (21.69%)	680 (22.83%)	5 (10.20%)	9 (5.00%)	1,472 (20.25%)
		Obese 1	108 (9.85%)	471 (15.89%)	500 (16.79%)	5 (10.20%)	9 (5.00%)	1,093 (15.04%)
		Obese 2	24 (2.19%)	123 (4.15%)	140 (4.70%)	0 (0.00%)	0 (0.00%)	287 (3.95%)
		Obese 3	3 (0.27%)	49 (1.65%)	40 (1.34%)	0 (0.00%)	0 (0.00%)	92 (1.27%)
Mean BSA(SD), m2			1.79 (0.2)	1.91 (0.23)	1.91 (0.24)	1.85 (0.19)	1.88 (0.19)	1.89 (0.23)
Mean Age (SD),	**years**		58.66 (10.44)	63.43 (9.21)	63.41 (9.39)	60.24 (7.44)	60.96 (8.56)	62.62 (9.61)
Sex	**Male**		575 (52.42%)	1,793 (60.47%)	1,807 (60.68%)	40 (81.63%)	109 (60.56%)	4,324 (59.49%)
	Female		522 (47.58%)	1,172 (39.53%)	1,171 (39.32%)	9 (18.37%)	71 (39.44%)	2,945 (40.51%)
WHO performance status	**0**		335 (30.54%)	2,134 (71.97%)	2,098 (70.45%)	30 (61.22%)	116 (64.44%)	4,713 (64.84%)
	1		627 (57.16%)	831 (28.03%)	880 (29.55%)	19 (38.78%)	59 (32.78%)	2,416 (33.24%)
	2		130 (11.85%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (2.78%)	135 (1.86%)
	3		5 (0.46%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (0.07%)
Race	**White**		20 (1.82%)	109 (3.68%)	76 (2.55%)	0 (0.00%)	0 (0.00%)	205 (2.82%)
	Non-white		1,077 (98.18%)	2,427 (81.85%)	2,482 (83.34%)	0 (0.00%)	0 (0.00%)	5,986 (82.35%)
	Missing		0 (0.00%)	429 (14.47%)	420 (14.10%)	49 (100.00%)	180 (100.00%)	1,078 (14.83%)
Disease site	**Colon**		1,097 (100.00%)	2,430 (81.96%)	2,439 (81.90%)	0 (0.00%)	0 (0.00%)	5,966 (82.07%)
	Rectum		0 (0.00%)	535 (18.04%)	539 (18.10%)	49 (100.00%)	180 (100.00%)	1,303 (17.93%)
(y)pT-stage	**pT0, pT1, pT2**		61 (5.56%)	370 (12.48%)	370 (12.42%)	23 (46.94%)	40 (22.22%)	864 (11.89%)
	pT3		832 (75.84%)	1,698 (57.27%)	1,709 (57.39%)	24 (48.98%)	138 (76.67%)	4,401 (60.54%)
	pT4		204 (18.60%)	897 (30.25%)	899 (30.19%)	2 (4.08%)	2 (1.11%)	2,004 (27.57%)
(y)pN-stage	**pN0**		443 (40.38%)	546 (18.41%)	541 (18.17%)	40 (81.63%)	39 (21.67%)	1,609 (22.14%)
	pN1		433 (39.47%)	1,686 (56.86%)	1,692 (56.82%)	6 (12.24%)	90 (50.00%)	3,907 (53.75%)
	pN2		221 (20.15%)	733 (24.72%)	745 (25.02%)	3 (6.12%)	51 (28.33%)	1,753 (24.12%)
AJCC Stage	**0**		0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (12.24%)	0 (0.00%)	6 (0.08%)
	I		0 (0.00%)	7 (0.24%)	12 (0.40%)	14 (28.57%)	2 (1.11%)	35 (0.48%)
	II		443 (40.38%)	539 (18.18%)	529 (17.76%)	20 (40.82%)	37 (20.56%)	1,568 (21.57%)
	III		654 (59.62%)	2,419 (81.59%)	2,437 (81.83%)	9 (18.37%)	141 (78.33%)	5,660 (77.86%)

Table 3.2 | *Continued*

		MOSAIC N = 1097	SCOT_3M N = 2965	SCOT_6M N = 2978	CHRONICLE N = 49	PS N = 180	Total N = 7269
Differentiation	**Poorly or un-diff**	144 (13.13%)	123 (4.15%)	116 (3.90%)	0 (0.00%)	0 (0.00%)	383 (5.27%)
	Well or moderately	894 (81.49%)	420 (14.17%)	413 (13.87%)	0 (0.00%)	0 (0.00%)	1,727 (23.76%)
	Missing	59 (5.38%)	2,422 (81.69%)	2,449 (82.24%)	49 (100.00%)	180 (100.00%)	5,159 (70.97%)
Perforation or obstruction	**No**	836 (76.21%)	391 (13.19%)	361 (12.12%)	0 (0.00%)	0 (0.00%)	1,588 (21.85%)
	Yes	261 (23.79%)	150 (5.06%)	168 (5.64%)	0 (0.00%)	0 (0.00%)	579 (7.97%)
	Missing	0 (0.00%)	2,424 (81.75%)	2,449 (82.24%)	49 (100.00%)	180 (100.00%)	5,102 (70.19%)
PNI	**No**	0 (0.00%)	485 (16.36%)	462 (15.51%)	0 (0.00%)	0 (0.00%)	947 (13.03%)
	Yes	0 (0.00%)	38 (1.28%)	48 (1.61%)	0 (0.00%)	0 (0.00%)	86 (1.18%)
	Missing	1,097 (100.00%)	2,442 (82.36%)	2,468 (82.87%)	49 (100.00%)	180 (100.00%)	6,236 (85.79%)
LVI	**No**	435 (39.65%)	250 (8.43%)	238 (7.99%)	0 (0.00%)	60 (33.33%)	983 (13.52%)
	Yes	157 (14.31%)	292 (9.85%)	294 (9.87%)	0 (0.00%)	39 (21.67%)	782 (10.76%)
	Missing	505 (46.03%)	2,423 (81.72%)	2,446 (82.14%)	49 (100.00%)	81 (45.00%)	5,504 (75.72%)
Median Lymph node harvest (IQR)		13.00 (8.00-19.00)	9.00 (7.00-14.50)*	8.000 (5.00-9.00)*	N R	11.00 (7.00-16.00)	12.00 (8.00-18.00)
Lymph node ≥ 10 nodes	**No**	353 (32.18%)	39 (1.32%)	44 (1.48%)	0 (0.00%)	67 (37.22%)	503 (6.92%)
	Yes	744 (67.82%)	502 (16.93%)	487 (16.35%)	0 (0.00%)	113 (62.78%)	1,846 (25.40%)
	Missing	0 (0.00%)	2,424 (81.75%)	2,447 (82.17%)	49 (100.00%)	0 (0.00%)	4,920 (67.68%)
Margins	**R0**	0 (0.00%)	2,965 (100.00%)	2,978 (100.00%)	49 (100.00%)	168 (93.33%)	6,160 (84.74%)
	R1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (4.44%)	8 (0.11%)
	Missing	1,097 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (2.22%)	1,101 (15.15%)
Median post-op CEA (IQR), ng/ml		1.300 (0.90-2.20)	1.60 (1.000-2.00)	1.60 (1.000-2.20)	N R	1.50 (1.000-2.70)	1.500 (1.000-2.20)
Chemo regimen	**LV5FU2**	1,097 (100.00%)	N A	N A	N A	N A	1,097 (15.09%)
	mFOLFOX6	N A	934 (31.50%)	936 (31.43%)	N A	N A	1,870 (25.73%)
	CAPOX	N A	1,959 (66.07%)	1,940 (65.14%)	49 (100.00%)	N A	3,948 (54.31%)
	mFOLFOX6/CAPOX	N A	72 (2.43%)	102 (3.43%)	N A	N A	174 (2.39%)
	Mayo-5FULV	N A	N A	N A	N A	27 (15.00%)	27 (0.37%)
	Nordic 5FULV	N A	N A	N A	N A	35 (19.44%)	35 (0.48%)
	CAP	N A	N A	N A	N A	118 (65.56%)	118 (1.62%)

Abbreviations: AJCC, American joint committee on cancer; **BMI,** Body mass index**; BSA,** body surface area; **CAP**, Capecitabine; **CAPOX,** Capecitabine + Oxaliplatin; **CEA**, carcinoembryonic antigen; **IQR**, Interquartile range; **LVI**, Lymphovascular invasion; **mFOLFOX6,** LV5FU2 + oxaliplatin; **NR**, Not recorded; **PNI**, Perineural invasion; **WHO**, World Health Organisation; **(y)pT,** (post-neoadjuvant treatment) pathological tumour stage, **(y)pN,** (post-neoadjuvant treatment) pathological nodal stage.
* High risk features only recorded for high-risk stage II patients, therefore high proportion of missing data.

3.3.3 BASELINE CHARACTERISTICS BY BMI AND TRIAL

Selected baseline characteristics by BMI category are presented for each trial in **Table 3.3**, with additional baseline characteristics in the appendix (**Table A3.1**). As expected, mean BSA increased with increasing BMI categories for each trial, with the mean BSA for obese patients in all trials being ≥2.0m^2. Age appeared to have an inverse-U relationship for MOSAIC and both SCOT arms, with younger patients in underweight and obese categories, suggesting the possibility of a selection of a healthier subset of obese patients. Underweight patients tended to be female, have higher performance status, higher t-stage, less likely to be node negative, supporting the argument of the potential risk of reverse causality in underweight patients. Patterns across overweight and obese BMI categories were less consistent across trials. Proportions of male and female patients varied across BMI categories and trials. Overweight and obese patients in MOSAIC and SCOT tended to have lower performance status, lower T-stage, and variable N-stage disease, potentially supporting the concept of a tendency for comparatively healthier overweight or obese patient enrolment.

Data on race, tumour differentiation, perforation, or obstruction, and perineural invasion were not collected for the CHRONICLE and PROCTORS-SCRIPT trials. Furthermore, lymphovascular invasion, lymph node harvest and post-operative CEA were not collected for CHRONICE, and perineural invasion was not collected for MOSAIC or PROCTOR. Hence, these were systematically missing. Significant amounts of missing data for those variables defining “high-risk” tumour features in the SCOT trial were due to this data only being collected for the stage II cancers **(Table A3.1)** but appeared to be similar across the BMI categories and for both arms**.**

In the MOSAIC and SCOT trials, the majority of patients were white, with the MOSAIC trial demonstrating some imbalance, with a higher proportion of underweight patients of “other” races than within the other BMI categories. The incidence of perforation and/or obstruction appeared to be highest in the underweight category and lowest in the obese categories for MOSAIC and SCOT_6M, with little difference across SCOT_3M. Similarly, the underweight patients had the highest proportions of lymphovascular invasions for MOSAIC and SCOT_6M, with less consistent relationships across the other BMI categories. Overall, there appeared to be a trend towards reducing lymph node harvest with increasing BMI (except for SCOT_6M).

Table 3.3 | Baseline characteristics by BMI and Trial

		Underweight	Normal	Overweight	Obese
Mean BSA (SD), m2					
MOSAIC		1.44 (0.10)	1.70 (0.16)	1.88 (0.16)	2.00 (0.19)
SCOT_3M		1.49 (0.12)	1.75 (0.17)	1.94 (0.17)	2.13 (0.21)
SCOT_6M		1.50 (0.11)	1.74 (0.17)	1.95 (0.17)	2.13 (0.20)
CHRONICLE			1.74 (0.14)	1.98 (0.18)	2.04 (0.08)
PS		1.69 (0)	1.78 (0.17)	1.99 (0.13)	2.10 (0.18)
Mean Age (SD), years					
MOSAIC		53.33 (14.66)	57.70 (11.05)	60.46 (9.49)	58.82 (8.01)
SCOT_3M		61.00 (11.58)	63.56 (9.64)	63.74 (9.09)	62.79 (8.44)
SCOT_6M		61.64 (9.63)	63.50 (9.90)	63.67 (9.19)	62.91 (8.90)
CHRONICLE			60.93 (7.56)	57.82 (6.58)	64.80 (8.11)
PS		62.85 (0)	60.32 (8.84)	61.46 (8.17)	63.58 (9.12)
Sex					
MOSAIC	**Male**	6 (16.67%)	282 (52.03%)	230 (59.90%)	57 (42.22%)
	Female	30 (83.33%)	260 (47.97%)	154 (40.10%)	78 (57.78%)
SCOT_3M	**Male**	11 (26.19%)	572 (53.51%)	820 (67.71%)	390 (60.65%)
	Female	31 (73.81%)	497 (46.49%)	391 (32.29%)	253 (39.35%)
SCOT_6M	**Male**	10 (27.78%)	545 (50.89%)	814 (68.35%)	438 (64.41%)
	Female	26 (72.22%)	526 (49.11%)	377 (31.65%)	242 (35.59%)
CHRONICLE	**Male**	N A	20 (74.07%)	15 (88.24%)	5 (100.00%)
	Female	N A	7 (25.93%)	2 (11.76%)	0 (0.00%)
PS	**Male**	1 (100.00%)	54 (55.10%)	49 (68.06%)	5 (55.56%)
	Female	0 (0.00%)	44 (44.90%)	23 (31.94%)	4 (44.44%)
WHO performance status					
MOSAIC	**0**	6 (16.67%)	156 (28.78%)	120 (31.25%)	53 (39.26%)
	1	20 (55.56%)	319 (58.86%)	219 (57.03%)	69 (51.11%)
	2	10 (27.78%)	64 (11.81%)	43 (11.20%)	13 (9.63%)
	3	0 (0.00%)	3 (0.55%)	2 (0.52%)	0 (0.00%)
SCOT_3M	**0**	20 (47.62%)	741 (69.32%)	906 (74.81%)	467 (72.63%)
	1	22 (52.38%)	328 (30.68%)	305 (25.19%)	176 (27.37%)
SCOT_6M	**0**	24 (66.67%)	756 (70.59%)	850 (71.37%)	468 (68.82%)
	1	12 (33.33%)	315 (29.41%)	341 (28.63%)	212 (31.18%)
CHRONICLE	**0**	N A	18 (66.67%)	10 (58.82%)	2 (40.00%)
	1	N A	9 (33.33%)	7 (41.18%)	3 (60.00%)
PS	**0**	0 (0.00%)	62 (63.27%)	49 (68.06%)	5 (55.56%)
	1	1 (100.00%)	33 (33.67%)	22 (30.56%)	3 (33.33%)
	2	0 (0.00%)	3 (3.06%)	1 (1.39%)	1 (11.11%)
Disease site					
MOSAIC	**Colon**	36 (100.00%)	542 (100.00%)	384 (100.00%)	135 (100.00%)
SCOT_3M	**Colon**	35 (83.33%)	882 (82.51%)	973 (80.35%)	540 (83.98%)
	Rectum	7 (16.67%)	187 (17.49%)	238 (19.65%)	103 (16.02%)
SCOT_6M	**Colon**	32 (88.89%)	863 (80.58%)	967 (81.19%)	577 (84.85%)
	Rectum	4 (11.11%)	208 (19.42%)	224 (18.81%)	103 (15.15%)
CHRONICLE	**Rectum**	N A	27 (100.00%)	17 (100.00%)	5 (100.00%)
PS	**Rectum**	1 (100%)	98 (100%)	72 (100%)	9 (100%)
T-stage					
MOSAIC	**(y)pT0-pT2**	1 (2.78%)	27 (4.98%)	18 (4.69%)	15 (11.11%)
	(y)pT3	27 (75.00%)	408 (75.28%)	302 (78.65%)	95 (70.37%)
	(y)pT4	8 (22.22%)	107 (19.74%)	64 (16.67%)	25 (18.52%)
SCOT_3M	**(y)pT0-pT2**	3 (7.14%)	121 (11.32%)	151 (12.47%)	95 (14.77%)
	(y)pT3	27 (64.29%)	600 (56.13%)	695 (57.39%)	376 (58.48%)
	(y)pT4	12 (28.57%)	348 (32.55%)	365 (30.14%)	172 (26.75%)
SCOT_6M	**(y)pT0-pT2**	4 (11.11%)	115 (10.74%)	160 (13.43%)	91 (13.38%)
	(y)pT3	20 (55.56%)	602 (56.21%)	679 (57.01%)	408 (60.00%)
	(y)pT4	12 (33.33%)	354 (33.05%)	352 (29.55%)	181 (26.62%)
CHRONICLE	**(y)pT0-pT2**	N A	17 (62.96%)	4 (23.53%)	2 (40.00%)
	(y)pT3	N A	8 (29.63%)	13 (76.47%)	3 (60.00%)
	(y)pT4	N A	2 (7.41%)	0 (0.00%)	0 (0.00%)
PS	**(y)pT0-pT2**	0 (0.00%)	19 (19.39%)	21 (29.17%)	0 (0.00%)
	(y)pT3	1 (100.00%)	78 (79.59%)	50 (69.44%)	9 (100.00%)
	(y)pT4	0 (0.00%)	1 (1.02%)	1 (1.39%)	0 (0.00%)

Table 3.3 | *Continued*

		Underweight	Normal	Overweight	Obese
N-stage					
MOSAIC	**(y)pN0**	12 (33.33%)	222 (40.96%)	159 (41.41%)	50 (37.04%)
	(y)pN1	13 (36.11%)	204 (37.64%)	155 (40.36%)	61 (45.19%)
	(y)pN2	11 (30.56%)	116 (21.40%)	70 (18.23%)	24 (17.78%)
SCOT_3M	**(y)pN0**	9 (21.43%)	200 (18.71%)	210 (17.34%)	127 (19.75%)
	(y)pN1	27 (64.29%)	621 (58.09%)	685 (56.56%)	353 (54.90%)
	(y)pN2	6 (14.29%)	248 (23.20%)	316 (26.09%)	163 (25.35%)
SCOT_6M	**(y)pN0**	7 (19.44%)	212 (19.79%)	215 (18.05%)	107 (15.74%)
	(y)pN1	23 (63.89%)	596 (55.65%)	661 (55.50%)	412 (60.59%)
	(y)pN2	6 (16.67%)	263 (24.56%)	315 (26.45%)	161 (23.68%)
CHRONICLE	**(y)pN0**	N A	20 (74.07%)	15 (88.24%)	5 (100.00%)
	(y)pN1	N A	5 (18.52%)	1 (5.88%)	0 (0.00%)
	(y)pN2	N A	2 (7.41%)	1 (5.88%)	0 (0.00%)
PS	**(y)pN0**	0 (0.00%)	23 (23.47%)	15 (20.83%)	1 (11.11%)
	(y)pN1	1 (100.00%)	47 (47.96%)	38 (52.78%)	4 (44.44%)
	(y)pN2	0 (0.00%)	28 (28.57%)	19 (26.39%)	4 (44.44%)
AJCC stage					
MOSAIC	**I**	0 0.00%	0 0.00%	0 0.00%	0 0.00%
	II	12 (33.33%)	222 (40.96%)	159 (41.41%)	50 (37.04%)
	III	24 (66.67%)	320 (59.04%)	225 (58.59%)	85 (62.96%)
SCOT_3M	**I**	0 (0.00%)	2 (0.19%)	2 (0.17%)	3 (0.47%)
	II	9 (21.43%)	198 (18.52%)	208 (17.18%)	124 (19.28%)
	III	33 (78.57%)	869 (81.29%)	1,001 (82.66%)	516 (80.25%)
SCOT_6M	**I**	0 (0.00%)	5 (0.47%)	6 (0.50%)	1 (0.15%)
	II	7 (19.44%)	207 (19.33%)	209 (17.55%)	106 (15.59%)
	III	29 (80.56%)	859 (80.21%)	976 (81.95%)	573 (84.26%)
CHRONICLE	**0**	N A	4 (14.81%)	2 (11.76%)	0 (0.00%)
	I	N A	10 (37.04%)	2 (11.76%)	2 (40.00%)
	II	N A	6 (22.22%)	11 (64.71%)	3 (60.00%)
	III	N A	7 (25.93%)	2 (11.76%)	0 (0.00%)
PS	**I**	0 (0.00%)	1 (1.02%)	1 (1.39%)	0 (0.00%)
	II	0 (0.00%)	22 (22.45%)	14 (19.44%)	1 (11.11%)
	III	1 (100.00%)	75 (76.53%)	57 (79.17%)	8 (88.89%)
Regimen					
MOSAIC	**5FULV**	36 (100.00%)	542 (100.00%)	384 (100.00%)	135 (100.00%)
SCOT_3M	**CAPOX**	28 (66.67%)	703 (65.76%)	799 (65.98%)	429 (66.72%)
	mFOLFOX6	12 (28.57%)	337 (31.52%)	384 (31.71%)	201 (31.26%)
	Both	2 (4.76%)	29 (2.71%)	28 (2.31%)	13 (2.02%)
SCOT_6M	**CAPOX**	23 (63.89%)	695 (64.89%)	761 (63.90%)	461 (67.79%)
	mFOLFOX6	12 (33.33%)	339 (31.65%)	394 (33.08%)	191 (28.09%)
	Both	1 (2.78%)	37 (3.45%)	36 (3.02%)	28 (4.12%)
CHRONICLE	**CAPOX**	N A	27 (100.00%)	17 (100.00%)	5 (100.00%)
PS	**MAYO**	0 (0%)	16 (16.33%)	10 (13.89%)	1 (11.11%)
	NORDIC	0 (0%)	20 (20.41%)	12 (16.67%)	3 (33.33%)
	CAP	1 (100%)	62 (63.27%)	50 (69.44%)	5 (55.66)

Abbreviations: **AJCC,** American joint committee on cancer; **BMI,** Body Mass Index; **BSA**, Body Surface area; **CAP**, Capecitabine; **CAPOX,** Capecitabine + Oxaliplatin; **CEA**, carcinoembryonic antigen; **IQR,** interquartile range; **mFOLFOX6,** LV5FU2 + oxaliplatin; **(y)pT,** (post-neoadjuvant treatment) pathological tumour stage, **(y)pN,** (post-neoadjuvant treatment) pathological nodal stage.

3.3.4 CHANGE IN BMI OVER CHEMOTHERAPY DURATION

Repeated BMI measures provided at the start of each cycle of chemotherapy were available for MOSAIC, SCOT_3M and SCOT_6M. **Figure 3.2** demonstrates the median change in BMI (in kg/m^2) across all cycles, according to baseline BMI category for each of the three trials and their respective regimens (excluding those patients changing regimen for the reasons discussed above). Overall, there was an increase in BMI with increasing cycle number. BMI change was, in general, inversely proportionally to starting BMI, with the largest changes in the underweight category.

Overall, at the trial level, median (IQR) change in BMI between first and last ACT cycle received according to baseline BMI categories were: 1.48 kg/m^2 (0.70, 1.97) for underweight, 1.35 kg/m^2 (0.34, 2.29) for normal, 1.17 kg/m^2 (0.32, 2.26) for overweight and 1.04 kg/m^2 (0.19, 2.21) for obese for the MOSAIC trial (p_{trend} = 0.203). For SCOT_3M these were: 0.24 kg/m^2 (-0.04, 0.98) for underweight; 0.06 kg/m^2 (-0.22, 0.83) for normal; 0.07 kg/m^2 (-0.27, 0.82) for overweight; and 0.00 kg/m^2 (-0.46, 0.72) for the obese categories (p_{trend} = 0.002). Finally, for SCOT_6M, these were: 0.66 kg/m^2 (0.00, 1.51); 0.48 kg/m^2 (-0.03, 1.51); 0.32 kg/m^2 (-0.31, 1.37); 0.00 kg/m^2 (-0.68, 1.37), respectively (p_{trned} <0.001).

These relationships were reflected in the proportions of patients changing BMI by ≥ 1kg/m^2 (**Figure 3.3**). In all trials and all BMI categories, the proportions of patients with stable BMI within 1kg/m^2 of their baseline BMI reduced with increasing cycle numbers. Furthermore, the proportion of patients with an increase in their BMI increased with increasing cycle numbers, in a manner that was inversely proportional to their starting BMI category (i.e., a higher proportion of patients increased their BMI in the underweight baseline BMI category). In SCOT_3M and SCOT_6M, the proportion of patients with reducing BMI was additionally seen to increase with increasing cycle numbers, in a manner proportional to starting BMI categories, explaining the relative zero change in median BMI and the wide interquartile ranges.

Figure 3.2 | Change in BMI over the duration of chemotherapy
Dot and line graphs demonstrating cycle-level median change in BMI (kg/m^2) for MOSAIC, SCOT_3M and SCOT_6M by baseline BMI category, with IQR demonstrated by whiskers.

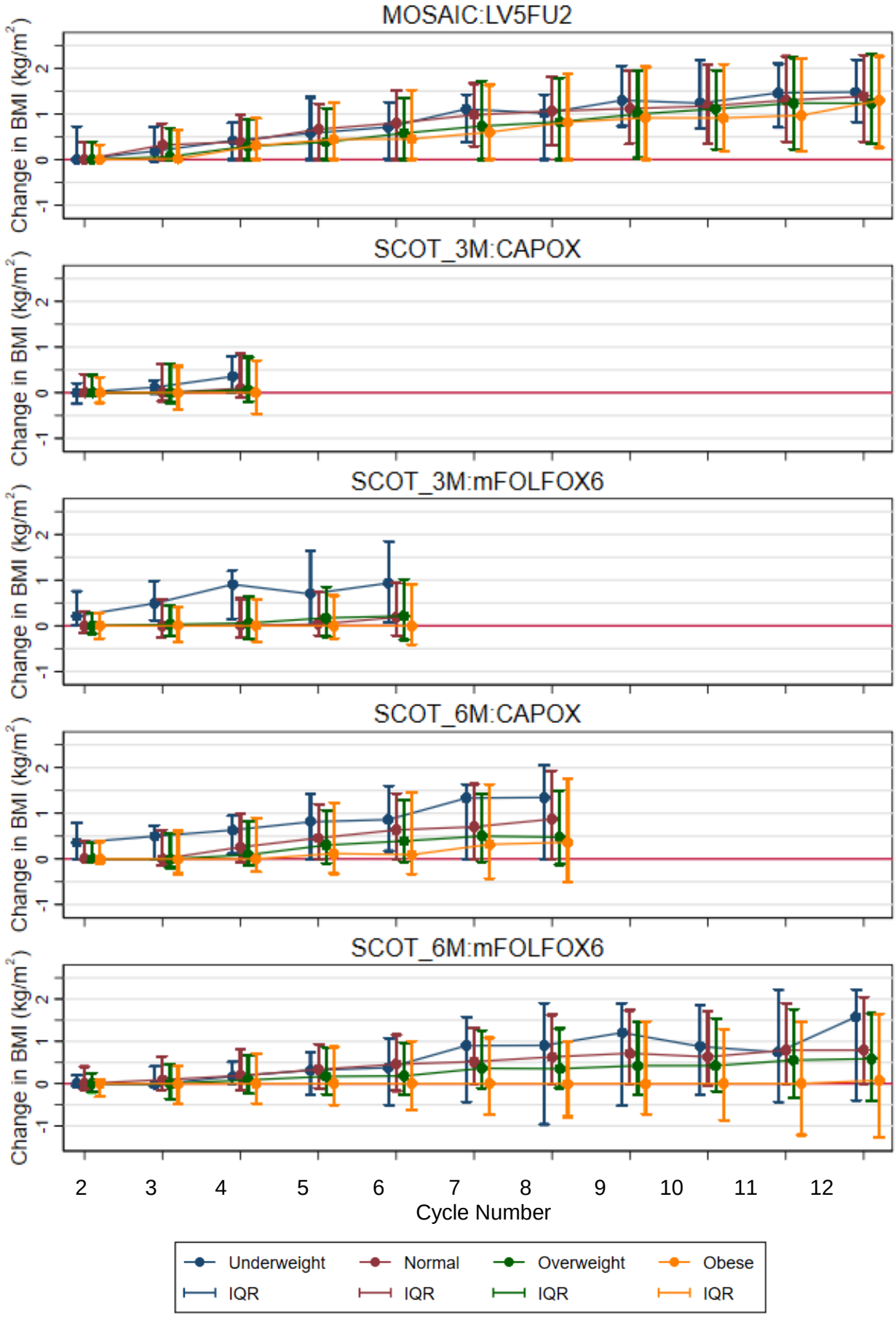
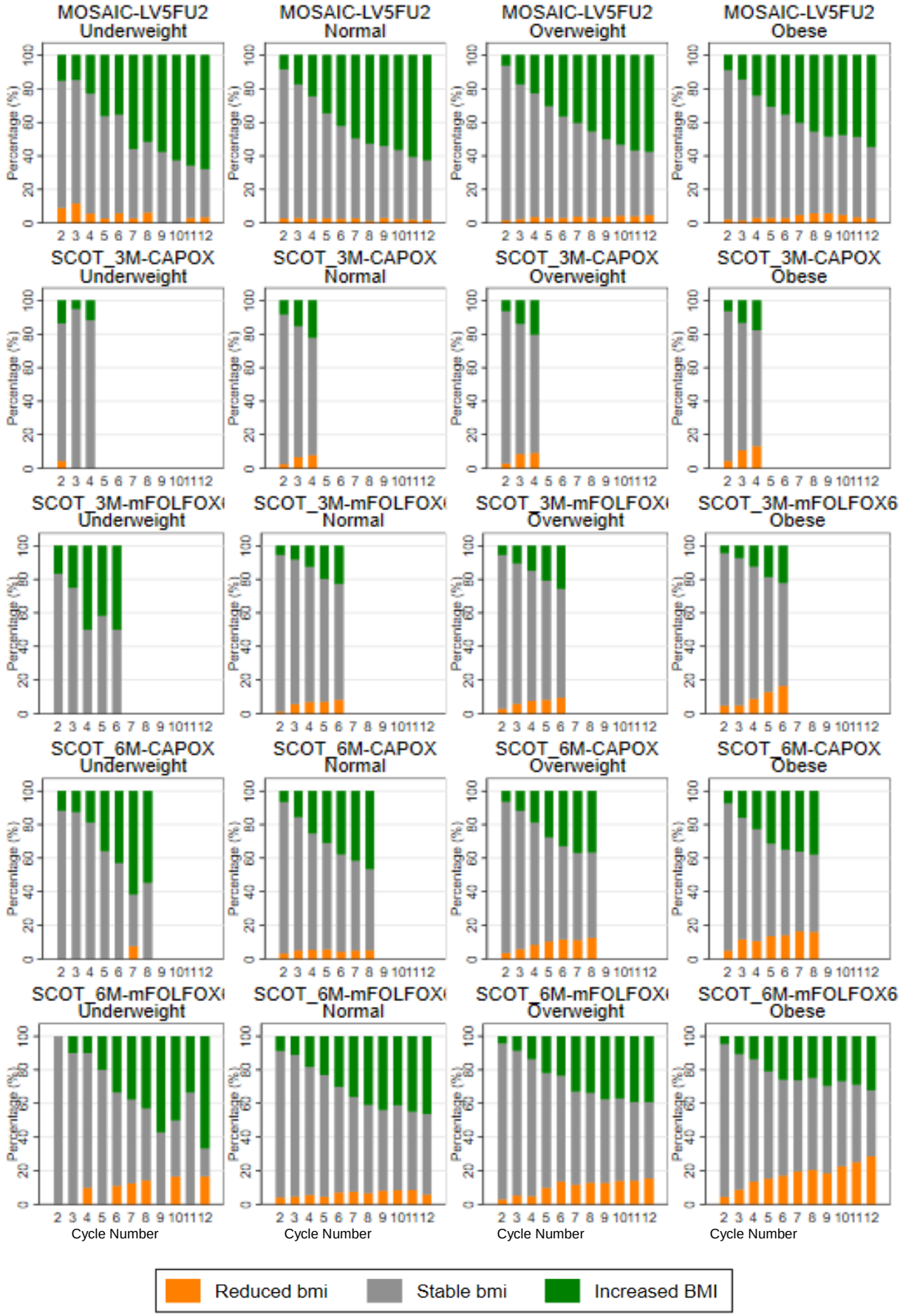


Figure 3.3 | Proportion of patients with a change in BMI

Bar graph demonstrating the proportion of patients with a >1kg/m^2 change or stable BMI for each cycle, according to their baseline BMI category for MOSAIC, SCOT_3M and SCOT_6M.



3.3.5 FIRST CYCLE DOSING AND DOSE CAPPING

Cycle one dosing

Cycle one average relative dose received (ARDR) for each trial is presented in **Figure 3.4a**. There was a significant inverse relationship between BMI and cycle 1 median ARDR for all trials (p_{trend} <0.05). In those trials with more than one regimen (SCOT and PROCTOR-SCRIPT), a similar significant inverse relationship (p_{trend} <0.05) was seen at regimen level (**Figure 3.4b)** except for the MAYO regimen, where numbers within each BMI category were generally small. Capecitabine-containing regimens tended to have slightly lower ARDRs than 5FU-containing regimens.

Cycle one median actual cycle dose (mg/m^2) and median RDR by BMI category at the drug-level within each trial and regimen are presented in the appendix (**Table A3.2**). Median actual total doses and relative doses were highest for the underweight categories and reduced with increasing BMI categories for each drug across all trials. Capecitabine doses tended to be lower, with larger reductions in the median RDR as BMI increased, and likely explained the lower cycle one ADR seen in capecitabine-containing regions.

Cycle one dose-capping

The proportion of patients receiving a capped cycle one dose, defined by receipt of <95% of the expected dose, by baseline BMI category at the trial level is demonstrated in **Figure 3.5a**. There was a significant relationship between increasing BMI category and increasing dose capping incidence for all trials, excluding CHRONICLE, which was borderline significant. Dose capping occurred for 0%, 2.2%, 4.4% and 29.6% of the underweight, normal, overweight and obese BMI categories in MOSAIC (p_{trend} <0.001); 21.4%, 26.6%, 33.0% and 62.2% in SCOT_3M (p_{trend} <0.001); 22.2% 27.7%, 36.4 and 61.4% in SCOT_6M (p_{trend}= <0.001); NA, 29.6%, 58.82% and 60.0% in CHRONICLE (p_{trend}= 0.057); and 0%, 24.5%, 34.7% and 55.6% in PROCTOR-SCRIPT (p_{trend}= 0.025), respectively. Similar relationships were seen by regimen, with capping more common in capecitabine-containing regimens and a J-shaped relationship in the mFOLFOX6 regimen of the SCOT_3M arm (**Figure 3.5b**).

Dose capping at the drug-level is demonstrated in the appendix (**Table A3.3**). In general, the incidence of dose capping was lowest for the underweight categories and increased with increasing BMI categories for each drug and across all trials, except for oxaliplatin in both SCOT_3M regimens, where dose capping displayed a J-shaped association with the normal BMI category being least likely to be dose capped. The most commonly capped drug was capecitabine consistent with the findings for cycle one dosing above.

Figure 3.4a | Cycle 1 average relative dose received by trial

Box and whisker plots demonstrating the average relative dose received (ARDR) by baseline BMI category for each trial (p values from Cuzick's test for trend).

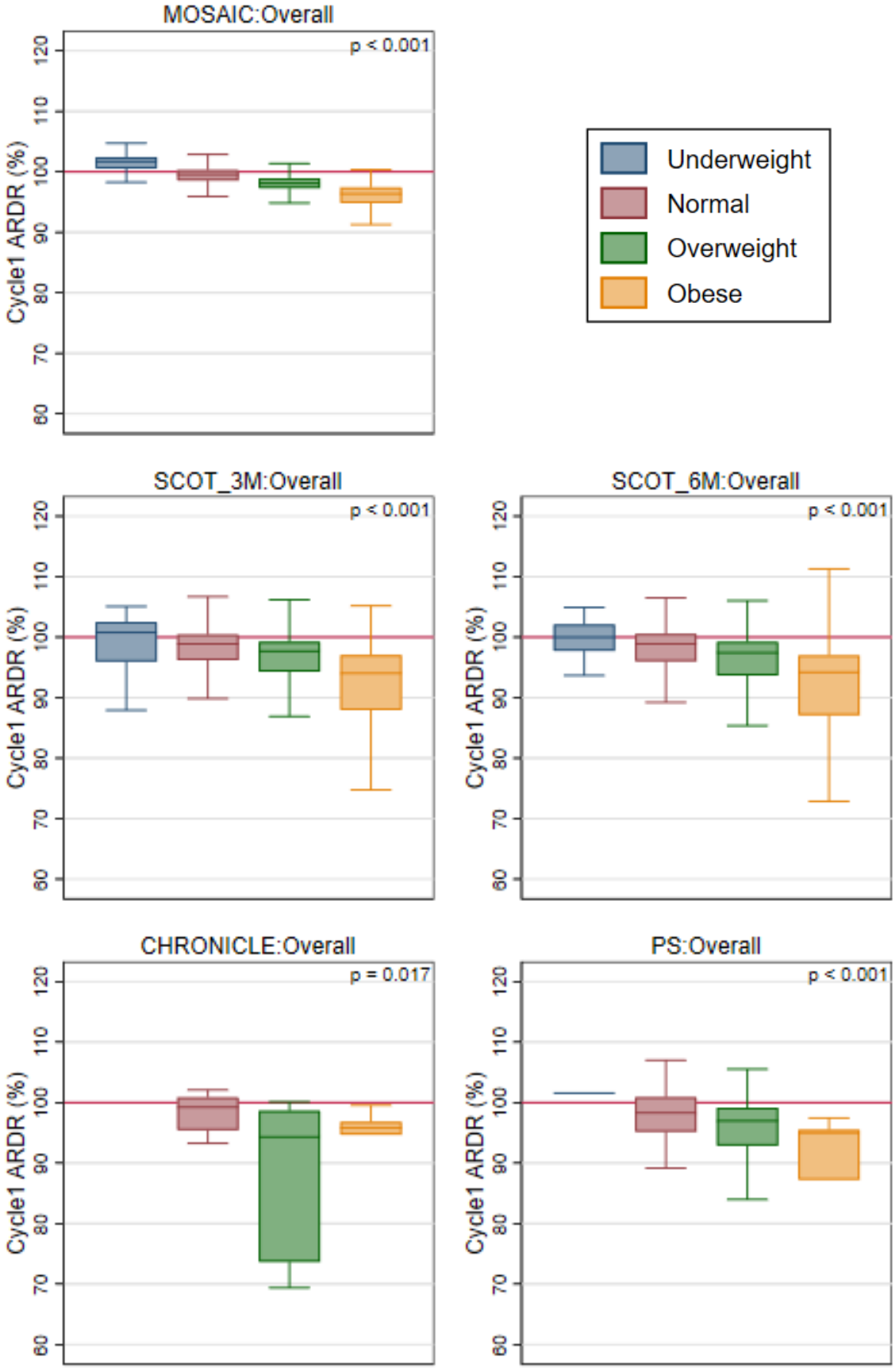


Figure 3.4b | Cycle 1 average relative dose received by regimen
Box and whisker plots demonstrating ARDR by baseline BMI category for each regimen in multi-regimen trials (p values from Cuzick's test for trend).

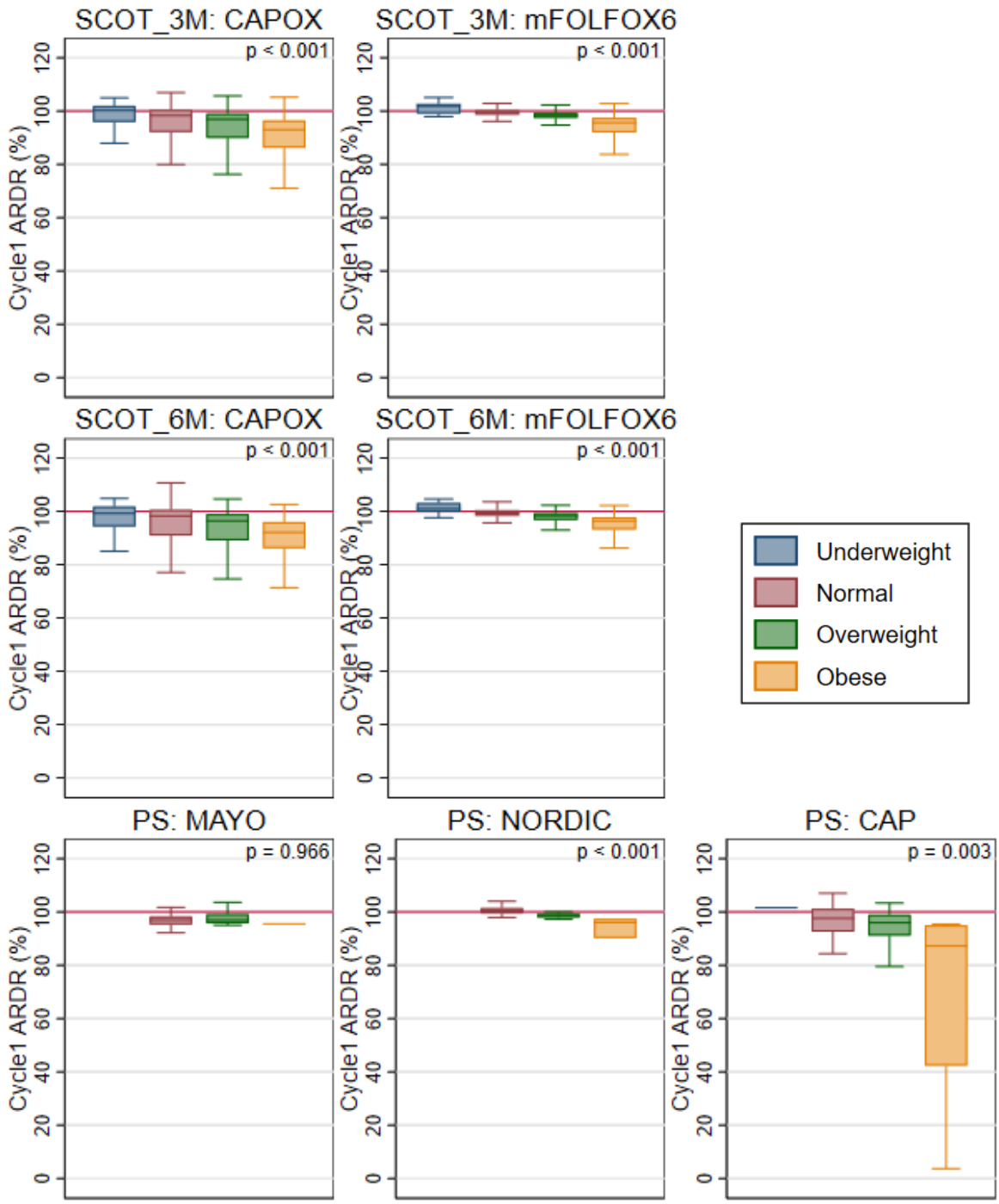


Figure 3.5a | Cycle 1 dose capping by trial
Bar charts demonstrating the percentage of patients receiving a capped cycle 1 dose by baseline BMI category for each trial (p values from Cochran Armitage test for trend).

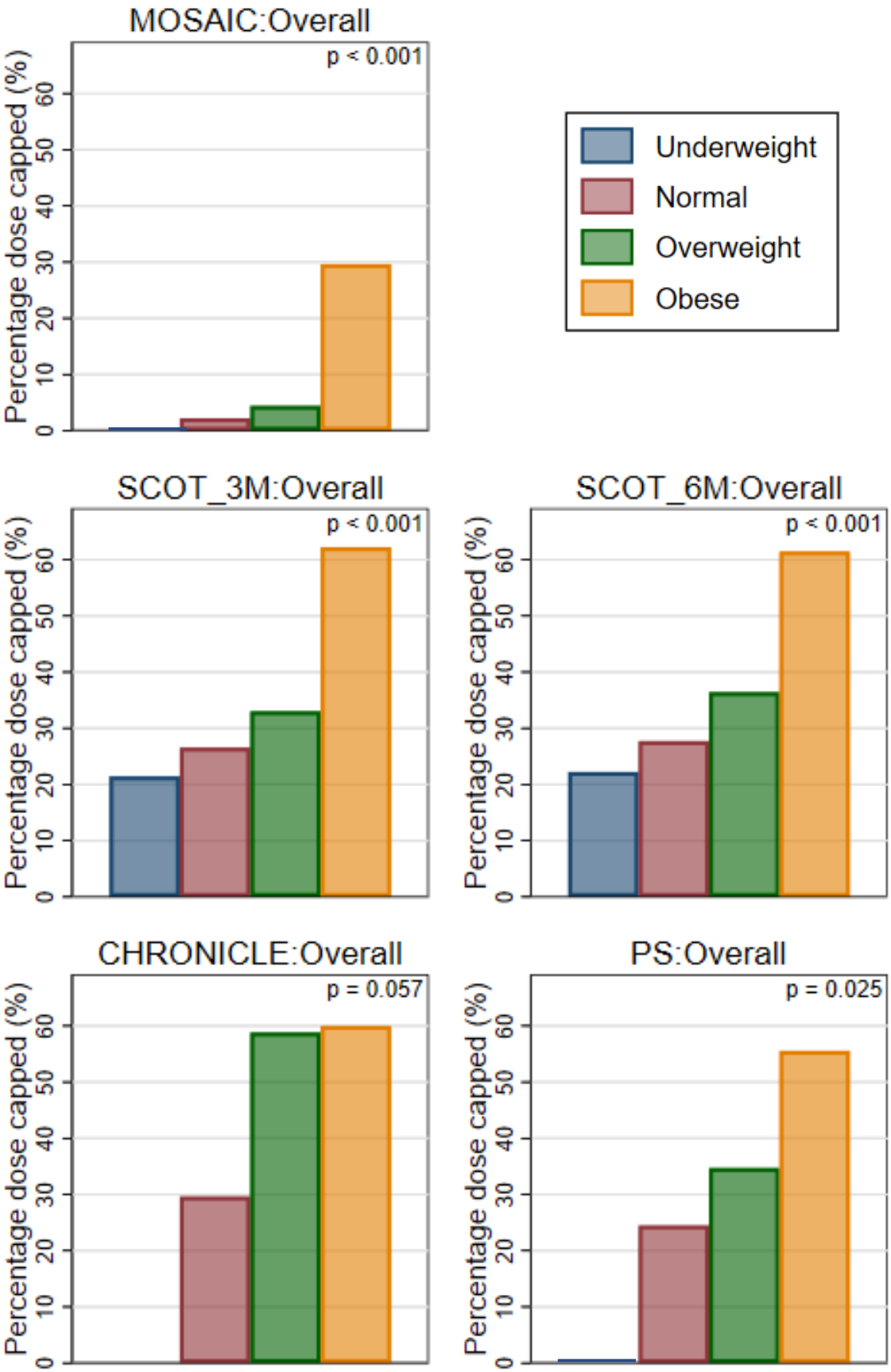
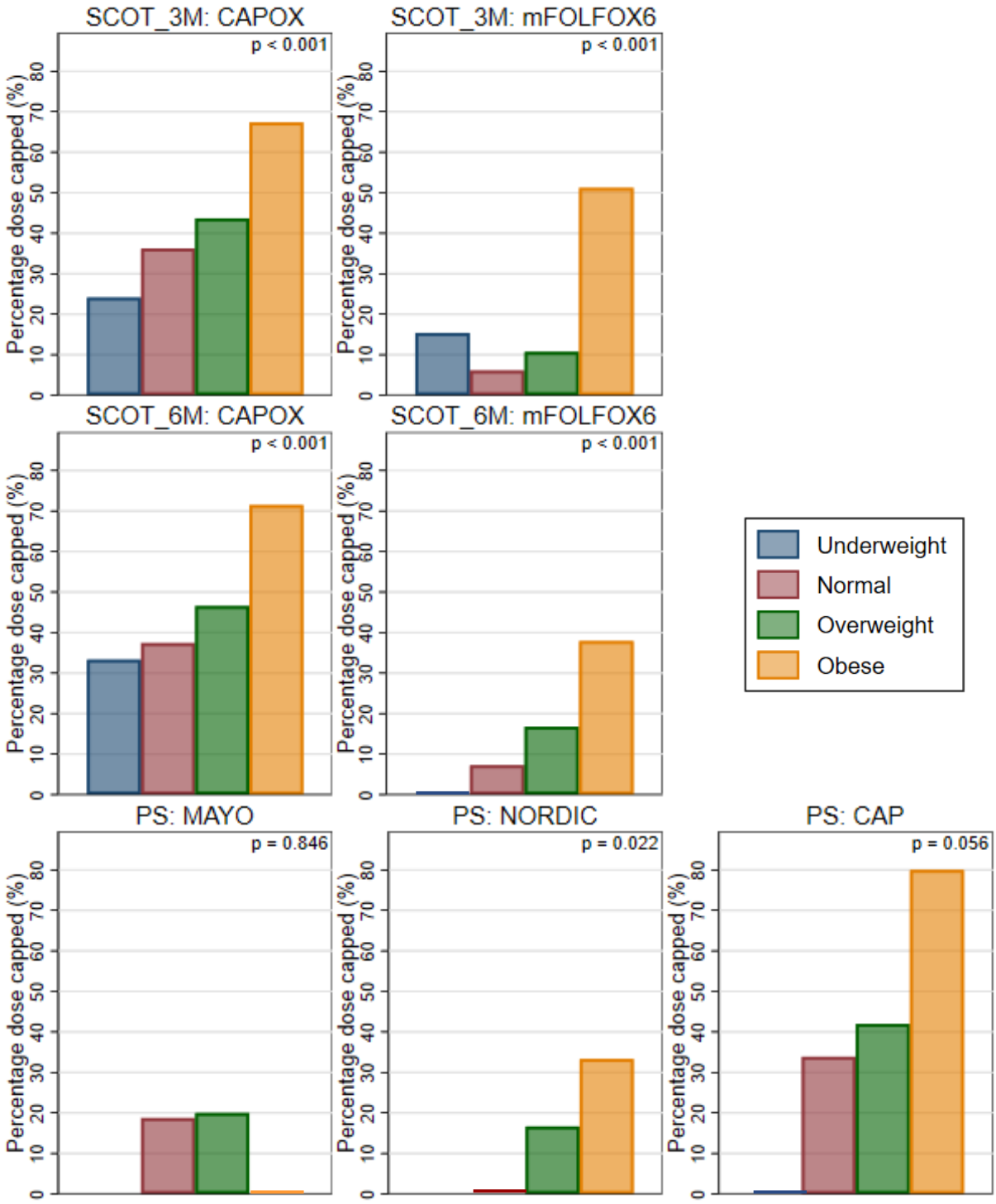


Figure 3.5b | Cycle 1 dose capping by regimen

Bar charts demonstrating the proportion of patients receiving a capped cycle 1 dose by baseline BMI category for each regimen, in multi-regimen trials (p values from Cochran Armitage test for trend).



3.3.6 ADHERENCE: CYCLE DOSING AND DOSE CAPPING

Cycle-level relative dose received

Cycle-level relative dose received was explored at the regimen and drug level only, due to differences in the numbers of cycles received across different regimens within SCOT_3M, SCOT_6M and PROCTOR-SCRIPT trials. Furthermore, excluding the small number of patients who changed regimen in the SCOT trial for the same reasons.

Cycle-level median (IQR) relative dose received for each cycle by baseline BMI category are presented graphically in **Figure 3.6a** and **3.6b** for each regimen and in **Appendix Figure A3.1** for each drug. Across all trials, regimens and BMI categories, there was, in general, a reduction in the median RDR as the cycle numbers increased.

For MOSAIC (LV5FU2), the significant inverse relationship seen at cycle 1 was relatively maintained across all cycles. Both 5FU bolus and 5FU infusion demonstrated the same relationship.

The SCOT_3M CAPOX and mFOLFOX6 regimens, displayed a similar relationship, however, the cycle 1 differences were less well maintained, with some convergence towards the end of the regimens. At the individual drug level, similar relationships were seen without differences being driven by any particular drug, though capecitabine doses tended to be lower.

Similarly, for the SCOT_6M CAPOX and mFOLFOX6 regimens, the cycle 1 differences, appeared to converge towards the mid-point of the regimens (cycles 3-4 and 6-7 respectively), following which the relationships inverted. Again, at the drug level there were similar relationships demonstrated. Capecitabine doses tended to be lower in the CAPOX regimen, and oxaliplatin doses lower towards the end of the mFOLFOX6 regimen.

For CHRONICLE (CAPOX), the differences between BMI categories were relatively well maintained throughout the 6 cycles, though here, the overweight BMI category was generally slightly lower dosed than the obese category.

Minimal differences in median ARDR were seen across BMI categories for the entirety of the PS MAYO regimen. Within the NORDIC regimen, however, there appeared to be a substantial reduction in the median ARDR for the obese category beyond the first cycle. Whereas in the CAP regimen, the inverse relationship between BMI and median ARDR converged around the mid-point of the regimen (cycle 4) and then inverted, similar to the patients in SCOT_6M. However, the numbers of patients within the obese category for both CHRONICLE and PS were small and therefore potentially less reliable.

Figure 3.6a | Cycle-level average relative dose received by regimen
Dot and line graphs plotting median ARDR values, with whiskers denoting IQR, for each cycle by baseline BMI category for each regimen within each trial *(continued overleaf)*.

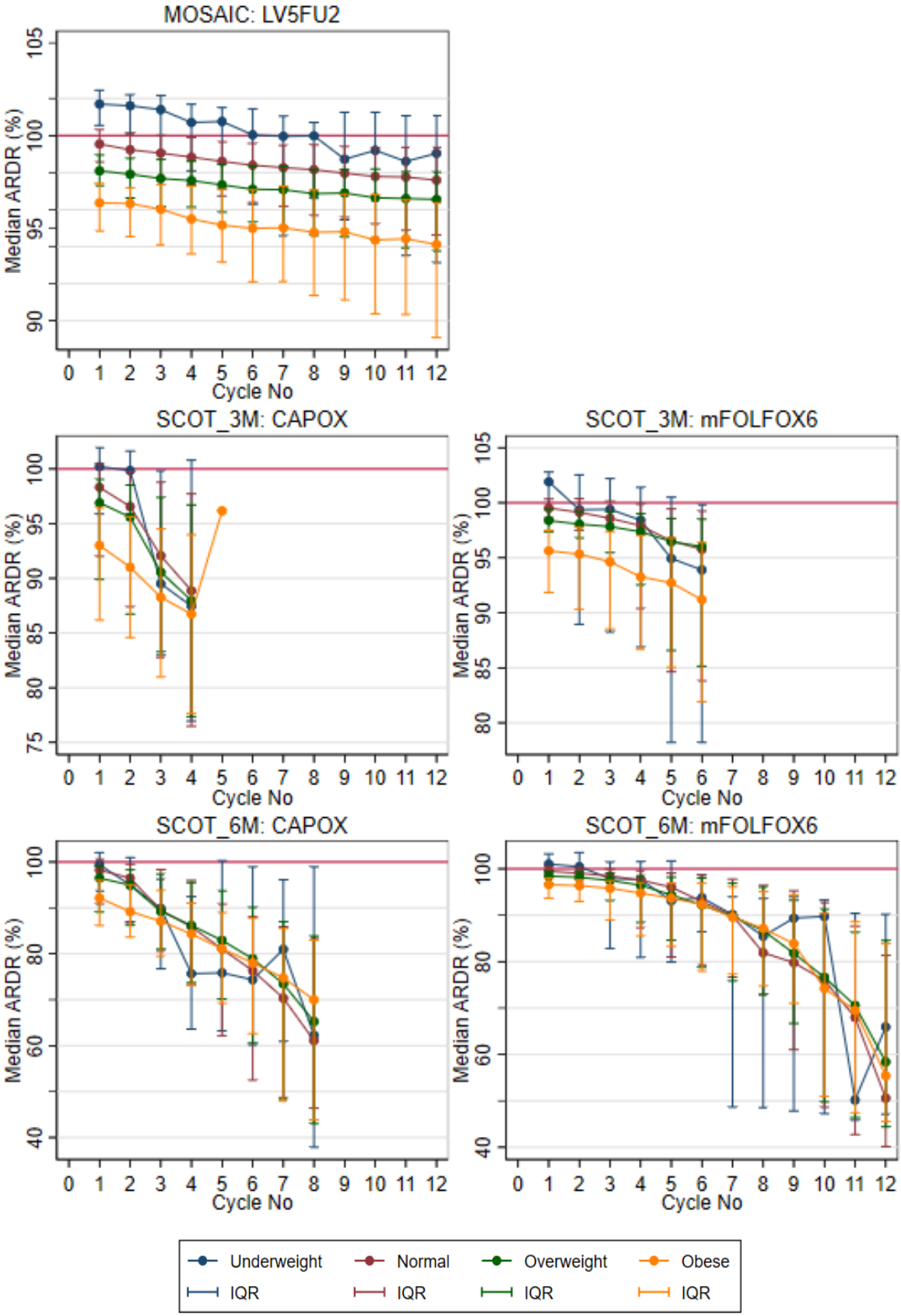
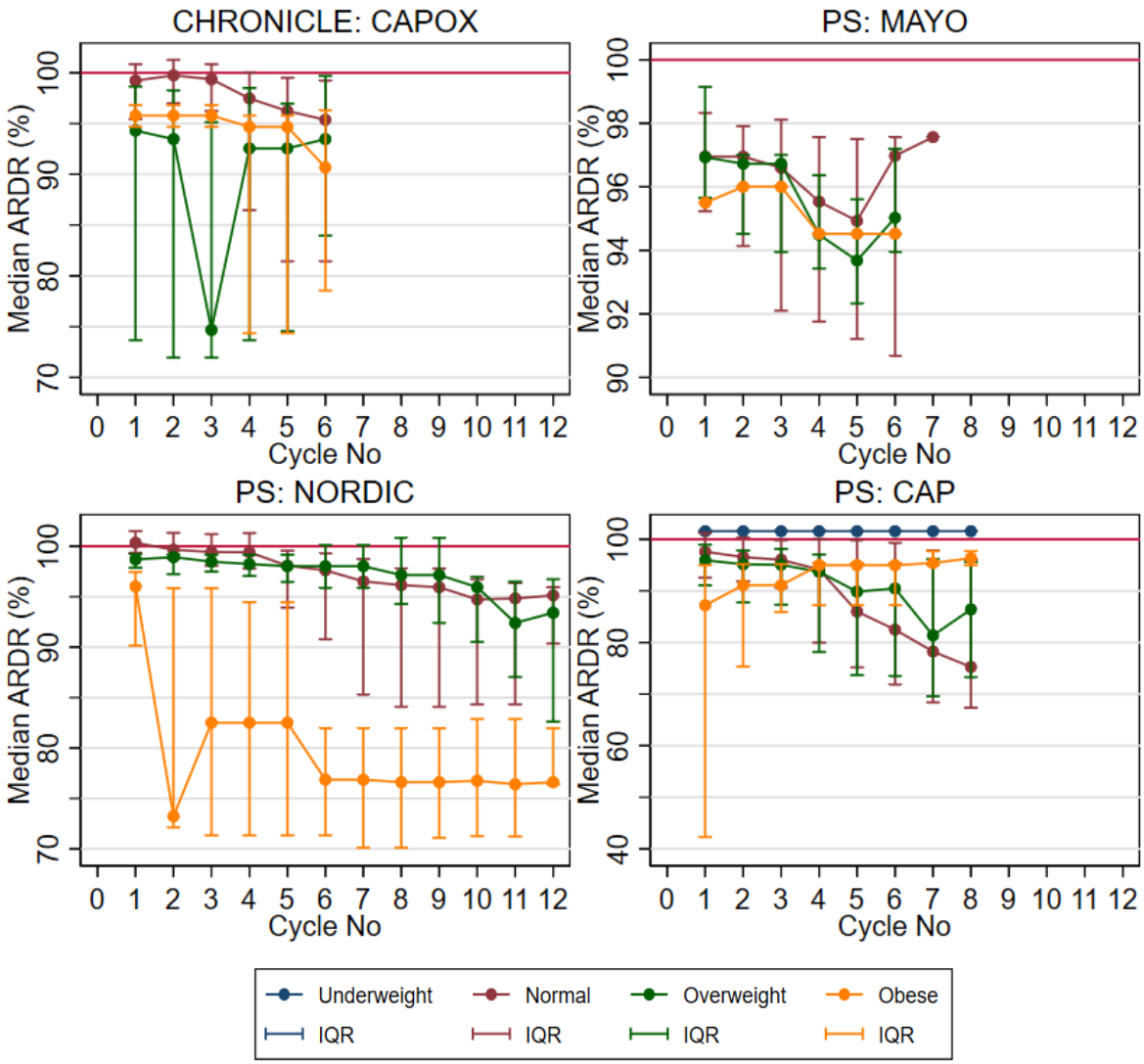


Figure 3.6b | Cycle-level average relative dose received by regimen (*continued*)
Dot and line graphs plotting median ARDR values, with whiskers denoting IQR, for each cycle by baseline BMI category for each regimen within each trial.



Cycle-level relative under-dosing

Cycle-level relative under-dosing (RUD) was defined in the same way as dose capping, that is receipt of less than 95% of the expected protocol dose. Again, this was explored at the regimen and drug level only, excluding those patients in the SCOT trial who changed dose.

Cycle-level proportions of patients who were relatively under-dosed are displayed graphically in **Figure 3.7a** and **3.7b** according to regimen, and **Appendix Figure A3.2** according to drug. Similar to the RDR, there was an increasing incidence of RUD as cycle numbers increased.

For MOSAIC (LV5FU2), the significant cycle 1 relationship between increasing BMI and increasing dose capping incidence was relatively maintained across the 12 cycles, with relative under-dosing reaching as high as 60% in the obese category. Both 5FU bolus and 5FU infusion demonstrated the same relationship.

A similar relationship was seen for the SCOT_3M CAPOX and mFOLFOX6 regimens, again these differences were less well maintained, with some convergence towards the end of the regimens (particularly in the mFOLFOX6 regimen) as seen for ARDR. The incidence of RUD in the obese category reached 78.4% within the CAPOX regimen, and 69.3% within the mFOLFOX6 regimen. At the drug-level, similar relationships were seen, although capecitabine RUD tended to be more common, likely driving the higher RUD incidence in the CAPOX regimen.

The BMI-cycle 1 dose capping relationship was relatively maintained across the SCOT_6M CAPOX regimen. Whereas, for the SCOT_6M mFOLFOX6 regimen, RUD incidence appeared to converge towards the mid-point of the regimens (cycles 6-7), similar to ARDR. The incidence of RUD of obese patients reached 88.0% for CAPOX, and 87.5% for mFOLFOX6. Again, this was mirrored at the drug level, however, capecitabine tended to display a higher RUD incidence from the start, with oxaliplatin RUD incidence increasing sharply to almost the same level by the end of the CAPOX regimen. Whereas, for the SCOT_6M mFOLFOX6 regimen, RUD incidence was similar for 5FU Bolus, 5FU infusion and oxaliplatin initially, the latter then increasing to a greater extent.

For CHRONICLE (CAPOX), there were generally high levels of RUD in the overweight and obese throughout, with the RUD incidence in the normal category increasing at the end of the regimen.

Minimal differences in RUD incidence were seen across normal and overweight BMI for the PS MAYO regimen, with few obese patients limiting interpretation. Within the NORDIC regimen, RUD rates were high for the obese category, with cycle 1 differences reducing between

overweight and normal categories. Whereas in the CAP regimen, the inverse relationship between BMI and RUD converged around the regimen mid-point (cycle 4) and then inverted.

Figure 3.7a | Cycle-level relative under dosing by regimen
Dot and line graphs plotting the percentage of patients who were relatively under-dosed, for each cycle by baseline BMI category for each regimen within each trial *(continued overleaf)*.

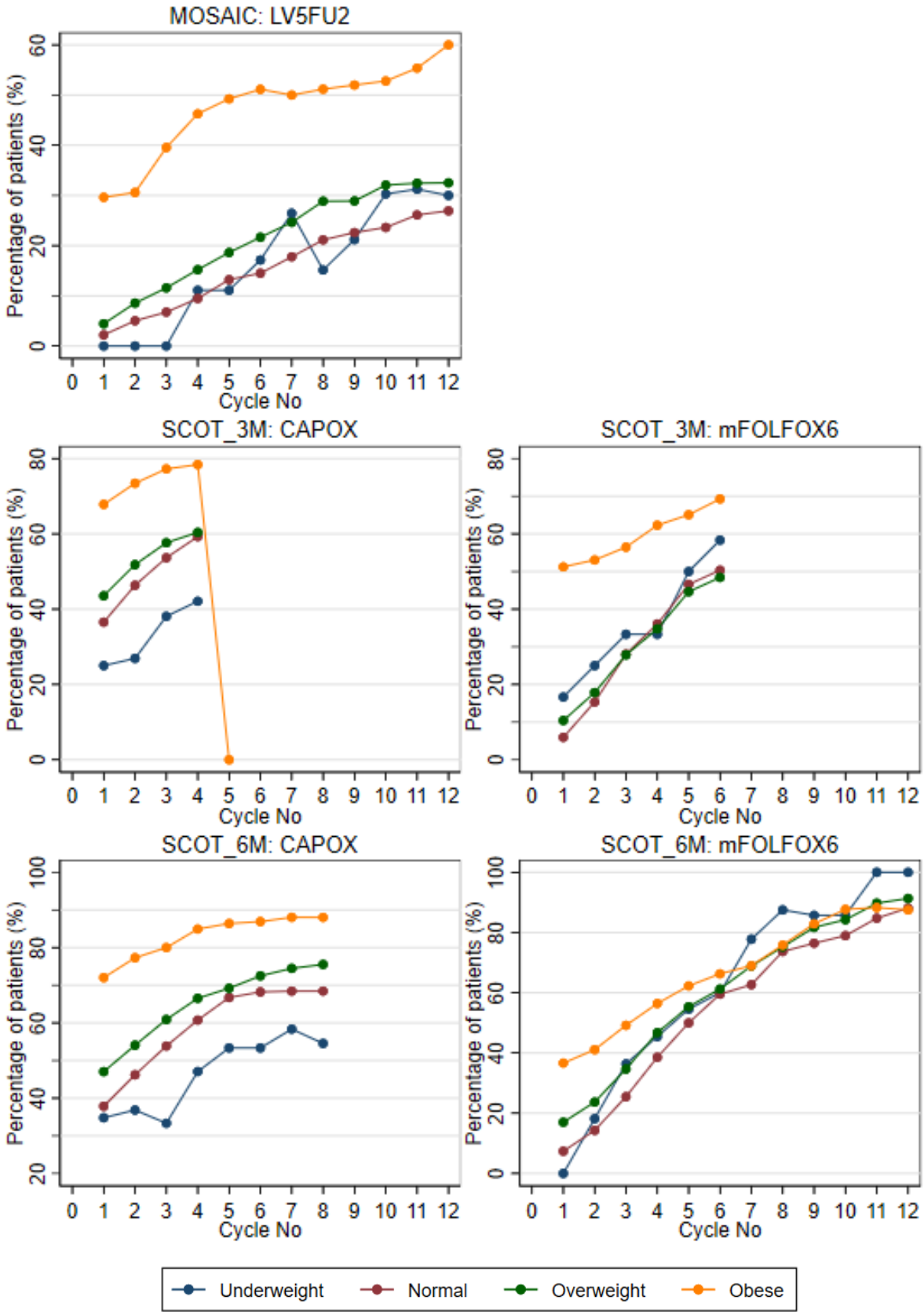
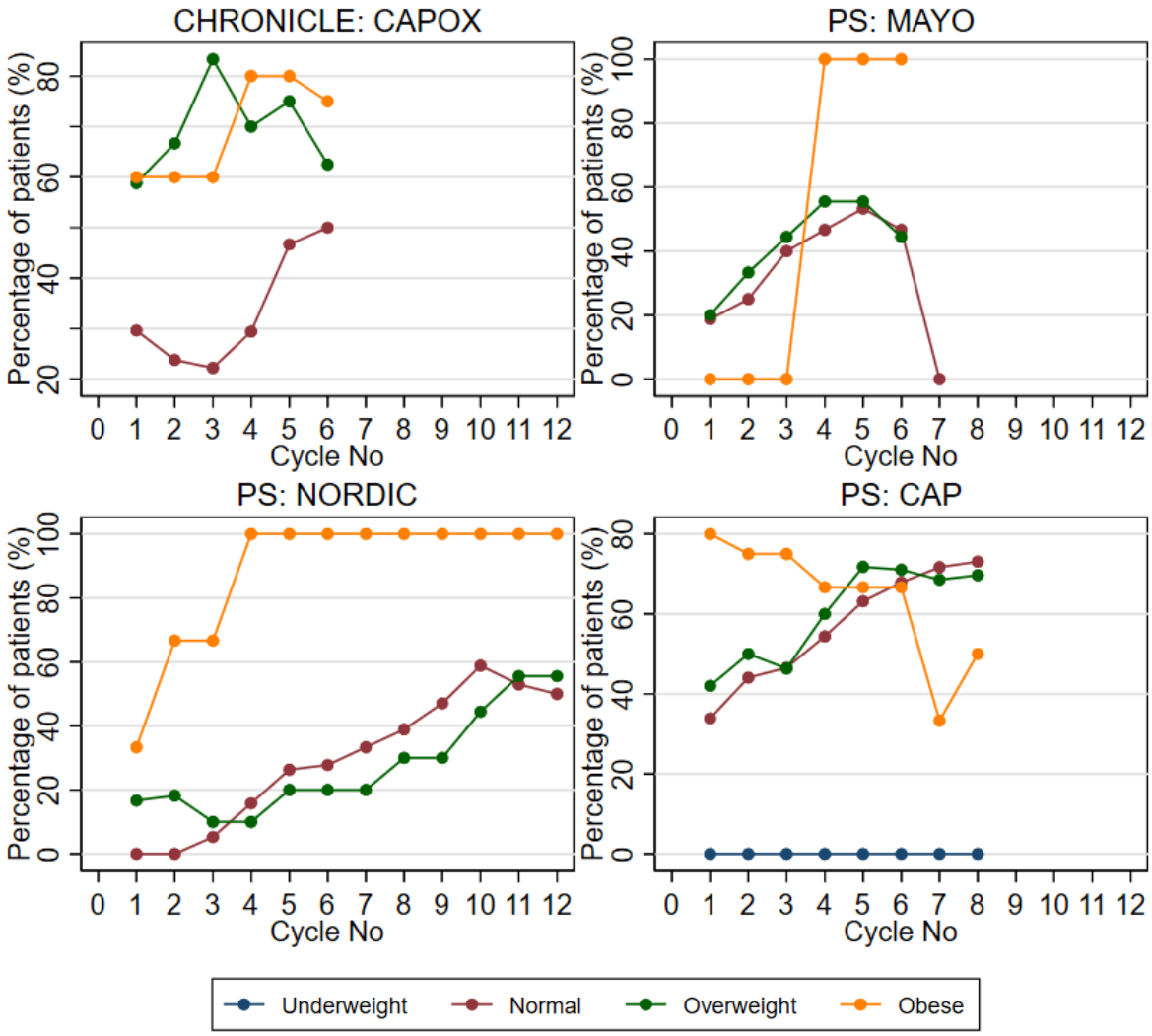


Figure 3.7b | Cycle-level relative under dosing by regimen (*continued*)
Dot and line graphs plotting the percentage of patients who were relatively under-dosed, for each cycle by baseline BMI category for each regimen within each trial.



3.3.7 ADHERENCE: DOSE REDUCTIONS

Figures 3.8a and **3.8b** demonstrate the proportion of patents receiving a dose reduction (defined as receipt of less than 95% of the preceding cycle dose) for each cycle, at the regimen level. **Figures A3.3** in the appendix, present the same at the drug-level.

There was no clear relationship between BMI and dose reductions for MOSAIC, at the regimen level (LV5FU2) or the drug-level, and dose reduction incidence was generally low (0 % – 11%) but tended to be highest for the underweight category.

Within the SCOT_3M CAPOX and mFOLFOX6 regimens, the BMI-dose reduction relationship was the reverse of the dose capping relationship, with slightly higher incidence of dose reductions at each cycle for the normal BMI category compared with overweight and obese. Drug-level relationships mirrored those at the regimen-level. Dose reduction incidence was higher in the CAPOX regimen, and generally higher than in the MOSAIC trial.

A similar relationship was demonstrated for the SCOT_6M CAPOX regimen and to a lesser extent for the mFOLFOX6 cycles, with dose reduction incidence more common in the CAPOX regimen initially only. At the drug level, capecitabine, 5FU bolus and 5FU infusion dose reduction incidence decreased with increasing cycle numbers. Whereas oxaliplatin dose reduction incidence continued at approximately the same level within CAPOX and increased within mFOLFOX6 regimens.

Dose-reduction incidence for cycles 2 and 3 of the CHRONICLE CAPOX regimen displayed an inverse relationship with BMI category, but then became less clear. Within the PS trial, dose reduction incidence was generally low, and tended to be lowest for the obese category in MAYO, NORDIC, and CAP regimens. Again, low numbers of patients within the obese categories limited interpretation.

Figure 3.8a | Cycle-level dose reductions by regimen
Dot and line graphs demonstrating the percentage of patents receiving a dose reduction at each cycle, by baseline BMI category. Dose reductions were defined as receipt of less than 95% of the preceding cycle dose (*continued overleaf*).

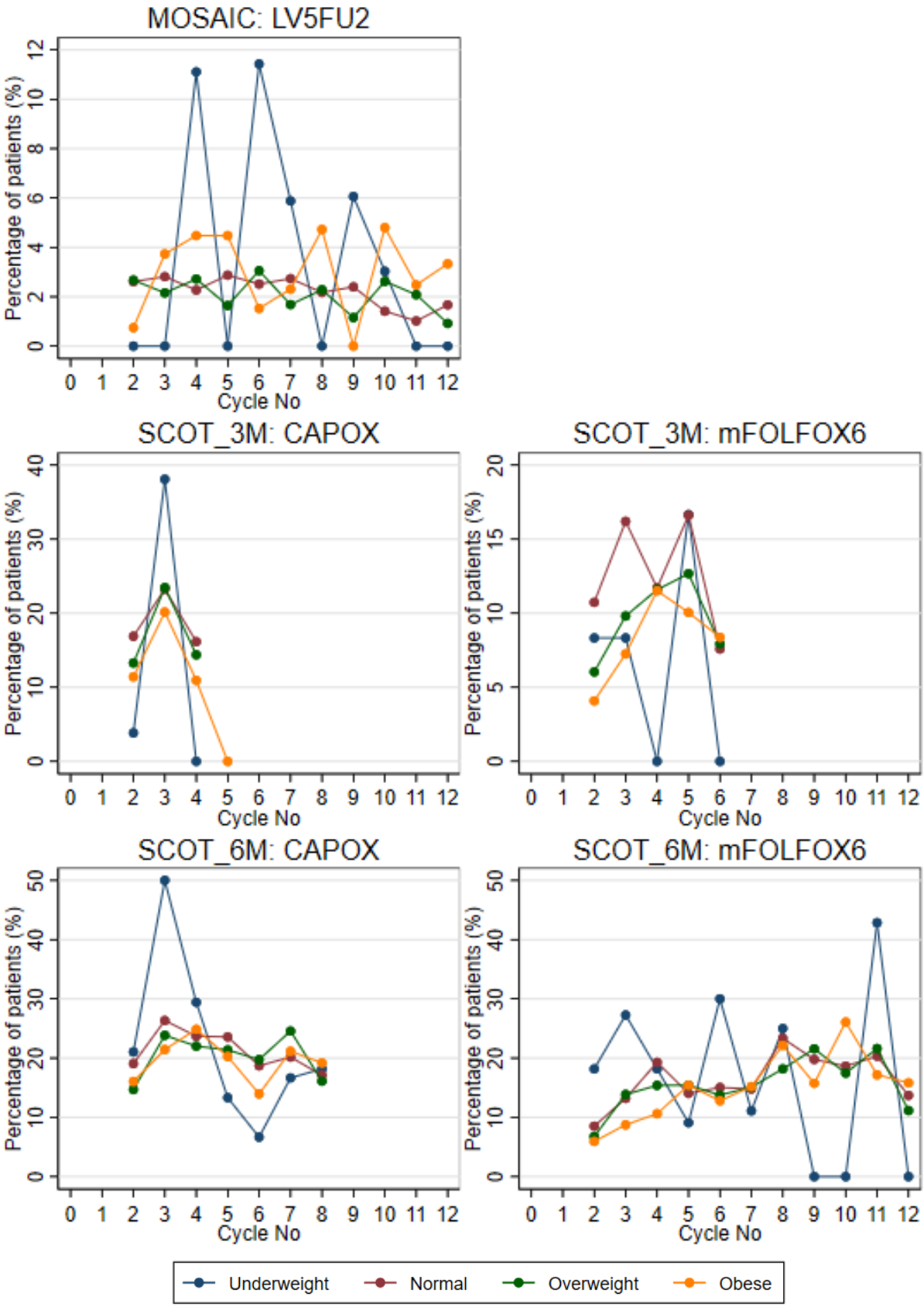
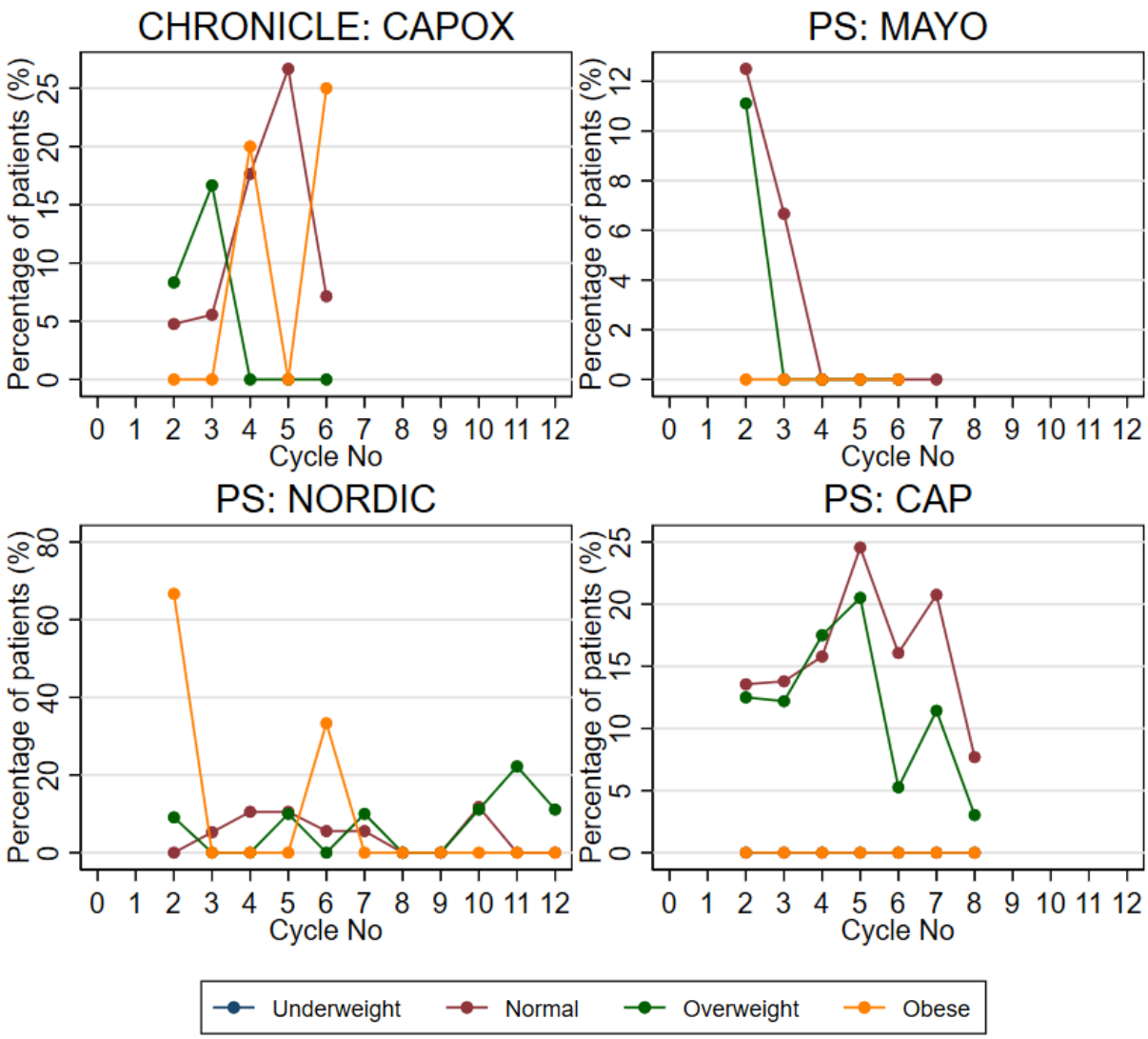


Figure 3.8b | Cycle-level dose reductions by regimen (*continued*)
Dot and line graphs demonstrating the percentage of patents receiving a dose reduction at each cycle, by baseline BMI category. Dose reductions were defined as receipt of less than 95% of the preceding cycle dose.



3.3.8 ADHERENCE: EARLY DISCONTINUATION

Cycle-level attrition of chemotherapy

Discontinuation of chemotherapy led to a degree of attrition in the numbers of patients receiving chemotherapy at each cycle. **Figures 3.9a** and **3.9b** plot the percentage of patients still receiving chemotherapy against the cycle number according to baseline BMI category for each trials' regimen.

Within the MOSAIC LV5FU2 regimen, the obese category had the lowest attrition rates throughout, whereas, overweight and underweight categories had the highest rates, mirrored at the drug level.

Attrition rates were similar across normal, overweight, and obese BMI categories for both regimens within SCOT_3M and SCOT_6M. However, attrition rates were highest for the underweight in SCOT_3M CAPOX, converse to none in the SCOT_3M mFOLFOX6 regimen. There was a modest inversely proportional relationship in SCOT_6M regimens (lowest attrition for obese), though not consistently so throughout mFOLFOX6 cycles. Similar relationships were seen at the drug-level, though oxaliplatin tended to have higher attrition rates than fluorouracil.

Within CHRONICLE, the obese category tended to have the lowest attrition, with similar rates in normal and overweight categories. Similarly, attrition was lowest amongst obese receiving PS MAYO and NORDIC regimens, with highest rates in the overweight. Whereas a proportional relationship was seen for the PS CAP regimen.

Early discontinuation of chemotherapy

Early discontinuation (receipt of fewer than the expected number of ACT cycles) is presented in **Figures 3.10a** and **3.10b** by trial and regimen, respectively. Overall, it occurred most frequently in CHRONICLE (46.9%) and SCOT_6M (38.2%), followed by PS (27.2%), then MOSAIC and SCOT_3M (both 12.9%). Early discontinuation tended to display an inverse relationship with BMI (excluding PS), reaching significance only for SCOT_3M. The percentage of patients discontinuing chemotherapy early in underweight, normal, overweight and obese categories were 16.7%, 11.6% 15.1% and 11.1% respectively for MOSAIC (p_{trend} = 0.8093); 22.5%, 15.2%, 10.8% and 12.2% for SCOT_3M (p_{trend} = 0.0101); 51.4%, 38.7%, 37.8% and 37.4% for SCOT_6M (p_{trend} =0.3396); NA, 48.2%, 52.9%, and 20.0% for CHRONICLE (p_{trend} = 0.4759); and 0.0%, 23.5%, 31.9% and 33.3% for PS (p_{trend} = 0.1835).

Regimen-level relationships mirrored these findings, with similar rates for CAPOX and mFOLFOX6 (except for no early discontinuation in SCOT_3M mFOLFOX6 underweight (**Figure 3.10b**)). Again, similar drug-level relationships were seen (excluding SCOT_6M regimens, where oxaliplatin was more frequently discontinued than fluorouracil; **Appendix Table A3.4**).

Figure 3.9a | Cycle-level retention of patients by regimen
Dot and line graphs demonstrating the percentage of patients receiving chemotherapy at each cycle, by baseline BMI category (*continued overleaf*).

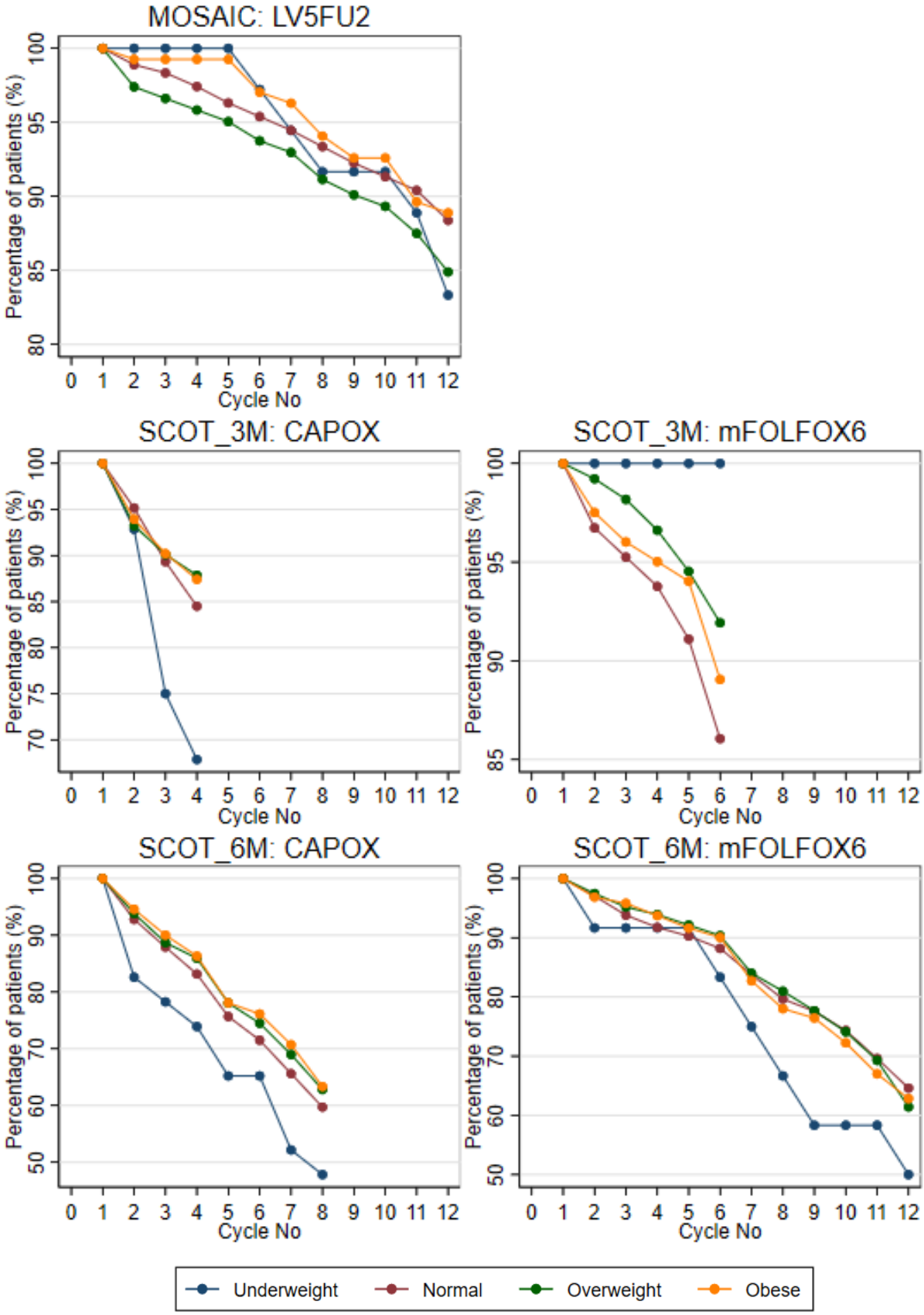


Figure 3.9b | Cycle-level retention of patients by regimen (*continued*)
Dot and line graphs demonstrating the percentage of patients receiving chemotherapy at each cycle, by baseline BMI category.

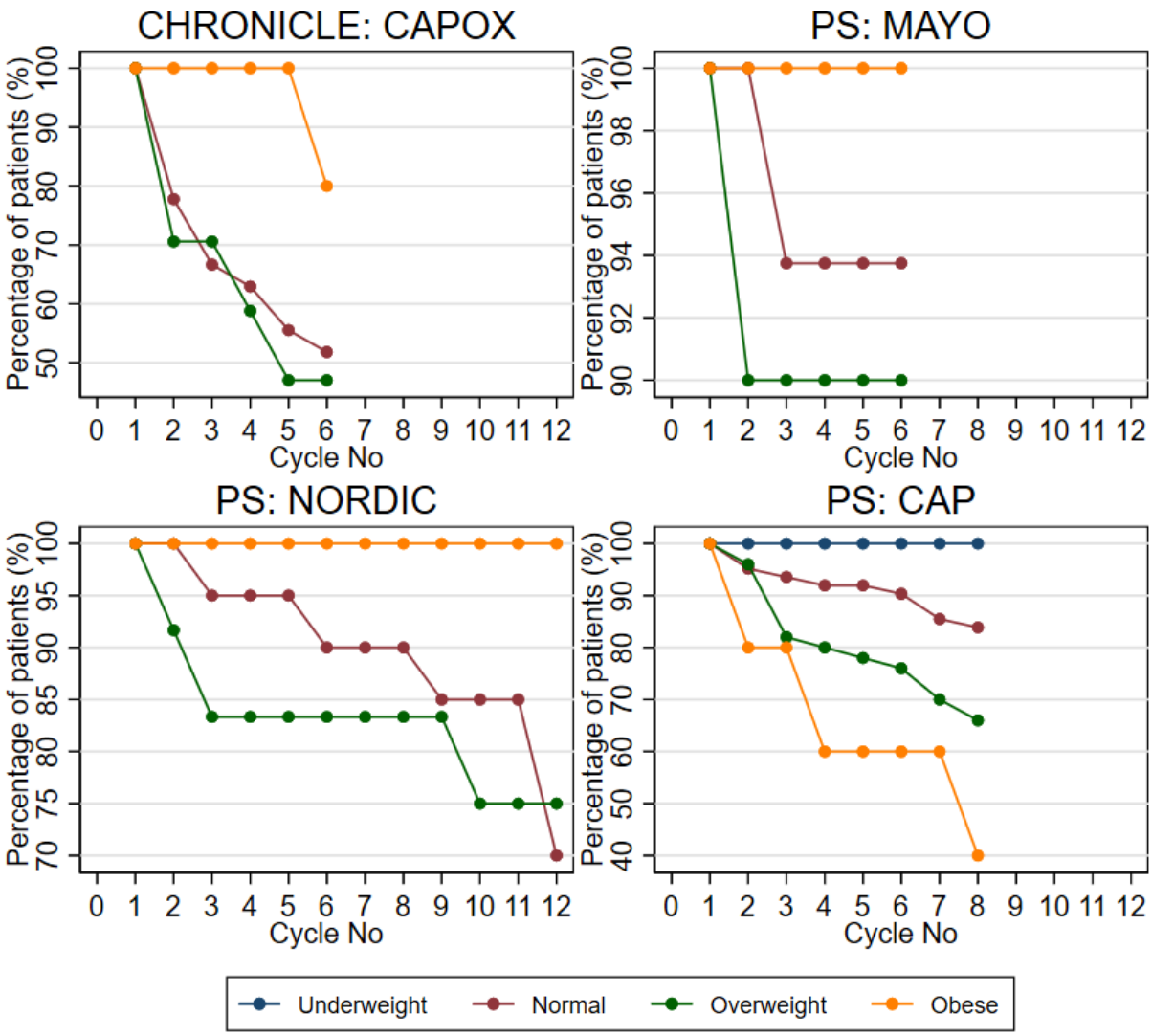


Figure 3.10a | Early discontinuation of chemotherapy by trial
Bar charts presenting the percentage of patients discontinuing chemotherapy early by baseline BMI category for each trial (p values from Cochran Armitage test for trend).

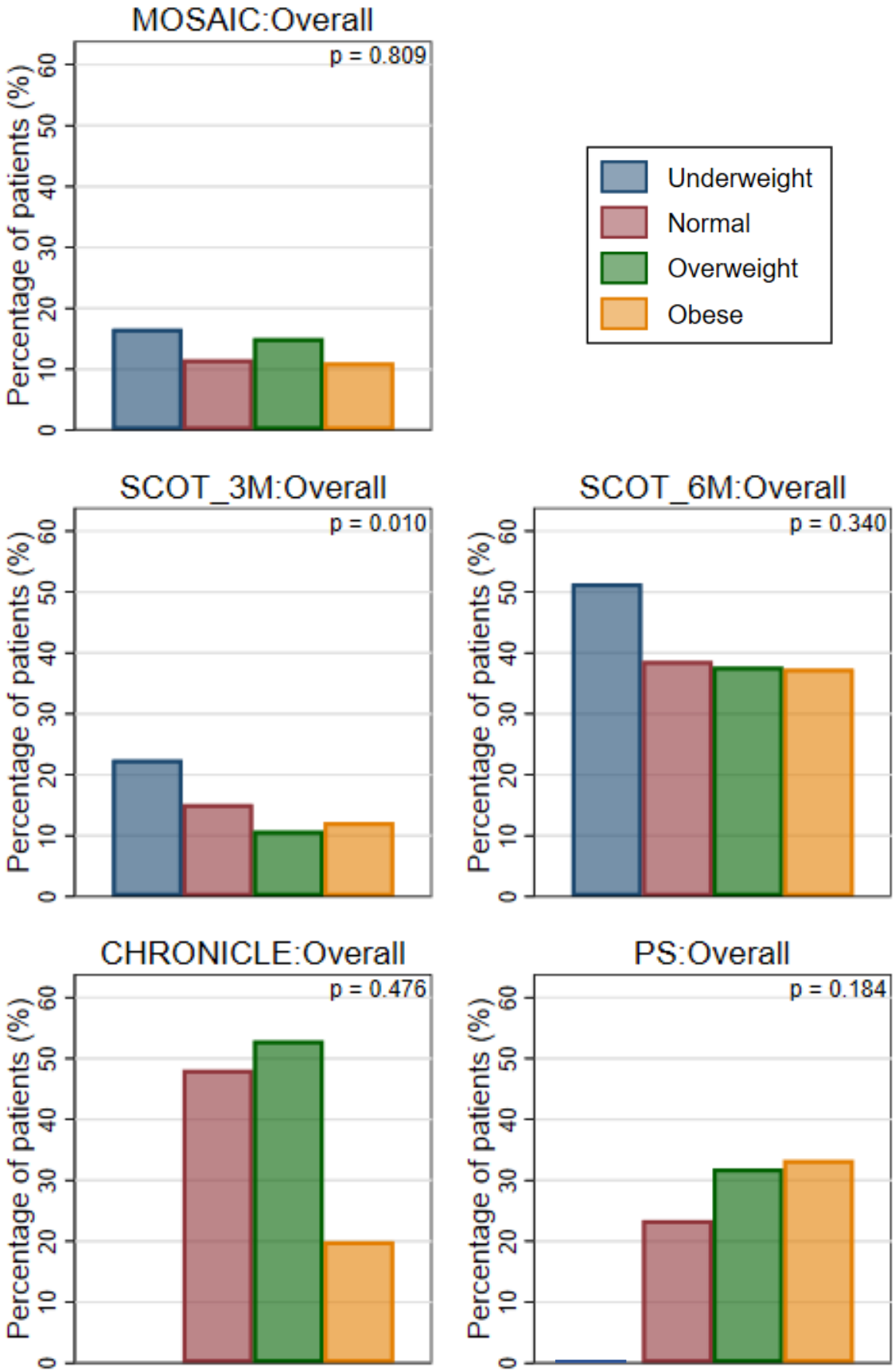
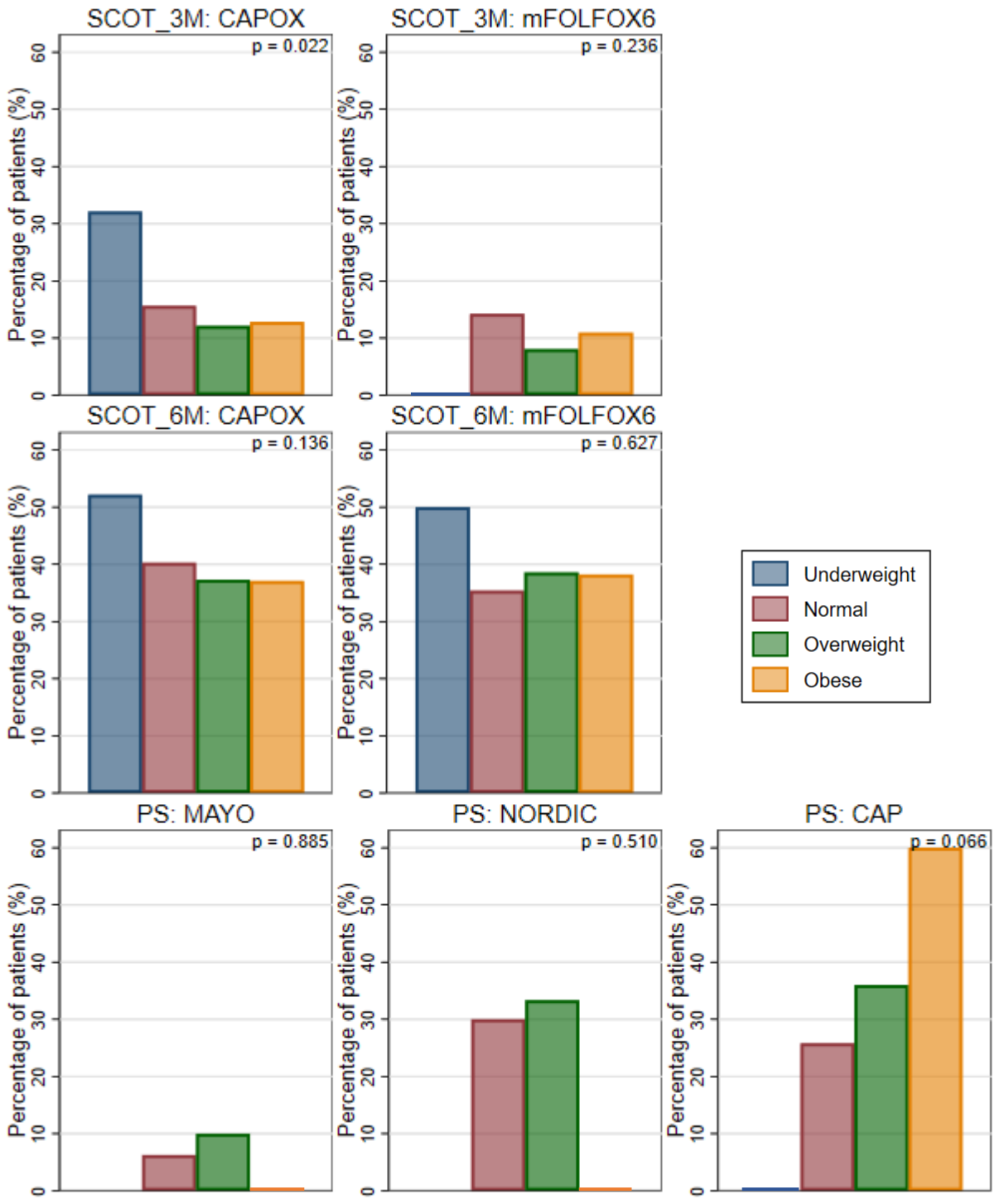


Figure 3.10b | Early discontinuation of chemotherapy by regimen
Bar charts presenting the percentage of patients discontinuing chemotherapy early by baseline BMI category for each regimen, in multi-regimen trials (p values from Cochran Armitage test for trend).



3.3.9 ADHERENCE: DOSE DELAYS

Delay in administration of chemotherapy cycles was defined as >7 days from the expected administration day. Overall, the incidence of any delay was highest in SCOT_6M (39.8%), followed by SCOT_3M (23.4%), MOSAIC (19.4%) and CHRONICLE (18.4%), and lowest for PS (16.7%). **Figures 3.11a** and **3.11b** present the incidence of any dose delay by baseline BMI category for each trial and regimen, respectively. For MOSAIC, the underweight category displayed the highest dose delay incidence (27.8%), with lower but similar rates in the other categories (normal 18.1%; overweight 19.5%; and obese 20%; p_{trend}=0.9430). SCOT_3M and SCOT_6M displayed significant inverse trends with lowest incidence in the obese category and highest incidence in the normal category, though the relationship appeared to be more of an inverted U-shape with lower dose delay incidence in the underweight (SCOT_3M: 21.43% of underweight, 26.01% of normal, 23.86% of overweight and 18.20% of obese (p_{trend}=0.0008); SCOT_6M: 30.56% of underweight, 42.86% of normal, 40.47% of overweight and 34.41% of obese (p_{trend}=0.0027)). This was mirrored at the regimen level (all inverted U relationships, except for SCOT_3M mFOLFOX6), with mFOLFOX6 regimens generally demonstrating a higher incidence of dose delay. Conversely, CHRONICLE displayed higher incidence in the obese category (40.0%) compared with normal (18.5%) and overweight categories (11.8%) (p_{trend}=0.5677). Whereas there were no dose delays within underweight and obese categories in the PS trial (18.4% of normal and 16.7% of overweight patients; p_{trend}=0.3457). Dose delays at the cycle level (**Figures 3.12a** and **3.12b**), generally mirrored the overall incidence relationships.

Figure 3.11a | Dose delay incidence by trial

Bar charts demonstrating the percentage of patients experiencing at least one dose delay by baseline BMI category for each trial (p values from Cochran Armitage test for trend).

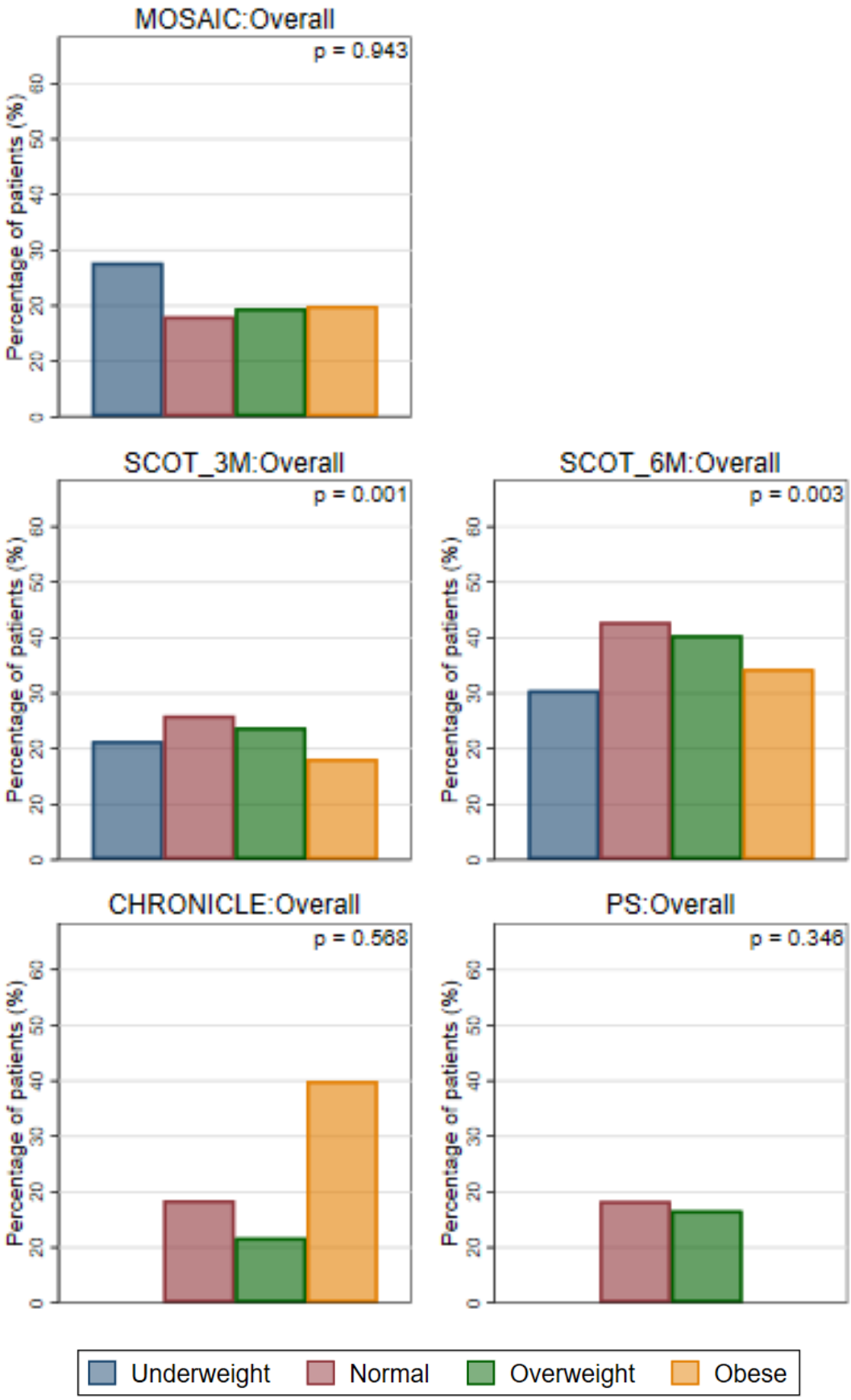


Figure 3.11b | Dose delay incidence by regimen
Bar charts demonstrating the percentage of patients experiencing at least one dose delay by regimen for multi-regimen trials (p values from Cochran Armitage test for trend).

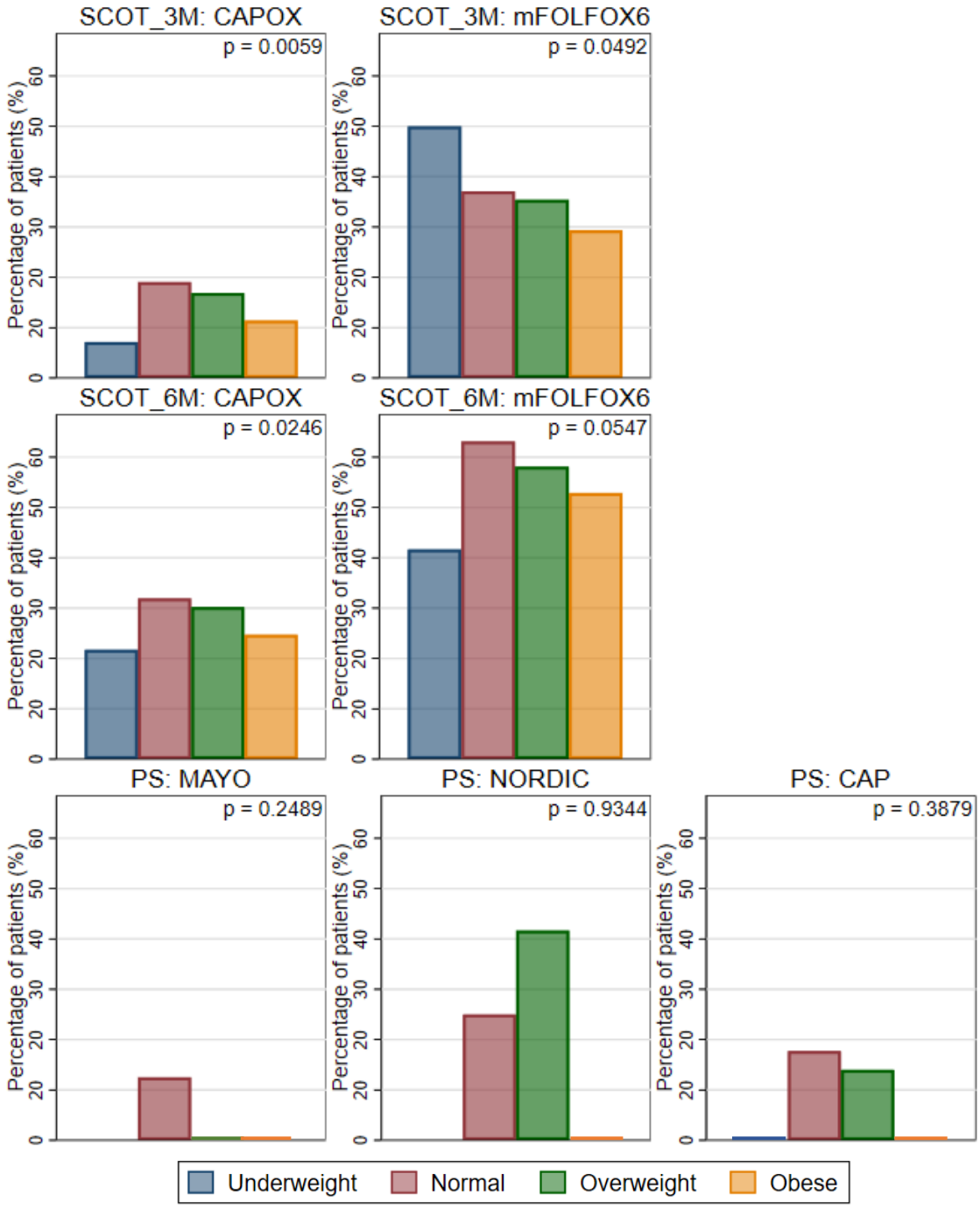


Figure 3.12a | Cycle-level dose delays by regimen
Dot and line graphs presenting the percentage of patients experiencing dose delays at each cycle by baseline BMI category for each trials' regimen (*continued overleaf*).

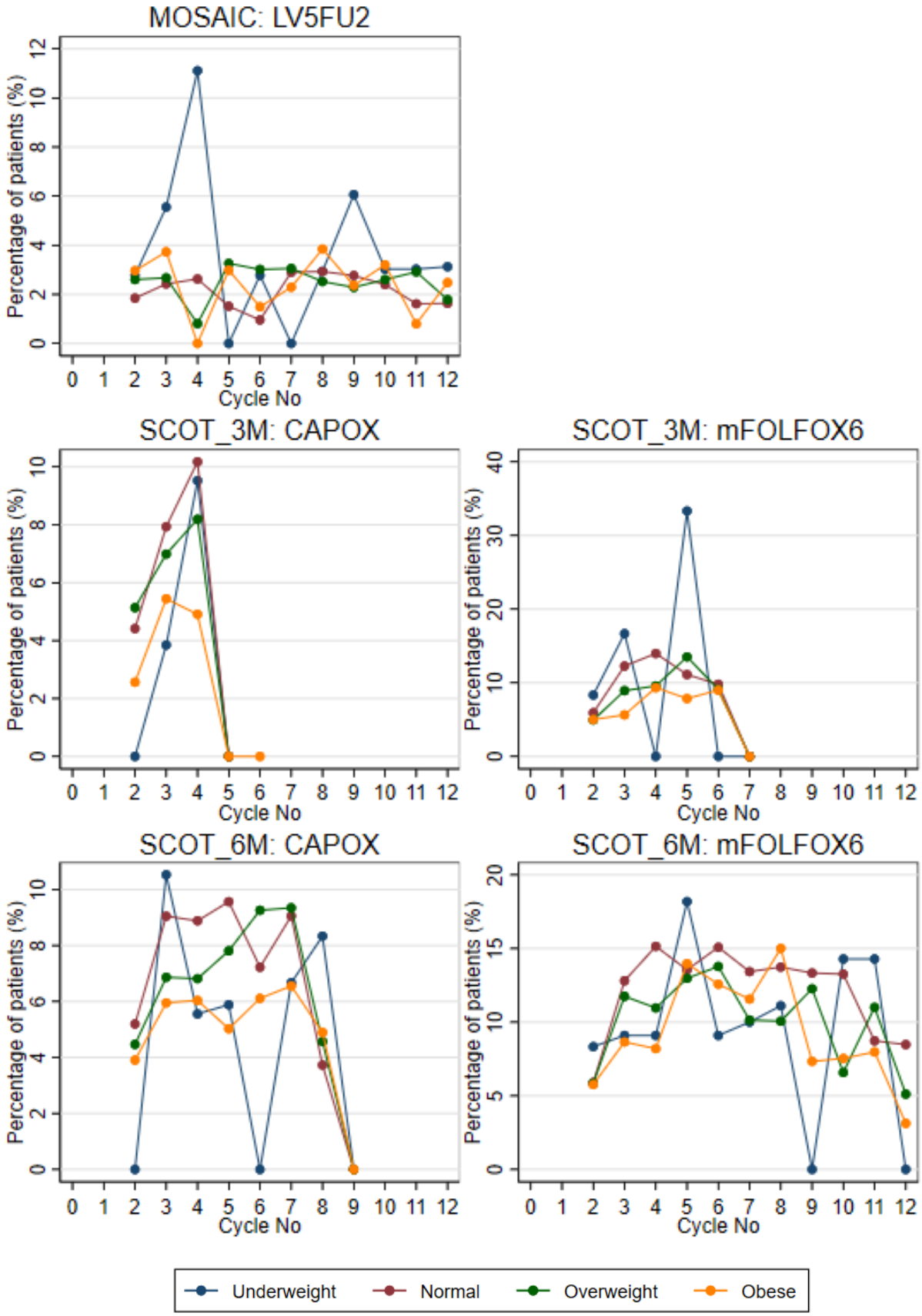
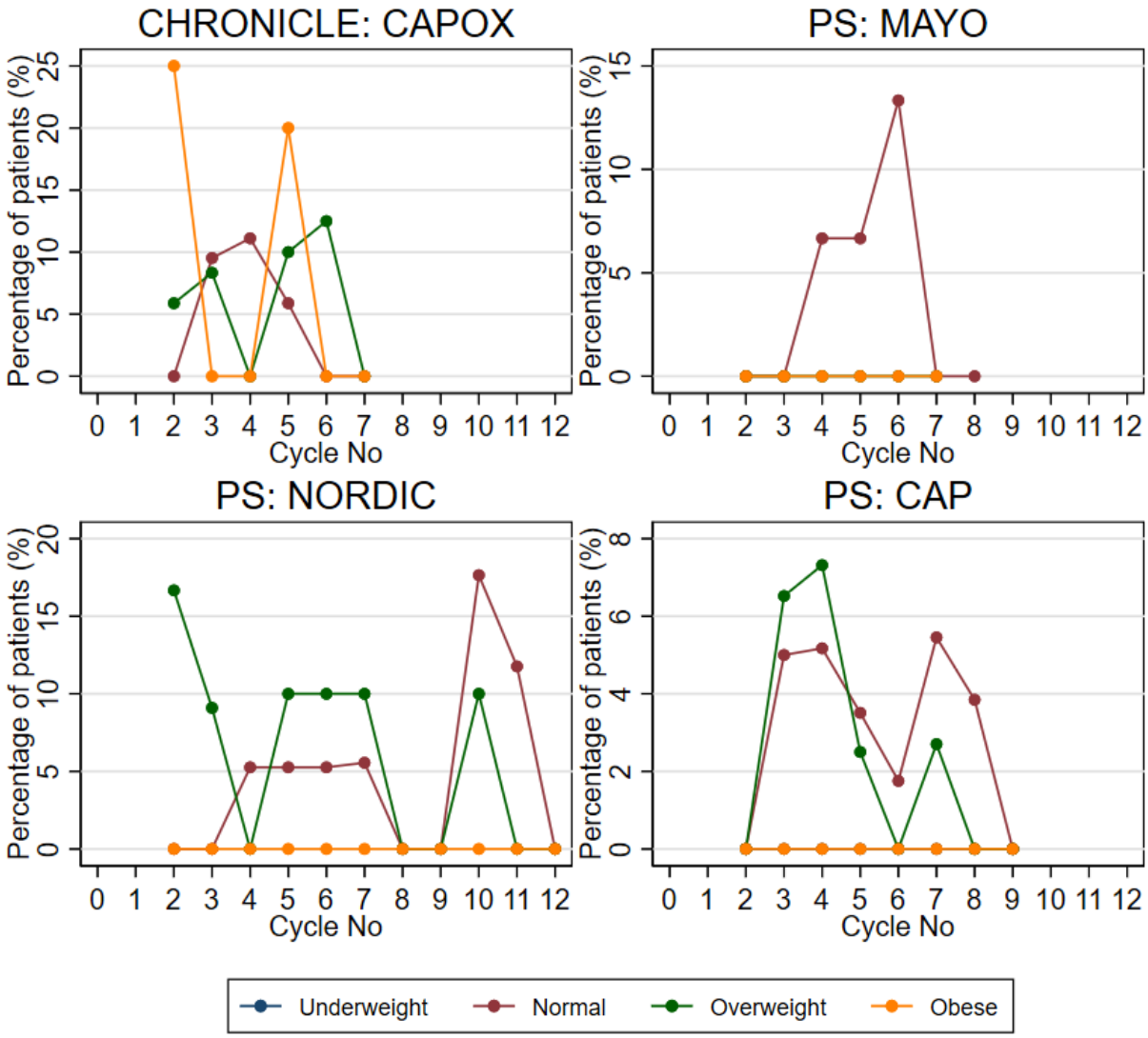


Figure 3.12b | Cycle-level dose delays by regimen (*continued*)
Dot and line graphs presenting the percentage of patients experiencing dose delays at each cycle by baseline BMI category for each trials' regimen.



3.3.10 ADHERENCE: RELATIVE DOSE INTENSITY AND CUMULATIVE RELATIVE DOSE

Relative dose intensity (RDI) and cumulative relative dose (CRD) were explored at the trial, regimen, and drug level.

Relative dose intensity

Cuzick's test for trend appeared to identify significant trends for MOSAIC (p_{trend} <0.001) and SCOT_3M (p_{trend} <0.001), but not SCOT_6M, CHRONICLE or PS. However, these relationships were less evident on examining the median average relative dose intensity (ARDI) with increasing BMI categories across majority of trials (**Table 3.4**). In general, obese patients tended to have the lowest median ARDI (excluding CHRONICLE) compared with other BMI categories, which may have been in part responsible for the significant trends demonstrated by Cuzick's test, in the context of a large sample size.

A similar, relationship was seen at the regimen-level (**Figure 3.13**). ARDI tended to be lower in capecitabine containing regimens, and RDI tended to be similar at the drug-level (**Table A3.5)**, with a generally lower capecitabine RDI, except for mFOLFOX6 containing regimens in SCOT_6M with lower oxaliplatin RDI.

Cumulative relative dose

The median average cumulative relative dose (ACRD) displayed a significant inverse relationship with increasing BMI categories for MOSAIC (p_{trend} <0.001) and PS (p = 0.045). However, despite a significant trend identified by Cuzick's test for SCOT_3M (p_{trend} <0.001), these relationships were less clear on examining median ACRD (**Table 3.4).** Obese patients again tended receive the lowest ACRD, except for SCOT_6M (where underweight received lower median ACRD) and CHRONICLE, and again may have overly influenced Cuzick's test. Regimen (**Figure 3.14**) and drug-level (**Table A3.5**) relationships mirrored trial-level and relative dose intensity relationships.

Table 3.4 | Overall adherence measures by baseline BMI for each trial

Trial	Underweight		Normal		Overweight		Obese		$P_{(trend)*}$
ARDI, median (IQR)									
MOSAIC	94.98	(85.99, 98.18)	95.81	(91.15, 98.59)	94.28	(88.77, 97.23)	92.10	(86.24, 95.47)	**<0.0001**
SCOT_3M	87.98	(77.99, 100.29)	87.62	(77.80, 97.05)	88.27	(79.08, 96.37)	86.23	(78.40, 93.03)	**<0.0001**
SCOT_6M	83.08	(70.23, 95.55)	78.20	(66.95, 88.89)	78.75	(68.35, 89.19)	78.41	(67.83, 86.41)	0.2220
CHRONICLE			94.74	(83.47, 98.99)	92.64	(73.35, 94.45)	89.04	(71.71, 94.66)	0.0817
PS	101.57	(101.57, 101.57)	88.84	(77.35, 95.52)	89.15	(79.19, 95.56)	81.51	(74.05, 92.27)	0.3032
ACRD, median (IQR)									
MOSAIC	98.44	(89.47, 100.86)	97.87	(94.68, 99.29)	96.49	(90.00, 97.95)	94.25	(87.84, 96.36)	**<0.0001**
SCOT_3M	89.41	(73.33, 99.63)	92.07	(80.10, 98.30)	92.48	(82.38, 97.55)	88.39	(79.38, 94.30)	**<0.0001**
SCOT_6M	72.83	(37.97, 85.93)	73.19	(50.73, 85.59)	73.86	(54.67, 86.74)	73.02	(51.00, 84.70)	0.8743
CHRONICLE			81.44	(30.92, 97.00)	61.57	(16.49, 80.92)	93.16	(74.56, 95.79)	0.7660
PS	101.57	(101.57, 101.57)	87.39	(75.44, 97.00)	85.25	(63.74, 95.61)	83.48	(73.17, 89.84)	**0.0452**

Abbreviations: ACRC, Average cumulative relative dose; **ARDI**, average relative dose intensity; **PS**, PROCTOR-SCRIPT
* Cuzick's test for trend

Figure 3.13 | Average relative dose intensity by regimen
Box plots demonstrating the average relative dose intensity by baseline BMI category for each regimen in multi-regimen trials (p values from Cochran Armitage test for trend).

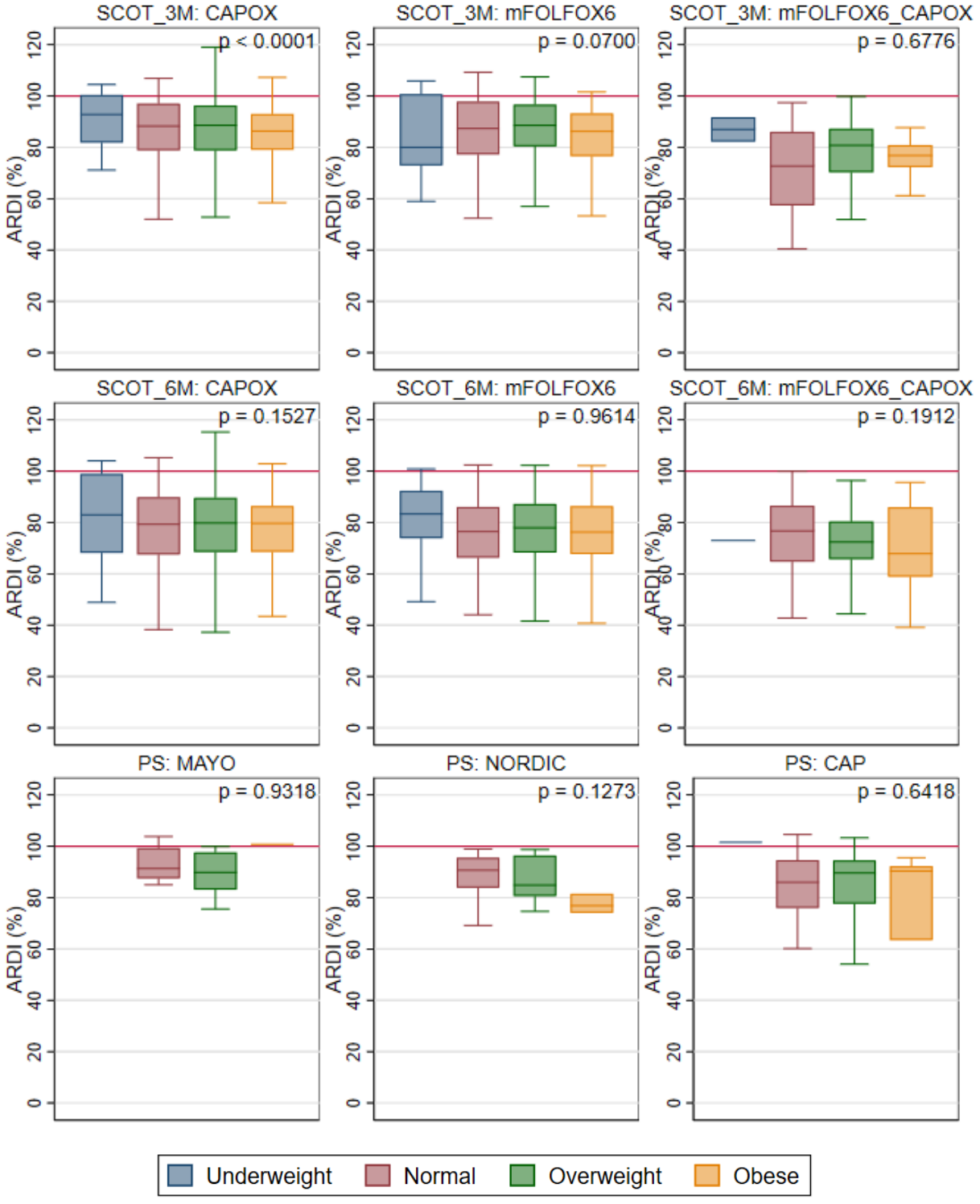
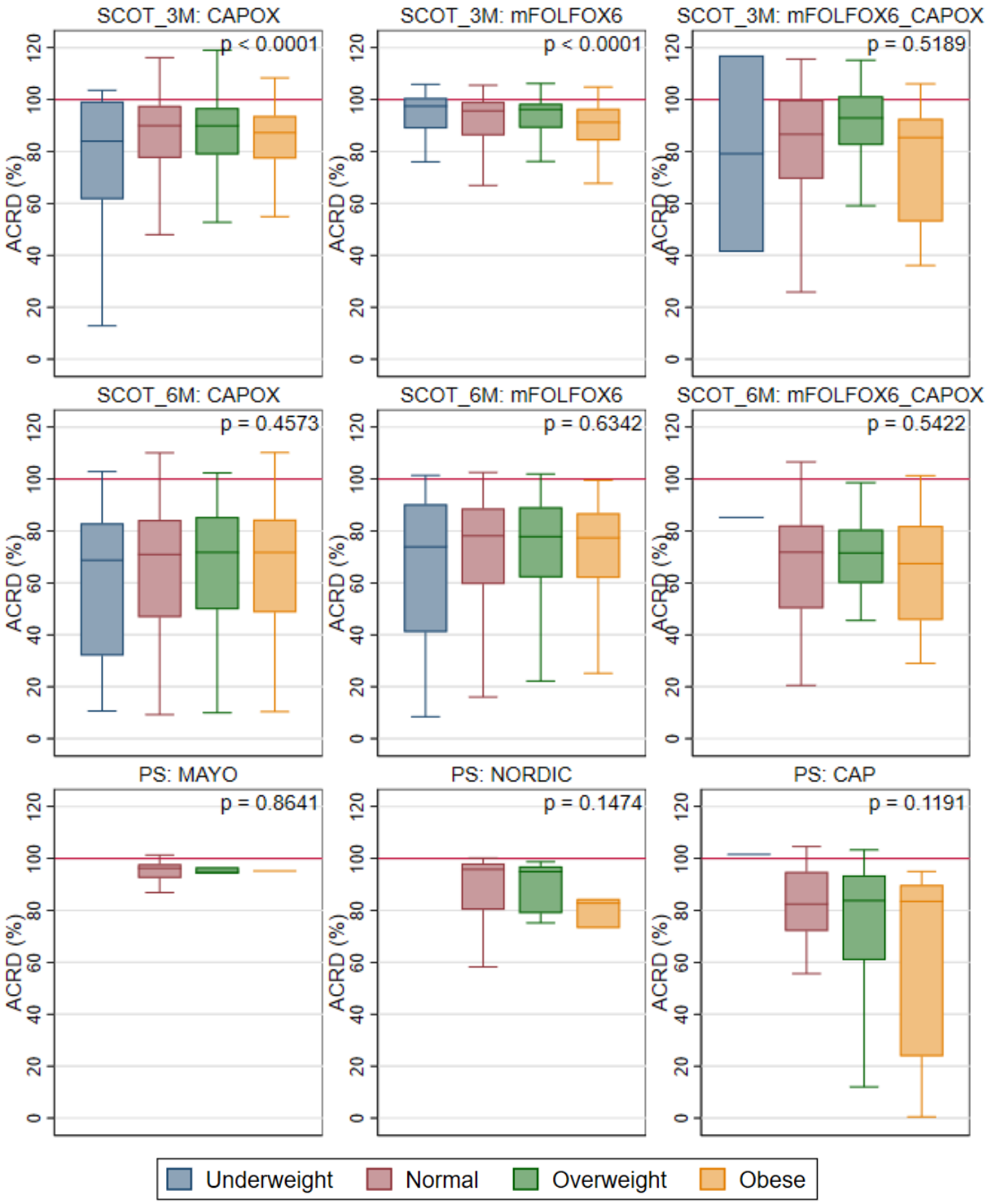


Figure 3.14 | Average cumulative relative dose by regimen
Boxplots demonstrating the average cumulative relative dose by baseline BMI category for each regimen within each trial (p values from Cochran Armitage test for trend).



3.4 DISCUSSION

3.4.1 SUMMARY AND INTERPRETATION OF RESULTS

The complexities of the chemotherapy data were explored, highlighting several key findings. First, differences in the distribution of BMI were noted across the trials, which may represent not only changing populations trends (with the more recent SCOT trial comprising of a higher proportion of obese patients), but also potential changes in recruitment practices for obese and older patients into randomised trials within oncology. The two purely rectal cancer trials had the lowest proportion of obese patients, consistent with what is frequently a super-selected patient population enrolled into such trials; having undergone neo-adjuvant (chemo)radiotherapy and then surgery, and may represent generally younger, fitter patients. Though there were variable patterns of baseline demographics across the trials, there was some suggestion of potentially healthier obese patients (younger ages, lower performance status, perforation/obstruction incidence and lower t-stage disease in MOSAIC and SCOT) at the trial level, which may introduce a degree of "healthy obese bias" and/or make results less representative of underlying populations.

Second, there was a tendency towards increasing BMI with each ACT cycle, compared with baseline BMI. Weight gain during adjuvant chemotherapy has previously been observed in patients with non-metastatic colorectal cacner.[119,229] Cancer-related weight loss is well-known, and furthermore there is likely to be a degree of weight loss associated with surgery, resulting from increased catabolism or periods of reduced nutrition (e.g., due to post-operative nausea or ileus).[229] Hence, such an increase in BMI is likely to represent some degree of recovery from surgery and disease-related weight loss, and as such highlights that peri-diagnosis or peri-treatment measurements, may not accurately represent life-time BMI risks. Additional factors that may cause weight gain include reduced activity as a result of fatigue, changes to dietary patterns (e.g., frequent, small, high calorie meals), intentional attempts at weight gain (particularly in the underweight), and steroid (glucocorticoid) use. The latter is known to be associated with weight gain (resulting from a combination of increased appetite (and increased energy intake), altered metabolism and water retention),[230] and is commonly used during chemotherapy.[231] Dexamethasone is frequently co-administered with oxaliplatin-containing regimens, given at the start of a cycle, and usually continued for several days. Here, the indication is supportive, for pre-emptive management of nausea and vomiting or hypersensitivity reactions, and may have additional benefit for fatigue and pain symptoms.[165] Included patients receiving doublet regimens are likely to have received steroids, Furthermore, the degree of cycle-level attrition across cycles due to early discontinuation of chemotherapy, may have influenced the cycle-level data, hence upward tendencies of BMI may also relate to the degree to which chemotherapy is tolerated, and the occurrence of chemotherapy-related toxicity, producing an upwards bias at the cycle level. Equally, during successive cycles there were

patients with BMI changes in the opposing direction, more common amongst those with a higher baseline BMI. Such weight loss may be intentional (e.g., the result of a patient's diagnosis, or generic advice to maintain a healthy weight in cancer survivors, prompting life-style changes), or unintentional (e.g., disease- or toxicity-related weight loss from nausea, vomiting, diarrhoea, or appetite changes). Data on steroid use, diet, physical activity, and patient intentions were unavailable, hence the relative contribution of these factors remains unclear. Furthermore, assumptions or conclusions of the composition of weight changes, i.e., adipose tissue vs. muscle, could not be made, but may be important in understanding how chemotherapy is tolerated, in addition to how adiposity and body composition are associated with survival.

Third, as hypothesised, there was an inverse relationship between BMI and cycle one average relative dose received, consistent across the drugs, regimens, and trials. Dose capping incidence mirrored this relationship with increasing incidence of cycle one capping with increasing BMI. Furthermore, capping was common in all trials, with incidence ranging approximately 30-60% amongst obese patients. Dose capping was common for all BMI categories within the SCOT trial and is likely to have been the result of dose banding, producing a degree of under- and over-dosing across all BMI categories.

Fourth, these relationships were relatively maintained throughout cycles for MOSAIC, ultimately leading to a significant inverse relationship between BMI and both ARDI and ACRD. Dose reduction incidence was generally low, with no clear relationship with BMI. Similarly, incidence of dose-delays, early discontinuation and cycle-level cumulative attrition were similar across normal, overweight, and obese categories. Overall, this suggested that initial dose-capping related differences might be maintained due to equivalent toxicity incidence across BMI categories.

Fifth, BMI-chemotherapy relationships were more variable for the other trials. The inverse cycle one RDR relationship, seen in both arms of the SCOT trial, reduced across the cycles, with some convergence of doses and indeed, changing (inverting) direction of association in SCOT_6M, mirrored by the incidence of relative under-doing. Dose reduction relationships displayed the inverse, with a higher percentage of patients receiving dose reductions in the normal BMI category, and a similar inverse dose delay incidence relationship. Cycle-level cumulative attrition of patients receiving chemotherapy was similar across BMI categories and overall, there was a significant inverse relationship between BMI and early discontinuation in SCOT_3M, but not SCOT_6M, with generally higher rates in the latter. These relationships suggested dose-limiting toxicity may have been greater in the lower BMI categories, potentially reducing the initial dosing differences. Indeed, the inverse relationship between BMI and both ARDI and ACRD was less obvious, however, obese patients appeared to receive lower median ARDI and ACRD.

Sixth, some differences between the drugs were demonstrated, and in general, capecitabine-containing regimens tended to have lower ARDRs, and were more commonly capped or underdosed. This was most likely explained by larger reductions in capecitabine median RDR, probably the result of administration in tablet form requiring rounding up or down doses, in addition to dose banding. Oxaliplatin relative under-dosing tended to be lower initially and increased more steeply to levels similar to capecitabine. Furthermore, oxaliplatin was more commonly discontinued than fluorouracil components of doublet regimens.

Finally, smaller numbers of patients within CHRONICLE and PS trials, particularly in the obese category, made for an overall more challenging interpretation of relationships within these trials, but in general followed similar relationships.

CHAPTER FOUR
RESULTS PART II

Characterising BMI-toxicity relationships

CHAPTER FOUR PREFACE

Chapter four summarises and characterises the relationship between BMI and toxicity. Toxicity data were available from each trial, and characteristics are described in relation to baseline BMI, prior to the formal statistical modelling undertaken in Chapters five and six. The complexity of the toxicity data is made evident, including the potential challenges of dealing with missing data during the statistical modelling undertaken in later chapters.

4.1 INTRODUCTION

Toxicity is common within regimens of adjuvant chemotherapy (ACT) and may be serious, posing a risk to life. The occurrence of grade 3+ toxicity is a common cause of dose reductions and/or early discontinuation of chemotherapy. Concerns over increased toxicity in full weight-based dosing of obese patients has historically resulted in the practice of dose capping. BMI has the potential to influence the development of toxicity and hence additionally impact on overall chemotherapy adherence, beyond initial dose capping.

4.2 METHODS

4.2.1 AIMS

The aims of Chapter four were to describe the toxicity datasets, characterising the relationship between BMI and toxicity, providing further insight into potential mechanisms of the BMI-chemotherapy adherence-toxicity pathways, prior to more formal statistical modelling.

4.2.2 DATA SOURCE & POPULATION

The two toxicity datasets (TOX1 and TOX2) were utilised, their derivation previously described in Chapter two (see also **Chapter 3, Figure 3.1**, for the patient population flow chart, and **Figure 4.1** below). For the majority of trials (MOSAIC, CHRONICLE and PROCTOR-SCRIPT [PS]), these consisted of the same patients as in the Main population (excluding five patients with completely missing toxicity data from PS) and are referred to as the TOX1 population throughout to reduce repetition. For SCOT_3M and SCOT_6M, the TOX1 population consisted of data from patients with protocol-mandated toxicity data collection, whereas the TOX2 population consisted of all patients with any available toxicity data. The majority of trials contributed cycle-level toxicity data, excluding CHRONICLE which had only overall summary (grade 3+) toxicity data for individual toxicities.

4.2.3 EXPOSURE

The primary exposure throughout this Chapter was BMI, again categorised according to WHO definitions as previously defined.

4.2.4 OUTCOMES

Intermediate toxicity outcomes were explored, summarised in **Table 4.1**, consisting of the various summary measures of toxicity defined in Chapter two.

4.2.5 Statistical Analysis

Baseline trial characteristics and selected chemotherapy adherence measures were summarised for SCOT_3M and SCOT_6M TOX1 and TOX2 populations, for comparison with the Main population (see Chapter three) to assess for potential issues with complete case analysis.

Intermediate toxicity outcomes were summarised at the trial level, and where appropriate, stratified at the regimen-level (**Table 4.1**). For the SCOT trial these were explored within both TOX1 and TOX2 populations. Regimen-level stratification was only performed for overall grade 3+ toxicity and grade 3+ toxicity stratified by cycle 1 dose-capping status, due to patient and event numbers being small within sub-strata for other analyses. Similarly, the small number of patients who changed regimen in the SCOT trial, as described in Chapters 2 and 3, were excluded from regimen-level analyses as these contained generally very small numbers within the context of the overall reduced numbers of TOX1 and TOX2 populations.

Continuous data are presented as median and interquartile range (IQR) and discrete data as n (%), as in Chapter three. Furthermore, statistical testing across ordinal BMI categories (using Cochran-Armitage test for trend) was again only performed on certain key analyses (**Table 4.1**) in order to reduce the number of statistical tests performed in attempt to reduce the problem of significance in the context of multiple testing. Definitive statistical modelling of BMI-toxicity relationships was undertaken in Chapters five and six. Statistical significance was attributed a p value threshold of 5%. All statistical analyses presented within this Chapter were performed in Stata® version 17 (StataCorp LLC, 2021, College Station, TX, USA).

Table 4.1 | Toxicity outcomes
The toxicity outcomes explored in relation to baseline BMI categories, the levels of stratification explored, and the statistical tests performed.

		Regimen	Trial
Overall toxicity	Overall occurrence of grade 3+ toxicity by BMI	✓	✓ [a]
	Overall occurrence of grade 3+ toxicity by BMI & dose capping	✓	✓ [a]
	Overall highest grade of toxicity by BMI	×	✓
	Early vs. late onset for first occurrence of grade 3+ toxicity	×	✓
Individual toxicities	Overall occurrence of grade 3+ neuropathy by BMI	×	✓
	Overall occurrence of grade 3+ diarrhoea by BMI	×	✓
	Overall occurrence of grade 3+ nausea by BMI	×	✓
	Overall occurrence of grade 3+ vomiting by BMI	×	✓
	Overall occurrence of grade 3+ neutropenia by BMI	×	✓
	Overall occurrence of grade 3+ mucositis by BMI	×	✓
	Overall occurrence of grade 3+ fatigue by BMI	×	✓
	Overall occurrence of grade 3+ skin toxicity by BMI	×	✓
	Overall occurrence of other grade 3+ toxicity by BMI	×	✓

Abbreviations: BMI, Body mass index.
[a] Cochran Armitage test for trend
*Excludes patients changing regimen.

4.3 RESULTS

4.3.1 PATIENT INCLUSION

A diagrammatic representation of the three study populations is presented in **Figure 4.1**. The TOX1 population (a complete-case dataset which excluded any missing toxicity data and SCOT patients not within the trial defined “safety’ population) consisted of 2171 patients. The TOX2 population (a complete case dataset including all patients with any available toxicity data) consisted of 3092 patients (see also **Chapter 3, Figure 3.1**).

4.3.2 TOXICITY POPULATION BASELINE CHARACTERISTICS

Trial-level baseline characteristics are presented in **Table 4.2**, for both toxicity populations of SCOT_3M and SCOT_6M, allowing comparison with the Main population characteristics previously presented in Chapter Three, **Table 3.2**. Median BMI, median BSA and the proportion of patients within each BMI category for each toxicity population was similar to the respective Main population. However, minor differences between the two toxicity populations and the Main population were observed. Performance status tended to be higher in all toxicity populations, with a higher proportion of performance status 1 in the TOX1 population (SCOT_3M: 36.2%; SCOT_6M: 39.1%) compared with TOX2 (SCOT_3M: 32.1%; SCOT_6M: 33.5%) and the Main population (SCOT_3M: 28%; and SCOT_6M: 29.6%). Though pT-stage was similar across the populations, pN-stage tended to be higher with the proportion nodal stage lower for pN0, similar for pN1 and higher pN2, for both toxicity populations compared with the respective Main population. This was reflected in a slightly higher proportion of patients with American Joint Committee on Cancer (AJCC) stage III within both TOX1 (SCOT_3M 86.4%; SCOT_6M 87.2%) and TOX2 (SCOT_3M 84.2%; SCOT_6M 84.3%) populations compared to the Main population (SCOT_3M 81.6%; SCOT_6M 81.8%).

Figure 4.1 | Study populations

Diagrammatic representation of the study populations, with coloured areas representing the data from each trial dataset that were included in the named population, and grey areas indicating data that were excluded. The Main population contains all data from eligible patients in each trial. The TOX1 population excluded any patients with missing toxicity data in addition to excluding SCOT patients who were not part of the protocol-defined safety population. The TOX2 population included all patients with any available toxicity data. Note that for MOSAIC and CHRONICLE, all three populations contain the same trial patients, whereas for PROCTOR-SCRIPT (PS), five patients had completely missing toxicity data, therefore TOX1 & TOX2 populations are the same.

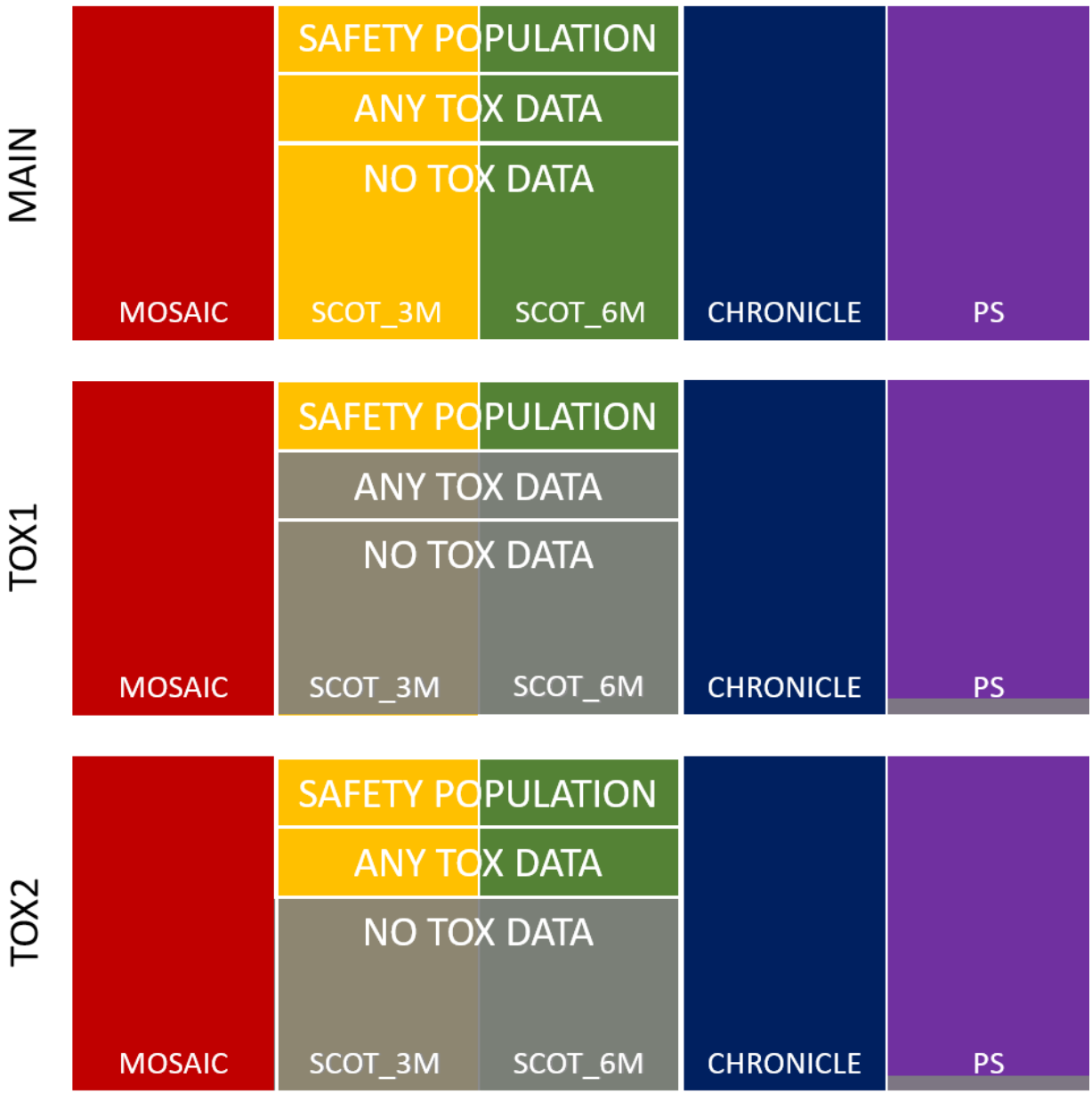


Table 4.2 | Trial characteristics for SCOT toxicity populations

		TOX1 Population		TOX2 Population	
		SCOT_3M N=420	SCOT_6M N=430	SCOT_3M N=885	SCOT_6M N=886
Mean BMI (SD), kg/m2		26.50 (4.74)	26.96 (4.84)	26.76 (4.98)	26.88 (4.70)
BMI WHO category	**Underweight**	10 (2.38%)	6 (1.40%)	18 (2.03%)	10 (1.13%)
	Normal	161 (38.33%)	156 (36.28%)	331 (37.40%)	327 (36.91%)
	Overweight	165 (39.29%)	173 (40.23%)	341 (38.53%)	358 (40.41%)
	Obese	84 (20.00%)	95 (22.09%)	195 (22.03%)	191 (21.56%)
	Obese 1	65 (15.48%)	68 (15.81%)	143 (16.16%)	140 (15.80%)
	Obese 2	15 (3.57%)	23 (5.35%)	38 (4.29%)	41 (4.63%)
	Obese 3	4 (0.95%)	4 (0.93%)	14 (1.58%)	10 (1.13%)
Mean BSA	**(SD), m2**	1.89 (0.23)	1.91 (0.23)	1.89 (0.23)	1.90 (0.23)
Mean Age	**(SD), years**	63.00 (9.01)	63.24 (10.04)	63.38 (9.39)	63.77 (9.63)
Sex	**Male**	257 (61.19%)	267 (62.09%)	530 (59.89%)	543 (61.29%)
	Female	163 (38.81%)	163 (37.91%)	355 (40.11%)	343 (38.71%)
Performance status	**0**	268 (63.81%)	262 (60.93%)	601 (67.91%)	589 (66.48%)
	1	152 (36.19%)	168 (39.07%)	284 (32.09%)	297 (33.52%)
Race	**White**	397 (94.52%)	406 (94.42%)	812 (91.75%)	823 (92.89%)
	Non-white	22 (5.24%)	20 (4.65%)	43 (4.86%)	34 (3.84%)
	Missing	1 (0.24%)	4 (0.93%)	30 (3.39%)	29 (3.27%)
Disease site	**Colon**	344 (81.90%)	351 (81.63%)	731 (82.60%)	733 (82.73%)
	Rectum	76 (18.10%)	79 (18.37%)	154 (17.40%)	153 (17.27%)
(y)pT-stage	**pT0-pT2**	52 (12.38%)	50 (11.63%)	104 (11.75%)	99 (11.17%)
	pT3	236 (56.19%)	247 (57.44%)	486 (54.92%)	506 (57.11%)
	pT4	132 (31.43%)	133 (30.93%)	295 (33.33%)	281 (31.72%)
(y)pN-stage	**pN0**	57 (13.57%)	55 (12.79%)	140 (15.82%)	139 (15.69%)
	pN1	242 (57.62%)	253 (58.84%)	500 (56.50%)	500 (56.43%)
	pN2	121 (28.81%)	122 (28.37%)	245 (27.68%)	247 (27.88%)
AJCC Stage	**0**	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	I	1 (0.24%)	0 (0.00%)	2 (0.23%)	3 (0.34%)
	II	56 (13.33%)	55 (12.79%)	138 (15.59%)	136 (15.35%)
	III	363 (86.43%)	375 (87.21%)	745 (84.18%)	747 (84.31%)
Differen-tiation	**Poor/un-diff**	14 (3.33%)	15 (3.49%)	33 (3.73%)	32 (3.61%)
	Well/mod	44 (10.48%)	41 (9.53%)	106 (11.98%)	100 (11.29%)
	Missing	362 (86.19%)	374 (86.98%)	746 (84.29%)	754 (85.10%)
Perforation/ obstruction	**No**	36 (8.57%)	33 (7.67%)	96 (10.85%)	84 (9.48%)
	Yes	22 (5.24%)	22 (5.12%)	42 (4.75%)	49 (5.53%)
	Missing	362 (86.19%)	375 (87.21%)	747 (84.41%)	753 (84.99%)
PNI	**No**	53 (12.62%)	48 (11.16%)	119 (13.45%)	112 (12.64%)
	Yes	4 (0.95%)	7 (1.63%)	11 (1.24%)	16 (1.81%)
	Missing	363 (86.43%)	375 (87.21%)	755 (85.31%)	758 (85.55%)
LVI	**No**	28 (6.67%)	29 (6.74%)	59 (6.67%)	64 (7.22%)
	Yes	30 (7.14%)	27 (6.28%)	80 (9.04%)	69 (7.79%)
	Missing	362 (86.19%)	374 (86.98%)	746 (84.29%)	753 (84.99%)
LNH		9.00 (8.00-9.00)	8.00 (8.00-9.00)	8.00 (6.00-9.00)	8.00 (6.00-9.00)
Lymph node ≥ 10 nodes	**No**	9 (2.14%)	8 (1.86%)	18 (2.03%)	15 (1.69%)
	Yes	49 (11.67%)	47 (10.93%)	120 (13.56%)	118 (13.32%)
	Missing	362 (86.19%)	375 (87.21%)	747 (84.41%)	753 (84.99%)
Post-op CEA (IQR), ng/ml		1.40 (1.00-2.05)	1.50 (1.00-2.10)	1.54 (1.00-2.20)	1.70 (1.00-2.20)
Regimen	**CAPOX**	265 (63.10%)	266 (61.86%)	580 (65.54%)	573 (64.67%)
	mFOLFOX6	143 (34.05%)	149 (34.65%)	284 (32.09%)	279 (31.49%)
	Both*	12 (2.86%)	15 (3.49%)	21 (2.37%)	34 (3.84%)

Abbreviations: AJCC, American joint committee on cancer; **BMI,** Body Mass Index; **BSA**, Body Surface area; **CAPOX,** Capecitabine + Oxaliplatin; **CEA**, carcinoembryonic antigen; **IQR,** interquartile range; **LNH**, Lymph node harvest; **LVI**, Lymphovascular invasion; **mFOLFOX6,** 5FU + oxaliplatin; **mFOLFOX6/CAPOX,** change of regimen with patients receiving both; **PNI**, perineural invasion; **(y)pT,** (post-neoadjuvant treatment) pathological tumour stage, **(y)pN,** (post-neoadjuvant treatment) pathological nodal stage; **WHO**, World Health Organisation.
*Patients changing regimen and receiving both CAPOX and mFOLFOX6

4.3.3 TOXICITY POPULATION BASELINE CHARACTERISTICS BY BMI AND TRIAL

Selected baseline characteristics according to baseline BMI category are presented in **Table 4.3** for both toxicity populations of SCOT_3M and SCOT_6M, for comparison with the Main population (previously presented in Chapter Three, **Table 3.3**).

Median BMI, median BSA and the proportion of patients within each BMI category for each toxicity population were similar to the respective full population. However, there were minor differences between the two toxicity populations and the Main population. Median age was slightly lower in underweight, overweight, and obese categories, but slightly higher in the normal category of both toxicity populations of SCOT_3M compared with the Main population. There were sex differences within the SCOT_3M arm with a higher percentage of obese patients who were female in the TOX1 and TOX2 populations compared with the Main populations. In the SCOT_6M arm proportions of males and females across BMI mirrored the Main population, with the exception of a higher proportion of underweight patients who were male in the TOX1 and TOX2 populations. Performance status tended to be higher across all BMI categories in the TOX1 and TOX2 populations compared with the Main population. Pathological N-stage tended to be higher with a higher proportion of pN2 for both SCOT_3M and SCOT_6M and both TOX1 and TOX2 populations compared with the Main population, this was most consistently the case for the obese category. Again, this was reflected in a slightly higher proportion of patients with American Joint Committee on Cancer (AJCC) stage III across the BMI categories, within both arms and both toxicity populations compared to the Main population. Furthermore, receipt of CAPOX vs. mFOLFOX6 was balanced across the baseline BMI categories in the Main population with approximately a 2/3 to 1/3 split respectively. However, within the TOX1 populations the obese category tended to have a slightly higher proportion of patients receiving mFOLFOX6 (SCOT_3M: 40.3%; SCOT_6M: 35.8%) compared with the TOX2 (SCOT_3M: 33.8%; SCOT_6M: 29.8%) and Main populations (SCOT_3M: 31.71%; SCOT_6M: 28.09%).

Table 4.3 | Baseline characteristics by Trial Toxicity population						
			Underweight	Normal	Overweight	Obese
Mean BSA (SD), m2						
TOX1	**SCOT_3M**		1.48 (0.12)	1.76 (0.17)	1.94 (0.17)	2.12 (0.19)
	SCOT_6M		1.52 (0.10)	1.73 (0.16)	1.96 (0.16)	2.13 (0.19)
TOX2	**SCOT_3M**		1.5 (0.11)	1.75 (0.17)	1.93 (0.17)	2.11 (0.21)
	SCOT_6M		1.5 (0.08)	1.73 (0.17)	1.94 (0.17)	2.12 (0.19)
Mean Age (SD), years						
TOX1	**SCOT_3M**		61.7 (12.94)	64.47 (9.18)	62.65 (8.97)	61.02 (7.82)
	SCOT_6M		63.33 (7.61)	62.04 (11.52)	64.17 (8.78)	63.49 (9.65)
TOX2	**SCOT_3M**		58.17 (15.09)	64.49 (9.58)	62.98 (9.39)	62.66 (8.10)
	SCOT_6M		66 (8.21)	63.27 (10.53)	64.24 (9.18)	63.63 (8.88)
Sex						
TOX1	**SCOT_3M**	**Male**	1 (10.00%)	95 (59.01%)	115 (69.70%)	46 (54.76%)
		Female	9 (90.00%)	66 (40.99%)	50 (30.30%)	38 (45.24%)
	SCOT_6M	**Male**	4 (66.67%)	75 (48.08%)	122 (70.52%)	66 (69.47%)
		Female	2 (33.33%)	81 (51.92%)	51 (29.48%)	29 (30.53%)
TOX2	**SCOT_3M**	**Male**	7 (38.89%)	185 (55.89%)	229 (67.16%)	109 (55.90%)
		Female	11 (61.11%)	146 (44.11%)	112 (32.84%)	86 (44.10%)
	SCOT_6M	**Male**	5 (50.00%)	169 (51.68%)	239 (66.76%)	130 (68.06%)
		Female	5 (50.00%)	158 (48.32%)	119 (33.24%)	61 (31.94%)
WHO performance status						
TOX1	**SCOT_3M**	**0**	5 (50.00%)	89 (55.28%)	119 (72.12%)	55 (65.48%)
		1	5 (50.00%)	72 (44.72%)	46 (27.88%)	29 (34.52%)
	SCOT_6M	**0**	3 (50.00%)	94 (60.26%)	103 (59.54%)	62 (65.26%)
		1	3 (50.00%)	62 (39.74%)	70 (40.46%)	33 (34.74%)
TOX2	**SCOT_3M**	**0**	8 (44.44%)	204 (61.63%)	255 (74.78%)	134 (68.72%)
		1	10 (55.56%)	127 (38.37%)	86 (25.22%)	61 (31.28%)
	SCOT_6M	**0**	7 (70.00%)	224 (68.50%)	230 (64.25%)	128 (67.02%)
		1	3 (30.00%)	103 (31.50%)	128 (35.75%)	63 (32.98%)
Disease site						
TOX1	**SCOT_3M**	**Colon**	10 (100.00%)	140 (86.96%)	128 (77.58%)	66 (78.57%)
		Rectum	0 (0.00%)	21 (13.04%)	37 (22.42%)	18 (21.43%)
	SCOT_6M	**Colon**	6 (100.00%)	131 (83.97%)	133 (76.88%)	81 (85.26%)
		Rectum	0 (0.00%)	25 (16.03%)	40 (23.12%)	14 (14.74%)
TOX2	**SCOT_3M**	**Colon**	15 (83.33%)	283 (85.50%)	275 (80.65%)	158 (81.03%)
		Rectum	3 (16.67%)	48 (14.50%)	66 (19.35%)	37 (18.97%)
	SCOT_6M	**Colon**	9 (90.00%)	271 (82.87%)	291 (81.28%)	162 (84.82%)
		Rectum	1 (10.00%)	56 (17.13%)	67 (18.72%)	29 (15.18%)
T-stage						
TOX1	**SCOT_3M**	**pT0-pT2**	1 (10.00%)	16 (9.94%)	19 (11.52%)	16 (19.05%)
		pT3	6 (60.00%)	88 (54.66%)	99 (60.00%)	43 (51.19%)
		pT4	3 (30.00%)	57 (35.40%)	47 (28.48%)	25 (29.76%)
	SCOT_6M	**pT0-pT2**	1 (16.67%)	12 (7.69%)	28 (16.18%)	9 (9.47%)
		pT3	4 (66.67%)	92 (58.97%)	90 (52.02%)	61 (64.21%)
		pT4	1 (16.67%)	52 (33.33%)	55 (31.79%)	25 (26.32%)
TOX2	**SCOT_3M**	**pT0-pT2**	1 (5.56%)	34 (10.27%)	40 (11.73%)	29 (14.87%)
		pT3	12 (66.67%)	183 (55.29%)	180 (52.79%)	111 (56.92%)
		pT4	5 (27.78%)	114 (34.44%)	121 (35.48%)	55 (28.21%)
	SCOT_6M	**pT0-pT2**	1 (10.00%)	31 (9.48%)	46 (12.85%)	21 (10.99%)
		pT3	7 (70.00%)	190 (58.10%)	190 (53.07%)	119 (62.30%)
		pT4	2 (20.00%)	106 (32.42%)	122 (34.08%)	51 (26.70%)

Table 4.3 | *Continued*

			Underweight	Normal	Overweight	Obese
N-stage						
TOX1	**SCOT_3M**	**pN0**	1 (10.00%)	19 (11.80%)	27 (16.36%)	10 (11.90%)
		pN1	6 (60.00%)	94 (58.39%)	94 (56.97%)	48 (57.14%)
		pN2	3 (30.00%)	48 (29.81%)	44 (26.67%)	26 (30.95%)
	SCOT_6M	**pN0**	0 (0.00%)	23 (14.74%)	17 (9.83%)	15 (15.79%)
		pN1	5 (83.33%)	82 (52.56%)	109 (63.01%)	57 (60.00%)
		pN2	1 (16.67%)	51 (32.69%)	47 (27.17%)	23 (24.21%)
TOX2	**SCOT_3M**	**pN0**	4 (22.22%)	52 (15.71%)	53 (15.54%)	31 (15.90%)
		pN1	10 (55.56%)	197 (59.52%)	190 (55.72%)	103 (52.82%)
		pN2	4 (22.22%)	82 (24.77%)	98 (28.74%)	61 (31.28%)
	SCOT_6M	**pN0**	0 (0.00%)	64 (19.57%)	49 (13.69%)	26 (13.61%)
		pN1	8 (80.00%)	175 (53.52%)	209 (58.38%)	108 (56.54%)
		pN2	2 (20.00%)	88 (26.91%)	100 (27.93%)	57 (29.84%)
AJCC stage						
TOX1	**SCOT_3M**	**I**	0 (0.00%)	0 (0.00%)	1 (0.61%)	0 (0.00%)
		II	1 (10.00%)	19 (11.80%)	26 (15.76%)	10 (11.90%)
		III	9 (90.00%)	142 (88.20%)	138 (83.64%)	74 (88.10%)
	SCOT_6M	**I**	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
		II	0 (0.00%)	23 (14.74%)	17 (9.83%)	15 (15.79%)
		III	6 (100.00%)	133 (85.26%)	156 (90.17%)	80 (84.21%)
TOX2	**SCOT_3M**	**I**	0 (0.00%)	0 (0.00%)	1 (0.29%)	1 (0.51%)
		II	4 (22.22%)	52 (15.71%)	52 (15.25%)	30 (15.38%)
		III	14 (77.78%)	279 (84.29%)	288 (84.46%)	164 (84.10%)
	SCOT_6M	**I**	0 (0.00%)	2 (0.61%)	1 (0.28%)	0 (0.00%)
		II	0 (0.00%)	62 (18.96%)	48 (13.41%)	26 (13.61%)
		III	10 (100.00%)	263 (80.43%)	309 (86.31%)	165 (86.39%)
Regimen						
TOX1	**SCOT_3M**	**CAPOX**	5 (50.00%)	102 (63.35%)	108 (65.45%)	50 (59.52%)
		mFOLFOX6	4 (40.00%)	53 (32.92%)	52 (31.52%)	34 (40.48%)
		Both*	1 (10.00%)	6 (3.73%)	5 (3.03%)	0 (0.00%)
	SCOT_6M	**CAPOX**	4 (66.67%)	96 (61.54%)	111 (64.16%)	55 (57.89%)
		mFOLFOX6	2 (33.33%)	56 (35.90%)	57 (32.95%)	34 (35.79%)
		Both*	0 (0.00%)	4 (2.56%)	5 (2.89%)	6 (6.32%)
TOX2	**SCOT_3M**	**CAPOX**	12 (66.67%)	211 (63.75%)	231 (67.74%)	126 (64.62%)
		mFOLFOX6	5 (27.78%)	108 (32.63%)	105 (30.79%)	66 (33.85%)
		Both*	1 (5.56%)	12 (3.63%)	5 (1.47%)	3 (1.54%)
	SCOT_6M	**CAPOX**	8 (80.00%)	216 (66.06%)	226 (63.13%)	123 (64.40%)
		mFOLFOX6	2 (20.00%)	102 (31.19%)	118 (32.96%)	57 (29.84%)
		Both*	0 (0.00%)	9 (2.75%)	14 (3.91%)	11 (5.76%)

Abbreviations: AJCC, American joint committee on cancer; **BMI,** Body Mass Index; **BSA**, Body Surface area; **CAPOX,** Capecitabine + Oxaliplatin; **IQR,** interquartile range; **mFOLFOX6,** 5FU + oxaliplatin; **mFOLFOX6/CAPOX,** change of regimen with patients receiving both; **(y)pT,** (post-neoadjuvant treatment) pathological tumour stage, **(y)pN,** (post-neoadjuvant treatment) pathological nodal stage; **WHO**, World Health Organisation.

4.3.4 CHEMOTHERAPY SUMMARY CHARACTERISTICS BY BMI AND TRIAL

Selected chemotherapy adherence summary characteristics are presented in **Table 4.4** according to baseline BMI category for toxicity populations of SCOT_3M and SCOT_6M, the Main population is additionally presented for ease of comparison across populations (where some data were only presented within the text of Chapter three).

Summary chemotherapy adherence outcomes for SCOT_3M appeared similar across the Main, TOX1 and TOX2 populations. Minimal differences were observed across BMI categories for dose capping, and similarly for the median average relative dose received (ARDR). The proportion of dose capped patients increased with increasing BMI in all populations, with a corresponding inverse relationship for median ARDR. Similarly, there were minimal differences in the median average relative dose intensity (ARDI) and median average cumulative relative dose (ACRD), except for the underweight category, which had a slightly lower median ARDI in the TOX1 population and ACRD in the TOX2 population.

Whereas for SCOT_6M, there were large differences in the proportion of underweight patients being dose capped (Main 22.2%; TOX1 33.3%; TOX2 40%), likely partly the result of small numbers. Though this resulted in virtually no difference in median ARDR, there was an obvious widening of the interquartile range, mainly the result of a reduction of the lower quartile. The obese category also had higher proportions of dose capping in the TOX1 (69.5%) and TOX2 (66.5%) populations compared with the Main population (61.5%), corresponding with a small reduction in the median ARDR (Main 94.20%, TOX1 92.42% and TOX2 92.95%). The inverse relationship between median ARDR and BMI was maintained. Median ARDI was similar across the populations, however the median ACRD was considerably lower for the underweight category of the TOX1 and TOX2 populations (55.64% and 52.18% respectively) compared with the Main population (72.83%). Furthermore, minor differences across the other BMI categories resulted in a reversal in the relationship with BMI, with a tendency for ACRD to increase with increasing BMI in the TOX1 and TOX2 populations.

Table 4.4 | Chemotherapy characteristics by BMI

Table summarising the chemotherapy characteristics for the Main and toxicity populations of SCOT_3M and SCOT_6M.

Trial	Population		Underweight		Normal		Overweight		Obese	
Dose capping, N (%)										
SCOT_3M	**Main**	**Full**	33	(78.57%)	785	(73.43%)	811	(66.97%)	243	(37.79%)
		Capped	9	(21.43%)	284	(26.57%)	400	(33.03%)	400	(62.21%)
	TOX1	**Full**	8	(80.00%)	113	(70.19%)	108	(65.45%)	29	(34.52%)
		Capped	2	(20.00%)	48	(29.81%)	57	(34.55%)	55	(65.48%)
	TOX2	**Full**	14	(77.78%)	235	(71.00%)	228	(66.86%)	68	(34.87%)
		Capped	4	(22.22%)	96	(29.00%)	113	(33.14%)	127	(65.13%)
SCOT_6M	**Main**	**Full**	28	(77.78%)	774	(72.27%)	757	(63.56%)	262	(38.53%)
		Capped	8	(22.22%)	297	(27.73%)	434	(36.44%)	418	(61.47%)
	TOX1	**Full**	4	(66.67%)	114	(73.08%)	113	(65.32%)	29	(30.53%)
		Capped	2	(33.33%)	42	(26.92%)	60	(34.68%)	66	(69.47%)
	TOX2	**Full**	6	(60.00%)	235	(71.87%)	225	(62.85%)	64	(33.51%)
		Capped	4	(40.00%)	92	(28.13%)	133	(37.15%)	127	(66.49%)
Median Cycle 1 Average Relative Dose Received (IQR) [%]										
SCOT_3M	**Main**		100.76	(95.98-102.51)	98.90	(96.20-100.44)	97.69	(94.29-99.24)	94.03	(87.98-97.05)
	TOX1		100.58	(95.89-101.88)	98.70	(94.20-100.22)	97.26	(93.87-99.14)	93.24	(88.84-96.65)
	TOX2		101.72	(95.89-102.91)	98.67	(95.20-100.21)	97.36	(94.24-99.19)	93.61	(88.09-96.70)
SCOT_6M	**Main**		99.99	(97.74-102.11)	98.91	(96.01-100.55)	97.42	(93.68-99.23)	94.20	(87.12-96.99)
	TOX1		99.43	(95.01-102.05)	98.64	(95.20-100.50)	97.58	(91.61-99.48)	92.42	(86.19-96.06)
	TOX2		99.43	(93.67-102.05)	98.74	(95.32-100.54)	97.27	(91.68-99.17)	92.95	(86.89-96.45)
Median Average Relative Dose Intensity (IQR) [%]										
SCOT_3M	**Main**		87.98	(77.99-100.29)	87.62	(77.80-97.05)	88.27	(79.08-96.37)	86.23	(78.40-93.03)
	TOX1		83.94	(79.70-96.13)	87.58	(80.32-95.56)	89.37	(81.51-96.65)	86.72	(77.50-93.78)
	TOX2		86.45	(79.70-97.77)	86.43	(77.57-95.91)	89.73	(81.56-96.81)	86.25	(78.88-93.76)
SCOT_6M	**Main**		83.08	(70.23-95.55)	78.20	(66.95-88.89)	78.75	(68.35-89.19)	78.41	(67.83-86.41)
	TOX1		84.28	(77.74-93.63)	82.14	(72.51-88.70)	80.42	(69.85-89.32)	77.50	(67.32-85.06)
	TOX2		84.28	(75.64-93.63)	81.43	(70.72-89.71)	79.27	(69.49-90.43)	78.67	(68.95-86.99)
Median Average Cumulative Relative Dose (IQR) [%]										
SCOT_3M	**Main**		89.41	(73.33-99.63)	92.07	(80.10-98.30)	92.48	(82.38-97.55)	88.39	(79.38-94.30)
	TOX1		88.34	(73.33-99.26)	94.26	(82.63-98.61)	94.20	(83.12-97.43)	89.54	(82.74-94.25)
	TOX2		82.83	(50.15-99.26)	92.40	(81.48-98.04)	93.46	(82.74-97.42)	88.42	(80.58-93.99)
SCOT_6M	**Main**		72.83	(37.97-85.93)	73.19	(50.73-85.59)	73.86	(54.67-86.74)	73.02	(51.00-84.70)
	TOX1		55.64	(12.37-86.98)	76.42	(49.68-86.37)	74.42	(53.42-88.30)	77.23	(66.19-85.72)
	TOX2		52.18	(21.82-75.72)	72.59	(46.90-84.85)	73.78	(51.18-86.18)	75.62	(55.86-85.72)

Abbreviations: IQR, Interquartile range.

4.3.5 Overall grade 3+ toxicity by BMI

Overall, any grade 3+ toxicity occurred in 30.90% of MOSAIC, 36.19% of SCOT_3M and 59.30% of SCOT_6M TOX1 patients, 37.78% of CHRONICLE, 40.57% of PS, and 32.77% of SCOT_3M and 46.84% of SCOT_6M TOX2 patients. There was no significant relationship demonstrated between baseline BMI category and the occurrence of grade 3+ toxicity in any trial or toxicity population (**Figure 4.2**). The MOSAIC and SCOT_6M TOX1 populations displayed a tendency for toxicity to increase with increasing BMI (though this was slightly J shaped for MOSAIC, with toxicity in the underweight almost as high as in the obese category). Whereas TOX1 SCOT_3M, CHRONICLE, PS, and TOX2 SCOT_3M populations displayed a tendency for reducing toxicity with increasing BMI. The TOX2 SCOT_6M population did not demonstrate any association, however toxicity was lowest in the underweight category. For multi-regimen trials, these relationships were mostly mirrored at the regimen level (**Figures 4.3a** and **4.3b**), with no significant associations demonstrated between BMI and grade 3+ toxicity occurrence. However, mFOLFOX6 regimens tended to display slightly higher levels of toxicity than CAPOX.

Figure 4.2 | Grade 3+ toxicity by trial
Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI category for each toxicity population and trial (p-values from Cochran Armitage test for trend).

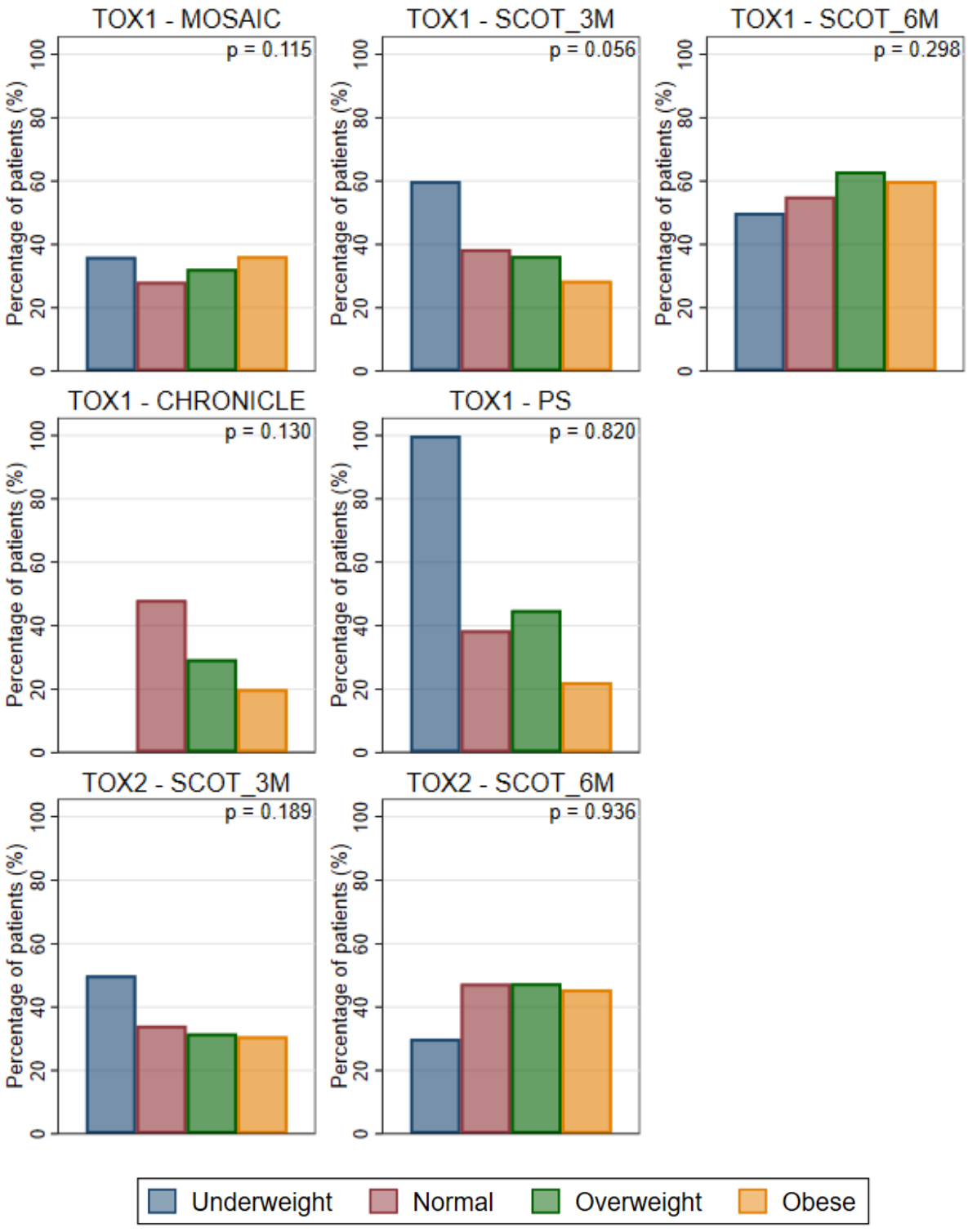


Figure 4.3a | Grade 3+ toxicity by regimen (TOX1 population)
Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI category for each regimen in multi-regimen trials for the TOX1 population (p-values from Cochran Armitage test for trend).

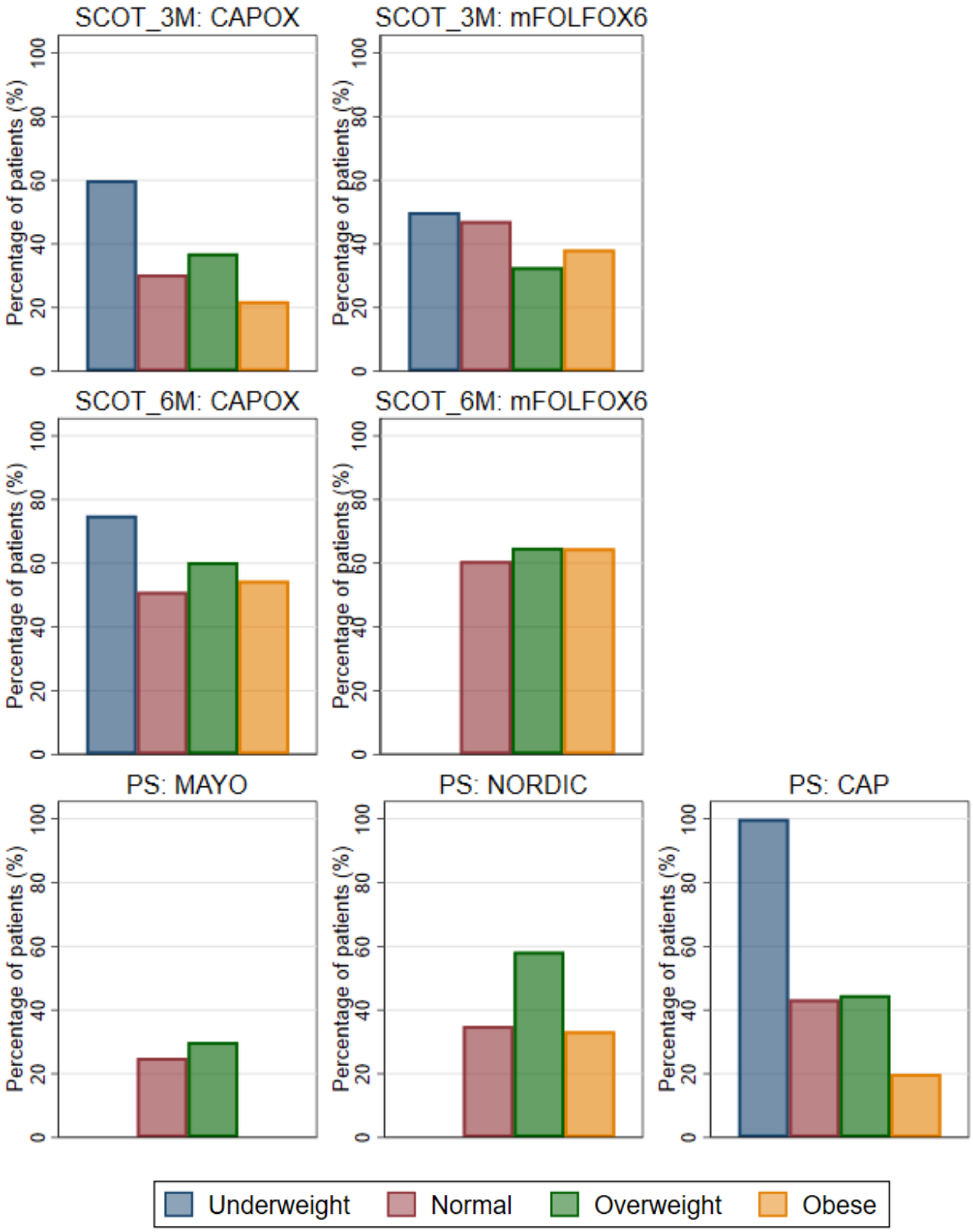
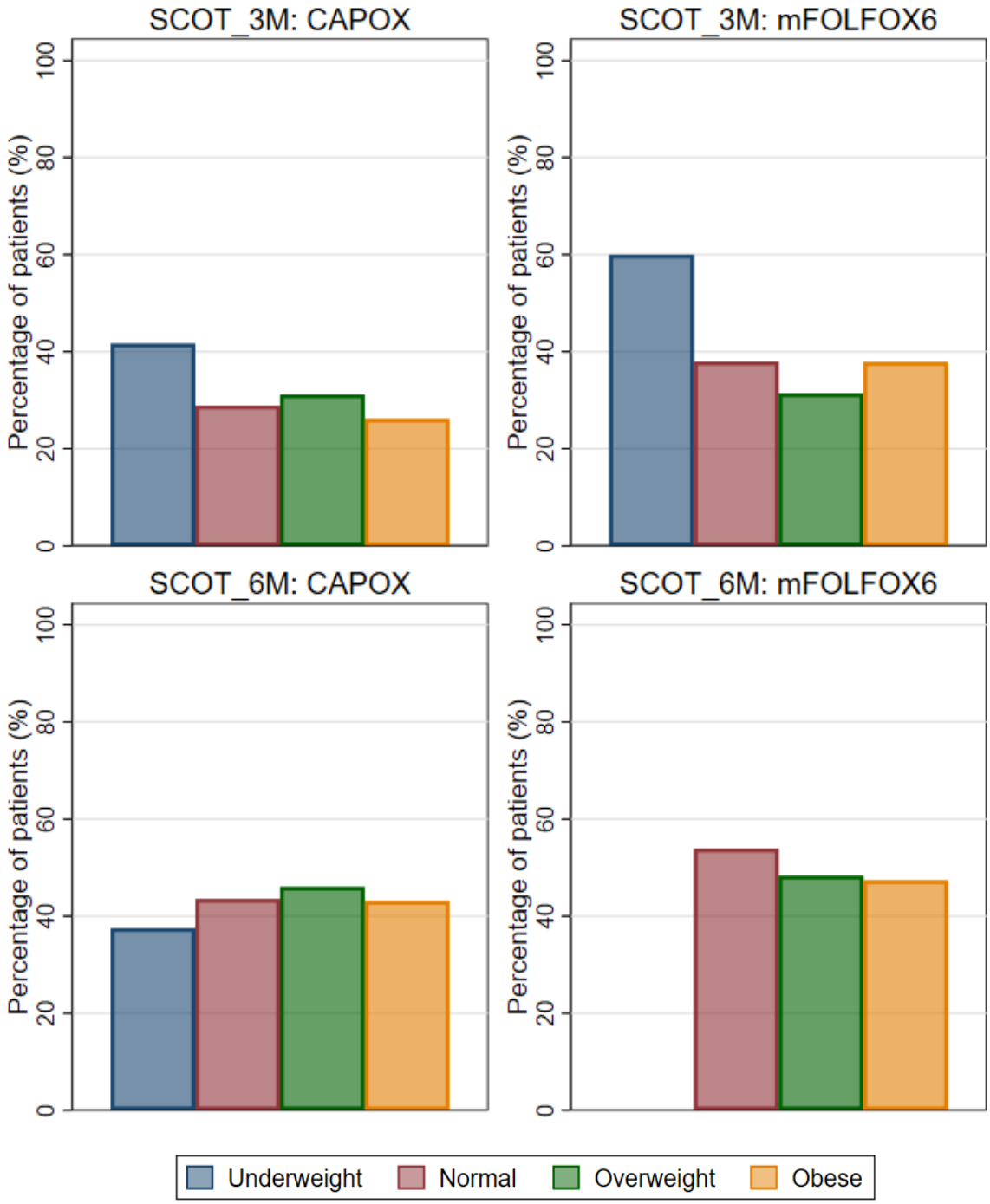


Figure 4.3b | Grade 3+ toxicity by regimen (TOX2 population)
Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI category for each regimen in multi-regimen trials for the TOX2 population (p-values from Cochran Armitage test for trend).



4.3.6 OVERALL GRADE 3+ TOXICITY BY BMI AND DOSE CAPPING STATUS

Figure 4.4 demonstrates the proportion of patients developing grade 3+ toxicity by baseline BMI category, further stratified according to receipt of cycle 1 dose capping status. In general, dose capping reduced the occurrence of toxicity for all baseline BMI categories, except for the underweight category within both TOX1 and TOX2 SCOT_6M populations and the normal category within MOSAIC. The overall relationships seen above were generally mirrored in fully dosed patients. A J-shaped and more linear tendency to increasing toxicity with increasing BMI was displayed by TOX1 MOSAIC and SCOT_6M populations respectively. Significant trends were not demonstrated in the other populations, however TOX1 SCOT_3M, CHRONICLE, PS displayed a tendency for reducing toxicity with increasing BMI, with no clear relationship for the TOX2 SCOT_3M and SCOT_6M populations. Within the dose capped subgroups, relationships between BMI and toxicity tended to be less clear and/or flattened off, and the underweight category tended to display the most variable patterns of toxicity, likely the result of small numbers of underweight patients within each trial. For multi-regimen trials, relationships at the regimen-level mirrored those at the trial level (**Figures 4.5a** and **4.5b**). Small numbers within the PS trial made interpretation at the regimen level more difficult.

Figure 4.4 | Grade 3+ toxicity by dose capping and trial

Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI and dose capping status, for each trial and toxicity population (p-values from Cochran Armitage test for trend).

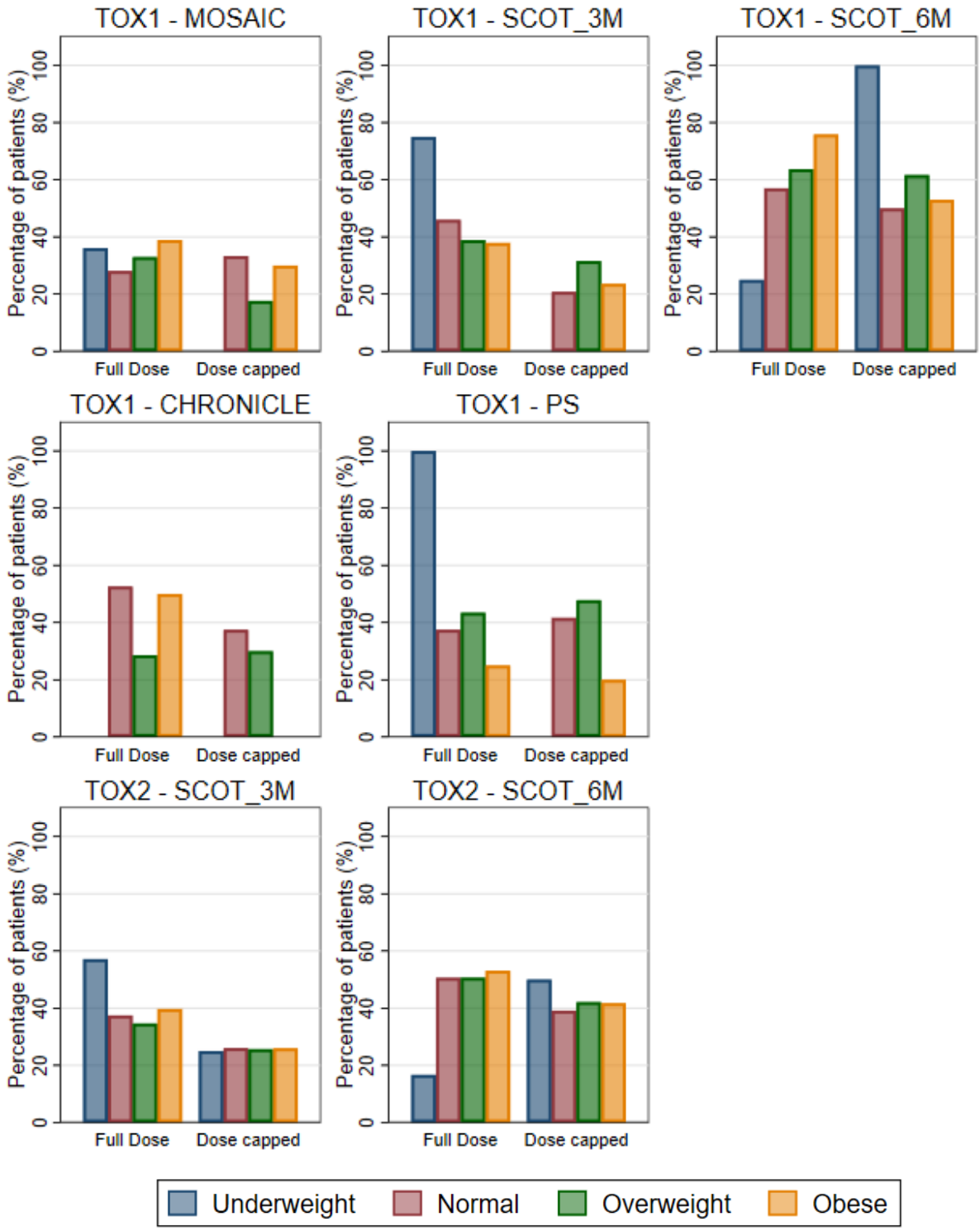


Figure 4.5a | Grade 3+ toxicity by dose capping and regimen (TOX1 population)
Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI and dose capping status, for each regimen in multi-regimen trials within the TOX1 population (p-values from Cochran Armitage test for trend).

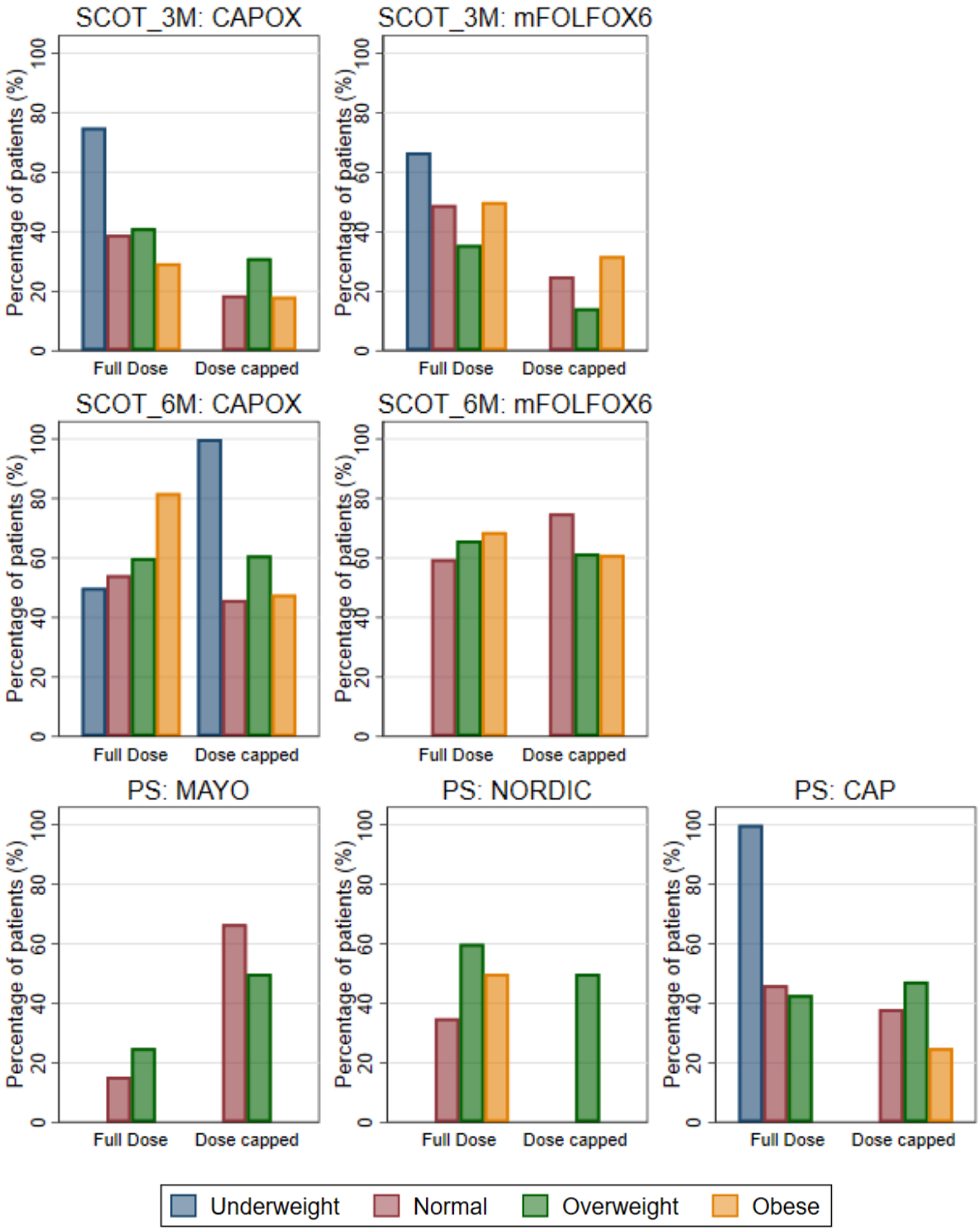
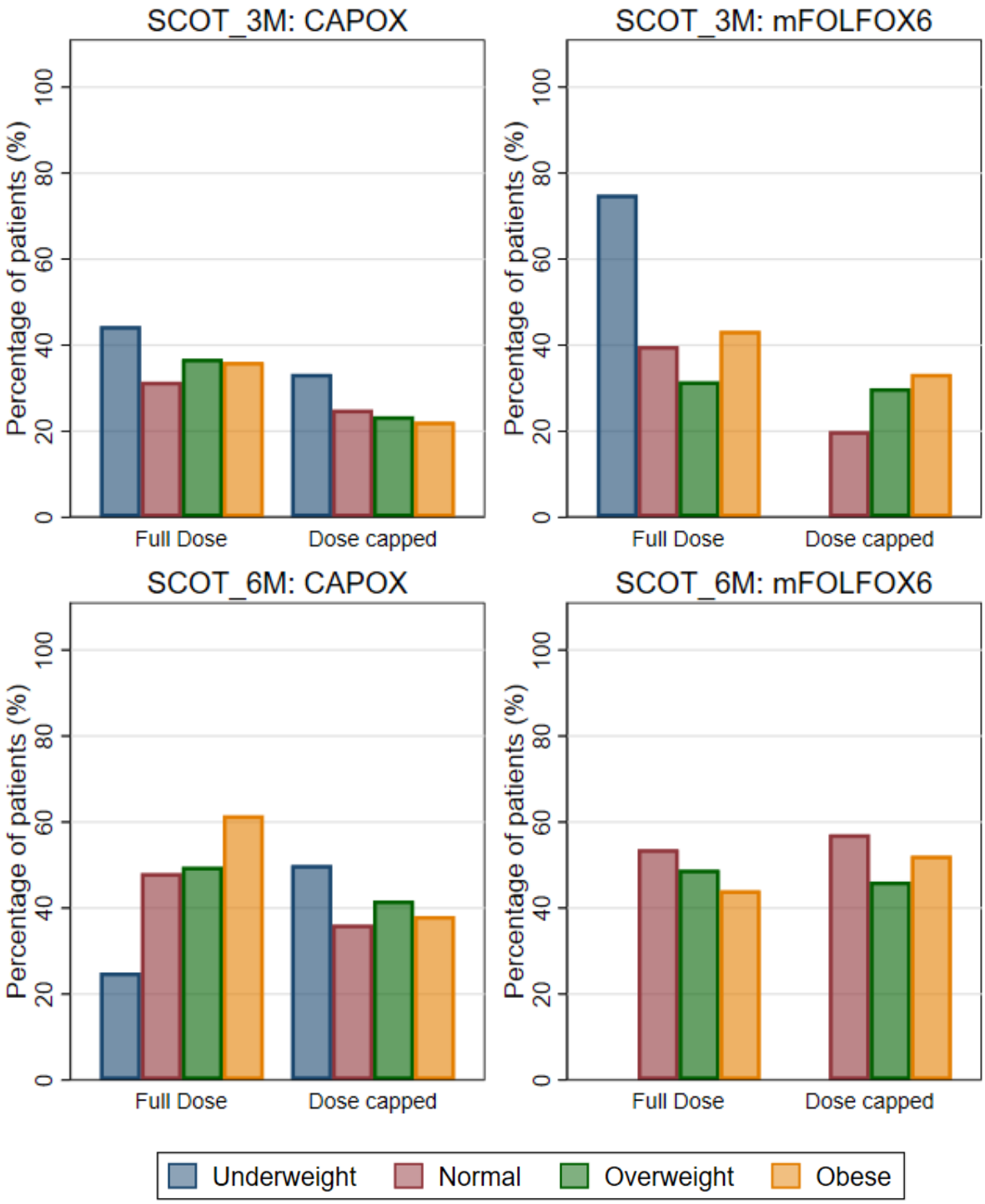


Figure 4.5b | Grade 3+ toxicity by dose capping and regimen (TOX2 population)
Bar graphs demonstrating the percentage of patients developing any grade 3+ toxicity by baseline BMI and dose capping status, for each regimen in multi-regimen trials within the TOX2 population (p-values from Cochran Armitage test for trend).



4.3.7 OVERALL HIGHEST GRADE OF TOXICITY BY BMI

The highest overall grade of toxicity (**Figure 4.6**) was grade two in all trials and populations, excluding both toxicity populations of SCOT_6M, where grade three toxicity was most the commonly occurring, and CHRONICLE (which only provided data on grade 3+). Similar patterns of toxicity distribution within each BMI category were seen within each trial (highest incidence of grade two or grade three toxicity, followed by grade one, grade four, grade five and then grade zero).

MOSAIC displayed a tendency for grade one toxicity to increase with BMI, a slight reverse U-shape distribution of grade two toxicity (highest incidence in the normal category and lowest in the obese category). There was no clear grade three toxicity relationship (highest in the overweight and lowest in the obese). Whereas there was a tendency for grade four toxicity to increase with BMI, the relative contribution of which is likely responsible for the overall grade 3+ relationship seen above.

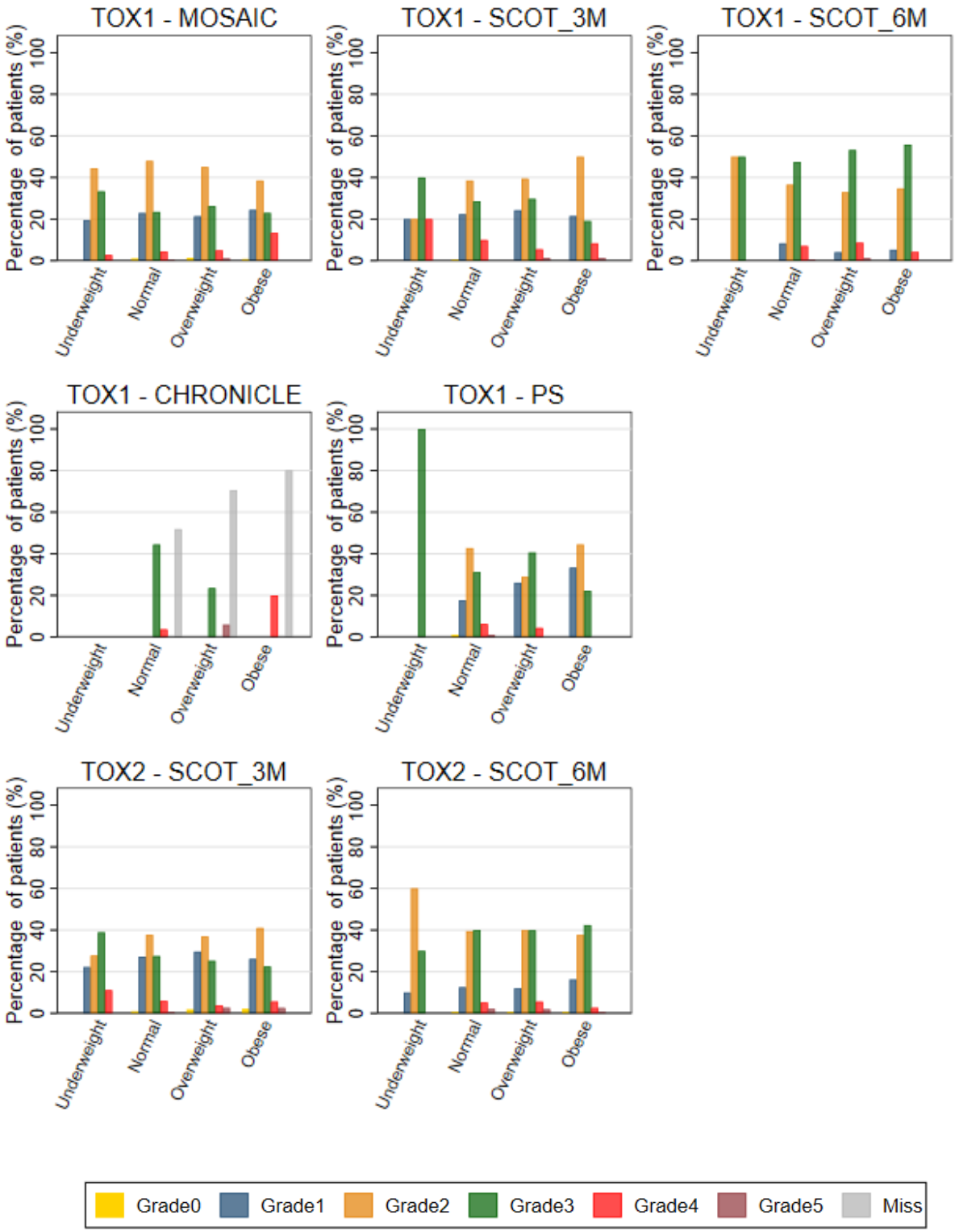
For both TOX1 and TOX2 populations of SCOT_3M, grade one toxicity displayed a slight inverse U-shape, highest in the overweight, with grade two toxicity tending to increase as BMI increased. However, both grade three and grade four incidence of toxicity tended to reduce with increasing BMI consistent with the overall BMI-grade 3+ relationship. Whereas the reverse was demonstrated for the TOX1 SCOT_6M population, with a tendency for both grade 1 and grade 2 toxicities to reduce with increasing BMI, grade three toxicity to increase with BMI, and grade four toxicity displaying an inverse U (highest in the overweight). The TOX2 SCOT_6M population however, displayed similar incidence of each toxicity grade for each BMI category, with the exclusion of the underweight category, consistent with the findings of relatively equivalent grade 3+ toxicity.

There was only one underweight patient in PS making interpretation of relationships including underweight more difficult. Excluding underweight, grade one toxicity tended to increase with BMI in PS, grade two toxicity demonstrated U-shaped distribution (lowest in overweight) with an inverted U-shape for grade three toxicity (highest in overweight). Whereas grade four toxicity tended to reduce with increasing BMI.

It was not possible to properly assess the highest toxicity grade in the CHRONICLE trial, as only grade 3+ toxicities were provided, hence there was a large proportion of patients with missing highest-grade data. Furthermore, highest grade of toxicity was not examined by regimen due to the small numbers of patients on stratification.

Figure 4.6 | Highest overall grade of toxicity by trial

Bar charts demonstrating the percentage of patients experiencing the highest grade of any toxicity by baseline BMI category for each toxicity population and trial. Highest grade of toxicity is graded 0 (none) to 5. CHRONICLE only provided data on grade 3+ toxicities and therefore the highest grade was missing in patients who did not experience a grade 3+ toxicity.



4.3.8 INDIVIDUAL GRADE 3+ TOXICITY BY BMI

The incidence of grade 3+ neuropathy, diarrhoea, nausea, vomiting, neutropenia, mucositis, fatigue, skin, and other toxicity was explored in relation to baseline BMI category at the trial level, but not at the regimen level due to small numbers of toxicity events and patients on stratification (**Figures 4.7 to 4.15**).

Neuropathy

Figure 4.7 demonstrates the percentage of patients developing grade 3+ neuropathy according to baseline BMI category. Within non-oxaliplatin-containing trials, only one patient in both overweight and obese categories in MOSAIC, and one patient in the normal category in PS developed neuropathy. Within the SCOT_3M TOX1 and TOX2 populations the incidence of grade 3+ neuropathy was low (<5%) and similar across all BMI categories. However, in the SCOT_6M TOX1 and TOX2 populations, the incidence was higher (up to 19%) with a tendency towards increasing incidence with increasing BMI, with no underweight patients developing grade 3+ neuropathy.

Diarrhoea

Grade 3+ diarrhoea (**Figure 4.8**) tended to display a U-shaped relationship with BMI within MOSAIC (highest incidence within underweight and obese categories), an inverse relationship within the SCOT_3M TOX1 population, no clear association within SCOT_6M TOX1, SCOT_3M and SCOT_6M TOX2, CHRONICLE and PS populations.

Nausea

The occurrence of grade 3+ nausea (**Figure 4.9**) tended to be most common in underweight patients within the SCOT_3M TOX1 and TOX2 populations, with low incidence (<5%) across the remainder of BMI categories for all trials, and no discernible pattern of association.

Vomiting

Similar, to the incidence of nausea, grade 3+ vomiting was most common in underweight patients within the SCOT_3M TOX1 and TOX2 populations, in addition to the normal BMI category in CHRONICLE. There was a low incidence (≤5%) across the remainder of BMI categories (**Figure 4.10**) for all trials, with no discernible pattern of association.

Figure 4.7 | Grade 3+ neuropathy by trial
Bar charts demonstrating the percentage of patients developing grade 3+ neuropathy by baseline BMI category for each trial and toxicity population.

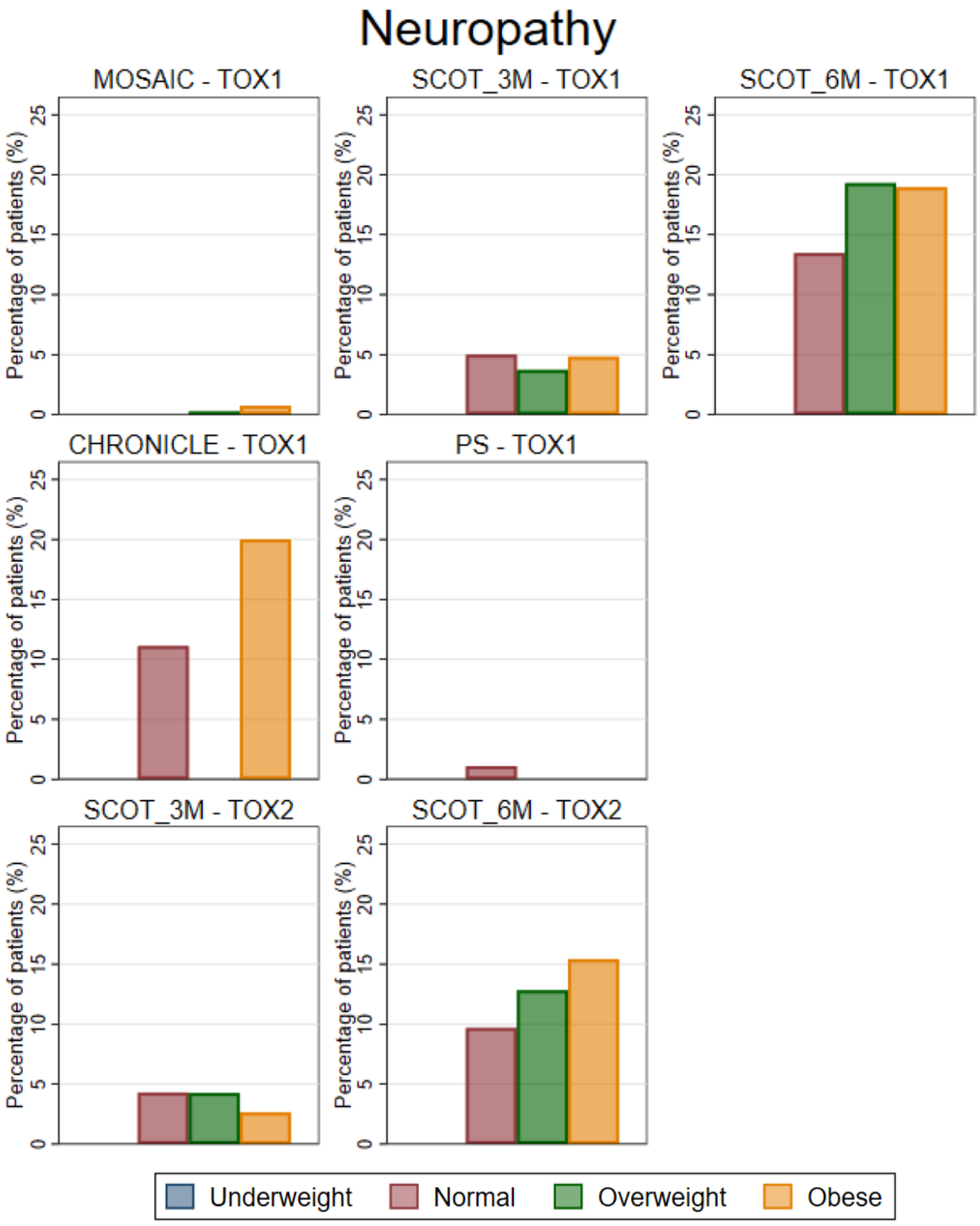


Figure 4.8 | Grade 3+ diarrhoea by trial
Bar charts demonstrating the percentage of patients developing grade 3+ diarrhoea by baseline BMI category for each trial and toxicity population.

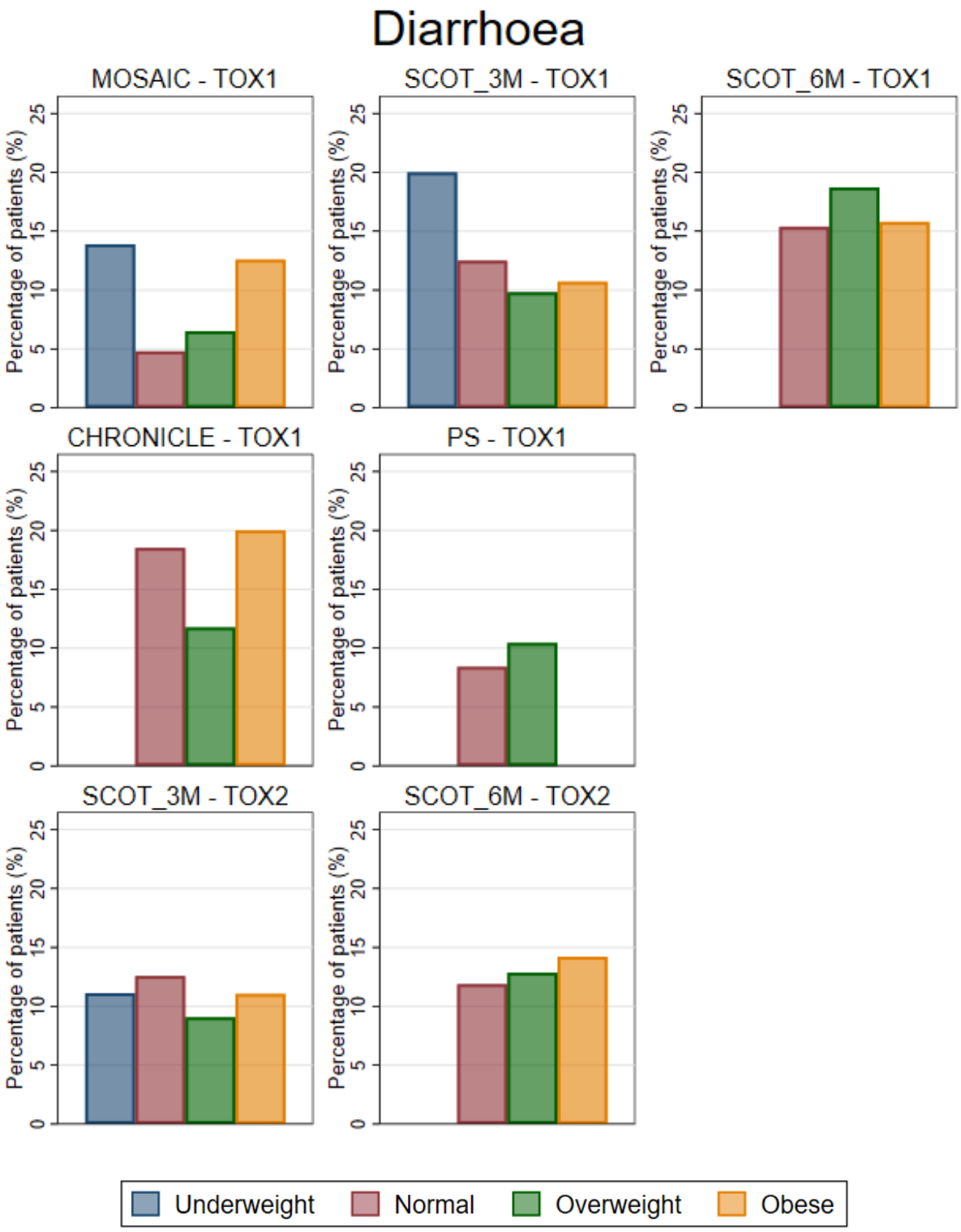


Figure 4.9 | Grade 3+ nausea by trial
Bar charts demonstrating the percentage of patients developing grade 3+ nausea by baseline BMI category for each trial and toxicity population.

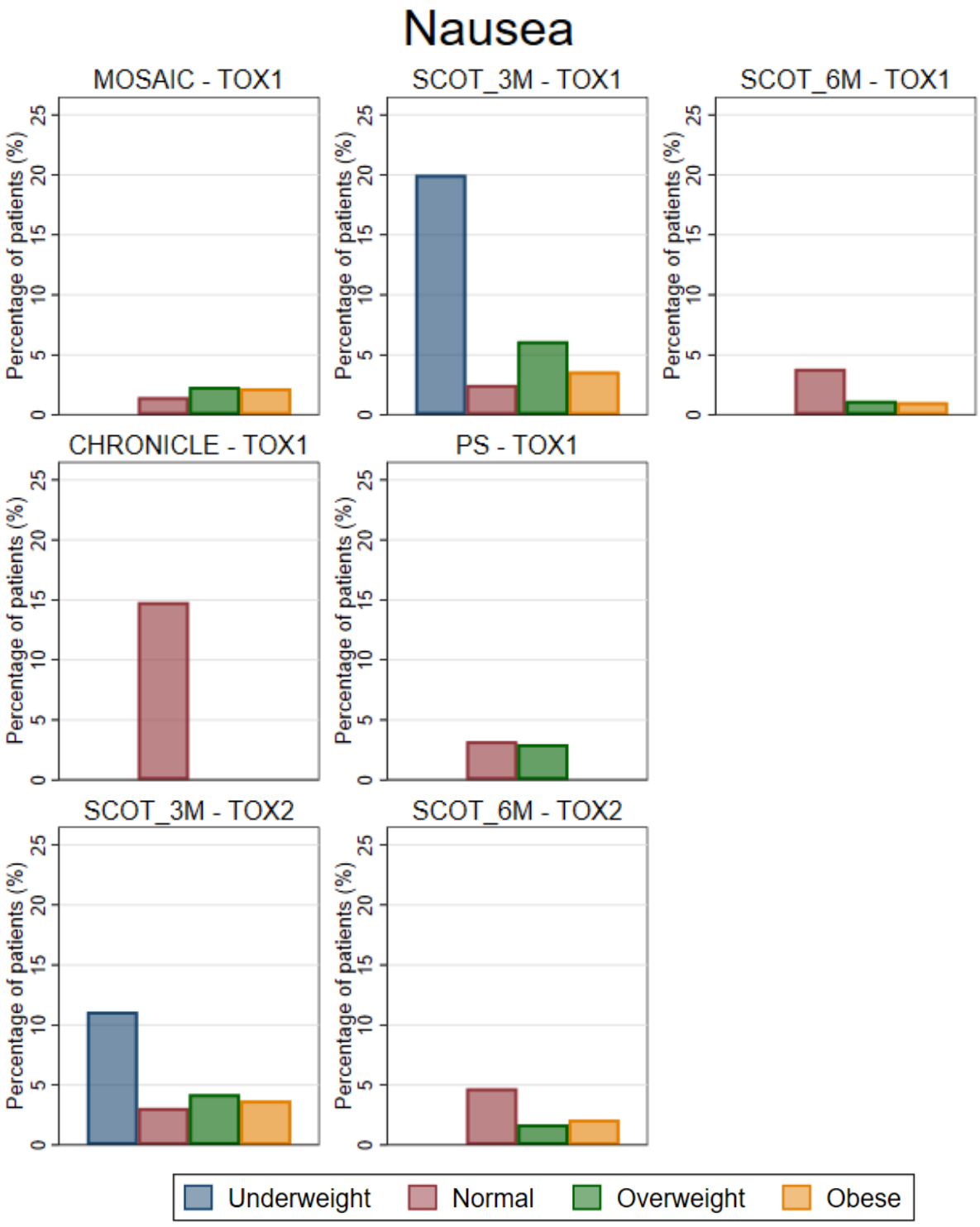
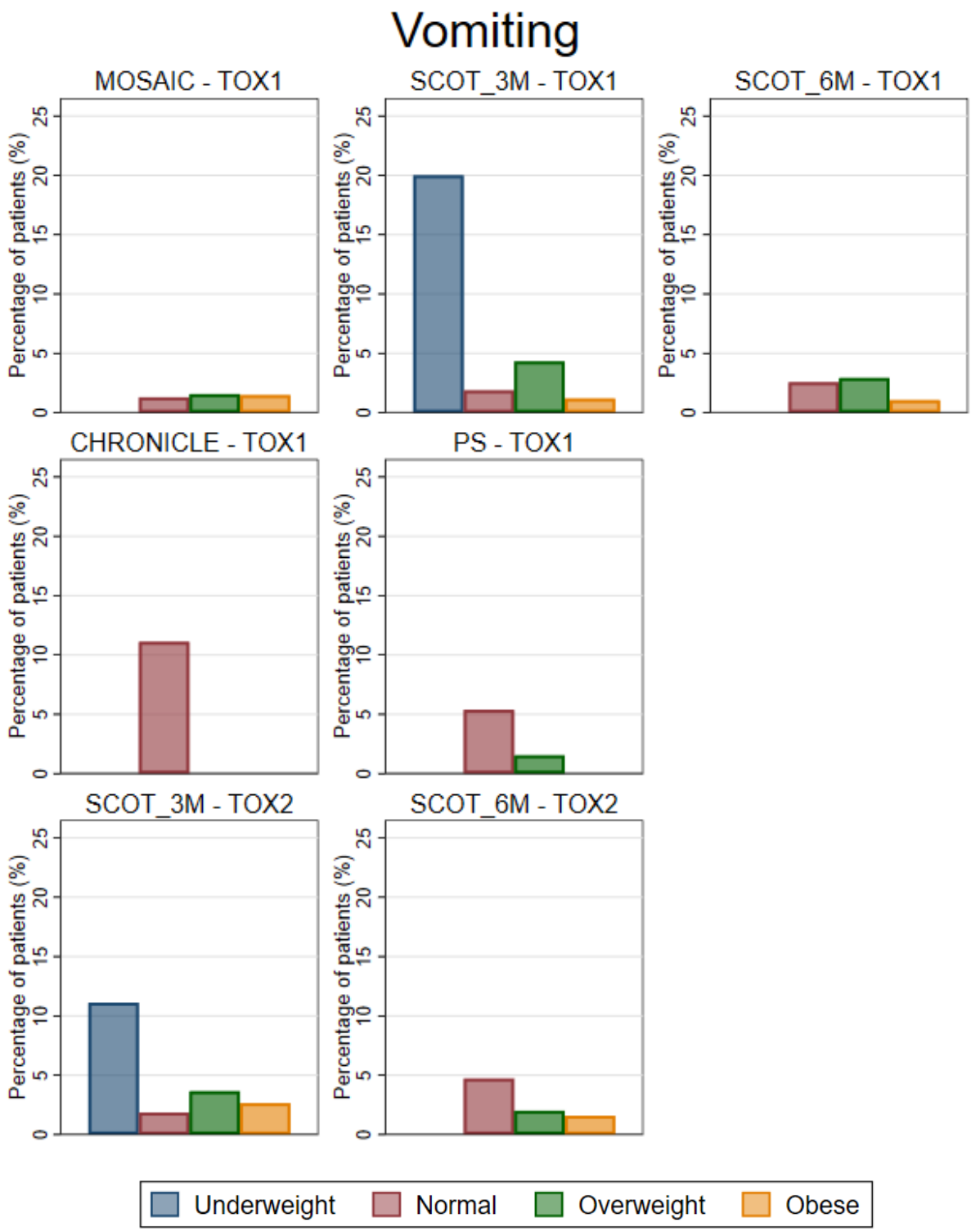


Figure 4.10 | Grade 3+ vomiting by trial
Bar charts demonstrating the percentage of patients developing grade 3+ vomiting by baseline BMI category for each trial and toxicity population.



Neutropenia

The relationship between BMI and neutropenia tended to be more consistent across the trials with, in general, reducing incidence of grade 3+ neutropenia with increasing BMI (**Figure 4.11**). This was most evident in MOSAIC and both SCOT_3M toxicity populations. Both SCOT_6M toxicity populations demonstrated the highest incidence of grade 3+ neutropenia in the normal BMI category and the lowest in the overweight BMI category. No grade 3+ neutropenia was demonstrated in overweight and obese categories in PS, nor in the obese category in CHRONICLE.

Mucositis

Figure 4.12 demonstrates the incidence of grade 3+ mucositis (including stomatitis). The incidence tended to be low (<5%) and similar across BMI categories for all trials and was consistent within TOX1 and TOX2 populations. There were no known occurrences of grade 3+ mucostomatitis within CHRONICLE and PS.

Fatigue

Grade 3+ fatigue occurred most frequently within the underweight category for each trial (**Figure 4.13**), with the remainder of the BMI categories displaying similar incidences and no clear association. However, within CHRONICLE and PS, grade 3+ fatigue did not occur within the obese categories and was lowest in the normal BMI categories, with incidence more than doubling in the overweight.

Skin

There was no obvious relationship between BMI and grade 3+ skin toxicities (including hand and foot syndrome) for any trial. No grade 3+ skin toxicity occurred in underweight patients within any SCOT_3M or SCOT_6M toxicity population or within PS (**Figure 4.14**). Furthermore, there was no grade 3+ skin toxicity within overweight and obese categories for CHRONICLE nor within the obese category for PS.

Other

The incidence of other grade 3+ toxicities displayed a tendency to increase with increasing BMI within MOSAIC, similar to the overall occurrence of grade 3+ toxicity (**Figure 4.15**). Within both toxicity populations of SCOT_3M and SCOT_6M, grade 3+ toxicity was most common in the underweight category, with no obvious relationship between BMI category and toxicity across normal, overweight, and obese BMI categories, and no obvious relationship for PS.

Figure 4.11 | Grade 3+ neutropenia by trial
Bar charts demonstrating the percentage of patients developing grade 3+ neutropenia by baseline BMI category for each trial and toxicity population.

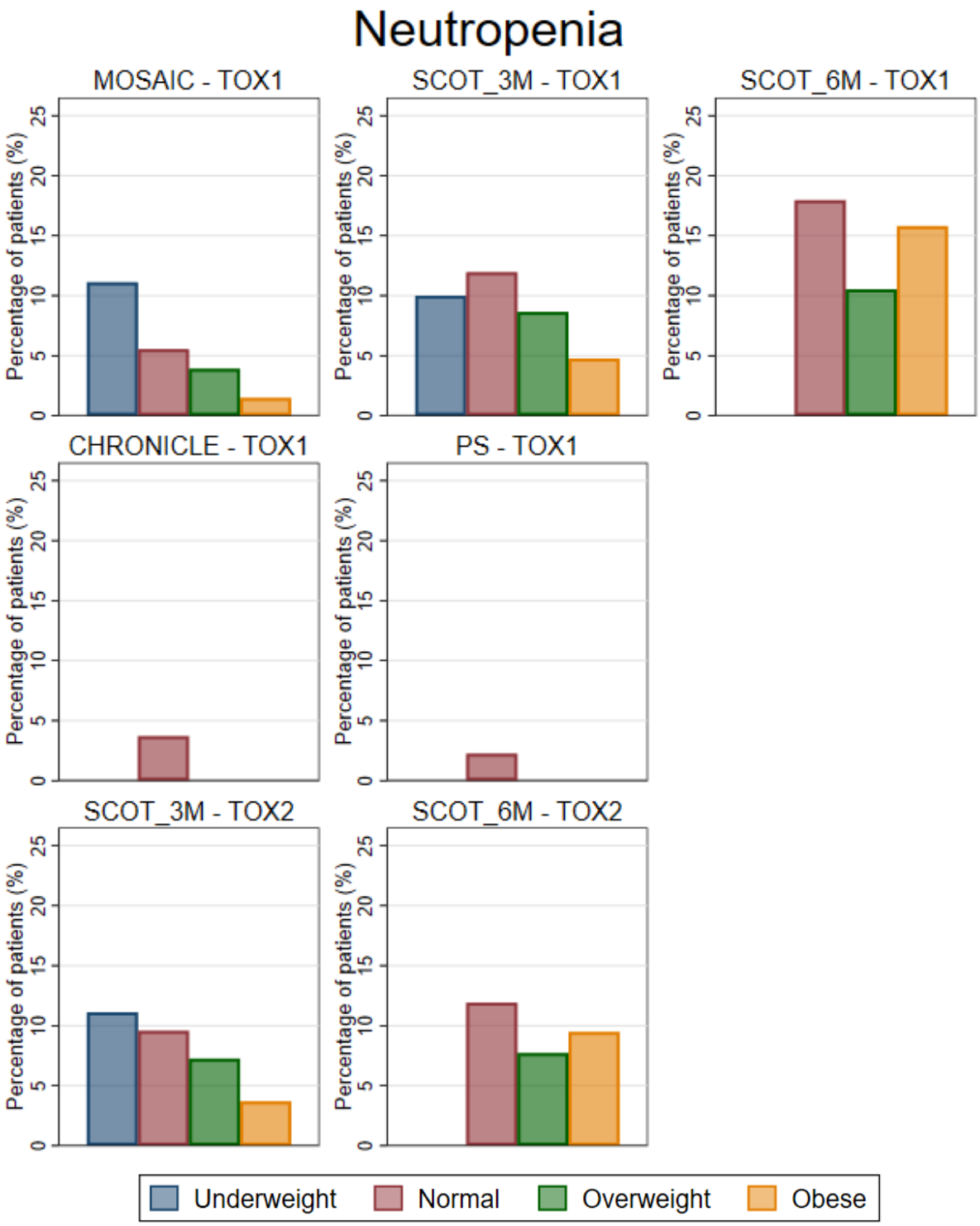


Figure 4.12 | Grade 3+ mucositis by trial
Bar charts demonstrating the percentage of patients developing grade 3+ mucositis (including stomatitis) by baseline BMI category for each trial and toxicity population.

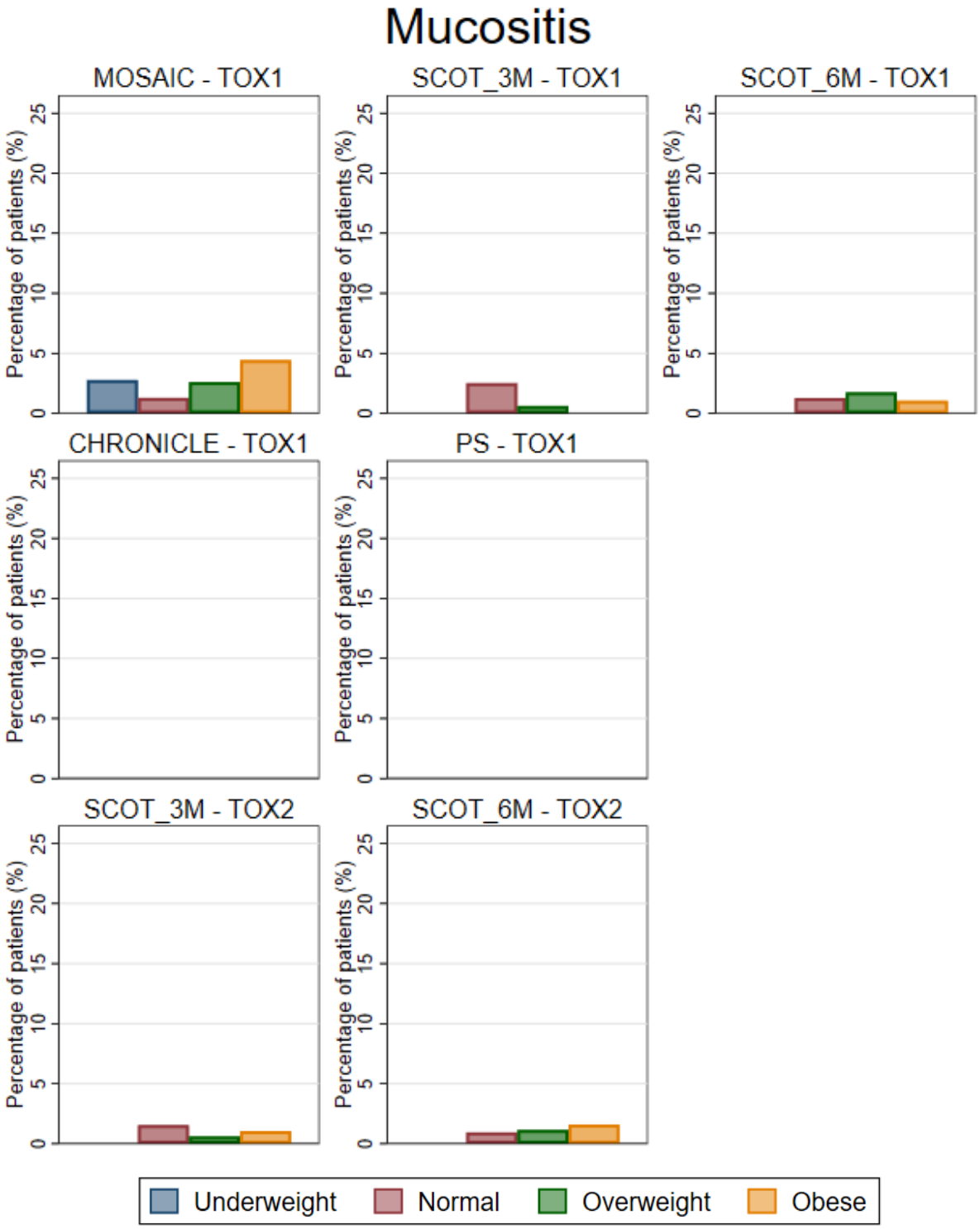


Figure 4.13 | Grade 3+ fatigue by trial
Bar charts demonstrating the percentage of patients developing grade 3+ fatigue by baseline BMI category for each trial and toxicity population.

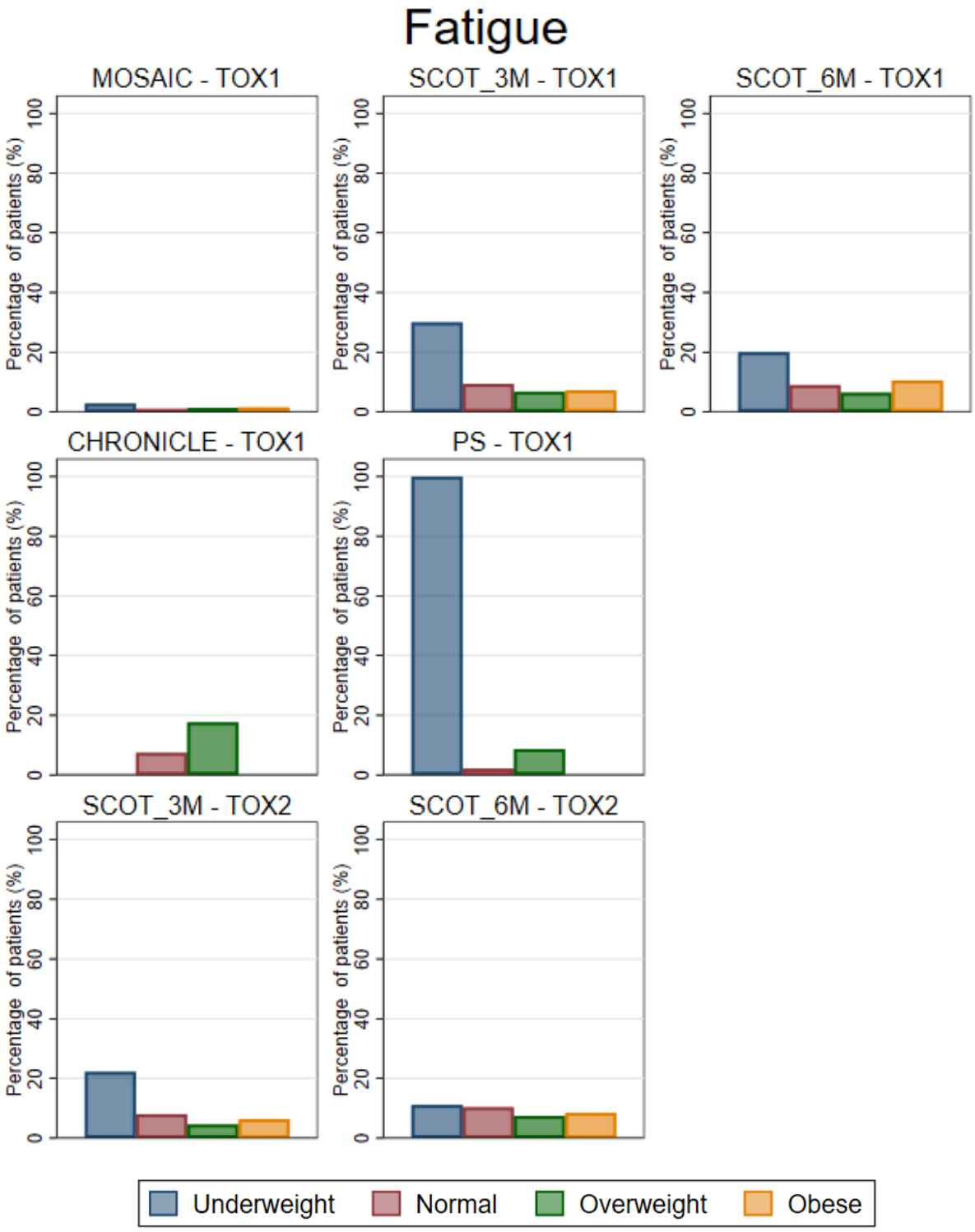


Figure 4.14 | Grade 3+ skin toxicity by trial
Bar charts demonstrating the percentage of patients developing grade 3+ skin toxicity by baseline BMI category for each trial and toxicity population.

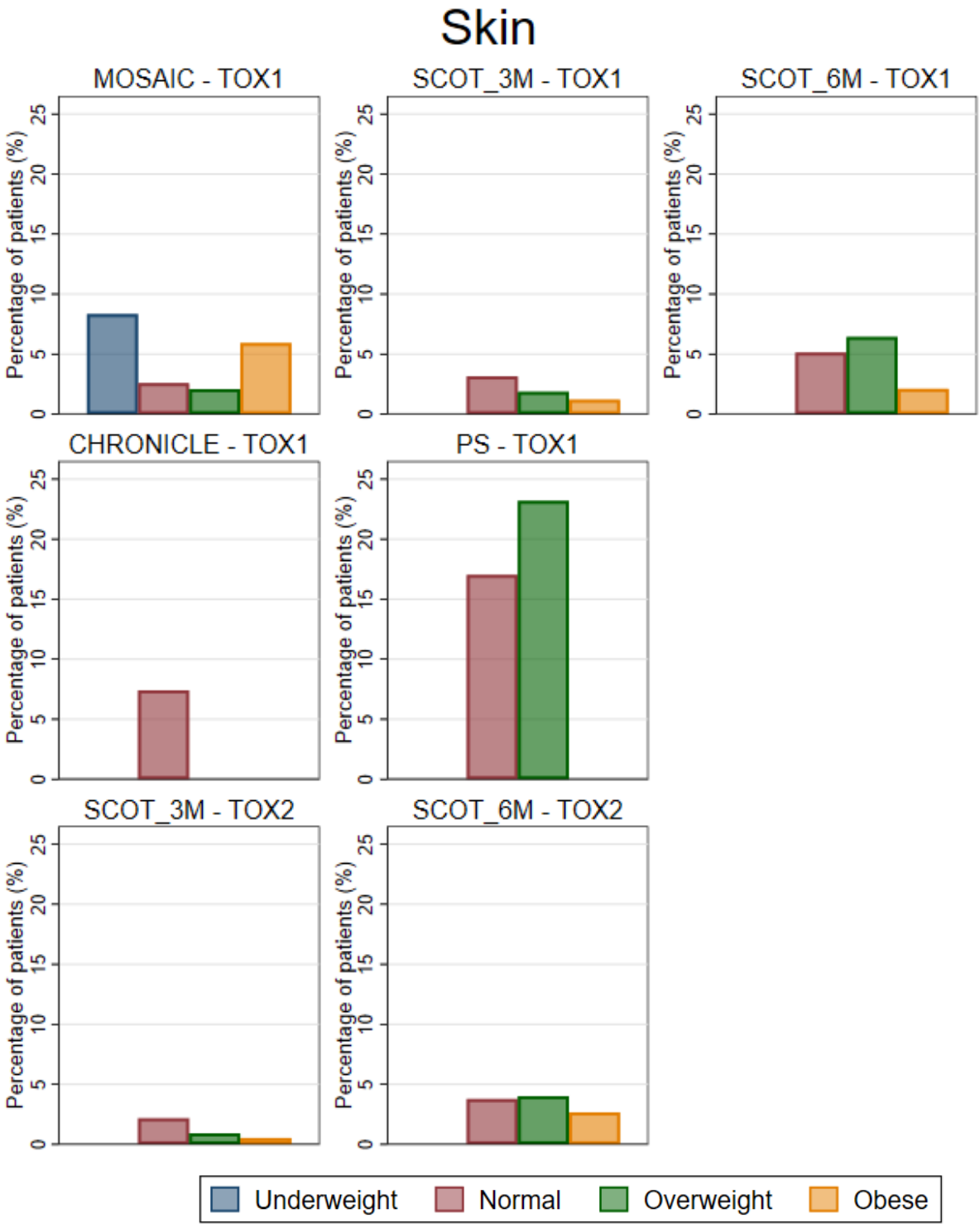
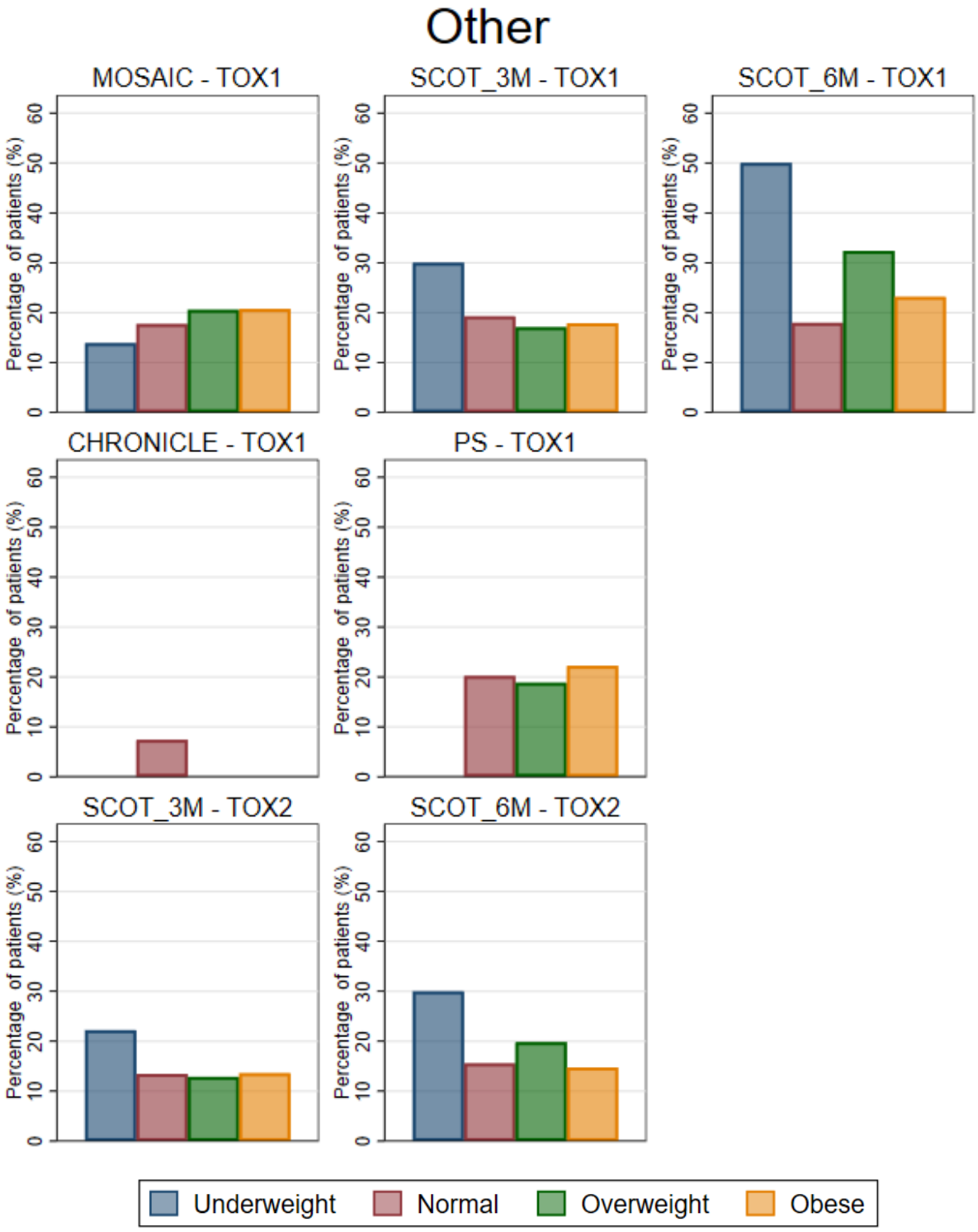


Figure 4.15 | Grade 3+ other toxicity by trial
Bar charts demonstrating the percentage of patients developing any other grade 3+ toxicity by baseline BMI category for each trial and toxicity population.



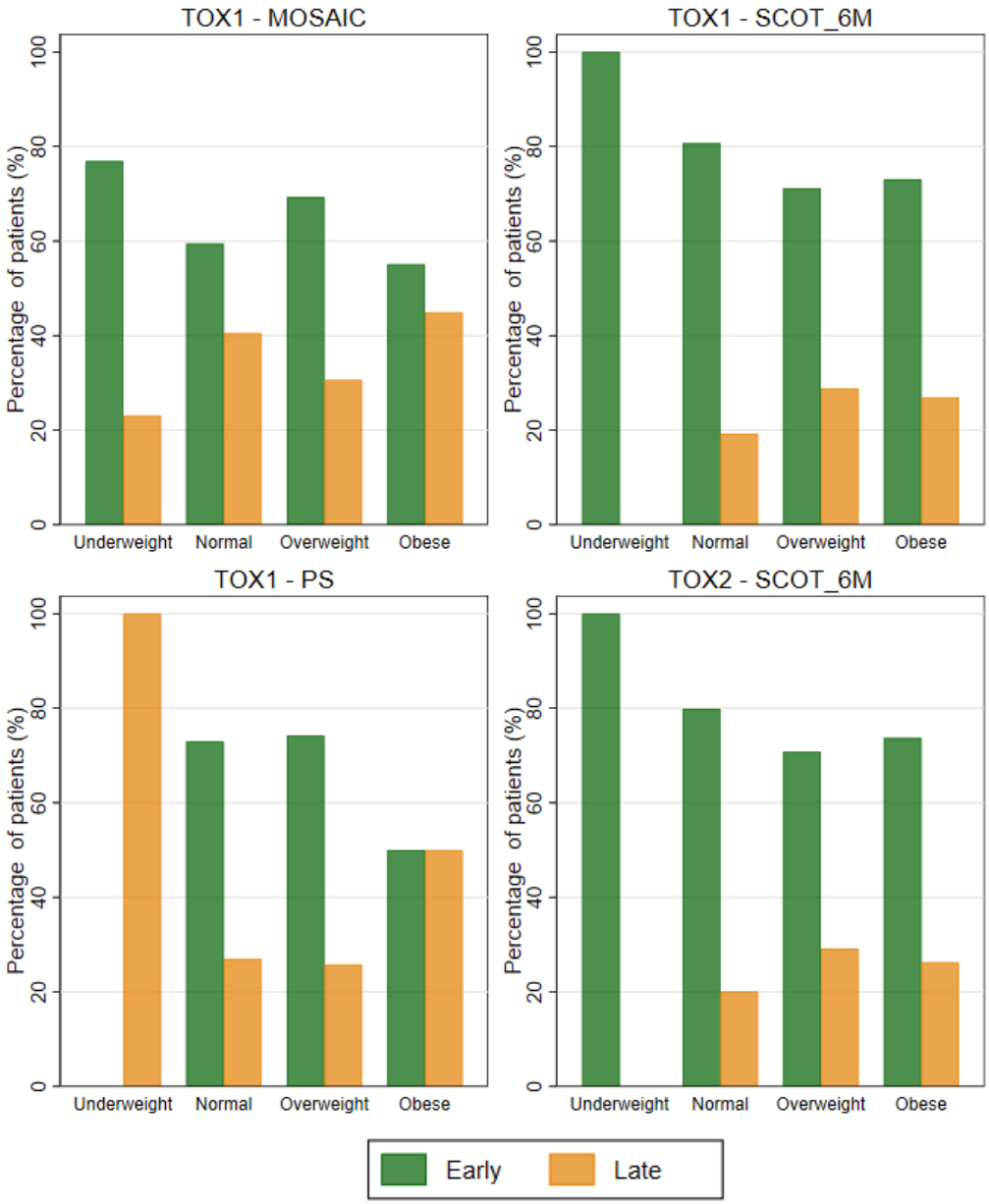
4.3.9 TIMING OF GRADE 3+ TOXICITY

The timing at which the first episode of grade 3+ toxicity occurred was examined by baseline BMI category. The subgroup of patients who developed grade 3+ toxicity was categorised according to whether the first occurrence of grade 3+ toxicity was early (during cycles expected to occur within the first 3months) or late (during cycles expected to occur after the first 3months) during their chemotherapy regimen. It was only possible to assess timing of toxicity for trials where cycle-level toxicity data were available and chemotherapy regimens lasted greater than 3 months (i.e., excluding CHRONICLE and SCOT_3M TOX1 and TOX2 populations).

Of the patients developing any grade 3+ toxicity, **Figure 4.16** demonstrates the percentage of the first episode occurring during early vs. late cycles. Overall, the first episode of grade 3+ toxicity tended to occur during early cycles for all BMI categories across all trials (excluding the underweight category within PS which consisted of a single patient). However, the percentage of early vs. late toxicity varied across BMI categories, and there appeared to be a tendency for the percentage of late toxicity to increase for overweight and/or obese patients compared with normal. For MOSAIC, the proportion of late toxicities was highest in the obese category (obese 44.9%; overweight 30.65%; normal 40.52%; underweight 23.08%). For both SCOT_6M populations it was highest in the overweight (TOX1 28.85%; TOX2 29.19%) followed closely by the obese (TOX1 26.92%; TOX2 26.25%) then normal categories (TOX1 19.28%; TOX2 20.13%), with no late toxicity in the underweight. In PS late toxicity was highest within the underweight (100%), however this was due to only 1 patient, followed by the obese (50.00%) then normal (27.03%) and overweight (25.81%) categories.

Figure 4.16 | Early vs. late grade 3+ toxicity by trial

Bar charts demonstrating the percentage of overall grade 3+ toxicity occurring during early vs. late cycles by baseline BMI category for each trial and population (trials without cycle-level data or chemotherapy regimen duration of ≤3 months were excluded.



4.4 DISCUSSION

4.4.1 SUMMARY AND INTERPRETATION OF RESULTS

The complexity of the toxicity data was explored, highlighting a number of findings in addition to potential issues for modelling of toxicity intermediate outcomes, arising from a significant proportion of missing data, mainly within the SCOT trial.

First, differences were noted for summary chemotherapy adherence measures across the two toxicity populations compared with the Main population, highlighting the limitations of complete-case analysis, which may result in loss of information and introduce bias.[232,233] It is possible that some of these differences were influenced by the differences observed in baseline characteristics. For example, small differences in median age, sex and an imbalance of chemotherapy regimen received across BMI categories in the TOX1 and TOX2 populations compared with the full population for the SCOT trial. Not only does this support the concept of careful selection of approaches for dealing with missing data, such as multiple imputation, it also underlines the importance of identification of possible confounders.[234] These principles were explored further within Chapters five and six. Furthermore, it is important to note the potential effects of missing cycle-level data on summary toxicity variables, which consisted of the highest known grades of toxicity. Summary toxicity variables (such as overall occurrence of any grade 3+ toxicity) were only missing if there was no toxicity data for any cycle for that patient. Hence, there is the potential to underestimate highest occurring toxicity grades or the occurrence of grade 3+ toxicity in those patients with some missing data. Overall, toxicity data distributions between SCOT TOX1 and TOX2 populations across BMI appeared similar, providing reassurance that BMI was unlikely to be a cause of missing data, and small variations more likely to be related to small sample sizes in the underweight. There was a suggestion, however, that toxicity incidence within the TOX2 population may have been underestimated, again supporting the assumption that grade of toxicity was unlikely to be related to missingness and hence that MAR assumptions were reasonable.

Second, no significant relationship was demonstrated between BMI and the occurrence of any grade 3+ toxicity for any trial or regimen within either toxicity population. Furthermore, possible directions of association appeared to be inconsistent. MOSAIC and TOX1 SCOT_6M displayed a tendency for toxicity to increase with BMI (possibly driven by an increase in grade 4 toxicity with increasing BMI for MOSAIC, and an increase in grade 3 toxicity with increasing BMI for SCOT_6M). Whereas the opposite was seen for TOX1 SCOT_3M, CHRONICLE, PS and TOX2 SCOT_3M, (driven by a combination of grade 3 to 5 toxicities) and TOX2 SCOT_6M not demonstrating any association.

Third, dose capping appeared to reduce the occurrence of any grade 3+ toxicity in general. The fully dosed strata generally mirrored the directions of association seen overall. Whereas, within the dose capped strata, there tended not to be any clear or consistent pattern of association.

Fourth, there did not appear to be a clear relationship between BMI and individual toxicities across trials. However, there was a slightly more consistent relationship between increasing BMI and reducing incidence of grade 3+ neutropenia across the majority of trials.

Fifth, when grade 3+ toxicity occurred, the first episode was most frequently seen during early cycles compared with late cycles, across all BMI categories. However, the proportion of first grade 3+ toxicity occurring late appeared to increase with increasing BMI and may partly explain opposing directions of BMI-toxicity relationships seen for the three-month and six-month arms of the SCOT trial. Thus, raising the hypothesis that dose capping might reduce earlier toxicity as BMI increases, producing a "catch-up" (convergence) effect seen with cycle-level dosing in Chapter Three.

Finally, it should be noted that summarising toxicity data as maximum grade, or as a grade 3+ indicator variable, may not have captured the extent of dosing-toxicity-adherence relationships. Such measures may not explain all dose delays and reductions, particularly those related to an accumulation of multiple lower grade toxicities. Alternative options for capturing cumulative toxicity include the Toxicity Index (TI)[235] and Toxicity over Time (ToxT).[236] The TI, a score which attempts to capture maximum toxicity in addition to the multiplicity and occurrence of other toxicity grades), does so only at a single time point. It also requires rank based methods for regression analysis, which are not currently supported within the mediation analysis literature, and furthermore, has been demonstrated to produce similar results in detecting toxicity differences to maximum grade of toxicity, when the sample sizes were above 250-300.[235] ToxT is a comprehensive collection of graphs, tabulation of adverse events and multiple longitudinal statistical techniques, and would be difficult to incorporate into a mediation framework.[236] Hence the approach taken forwards for summarising toxicity (use of a grade 3+ toxicity indicator variable [see Chapters five and six]), were selected as a result of data and methodological limitations, including the lack of cycle-level and lower grade toxicity data from CHRONICLE and the requirement of a standardised approach across the trials.

CHAPTER FIVE

RESULTS PART III

Path Analysis

CHAPTER FIVE PREFACE

Chapter five focuses on defining the causal pathways within BMI-Chemotherapy Adherence-Toxicity-Survival relationships, using causal inference and individual participant data (IPD) meta-analysis approaches. In particular directed acyclic graphs are used to facilitate definition of the hypothesised causal pathways and make the relevant assumptions explicit. Subsequently, this allows modelling of the individual pathways, providing two functions. First, early mechanistic insight is obtained prior to definitive mediation modelling in Chapter Six, and second, it ensures that the subsequent mediation models are correctly specified. Therefore, also introduced here are the concepts of traditional mediation approaches and the definitions of total, direct and indirect effects within this context.

5.1 INTRODUCTION

Chapters three and four summarised the characteristics of dosing and toxicity data according to BMI and highlighted the complexity and richness of the trial data in use. There appeared to be a relationship between increasing BMI and increased rates of dose capping, translating to a reduction in the cycle 1 relative dose received. These initial differences seemed to somewhat attenuate across cycle doses, producing a smaller inverse BMI-adherence measure relationship at the trial level. Here, these initial results were taken forwards and formally modelled, with trial-level results aggregated using IPD meta-analysis approaches.

5.2 METHODS

5.2.1 AIMS

The aims of Chapter five were two-fold. First, to define the hypothesised causal pathways through use of directed acyclic graphs (DAGs). Second, to model the individual pathways which make up the DAGs, in order to identify whether hypothesised associations exist and additionally ensure correct model specification to be taken forwards to mediation modelling.

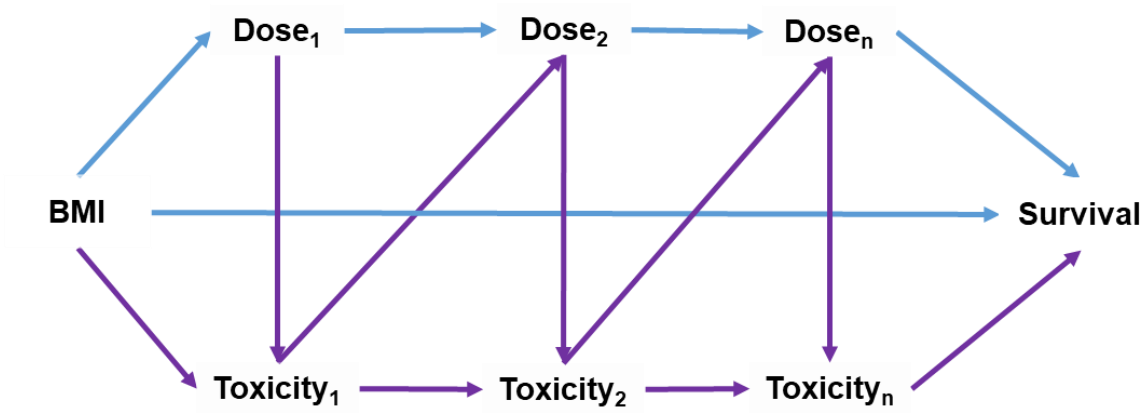
5.2.2 DATA SOURCE & POPULATION

All three datasets (the Main dataset and the two additional toxicity datasets, TOX1 and TOX2), as previously described in Chapters two, three and four, were utilised.

5.2.3 DIRECTED ACYCLIC GRAPHS

Using a causal inference approach, hypothesised causal pathways and therefore analyses were pre-defined, in addition to identification of confounders, facilitated by the construction of directed acyclic graphs (DAGs). With the overarching hypothesis that elevated BMI is associated with adverse colorectal cancer survival, which may be mediated through underdosing (resulting from dose capping), the DAG in **Figure 5.1** was constructed to demonstrate these relationships throughout a course of chemotherapy. Here, baseline BMI is the exposure, survival is the outcome, and each cycle dose of adjuvant chemotherapy received is a mediator. Added to which, toxicity acts as a time-varying (intermediate) confounder, as it may result in a reduction of the subsequent dose.

Figure 5.1 | Directed acyclic graph 1
A simplified directed acyclic graph (DAG) of the hypothesised causal relationship between BMI, cycle-level chemotherapy doses and toxicity, and survival. Baseline BMI (exposure) is causally associated with survival (outcome) and cycle-level dosing (mediators), affecting survival. Each cycle dose will in turn influence subsequent doses. Cycle 1 dosing may also affect toxicity (additionally influenced by baseline BMI), which will then influence subsequent cycles' dosing, and is hence a time-varying confounder. Each dose and toxicity may additionally affect survival (arrows not depicted to improve readability). Though not displayed for simplicity, this relationship can be further complicated by adding in repeated BMI measures prior to each dose, and survival status for each cycle time-point. Both the repeated BMI and survival measures would be influenced by preceding BMI, dose and toxicity and survival statuses, and similarly go on to affect these same variables.



The first DAG can be condensed down to that in **Figure 5.2,** where chemotherapy and toxicity are summarised with single measures. BMI is hypothesised to be causally associated with survival, the total effect [path *c'*], which can be decomposed into a direct effect [path *c*] and an indirect effect [path *ab*], via the association between BMI and chemotherapy adherence [path *a*] (as a result of cycle1 dosing/dose capping), which is subsequently associated with survival [path *b*]. BMI may furthermore be indirectly associated with survival, mediated through the development of grade 3+ toxicity [path *df*], which in turn is associated with adherence (through dose reductions [path *e*]) and survival (through severe toxicity and treatment-related death [path *f*]). This dual role of toxicity, as a mediator of exposure-outcome and exposure-mediator relationships, and confounder of the mediator-outcome relationship, defines it as an intermediate confounder, producing additional complexity within the causal inference framework for mediation analysis (see Chapter six).

Confounders are common causes for both an exposure and an outcome and were carefully considered for each pathway (**Figure 5.3**). Age and sex are known to be associated with BMI,[237,238] and are prognostic for colorectal cancer survival,[165,239] in addition to being associated with dosing chemotherapy, [124,165] and the development of toxicity.[240] Performance status may also affect BMI, with worse performance status associated with reduced activity, which may result in weight gain, furthermore poorer performance status is often associated with reduced dosing,[124] is an adverse prognostic factor,[165] and is associated with increased toxicity.[241] Finally, disease stage may affect BMI through weight loss resulting from more aggressive disease, is prognostic for survival, and might influence dosing decisions, particularly after the occurrence of toxicity (e.g. a clinician might be less concerned about the risks of early discontinuation on prognosis in high risk stage II disease, where the benefit of chemotherapy is less clearly established). Finally, the regimen of chemotherapy may influence both adherence (through for example, dose-banding of capecitabine), and survival in certain circumstances (e.g. where 3 months of chemotherapy is given in high risk stage III disease),[242] and may further influence the development of certain toxicities.

DAGs two and three (**Figures 5.2** and **5.3**) can be broken down into two additional mediated relationships: a BMI-toxicity-adherence mediated pathway (**Figure 5.4a**) and a toxicity-adherence-survival relationship (**Figure 5.4b**). In the latter BMI becomes a confounder, thus demonstrating the additional requirement to adjust for BMI when examining pathways *b*, *e,* and *f*.

Figure 5.2 | Directed acyclic graph 2
Directed acyclic graph (DAG) of the hypothesised causal relationship between BMI, chemotherapy adherence, toxicity, and survival. Baseline BMI (exposure) is causally associated with survival (total effect [path *c'*], which can be decomposed into a direct effect [path *c*] and indirect effect [path ab], the mediated pathway through the BMI-chemotherapy adherence [path *a*] and chemotherapy adherence-survival [path *b*] pathways. The occurrence of grade 3+ toxicity acts as an intermediate confounder, due to its dual role as a mediator of both chemotherapy adherence [via path *de*] and survival [via path *df*], and as a cofounder of the chemotherapy adherence-survival pathway [path *b*] (as a common cause of adherence [path *e*] and survival [path *f*]).

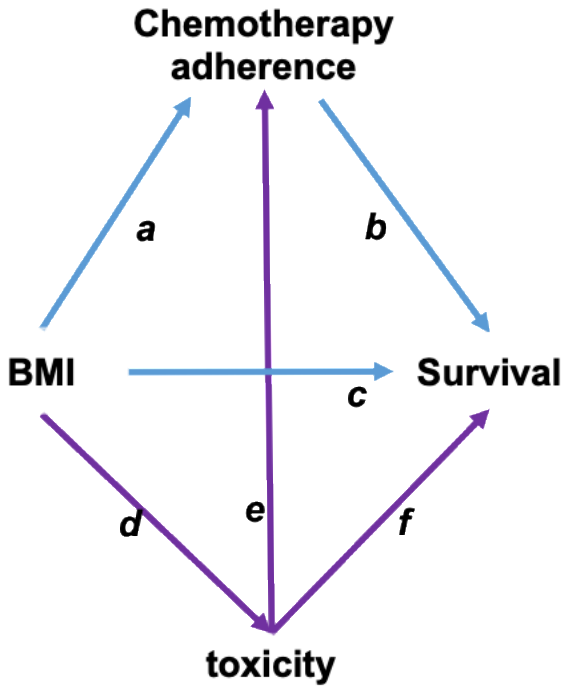


Figure 5.3 | Directed acyclic graph 3
Addition of confounders to DAG 2. Confounders are common causes of an exposure and outcome. Baseline age, sex, ECOG performance status (PS), (y)pT-stage and (y)pN-stage are confounders of all pathways as they are likely to influence BMI and all outcomes. Note that where the regimen is not randomised (mainly the SCOT trial) it cannot be a cause of baseline BMI and therefore does not confound pathways *a, d,* or *c*, and where randomised cannot be a confounder of any pathway.

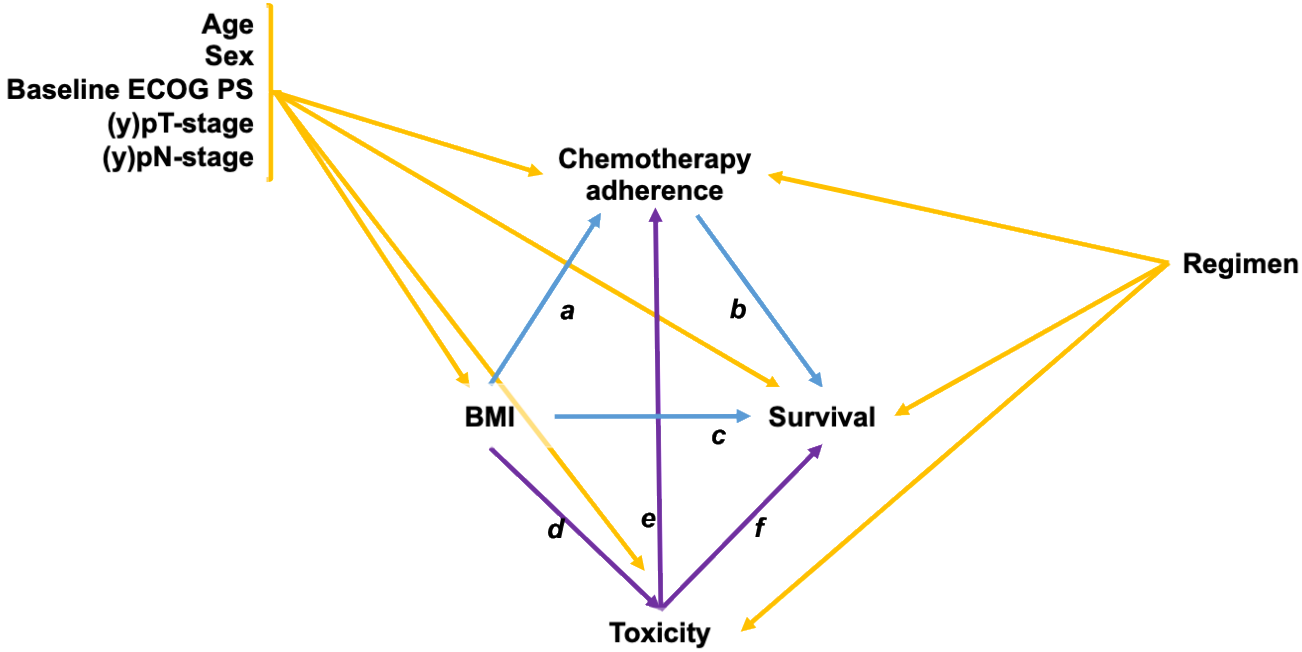
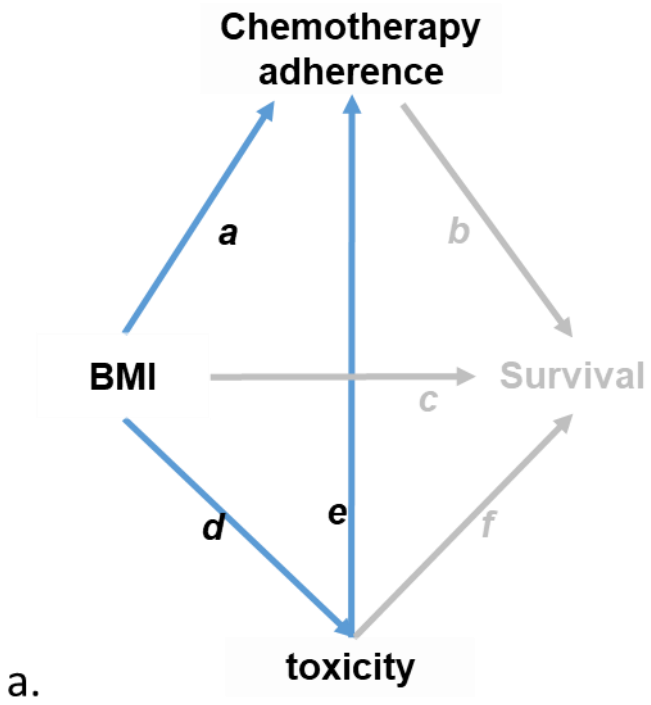
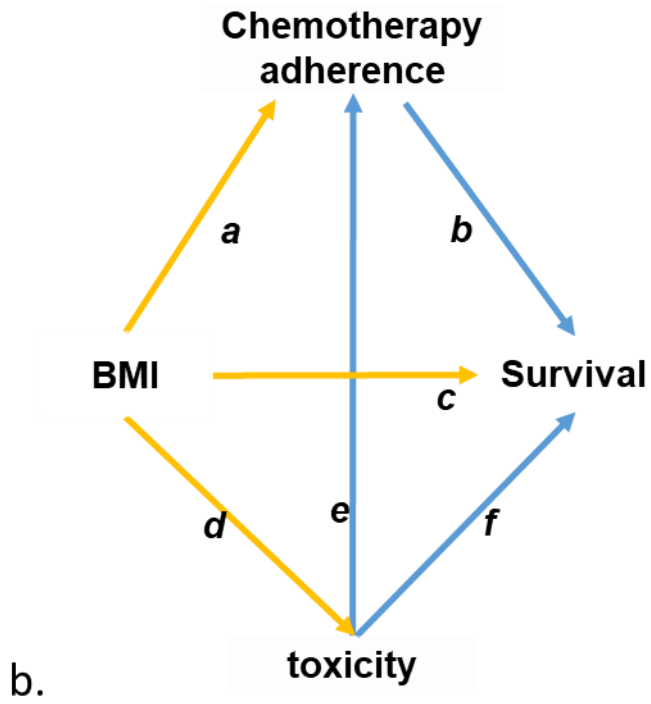


Figure 5.4 | Directed acyclic graphs 4 and 5
DAGs 2 and 3 can be broken down in to two additional mediated relationships. **a.** DAG 4: The relationship between BMI and chemotherapy adherence, mediated by grade 3+ toxicity, and **b.** DAG 5 the relationship between grade 3+ toxicity and survival, mediated by chemotherapy adherence, where BMI becomes a confounder.



a.



b.

5.2.4 TRADITIONAL MEDIATION ANALYSIS

Difference of coefficients model

The traditional difference of coefficients approach to mediation analysis involves fitting two regression models for the outcome.[243] First, regressing outcome (Y) on exposure (X) and covariates (C).

$$Y \mid X, C$$

Second, adding the putative mediator (M) such that Y is regressed on X, M and C.

$$Y \mid X, M, C$$

The total effect is then defined as the effect of the exposure given the covariates and hence is the beta coefficient for the exposure from the first regression model. The direct effect is defined as the effect of X given M and C and is thus the beta coefficient for the exposure from the second regression model. The indirect effect can then be calculated as the direct effect subtracted from the total effect. Though, this method cannot generate standard errors or confidence intervals for the indirect effect, the difference in the coefficient can give some idea of the potential for a mediated pathway. Thus, for the relevant pathways, both the total effect (excluding the mediator) and direct effect (including the mediator) were modelled. [243]

Product of coefficients model

The alternative traditional method to mediation analysis is known as the product of coefficients model. The principles of this approach are applied within the counterfactual mediation analysis approaches (described in detail within Chapter six) to obtain direct, indirect, and total effects. Again, this requires fitting two regression models. [243] First the mediator is regressed on exposure and covariates:

$$M \mid X, C$$

Second, the outcome is regressed on exposure, mediator, and covariates.

$$Y \mid X, M, C$$

The direct effect is given by the beta coefficient for X from the outcome model. The indirect effect is given by the product of the beta coefficient for M in the outcome model and the beta-coefficient for X from the mediator model. The total effect is the sum (or product, on the multiplicative scale) of direct and indirect effects.[243] Thus, considering formal mediation analysis in the following chapters, correct specification of the mediator and outcome regression models are particularly important.

5.2.5 EXPOSURE

The primary exposure throughout this Chapter was BMI, modelled continuously to reduce loss of information. However, during analysis of certain individual pathways, chemotherapy adherence and toxicity were additionally treated as exposures.

5.2.6 MEDIATORS

The two measures of adherence, the average relative dose intensity (ARDI) and average cumulative relative dose (ACRD) as previously defined in Chapter Two, were explored as mediators. In addition, toxicity was explored as a potential mediator of the BMI-Adherence pathway [path *a*] described in **Figure 5.4a**.

5.2.7 OUTCOMES

The primary outcome was overall survival (OS), as previously defined. Secondary outcomes were disease-free survival (DFS) and cancer-specific survival (CSS). Additional secondary outcomes during analysis of certain individual pathways were: cycle 1 dose capping, average relative dose received (ARDR), chemotherapy adherence and the occurrence of grade 3+ toxicity.

5.2.8 STATISTICAL ANALYSIS

Patient inclusion and baseline characteristics were previously detailed for all three datasets within Chapters three and four, and hence were not summarised again. A two-stage IPD meta-analysis, to maintain trial clustering and allow for between-trial heterogeneity, was undertaken for each pathway (labelled *a* - *f* in **Figures 5.2** to **5.5**). Additionally, the relationship between BMI and cycle 1 dose capping, cycle 1 ARDR, grade 3+ individual toxicities, and early vs. late cycle toxicity were explored.

Stage one

First, analyses for each path were undertaken at the trial level. Continuous outcomes were modelled with linear regression, binary outcomes with logistic regression, and categorical outcomes with multinomial logistic regression. Both Cox proportional hazards (PH) and Weibull survival models were used to model time-to-event. Though Cox PH models are commonly used for survival analysis, when used in mediation models with a common outcome, VanderWeele [244] has demonstrated that their use is limited to describing the existence of mediation as models do not provide a valid measure of effect. However, parametric survival models utilising Weibull or exponential hazard functions on the log mean survival time difference scale, have been demonstrated to provide valid estimates of mediation.[244] Hence, Weibull models form the main analysis and Cox PH models were performed for comparison, and to aid in assessing that the Weibull distribution was appropriate to model the baseline hazard.

The total effect was examined for each pathway, and where appropriate, the direct effect was also explored by addition of the putative mediator into the regression model. This was to assess for potential mediation, through evaluation of the extent and direction of change of the effect estimate. All models were adjusted for the same confounders: (age, sex, (y)pT-stage, (y)pN-

stage, and ECOG performance status). BMI was also adjusted for in paths *b, e,* and *f* models*,* in addition to toxicity for path *b*. Dichotomising or categorising continuous variables was avoided to reduce information loss.

Due to the missing toxicity data, pathways that required adjustment for toxicity (paths *b* and *c*) to produce unbiased total effect estimates were modelled utilising multiple imputation for missing toxicity data (fully adjusted), and additionally modelled without toxicity (partially adjusted). This was to assess for potential bias as a result of residual confounding, and the necessity to adjust for toxicity. Such partially adjusted models are referred to as "biased", to distinguish them from the fully adjusted models (see **Table 5.1** and below).

Stage two

The second stage of meta-analysis involved combining the trial-level coefficients and standard errors for each analysis. Random effects were assumed, as the true effect of an exposure is likely to differ across populations (between-study heterogeneity) resulting from varying distributions of participant level characteristics, and random effects meta-analysis will take into account both within- and between-study variances (the latter known as Tau^2). Meta-analysis models are weighted according to the inverse of variance which, for the random effects models, takes into account both within- and between-study variance of the effect estimate.[245] Models were estimated using restricted maximum likelihood (REML) estimation, which estimates both the summary effect estimate and the between-study variance simultaneously. REML has been demonstrated to out-perform several other methods, such that it is the current preferred method of estimation.[246,247]

Heterogeneity measures

Quantification of between-trial heterogeneity is important and can be reported in several ways. Recently there has been a shift towards presentation of Tau^2, where no heterogeneity will result in a value of zero. The I^2 statistic is a percentage of the variability of the effect estimate that occurs due to between-study heterogeneity (Tau^2). Historically it has often been used alone, as a direct measure of heterogeneity. However, I^2 should be interpreted with caution; it depends on within-study variance and tends to increase as the numbers of patients within studies increases, and therefore may be misleading. Hence, it is best utilised in combination with Tau^2.[248]

Trial-level model specification

Though multiple pathways were examined, these condensed down to a smaller number of regression models from which the relevant effect estimates, and their standard errors, were taken depending on the pathway of interest. These models varied in the additional covariates included, depending on whether direct or total effect pathways were assessed (**Table 5.1**) or additional confounder adjustment was required. Pathways *a* and *e* were based on the same

regression models (with or without toxicity), and pathways *b, c,* and *f* on the same survival models (with or without toxicity and/or adherence measures).

Age is an important confounder of observational studies, and frequently demonstrates non-linear relationships, hence its functional form was assessed at the trial level. Within linear regression models for ACT adherence outcomes, age was frequently found to be non-linear for both SCOT trial arms, however best fitting fractional polynomials were inconsistent across arms, trial toxicity sub-populations and adherence outcomes. Hence, age was modelled using restricted cubic splines with three knots, initially positioned at ages 50, 64 and 74 years, according to Harrell's recommended percentiles (10^{th} 50^{th} and 90^{th} centiles of the pooled data).[249] Due to differences in the upper ages within the trials, the upper knot required reducing to 70 years to ensure better coverage of the data (e.g., the maximum age for MOSAIC was 75 years). Likelihood ratio tests were used to compare nested models and supported the use of spline models in the SCOT trial. Due to the nature of mediation analysis, requiring the same variables and functional forms to be utilised for all analyses, and to allow comparison of conditional effect estimates, age was included as restricted cubic splines in all models.

Assessment of linear regression model assumptions demonstrated some evidence of non-normally distributed residuals and/or heteroskedasticity for some of the trials. Transformation of adherence measures was explored with the Stata "ladder" command[250] that attempts multiple power transformations (cubic, square, square root, log, 1/square root, inverse, 1/square and 1/cubic) and tests for normality in the transformed variable. None of the eight transformations were able to produce a normally distributed variable, thus adherence measures were consequently left untransformed and bootstrapping of confidence intervals was assessed as a sensitivity analysis. Logistic regression models were assessed for specification, goodness of fit, area under the curve and effect of influential observations, with no substantial issues identified. Though the proportional hazards assumption is not assessable for Weibull models within Stata packages, it can, however, be tested for Cox regression models. Hence, this was performed for continuous variables by addition of an exposure-time interaction, in addition to calculating and plotting scaled Schoenfeld residuals. For categorical or binary covariates log-minus log plots were also examined.

Table 5.1 | Path analysis regression models

Path	Effect	Model	Outcome	Exposure	Additional Confounders	Standard Confounders
a	**Total**	Linear Regression	ARDI or ACRD	BMI	NA	All analyses adjusted for: Age Sex (y)pT-stage (y)pN-stage ECOG performance status (Regimen for multi-regimen trials)
a'	**Direct**	Linear Regression*	ARDI or ACRD	BMI	Toxicity	
e	**Total**	Linear Regression*	ARDI or ACRD	Toxicity	BMI	
d	**Total**	Logistic Regression	Toxicity	BMI	NA	
b	**Total**	Cox or Weibull*	OS; DFS; CSS	ARDI or ACRD	BMI; Toxicity	
b	**Biased† total**	Cox or Weibull	OS; DFS; CSS	ARDI or ACRD	BMI	
c'	**Total**	Cox or Weibull*	OS; DFS; CSS	BMI	Toxicity	
c	**Direct**	Cox or Weibull*	OS; DFS; CSS	BMI	Toxicity; ARDI or ACRD	
c'	**Biased† Total**	Cox or Weibull	OS; DFS; CSS	BMI	NA	
c	**Biased† Direct**	Cox or Weibull	OS; DFS; CSS	BMI	ARDI or ACRD	
f	**Total**	Cox or Weibull*	OS; DFS; CSS	Toxicity	BMI	
f'	**Direct**	Cox or Weibull*	OS; DFS; CSS	Toxicity	BMI; ARDI or ACRD	

Abbreviations: **ACRD**, average cumulative relative dose; **ARDI**, average relative dose intensity; **BMI**, Body mass index; **CSS**, Cancer specific survival; **DFS,** Disease-free survival; **OS**, Overall survival

*For the SCOT trial, analyses which required inclusion of toxicity as a covariate or exposure required multiple imputation approaches for the of the Main population.

†Biased pathways are those that are partially adjusted (i.e., not adjusted for toxicity where they should ideally be) and hence effect estimates are potentially biased.

Meta-analysis model specification

At the meta-analysis level, non-linearity of continuous exposures was assessed using multivariate (MV) meta-analysis of restricted cubic splines. MV meta-analysis allows the estimation of summary effects whilst accounting for the correlation of multiple outcomes (and hence can combine estimation of correlated spline terms). Specifically, it accounts for both within study and across study correlations.[247] It is implemented within Stata through the user-written the `mvmeta` command.[251,252]

Knots were fit on the pooled data, initially according to Harrell's recommended percentile.[249] However, similar to age, after exploring the distributions of the variables from which spline terms were generated, these were modified to ensure that they were sensibly placed for all trials. Hence knots were positioned at BMIs of 20, 25 and 30 for three knots; 20, 23.3, 26.6 and 30 for four knots; 20, 22.5, 25, 27.5 and 30 for five knots. Multivariate random-effects meta-analysis with REML estimation was then performed using the correlated spline terms' effect estimates and their variances and co-variances. Predicted values for the outcome (on the log scale for odds or hazard ratios) were then plotted against the exposure to assess for evidence of non-linearity.[247] Models were run with three, four and five knots, and Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values were additionally examined to assess for the best fitting models, and comparison with linear models. Finally, because MV meta-analysis requires co-variances to be calculated from the trial-level models, it was not possible to perform on multiple imputation analyses (see below). This would require a substantially large number of imputed datasets to be valid (akin to bootstrapping), and post-estimation commands to obtain variance-covariance matrices are not available as standard through the estimation suite for multiple-imputation in Stata.[250]

Missing toxicity data and multiple imputation

The SCOT trial contained a high proportion of patients with missing toxicity data due to the pre-defined safety-monitoring protocol (see Chapter 2). To explore the potential influence on the estimated effects from complete-case analysis, all IPD meta-analyses were performed on all three previously described populations (Main, TOX1 and TOX2). Within the Main population, for any analysis that included toxicity, multiple imputation (MI) was undertaken for missing SCOT toxicity data, assuming data were missing at random. As discussed in Chapters two and four, the assumption of missing at random was felt to be appropriate due to the missingness patterns observed appearing to relate to randomisation time (for which data were available), rather than, for example, grade of toxicity itself. Though the latter is possible, and would have rendered missing data MNAR, the similar distribution of toxicity grades between patients with "safety" and "ad hoc" toxicity data collection suggested that this was less likely to be the case. Other potential causes of missingness such as site or investigator could not be explored due to lack of such data. Hence there was a residual risk of bias, though overall, the use of multiple imputation was felt to reduce bias that might otherwise have resulted from complete case

analysis. Imputation of toxicity for patients with some “ad hoc” data collection was considered, however, it was felt that this might have resulted in the loss of some “true” toxicity information and relationships. These assumptions could have been tested with additional sensitivity analysis comparing the two approaches, should time have allowed.

Multiple imputation with random forests (RF) was utilised, which is a machine learning approach and has been demonstrated to outperform MI with chained equations (MICE) in the setting of non-linearity and/or the presence of unidentified interactions, in addition to performing well in settings with high percentages of missing data.[253] Generation of multiple imputed datasets was performed in R using the `mice.impute.rf` package within the `mice` package[254] with 10 random forests (demonstrated equivalent to 100 random forests) and 10 iterations to generate 10 imputed datasets. The predictor variables used for the imputation models included all those used for the regression models (BMI, splines of age, sex, ECOG performance status, pT stage, pN stage, chemotherapy regimen, ARDI and ACRD). In addition, several auxiliary variables were included: randomisation date, surgery date, cycle 1 RDR, tumour site, baseline BSA, weight and height. Randomisation date was an important potential missingness mechanism that may aid imputation under MAR conditions, as previously discussed. Surgery date was also included, as longer durations between surgery and randomisation may have been the result of complications, with possible increased risk of toxicity resulting from a degree of deconditioning. Tumour site (colon or rectum) was added, as patients with rectal cancer might display worse diarrhoeal-type toxicity, because of e.g., neoadjuvant radiotherapy. Furthermore, cycle 1 relative dose was selected rather than the dose-capping indicator variable, to reduce the potential for information loss within the context of cycle1 dosing-toxicity relationships. Finally, though likely correlated with BMI, baseline BSA in addition to height and weight were added because of the possible association between BSA and toxicity that might result from dose banding. Such associations may be non-linear and hence the RF approach is useful in this context. Furthermore, the multiple imputation with RF approach allows the use of a large number of potentially correlated variables without encountering problems from collinearity.[253] The regression models were then run on each imputed dataset and the coefficients and standard errors combined using Rubin’s Rules[255] prior to performing the second stage of meta-analysis. The potential bias from residual confounding as a result of not additionally adjusting for toxicity in key pathways (*b* and *c*) was assessed as described above.

Effect Modification (Interactions)

Within the setting of meta-analysis, approaches to test effect modification, such as stratification and meta-regression are problematic and result in effect estimates that are biased by ecological bias.[180] Hence an alternate approach is required, where interactions are modelled at the trial level, within-study interaction terms are subsequently meta-analysed to produce a summary within-study interaction effect estimate.[247] Two pre-planned interactions were examined for the total effects of all pathways: sex (female vs. male) and disease stage categorised using the

SCOT trial definitions (stage II-high risk [node negative disease with high-risk features], stage III-low risk [pT1-3, pN1] and stage III-high risk [pT4 with pN1-2 or pN2 with any T-stage], with the middle category set as the reference).

Sensitivity analyses

Finally, a number of sensitivity analyses were planned *a priori*, falling into three broad categories: clinical, potential data errors, and statistical/methodological (**Table 5.2**).

Statistical analyses were performed in Stata version 17 (StataCorp LLC, 2021, College Station, TX, USA), and multiply imputed datasets were generated in R version 3.6.2. and R Studio (version 1.4.1106).

Table 5.2 | Planned sensitivity analyses

Category	Sensitivity Analysis	Method
Clinical	S1. Effects of 6 months of planned treatment alone.	Exclusion of the SCOT 3-month arm.
	S2. Influence of dose banding.	Exclusion of patients receiving capecitabine.
	S3. Effect of reverse causality.	Exclusion of patients with deaths within the first 6 months.
Data Errors	S4. Effect of suspected chemotherapy cycle numbering or date errors.	Exclusion of patients with apparent chemotherapy cycle numbering or date errors found during data cleaning.
	S5. Effect of suspected height / weight errors.	Exclusion of patients with suspected height / weight errors found during data cleaning.
	S6. Effect of suspected chemotherapy dose errors.	Exclusion of patients with suspected chemotherapy dose errors found during data cleaning.
	S7. Effect of suspected toxicity data errors.	Exclusion of patients with suspected toxicity data errors found during data cleaning.
	S8. Effects of S4 – S7 combined.	S4 – S7 combined.
Statistical	S9. Small trial effects.	Exclusion of CHRONICLE & PROCTOR-SCRIPT.
	S10. Heteroscedasticity / non-normally distributed residuals.	Bootstrapping regression models.
	S11. Confidence interval construction (resulting in more conservative estimates).	Hartung-Knapp-Sidik-Jonkman (HKSJ) method for confidence interval construction.

5.3 RESULTS

5.3.1 CYCLE 1 DOSING

The effect of 5kg/m^2 increments of BMI on the odds of receiving a capped cycle 1 dose, and on the cycle 1 average relative dose received are displayed in **Figures 5.5a** and **5.5b**, for all three populations. BMI 5kg/m^2 increments were significantly associated with almost three times the odds of receiving a capped cycle 1 dose (Main population OR 2.70; 95%CI 2.00, 6.64; **Figure 5.5a**). This relationship was consistent across all trials and all populations, with slightly higher odds for the TOX1 population. Heterogeneity was moderate with a Tau^2 of 0.077 for the Main population. Consistent with dose capping, there was a significant relationship between increasing BMI and a reduced cycle 1 ARDR (**Figure 5.5b)**, for all three populations. Hence, the increased odds of dose capping equated to a reduction in the cycle 1 ARDR of 2.12% for each 5kg/m^2 BMI increment. Heterogeneity was relatively high, with a Tau^2 of 0.149 for the Main population.

Comparing models of splines of BMI against the linear model (**Figure 5.6**), that the three-knot spline model appeared to perform slightly better than the linear model, with the lowest AIC and BIC values. Hence, possible non-linearity was suggested, with the odds of dose capping starting to increase at approximately the threshold for an overweight BMI (25kg/m^2) and a reduction in ARDR mirroring this relationship.

Effect modification by sex and disease stage was explored, summary effect estimates for the exposure when interaction terms were added to the models are demonstrated in the appendix (**Tables A5.1** and **A5.2**). Addition of a BMI-sex interaction term to the models resulted in an increase in overall effect of 5kg/m^2 on the odds of cycle 1 dose capping (OR 3.53; 95%CI 2.81, 4.14) compared with the non-interaction model (**Tables A5.1)**. Meta-analysis of the within-trial interaction effects demonstrated a significant effect modification by sex ($OR_{interaction}$ 0.53; 95%CI 0.46, 0.61), meaning that the effect of 5kg/m^2 BMI increments on the odds of dose capping was almost halved in females compared with males (**Figure 5.7a**). This was similar for ARDR, with a slight increase in the overall effect after including the interaction term (Coef. -2.73%; 95%CI -3.52, -1.93), and a significant within trial interaction (**Figure 5.7b**; $Coef._{interaction}$ 1.23, 95%CI 0.31, 2.15). Again, the effect of 5kg/m^2 BMI increments was almost halved in females, resulting in an overall smaller reduction of ARDR with increasing BMI, compared with males. These results were consistent across the toxicity populations.

Disease stage was categorised as stage II-high risk (HR), stage III-low risk (LR) and stage III-HR, with the middle category as the reference. Addition of BMI-stage interaction terms into the model minimally altered the overall effect estimates for dose capping and ARDR compared with the non-interaction models (**Table A5.2**). Though the interaction for stage III-HR vs. stage III-LR

disease did almost reach significance (**Figure 5.8a**; $OR_{interaction}$ 0.88; 95%CI 0.77, 1.02), suggesting a tendency to avoid dose capping in higher risk disease as BMI increased, this equated to a non-significant minimal increase in ARDR (**Figure 5.8b**; Coef. $_{interaction}$ 0.06%; 95%CI -0.19, 0.32). There was no significant within-trial interaction demonstrated for stage II-HR vs. stage III-LR disease, with some inconsistency for the TOX1 population.

Figure 5.5 | The relationship between BMI and cycle 1 dosing

Forest plots demonstrating the effect of 5kg/m^2 BMI increments on **a.** the odds of receiving a capped first cycle dose and **b.** on cycle 1 average relative dose received (ARDR), for all three study populations.

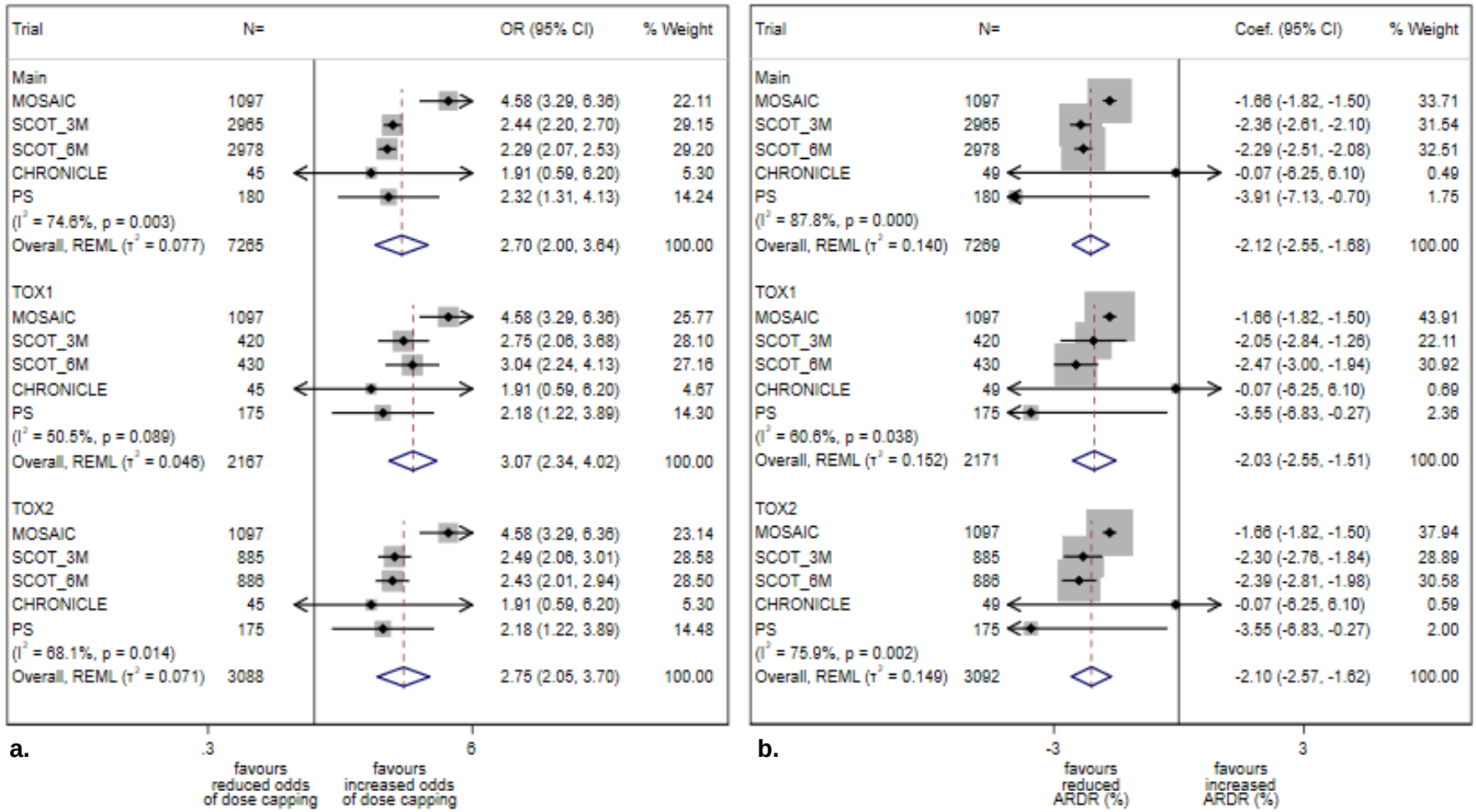
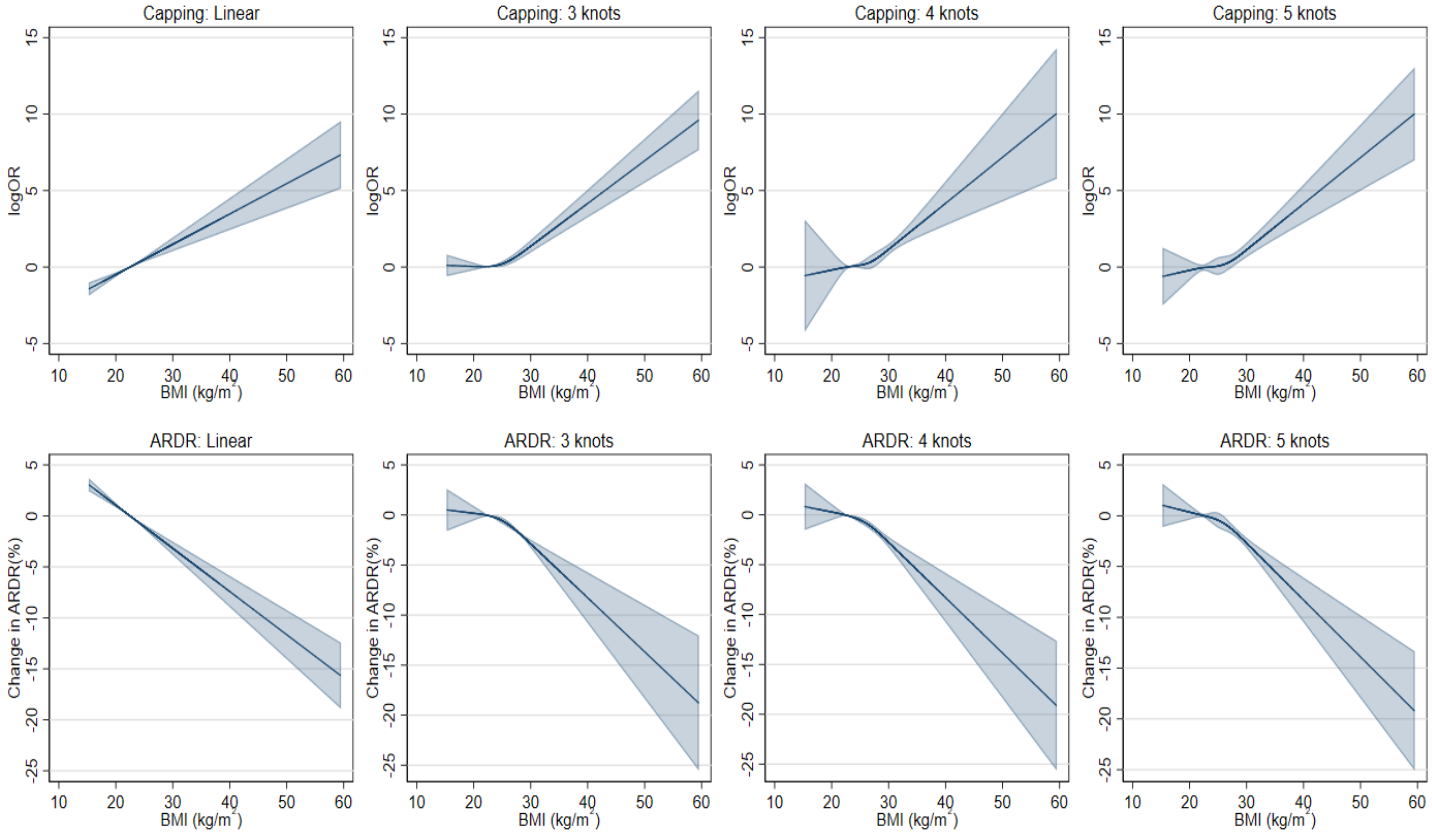


Figure 5.6 | Linearity of BMI and cycle 1 dosing relationships

Graphs demonstrating the predicted log odds ratios (logOR, line) and 95% confidence intervals (shaded area) from linear and spline (3, 4 or 5 knots) multivariate meta-analyses of BMI effects on cycle 1 dose capping and average relative dose received (ARDR). Referent BMI is 22.5kg/m^2. Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are presented for the respective models.



AIC and BIC values					
			Spline model no. knots		
		Linear	3	4	5
Capping	**AIC**	8.70	**-6.58**	14.61	48.53
	BIC	7.92	**-8.54**	11.09	43.07
ARDR	**AIC**	15.67	**11.46**	42.01	79.90
	BIC	14.89	**9.51**	38.49	74.44

Figure 5.7 | Effect modification of BMI-dose capping and average relative dose received relationships by sex

Forest plots presenting the meta-analysed within-trial BMI-sex interaction terms (females vs. male) for the effect of 5kg/m^2 BMI increments on **a.** the odds of dose capping (logistic regression models), and **b.** on cycle 1 average relative dose received (linear regression models).

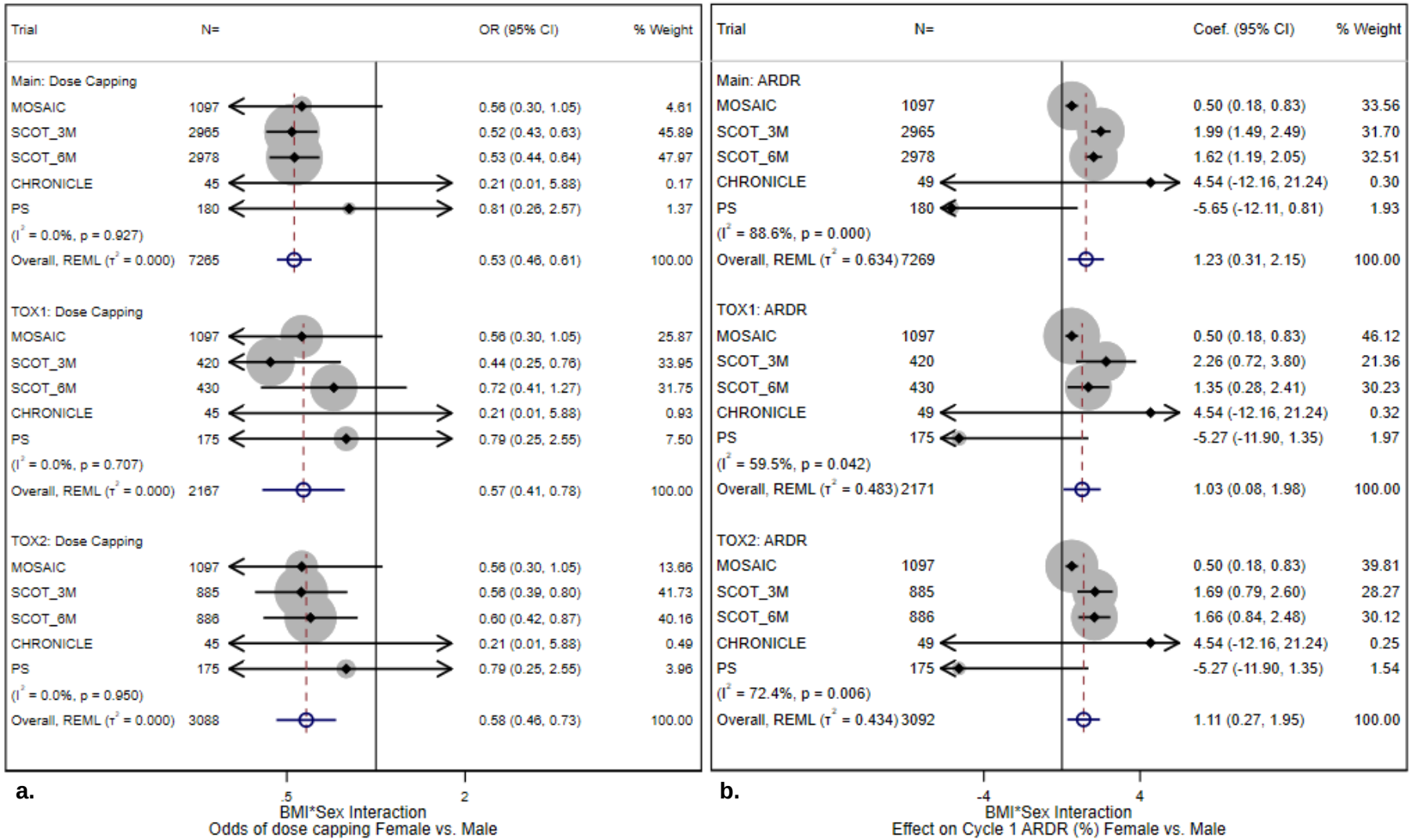
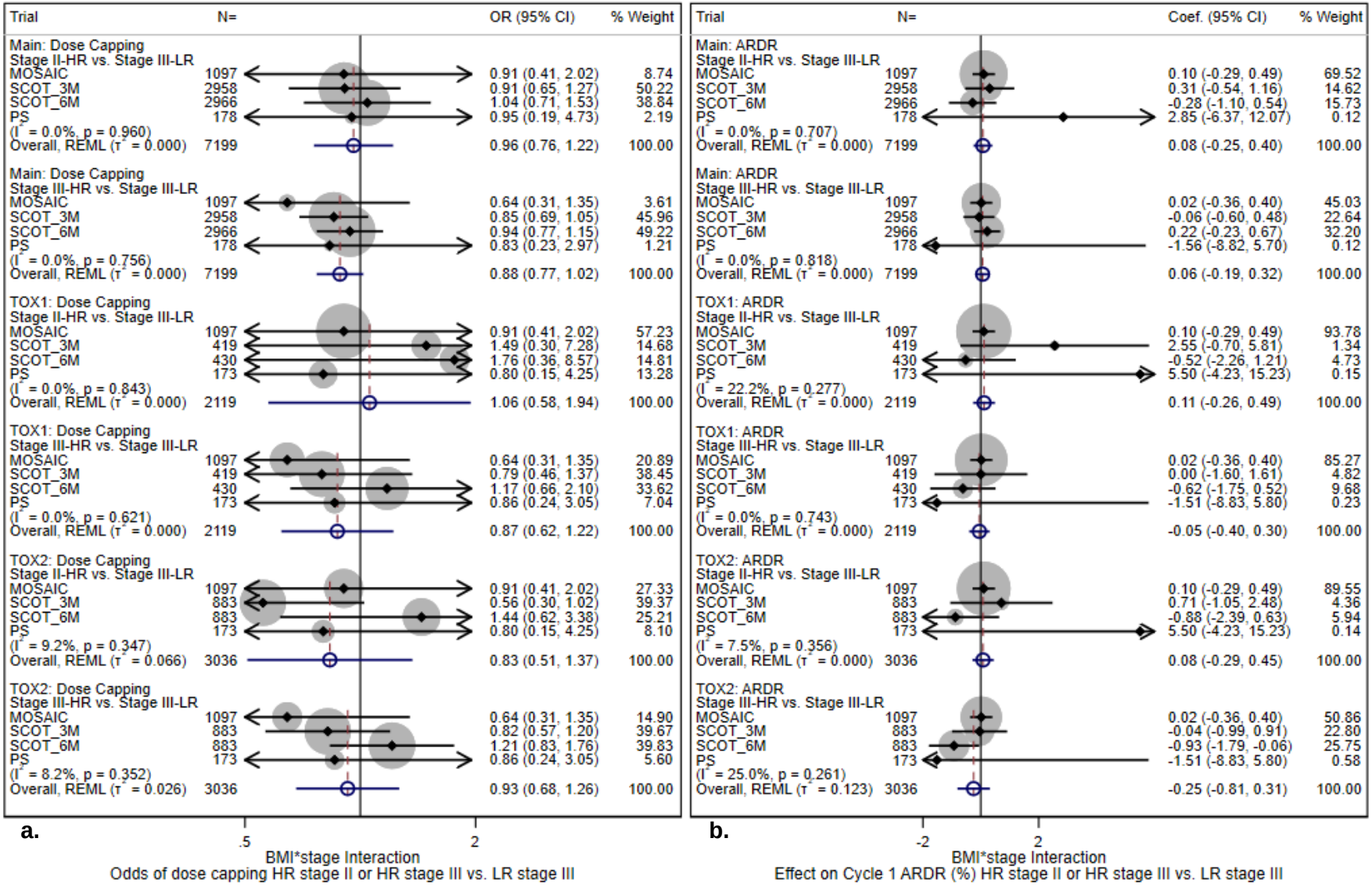


Figure 5.8 | Effect modification of BMI-dose capping and average relative dose received relationships by stage

Forest plots presenting meta-analysed within-trial BMI-stage interaction terms (stage II-High Risk (HR) or stage III-HR vs. stage III-Low Risk (LR)) for the effect of 5kg/m^2 BMI increments on **a.** the odds of dose capping (logistic regression models), and **b.** cycle 1 average relative dose received (linear regression models).



5.3.2 PATH *A*

The relationship between BMI and adjuvant chemotherapy adherence is depicted as path *a* in the DAG from **Figure 5.4a**. IPD meta-analysis of path *a* was undertaken for both the total and direct effects (without and with toxicity included as a covariate respectively) of BMI on both adherence measures, to explore both the effect of BMI and the potential for mediation via grade 3+ toxicity.

BMI increments of 5kg/m^2 were associated with a reduction of ARDI and ACRD of 1.08% (95%CI -1.44, -0.72) and 1.14% (95%CI -1.91, -0.38) respectively (**Figure 5.9a** and **5.10a**), and hence a significant total effect, with varying heterogeneity (ARDI Tau^2 = 0.0358 and ACRD Tau^2 = 0.235). This was consistent across the three different populations for ARDI, though a slightly larger effect estimate of -1.37% was demonstrated in the TOX1 population, likely the result of a higher percentage of weighting attributed to the MOSAIC trial. Similarly, effect estimates were consistent across the three populations for ACRD (all approximately -1%), however TOX1 and TOX2 populations did not reach significance for ACRD. This was likely a combination of reduced power with complete case analysis in addition to the SCOT_6M trial displaying a tendency for increased ACRD with increasing BMI within the TOX1 and TOX2 populations, highlighting both the potential loss of statistical efficiency and the risk of bias introduced by complete case analysis.

Addition of grade 3+ toxicity as an indicator variable did not substantially change the effect estimates (**Figure 5.9b** and **5.10b**), with the direct effect results consistently demonstrating an approximately 1% reduction in ARDI or ACRD for 5kg/m^2 increments in BMI, suggesting no clear evidence of mediation.

Linearity was assessed using multivariate meta-analysis of restricted cubic splines of BMI with three to five knots for the total effect of path *a*. **Figure 5.11** demonstrates meta-analysed linear and spline models with varying numbers of knots, and the corresponding AIC and BIC values. For BMI-ARDI relationships, both AIC and BIC were slightly lower for the 3knot spline model. Here the graphs demonstrated some departure from linearity and a flattened relationship with BMIs of approximately less than 25kg/m^2. There was less substantial evidence of non-linearity in BMI-ACRD relationships, with linear models resulting in the lowest AIC and BIC values, though 3 knot spline model demonstrated a similar shape to ARDI.

Figure 5.9 | Path a: ARDI Forest plots demonstrating **a.** the total effect (TE) and **b**. the direct effect (DE, additionally adjusted for toxicity) of 5kg/m^2 BMI increments on ARDI.

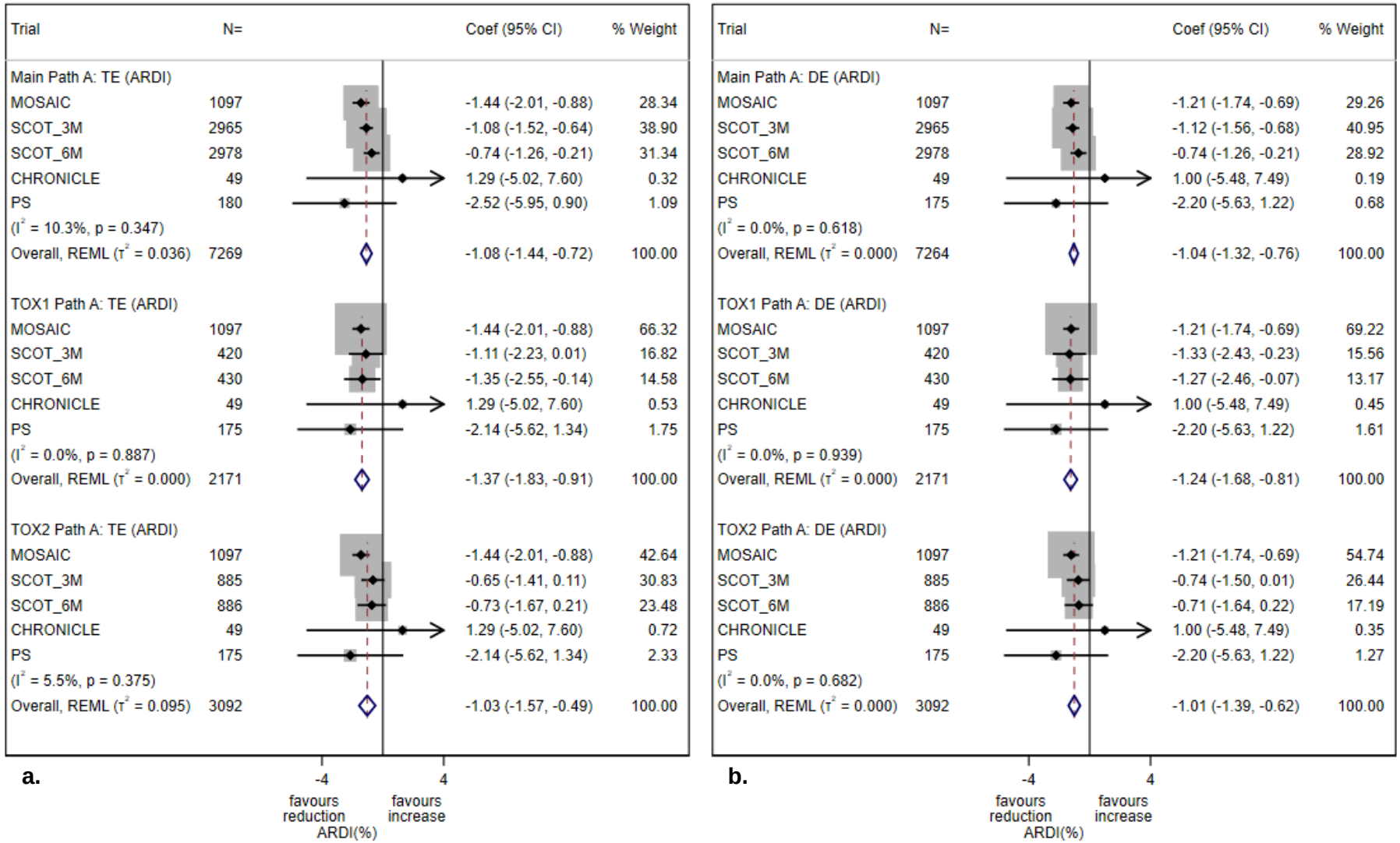


Figure 5.10 | Path *a*: ACRD

Forest plots demonstrating **a.** the total effect (TE) and **b**. the direct effect (DE, additionally adjusted for toxicity) of 5kg/m^2 BMI increments on ACRD.

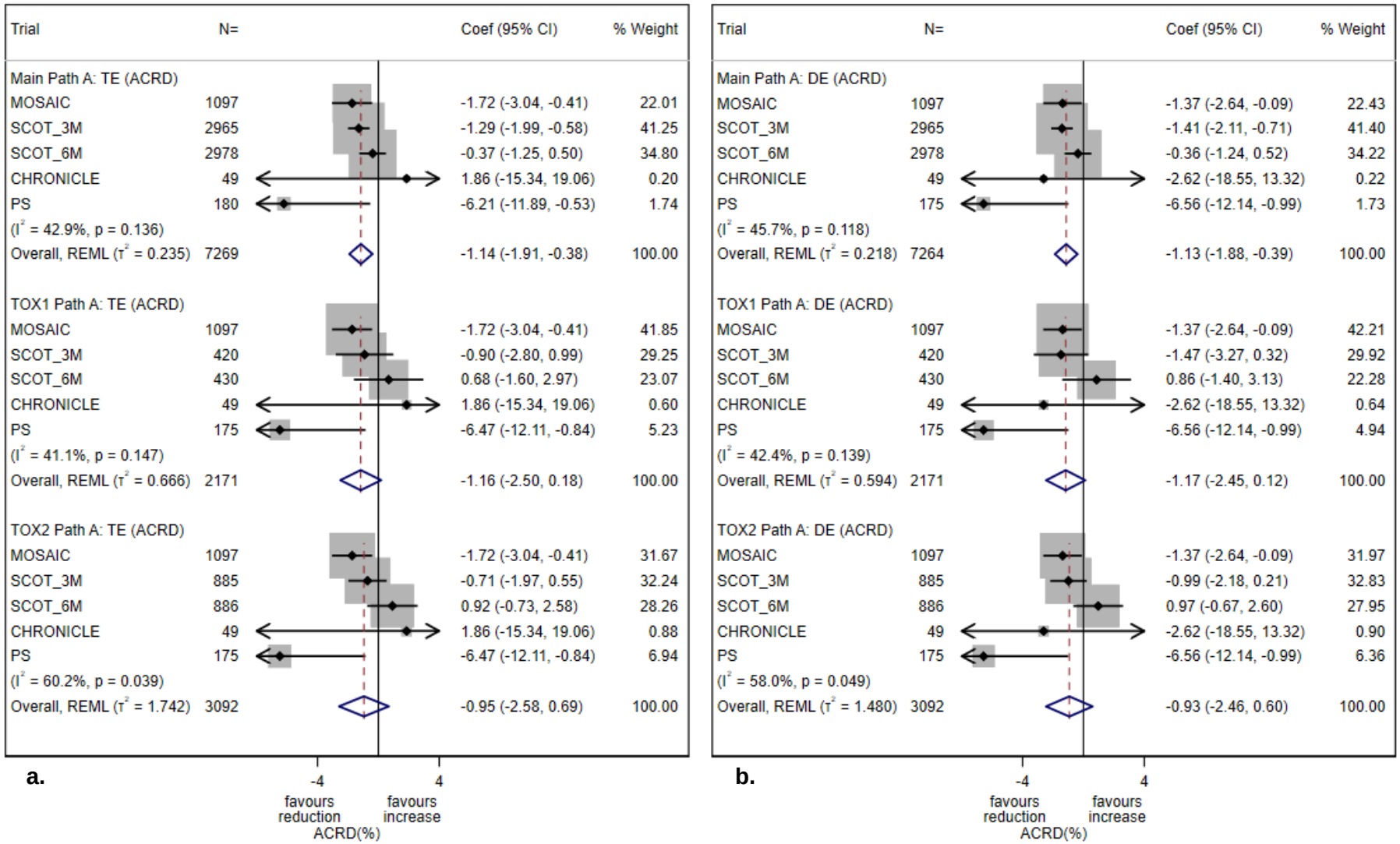
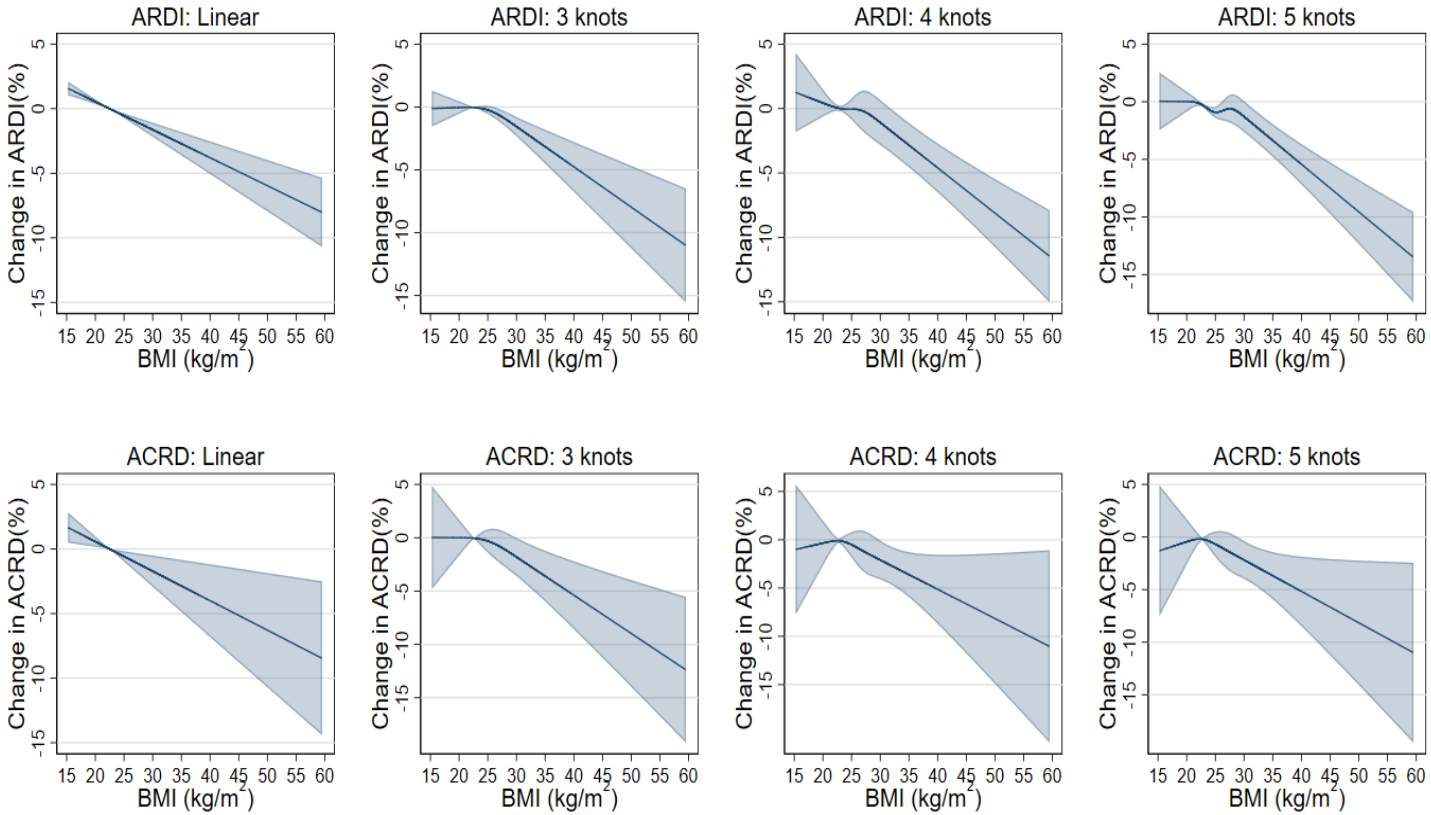


Figure 5.11 | Path *a* (total effect) linearity

Graphs demonstrating the predicted values of change in ARDI or ACRD (coefficient, line) and 95% confidence intervals (shaded area) from linear and spline (3, 4 or 5 knots) multivariate meta-analysis models for the total effect of path *a* plotted against BMI (centred on 22.5kg/m^2). Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are presented for the respective models.



AIC and BIC values

			Spline model no. knots		
		Linear	3	4	5
ARDI	**AIC**	14.90	**13.07**	48.17	90.37
	BIC	14.12	**11.12**	44.65	84.90
ACRD	**AIC**	**22.62**	27.29	65.80	108.30
	BIC	**21.83**	25.34	62.29	103.61

Effect modification by sex and stage was examined for the total effect models. Addition of a BMI-sex interaction term resulted in a larger effect estimate for ARDI (**Table A5.1;** Coef. -1.93; 95%CI -2.85, -1.27) compared with the non-interaction model, with evidence that this effect was substantially reduced in females (**Figure 5.12a**; Main population $Coef._{(interaction)}$ 1.63; 95%CI 1.05, 2.20). Furthermore, these relationships were consistent across all populations. Similarly, addition of a BMI-sex interaction term resulted in a larger effect estimate for ACRD (**Table A5.1**; Main population Coef. -1.55; 95%CI -2.61, -0.49) compared with the non-interaction model, with low heterogeneity (Tau^2 = 0.000). However, despite a tendency towards a reduction in this effect for females, effect modification was not significant (**Figure 5.12b**; Main population $Coef._{(interaction)}$ 0.92; 95%CI -0.25, 2.08), with relatively high heterogeneity (Tau^2 = 0.236). Again, these relationships were consistent across all populations.

Addition of BMI-stage interaction terms into the models resulted in small changes in the effect estimates for ARDI and ACRD with both remaining significant for the Main population (**Table A5.2)**. Furthermore, there was no convincing evidence of effect modification by disease stage within the Main population for ARDI (**Figure 5.13b**) or ACRD (**Figure 5.13b**), with some variability across toxicity populations.

Sensitivity analyses summary estimates for path *a* are presented in **Figure A5.1** for ARDI and **Figure A5.2** for ACRD, within the appendix. None of the sensitivity analyses resulted in a substantial change in effect estimates of total or direct effects for ARDI, with all results remaining significant for all analyses and populations. Similarly, for ACRD, effect estimates did not substantially change, however slightly larger effect estimates were seen when excluding patients receiving 3 months ACT only (Coef. -1.32; 95%CI -2.91, 0.26) and excluding patients receiving capecitabine (Coef. -1.28; 95%CI -2.02, -0.54), though the former had substantially widened confidence intervals. Furthermore, the conservative confidence intervals produced by the Hartung-Knap-Siddik-Jonkmann (HKSJ) method widened confidence intervals such that they just crossed the null effect line (Coef. -1.14; 95%CI -2.35, 0.06). Despite more variability in effect estimates for the TOX1 and TOX2 populations, overall direction of relationships remained the same with wider confidence intervals, as would be expected from a smaller sample size. Overall, there remained convincing evidence of a reduction in ARDI an ACRD with increasing BMI.

Figure 5.12 | Effect modification of Path *a* total effect by sex

Forest plots presenting meta-analysed within-trial BMI-sex interactions. Summary effect estimates represent the additional effect for females vs. males for a 5kg/m^2 BMI increments on **a.** the average relative dose intensity (ARDI) and **b.** the average cumulative relative dose (ACRD).

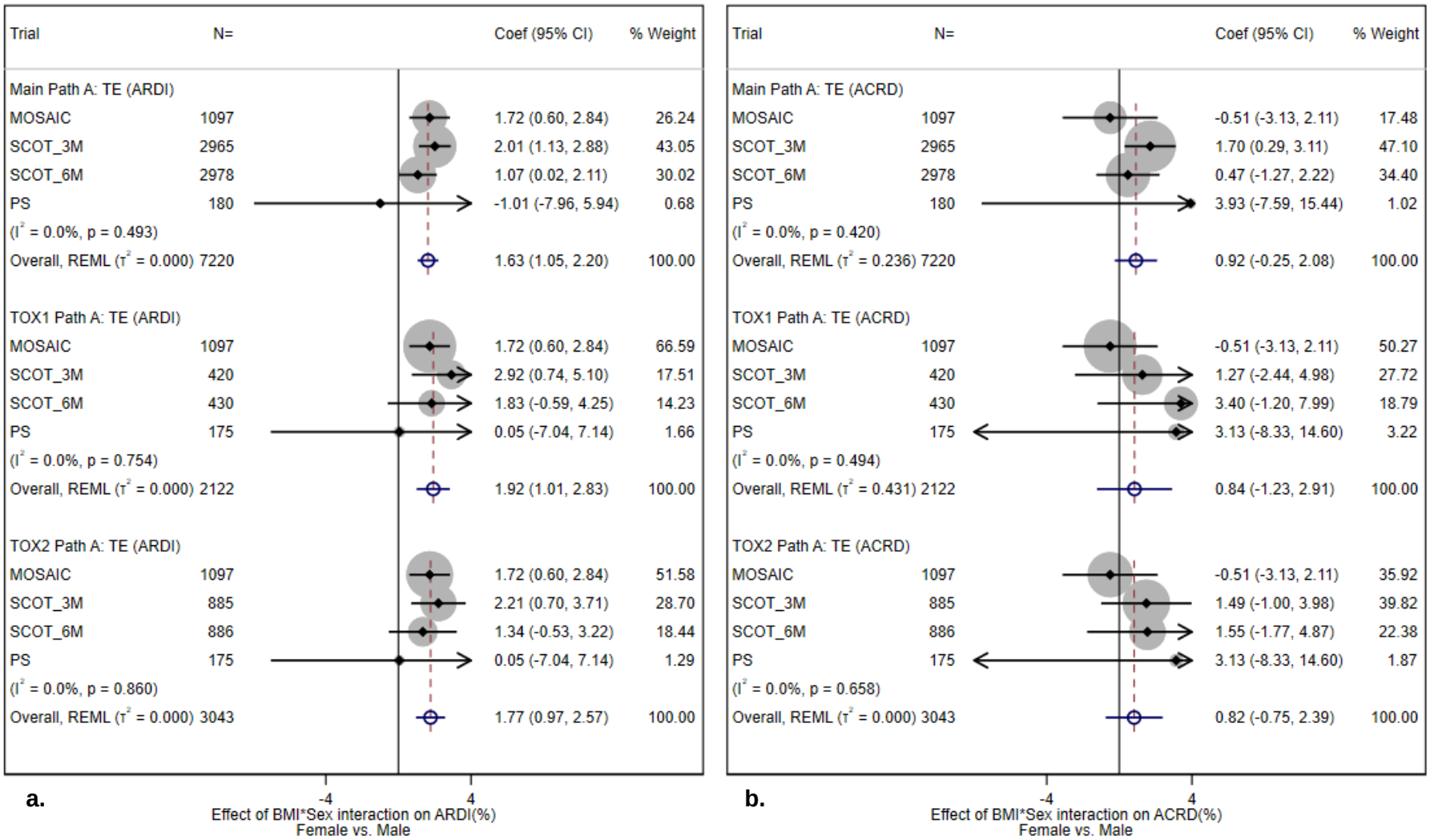
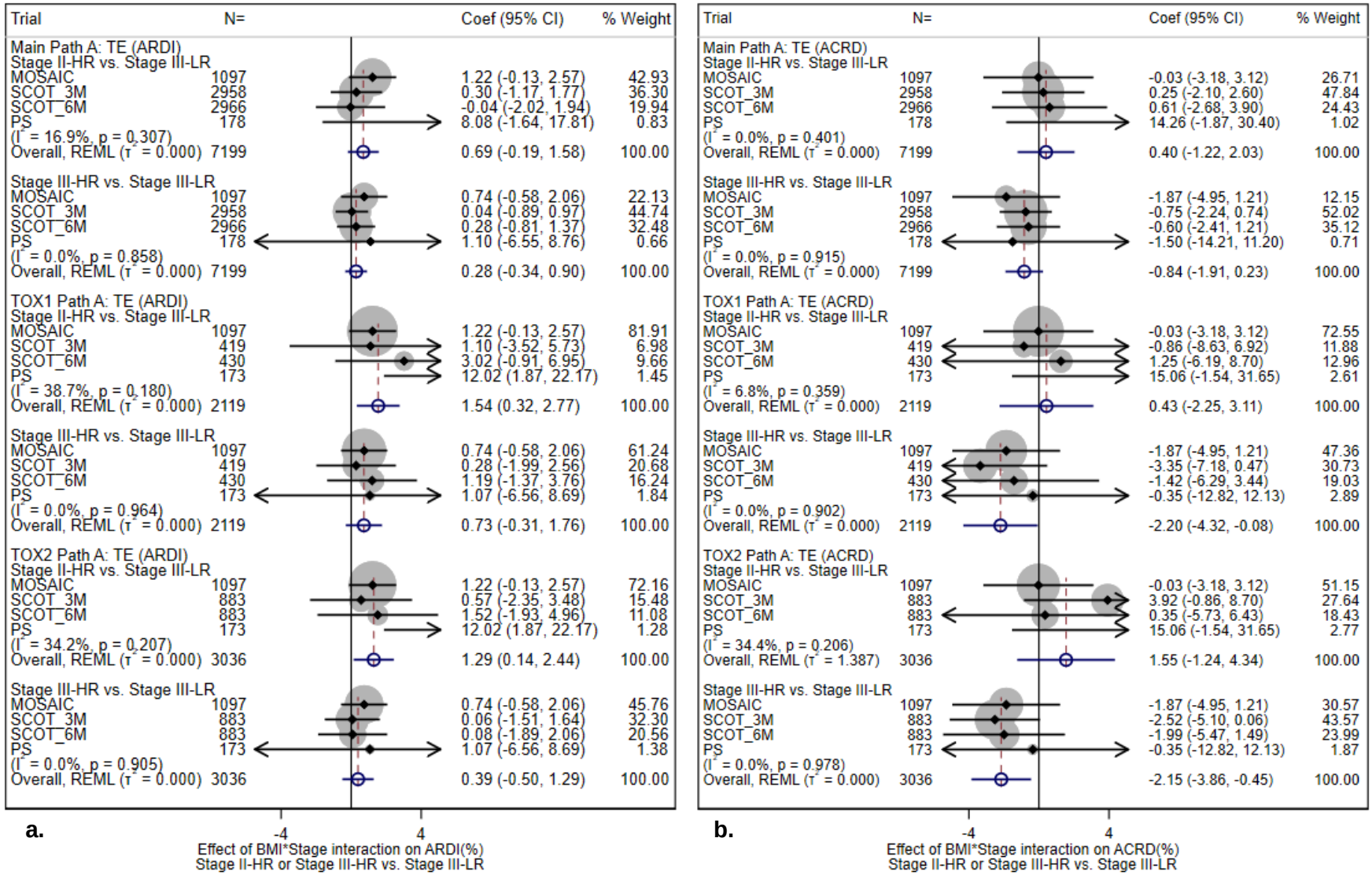


Figure 5.13 | Effect modification of Path *a* total effect by disease stage

Forest plots presenting meta-analysed within-trial BMI-stage interaction terms. Summary effect estimates represent the additional effect for stage II-high risk (HR) or stage III-high risk (HR) vs. stage III-low risk (LR) disease for 5kg/m^2 BMI increments on **a.** the average relative dose intensity (ARDI) and **b.** the average cumulative relative dose (ACRD).



5.3.3 PATH *D*

The relationship between BMI and grade 3+ toxicity is depicted as path *d* in the DAG from **Figure 5.4a**. IPD meta-analysis results for path *d* are demonstrated in **Figure 5.14** and display no significant relationship between BMI and toxicity (Main OR 1.01; 95%CI 0.91, 1.14), with low heterogeneity (Tau^2 = 0.006) and consistent results across the three study populations

Linearity was assessed using multivariate meta-analysis of restricted cubic splines of BMI, and only possible for TOX1 and TOX2 populations. Linear and non-linear models are presented in **Figure 5.15,** and were similar for the two toxicity populations, with narrower confidence intervals for TOX2, reflecting a larger sample size. AIC and BIC values were smallest for the 3 knots linear model, suggesting some possible inverse u-shaped non-linearity with a tendency for toxicity to reduce with increasing BMI, above approximately 27kg/m^2. However, with confidence intervals consistently crossing zero and increasingly wide as BMI increased, there was no convincing evidence of a significant non-linear relationship.

Effect modification by dose capping was examined in addition to sex and stage. Addition of a BMI-dose-capping interaction term resulted in a small increase in the odds ratio (**Figure 5.16a**, OR 1.07; 95%CI 0.95, 1.20) compared with the non-interaction model, with larger increases in the TOX1 and TOX2 populations and the latter borderline significant. However, there was no significant within trial interaction demonstrated for capped vs. full cycle 1 dosing for any population (**Figure 5.16b** Main OR 0.98; 95%CI 0.83, 1.16), with low heterogeneity (Tau^2 0.000). There was no substantial change in the OR when including either a BMI-sex or a BMI-stage interaction term (**Tables A5.1 and A5.2**), with no evidence of effect modification by sex or disease stage.

Summary estimates of sensitivity analyses are presented in **Figure A5.3**, within the appendix. None of the sensitivity analyses resulted in a substantial change in effect estimates of path *d,* with two exceptions. The odds ratio increased and became borderline significant after exclusion of patients receiving 3 months of chemotherapy in the TOX1 population (OR 1.13, 95%CI 1.00, 1.27). Furthermore, exclusion of patients receiving capecitabine resulted in an increased OR which was significant in the TOX1 population (OR 1.15, 95%CI 1.01, 1.32) and borderline significant in TOX2. However, these relationships were not convincing within the Main population.

Figure 5.14 | Path D - Toxicity

Forest plot demonstrating the relationship between 5kg/m^2 increments of BMI and the occurrence of any grade 3+ toxicity during adjuvant chemotherapy regimens for the three populations. Number of events relates to the number of patients developing grade 3+ toxicity, where multiple imputation was used for the SCOT trial, this is the average across the imputed datasets.

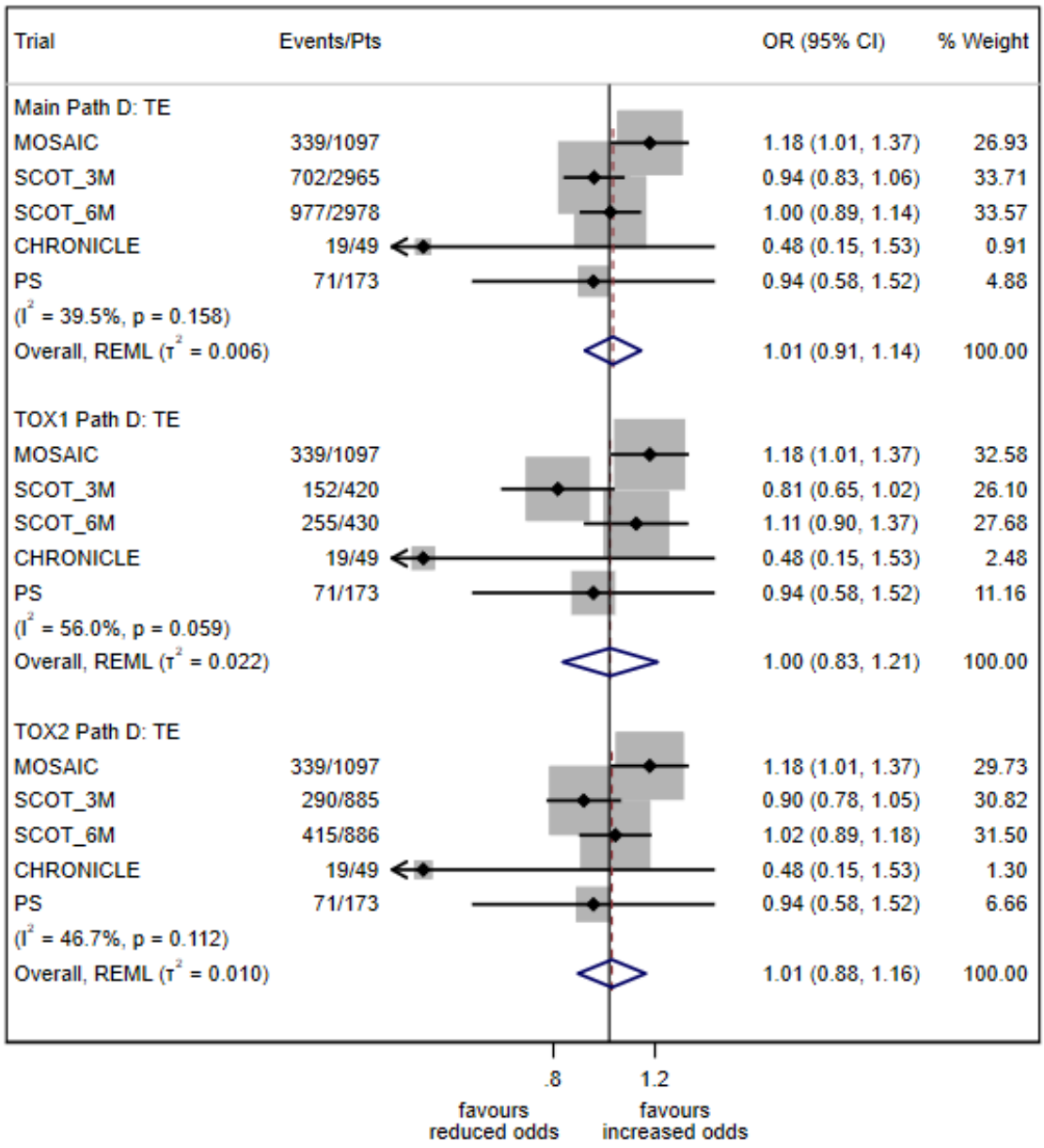


Figure 5.15 | Path D linearity
Graphs demonstrating predicted values of log odds ratios (logOR, line) and 95% confidence intervals (shaded area) from linear and spline (3, 4 or 5 knots) multivariate meta-analysis models for the total effect of path *d* plotted against BMI (centred on 22.5kg/m^2). Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are also presented.

AIC and BIC values					
			Spline model no. knots		
		Linear	3	4	5
TOX1	**AIC**	6.24	**-9.16**	9.96	41.19
	BIC	5.46	**-11.12**	6.14	35.72
TOX2	**AIC**	4.44	**-12.05**	9.11	39.57
	BIC	3.66	**-14.00**	5.59	34.10

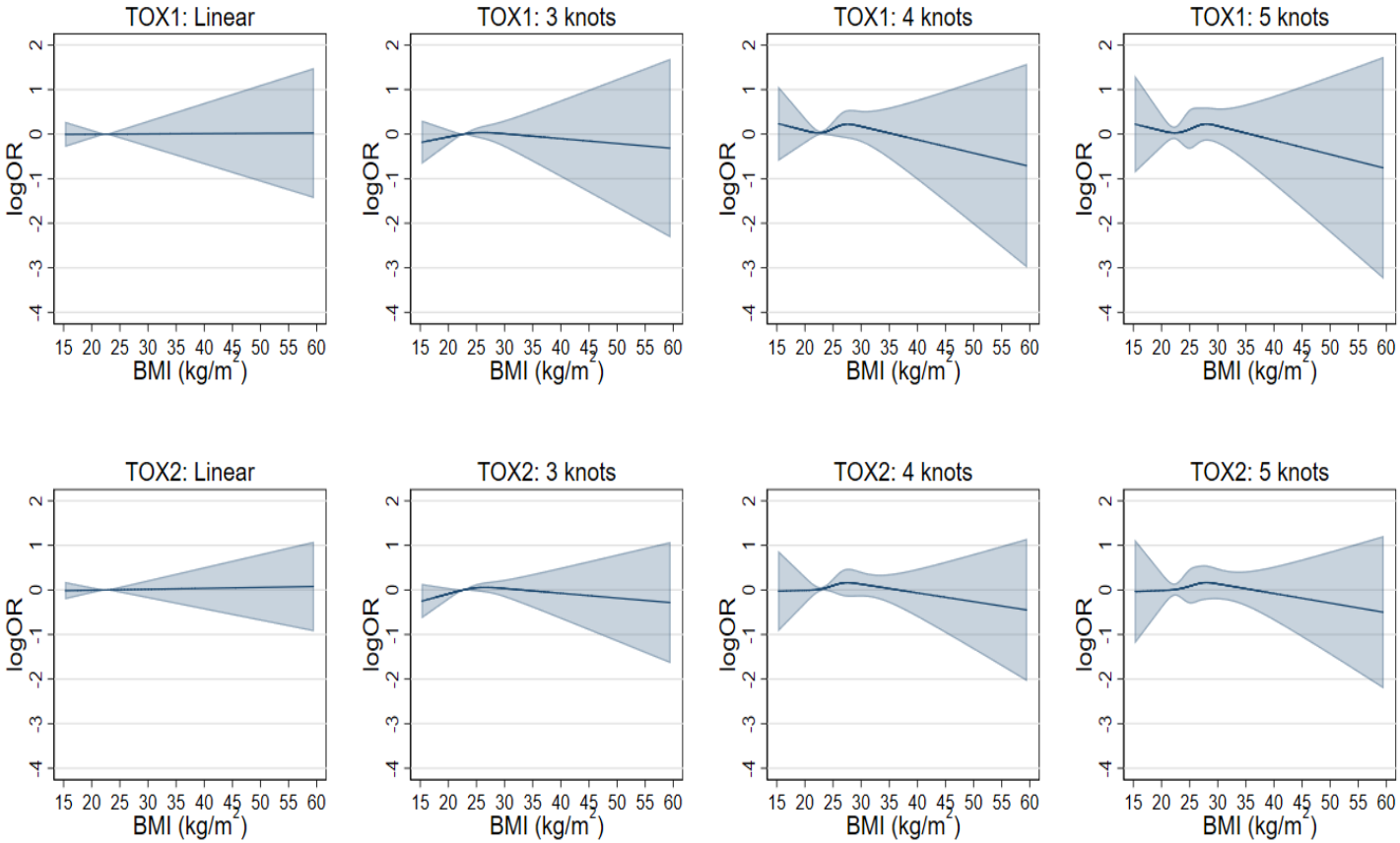
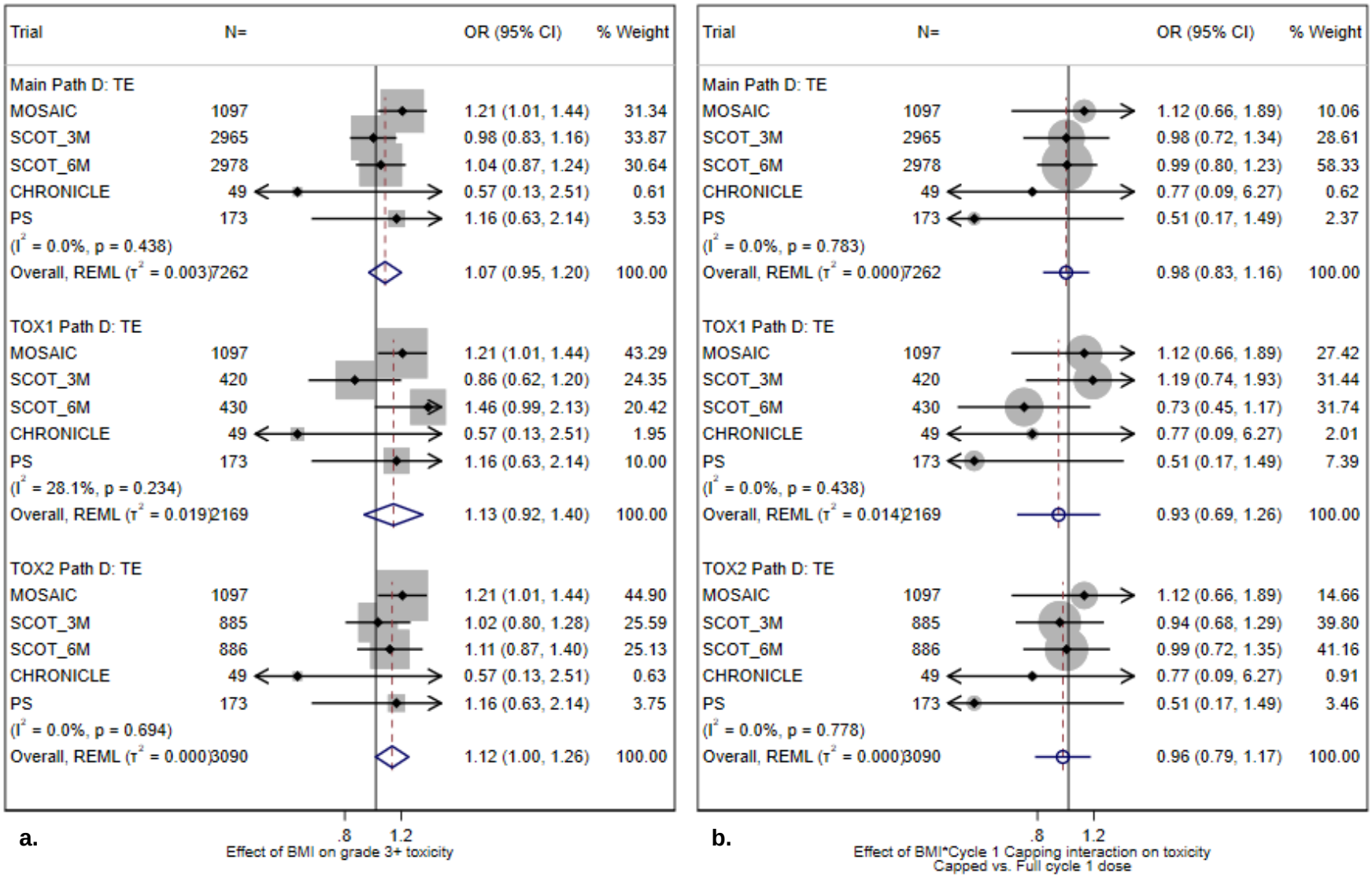


Figure 5.16 | Effect modification of Path *d* by cycle 1 dose capping

Forest plots demonstrating **a**. the total effect of 5kg/m^2 BMI increments on toxicity when the BMI-dose-capping interaction term is included in the model and **b.** the meta-analysed within-trial BMI-dose-capping interaction term, indicating the additional effect on the BMI-toxicity relationship of a capped cycle 1 dose vs. full dose.



Meta-analysis was additionally undertaken to investigate the effects of BMI on the occurrence of individual grade 3+ toxicities within the TOX1 and TOX2 populations only. There was a borderline significant relationship between BMI and increased odds of developing grade 3+ neuropathy within the TOX1 population (**Figure 5.17a**; OR 1.24; 95%CI 0.99, 1.56) with low heterogeneity (Tau^2 = 0.000), however, this was not consistent within the TOX2 population (**Figure 5.17b**, OR 1.10; 95%CI 0.75, 1.62). Furthermore, there was a significant reduction in the odds of developing grade 3+ neutropenia with increasing BMI which was consistent for both toxicity populations (**Figures 5.18a** and **5.18b**) with an odds ratio of 0.71 for both (TOX1 95%CI 0.56, 0.90; TOX2 95%CI 0.57, 0.89). There was no convincing relationship between BMI and the development of grade 3+ diarrhoea, nausea (**Figure 5.17a** and **5.17b**), vomiting, mucositis (**Figure 5.18a** and **5.18b**), fatigue, skin, or other toxicities **(Figures 5.19a** and **5.19b**).

Finally, the relationship between BMI and timing of the first occurrence of grade 3+ toxicity was explored. Firstly, a meta-analysed multinomial logistic regression model for the effect of BMI on the risk of toxicity occurring during early cycles vs. no grade 3+ toxicity demonstrated no significant relationship (relative risk ratio (RRR) 1.01, 95%CI 0.84, 1.21) **(Figures 5.20i)**, however there did appear to be an increased risk of toxicity occurring during late cycles vs. no toxicity (RRR 1.20, 95%CI 1.01, 1.43), with increasing BMI **(Figures 5.20ii)**. Furthermore, within the subgroup of patients experiencing grade 3+ toxicity, there was a tendency for the odds of the first episode of grade 3+ toxicity occurring during early vs. late cycles to be reduced as BMI increased (**Figure 5.20.iii**). Finally, meta-analysed Cox proportional hazards models assessing time to first occurrence of toxicity from randomisation demonstrated no significant relationship between BMI and grade 3+ toxicity (**Figure 5.20.iv**). Relationships were similar for both toxicity populations and heterogeneity was generally low (**Figures 5.20a** and **20b**). Overall, these results suggested that although BMI is not associated with the occurrence of grade 3+ toxicity, it might be associated with the timing of toxicity, where toxicity was more likely to be a later event as BMI increased.

Figure 5.17 | Path *d* – Grade 3+ neuropathy, diarrhoea, and nausea toxicities

Forest plots demonstrating the effects of 5kg/m^2 BMI increments on the occurrence of grade 3+ neuropathy, diarrhoea, and nausea toxicities during adjuvant chemotherapy regimens in the **a.** TOX1 and **b.** TOX2 populations.

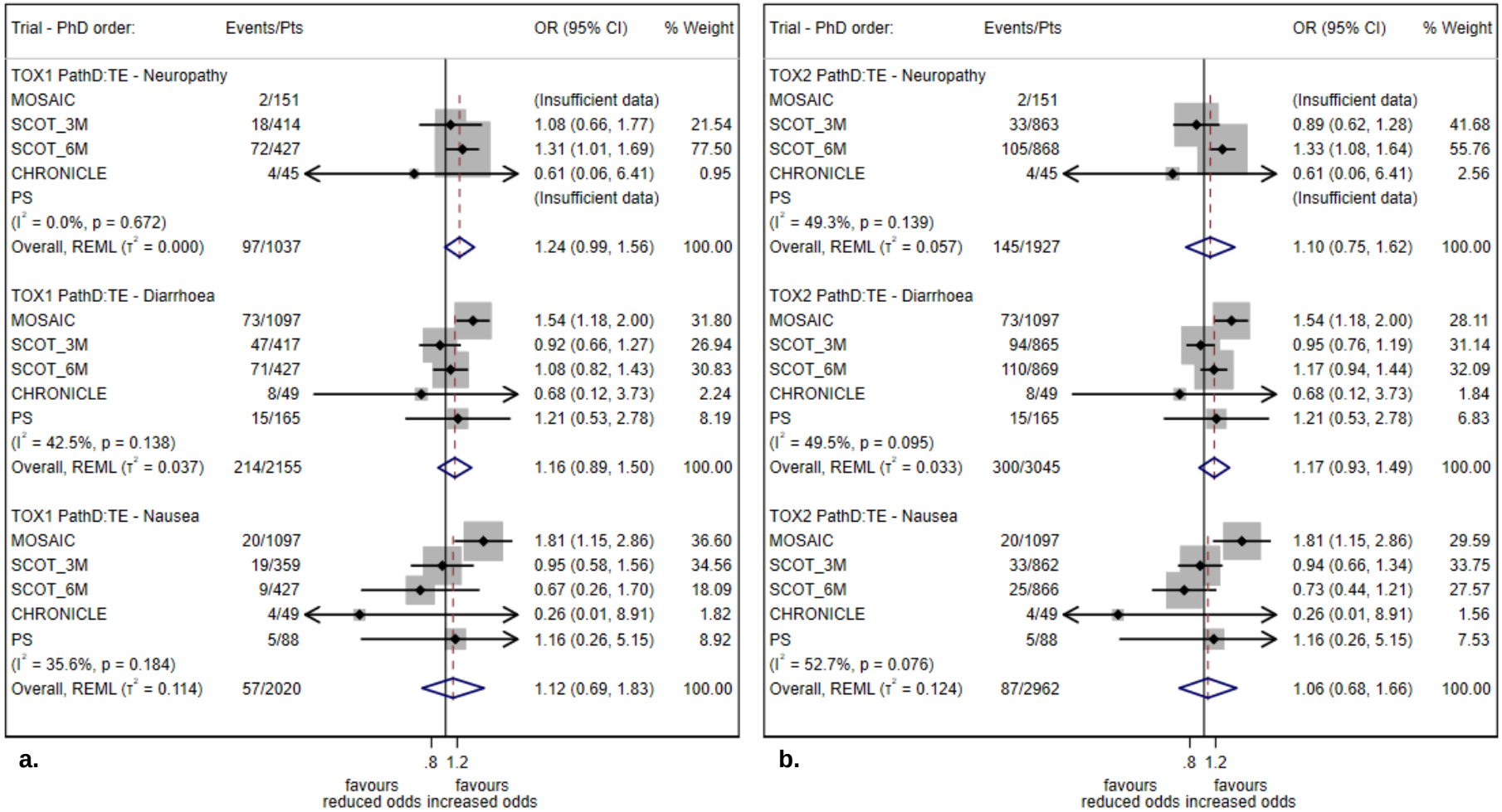


Figure 5.18 | Path *d* – grade 3+ vomiting, neutropenia, and mucositis toxicities

Forest plots demonstrating the effects of 5kg/m^2 BMI increments on the occurrence of grade 3+ vomiting, neutropenia, and mucositis toxicities during adjuvant chemotherapy regimens in the **a.** TOX1 and **b.** TOX2 populations.

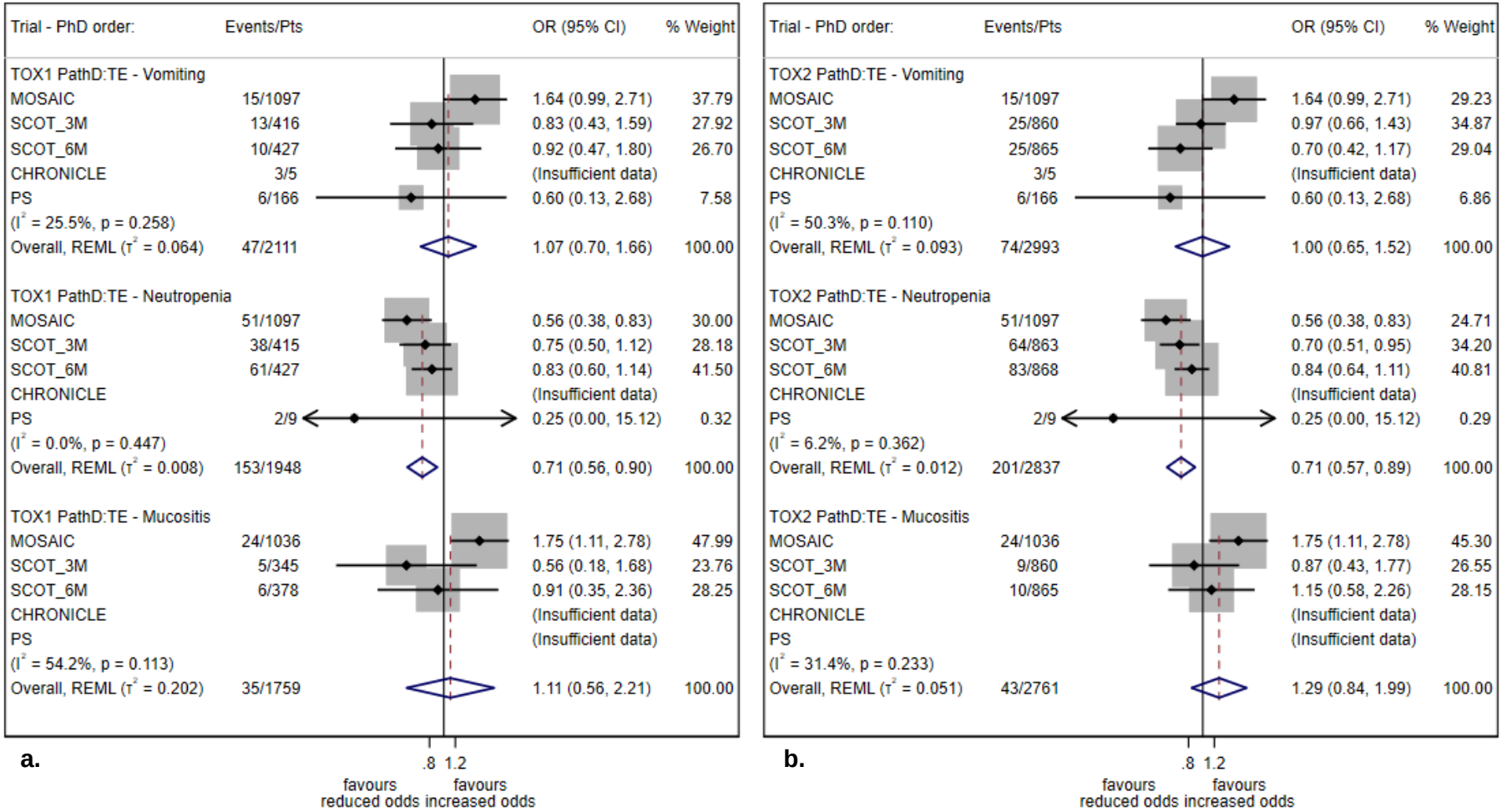


Figure 5.19 | Path *d* – grade 3+ fatigue, skin, and other toxicities

Forest plots demonstrating effects of 5kg/m^2 BMI increments on the occurrence of any grade 3+ fatigue, skin, and other toxicities during adjuvant chemotherapy regimens in the **a.** TOX1 and **b.** TOX2 populations.

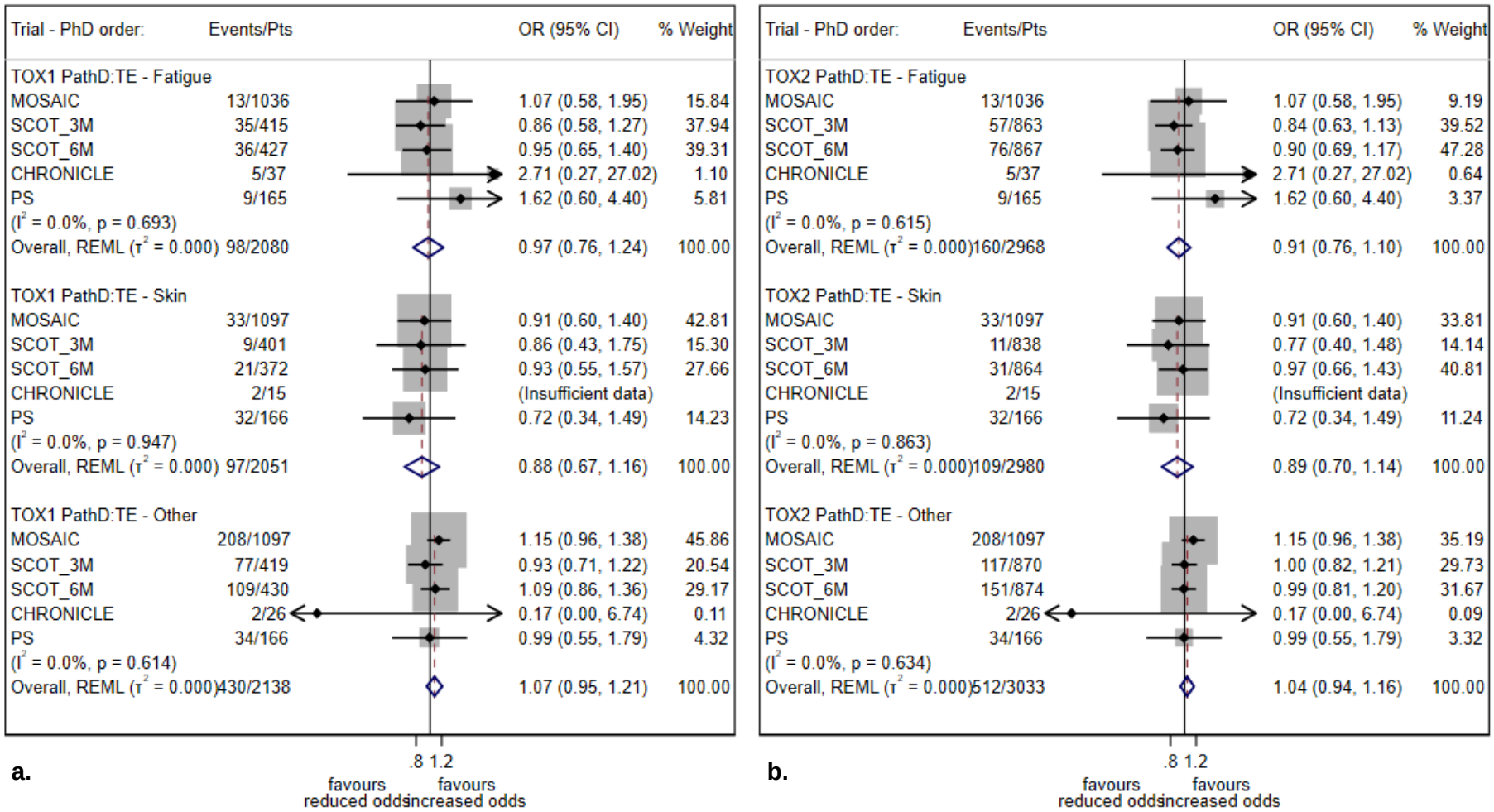
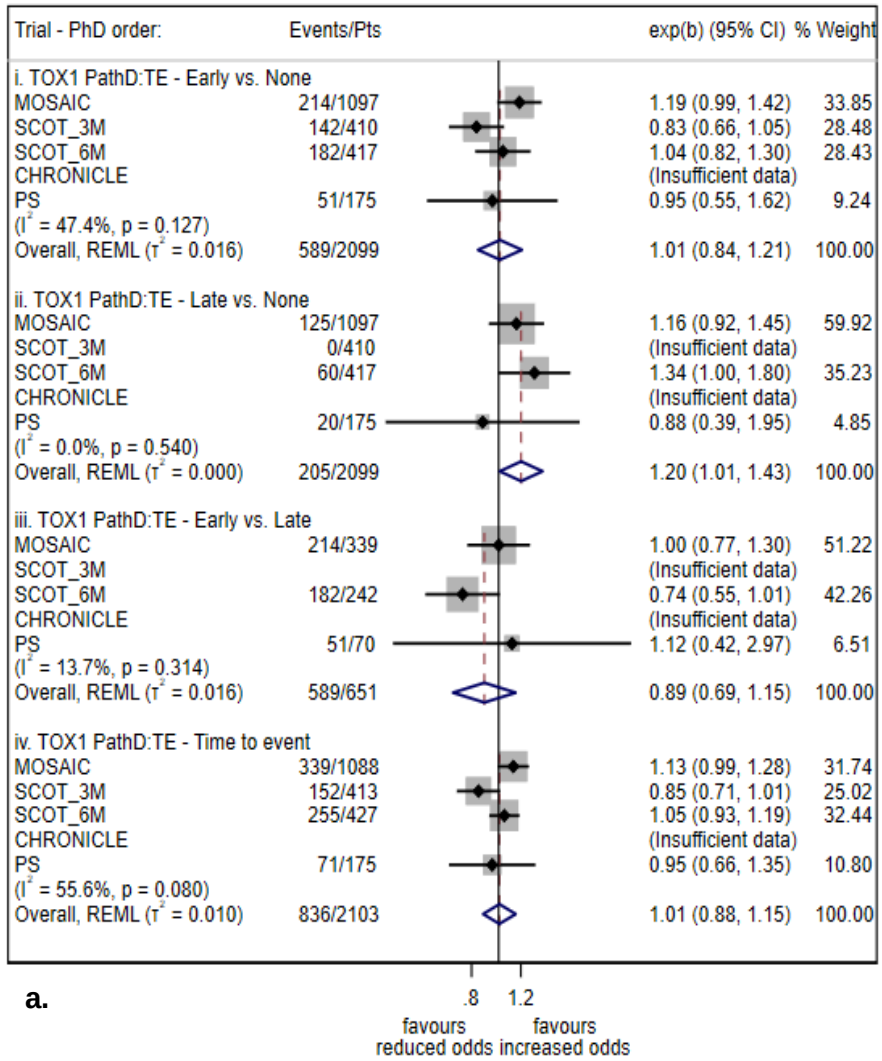
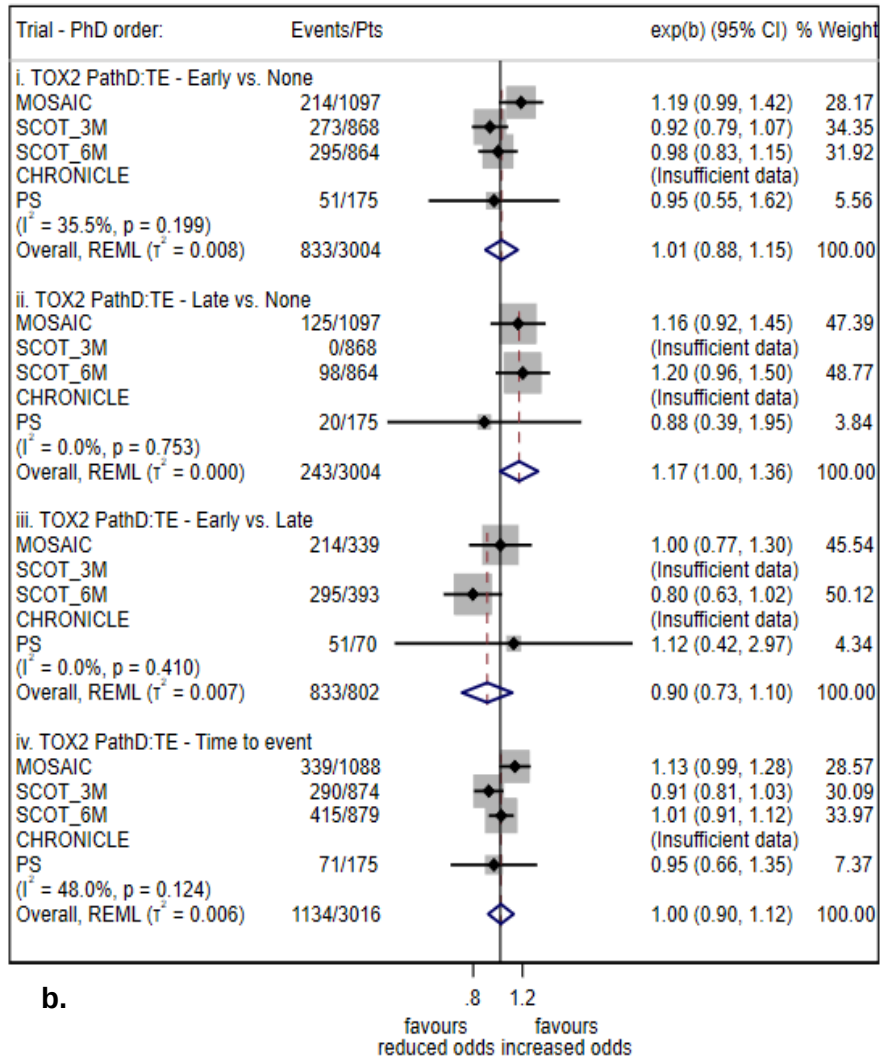


Figure 5.20 | Path *d* – Timing of grade 3+ toxicity occurrence

Forest plots demonstrating effects of 5kg/m^2 BMI increments on **i.** early and **ii.** late cycle grade 3+ toxicity (relative to no grade 3+ toxicity [multinomial models reporting relative risk ratios]); **iii** early cycle vs. late cycle toxicity among patients experiencing grade 3+ toxicity (logistic models [OR]); **iv.** Risk of grade 3+ toxicity (Cox PH models [HR]); within **a.** TOX1 and **b.** TOX2 populations.





5.3.4 PATH *B*

The relationship between adherence and survival is presented as path *b* in the DAG from **Figure 5.4b** and was explored for both ARDI and ACRD as exposures, and for all three survival outcomes. Models were meta-analysed with and without the addition of toxicity, to explore potential residual confounding bias by not including toxicity, in addition to utilising both Weibull and Cox proportional hazards survival models, as described above.

The total number of OS events occurring during a median of 3.05 (IQR 2.90, 4.00) years follow-up was 964 (13.26%). Across the five trials, the rate of OS events ranged from 12.94% to 16.33% with median follow-up of ranging 2.78 years to 5.57 years. Median overall, disease-free or cancer specific survival was not reached by any trial, and hence was not calculable. Disease-free and cancer-specific events, in addition to cause of death, are presented in **Table 5.3**.

Kaplan Meier curves and risk tables are presented in the appendix (**Figures A5.4 to A5.8**) for ARDI and ACRD (categorised for exploration of the data only) at the trial level. Some trials (namely SCOT and MOSAIC) displayed occasional evidence of non-proportional hazards for ACRD and to a lesser extent ARDI (**Figures A5.9** and **A5.10**) for some survival models, which generally appeared to be small deviations. For ACRD, when addition of exposure*time interactions into the models were explored, these resulted in a strengthening of path *b* relationships, with small effect estimates for the time varying effects, in the opposing direction. Furthermore, a small degree of non-proportional hazards may have been related to the extent of right censoring beyond 3-5 years in most trials, in addition to competing risks (comparatively smaller time-varying effects were generally noted for CSS), and finally the possibility of non-linear relationships (explored below). Hence, the obtained hazard ratios should be considered as an average hazard ratio across a median follow-up of 3 years. It was assumed that the independent censoring assumption held. For all trials, censoring appeared to be the result of cessation of trial follow-up, with no data suggesting substantial numbers of patients being lost to follow-up, which might have violated this assumption. For SCOT, CHRONICLE and PS trial recruitment was slower than expected, with all three not meeting recruitment targets, and SCOT requiring an extension for requirement and follow-up duration. For MOSAIC, the complete 10 year follow-up data were not available (see **Section 6.2.6** for more detail), with the dataset appearing to correspond to the first published paper with 3 year data, for which “good compliance with follow-up visits” was described.[183] Hence right censoring was most likely to relate to the last trial follow-up, rather than patient-dependent factors.

For ARDI, 5% increments were associated with a significantly reduced overall survival (**Figure 5.21a**, HR 1.05; 95%CI 1.01, 1.09), and displayed a non-significant tendency towards worse disease free (**Figure 5. 22a**, HR 1.03; 95%CI 0.99, 1.07) and cancer specific survival (**Figure 5.23a**, HR 1.03; 95%CI 1.00, 1.06) with effects consistent across toxicity populations. Exclusion

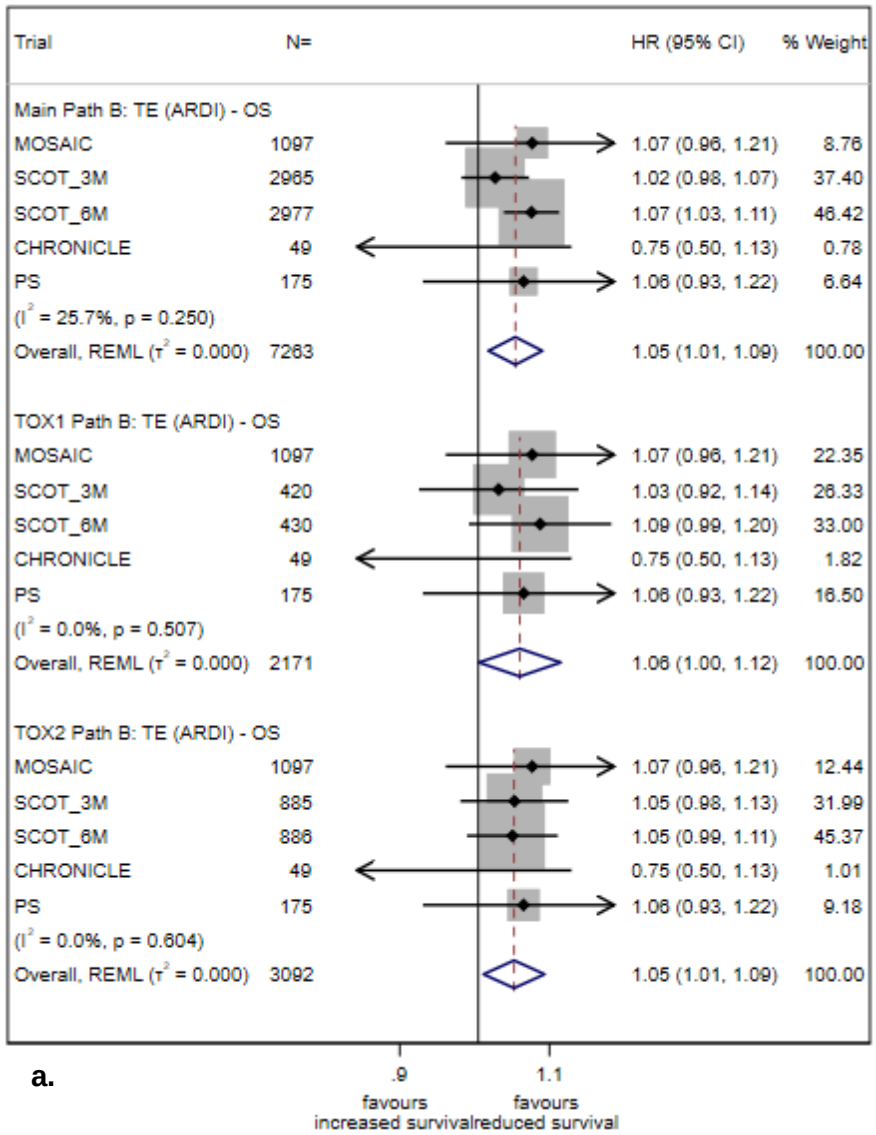
of toxicity as a covariate resulted in minimal changes of the effect estimates towards the null effect and made OS relationships non-significant (**Figure 5.21b, 5.22b and 5.23b**), suggesting a minimal degree of bias from residual cofounding by toxicity. Heterogeneity was low, with small Tau^2 estimates, and Cox models resulted in virtually identical outcomes (**Figure A5.11a**).

Table 5.3 | Survival outcomes and median follow up by trial

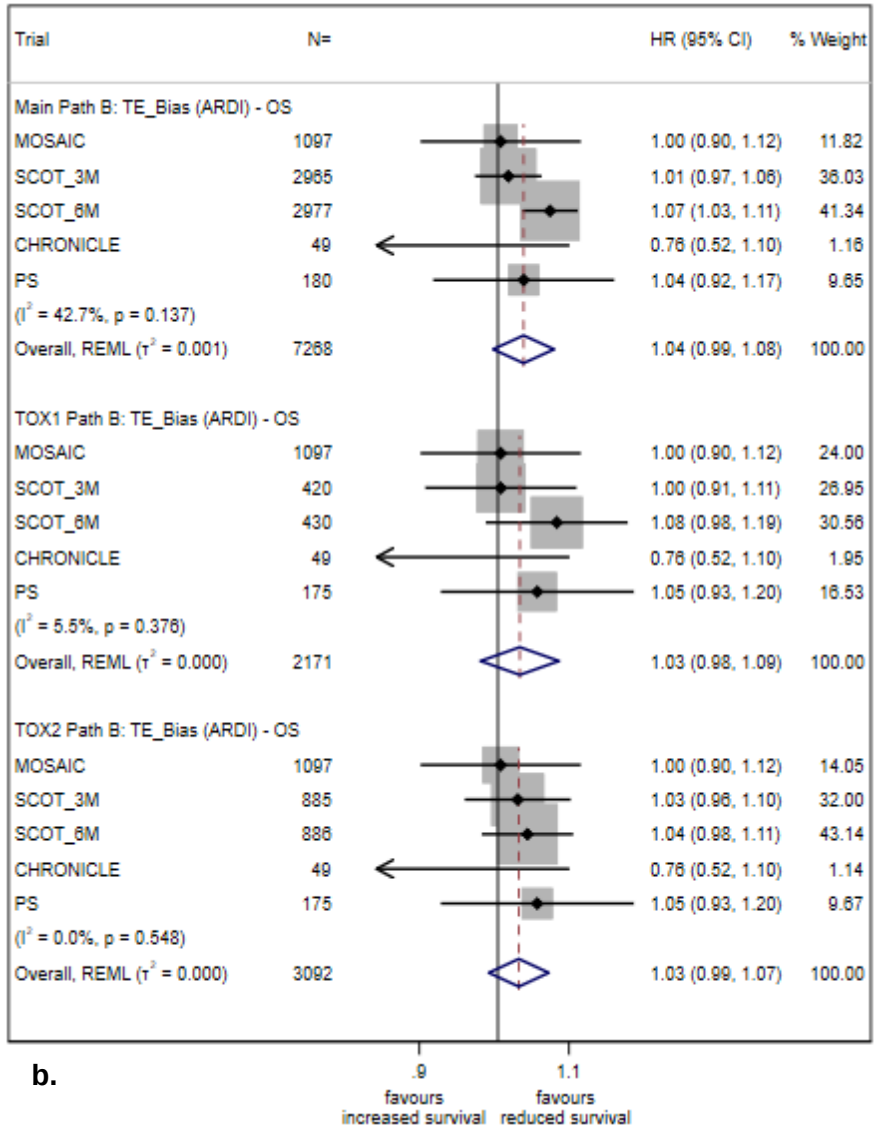
	MOSAIC	SCOT_3M	SCOT_6M	CHRONICLE	PS	Total
OS events, N (%)	142 (12.94)	386 (13.02)	385 (12.93)	8 (16.33)	43 (23.89)	964 (13.26)
DFS events, N (%)	281 (25.62)	726 (24.49)	728 (24.45)	11(12.45)	73 (40.7)	1819 (25.02)
CSS events, N (%)	120 (10.94)	272 (9.17)	269 (9.03)	6 (12.24)	35 (19.44)	702 (9.66)
Mean follow-up (IQR), years	2.78 (2.37, 3.25)	3.07 (2.96, 4.02)	3.06 (2.96, 4.04)	3.26 (2.47, 4.20)	5.57 (4.78, 7.21)	3.05 (2.90, 4.00)
Cause of death						
Colorectal Cancer	120 (10.94)	272 (9.17)	269 (9.03)	6 (12.4)	35 (19.44)	702 (9.66)
Adverse Event	6 (0.55)	16 (0.54)	15 (0.50)	1 (2.04)	0 (0.00)	38 (0.52)
Other	15 (1.37)	97 (3.27)	100 (3.36)	1 (2.04)	7 (3.89)	220 (3.03)
Unknown	1 (0.09)	1 (0.03)	1 (0.03)	0 (0.00)	1 (0.56)	4 (0.06)

CSS, Cancer-Specific Survival; **DFS,** Disease-Free Survival; **IQR,** Inter-Quartile Range **OS,** Overall Survival;

Figure 5.21 | Path *b* – ARDI effect on overall survival
Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ARDI increments on overall survival



a.



b.

Figure 5.22 | Path *b* – ARDI effect on disease free survival
Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ARDI increments on disease free survival.

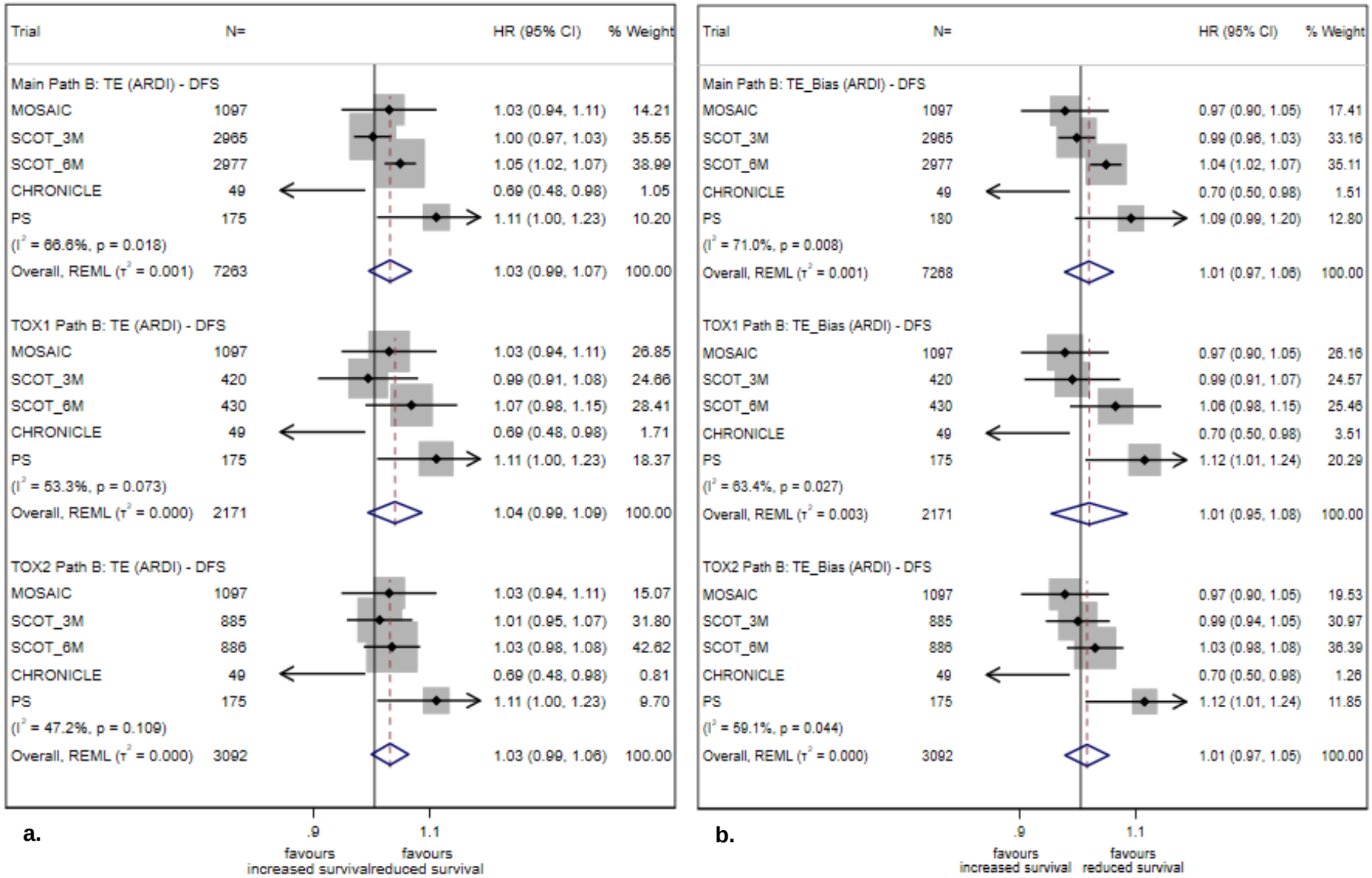
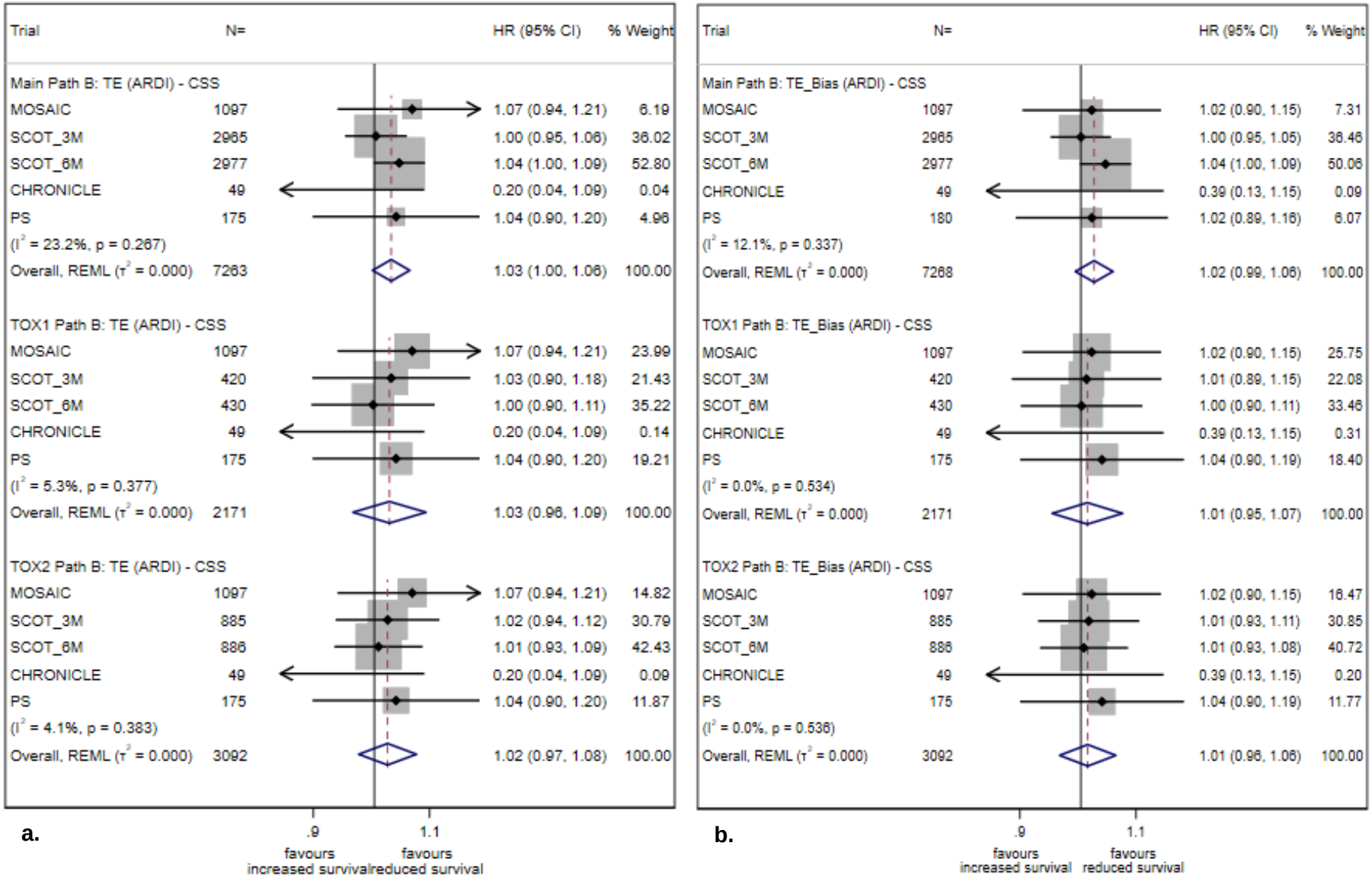


Figure 5.23 | Path *b* – ARDI effect on cancer specific survival

Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ARDI increments on cancer specific survival.



Conversely, 5% increments of ACRD resulted in a significant improvement of all survival outcomes: 6% for OS (**Figure 5.24a**, HR 0.94; 95%CI 0.91, 0.96), 4% for DFS (**Figure 5.25a**, HR 0.96; 95%CI 0.92, 1.00), and 6% for CSS (**Figure 5.26a**, HR 0.94; 95%CI 0.92, 0.96), with effects consistent across toxicity populations. Again, there appeared to be minimal bias introduced as a result of excluding toxicity as a covariate, with minimal changes to the effect estimates in the direction of strengthening of associations (**Figure 5.24b, 5.25b and 5.26b**). Cox models again resulted in very similar outcomes (**Figure A5.11b**) and again heterogeneity was low throughout all analyses, with small Tau^2 estimates.

Assessment of linearity using multivariate meta-analysis of restricted cubic splines of BMI was only possible for models excluding toxicity. Linear and spline models with varying knots for ARDI and ACRD are presented in **Figures 5.27** and **5.28** respectively.

AIC and BIC values were smallest for the 3 knots model for ARDI and ACRD, with linear and 4-knots models demonstrating similar values for both. ARDI models suggested a small degree of non-linearity with no association followed by the logHR increasing above an ARDI of approximately 80%. However, confidence intervals consistently crossed zero, implying no convincing evidence of a significant relationship between ARDI and overall, disease-specific, or cancer-specific survival. Linear models similarly did not convincingly demonstrate an association with predicted confidence intervals also covering zero. Conversely, the 3-knot model for ACRD demonstrated minimal non-linearity (some flattening effect above an ACRD of approximately 80%), with strong evidence of a significant relationship between ACRD and overall and cancer-specific survival, including a slightly steeper slope, and borderline significance for DFS. These results suggested that a linear model was a reasonable approximation of the relationship but might slightly underestimate effect estimates with lower ACRD values, particularly for OS.

Figure 5.24 | Path *b* – ACRD effect on overall survival

Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ACRD increments on overall survival

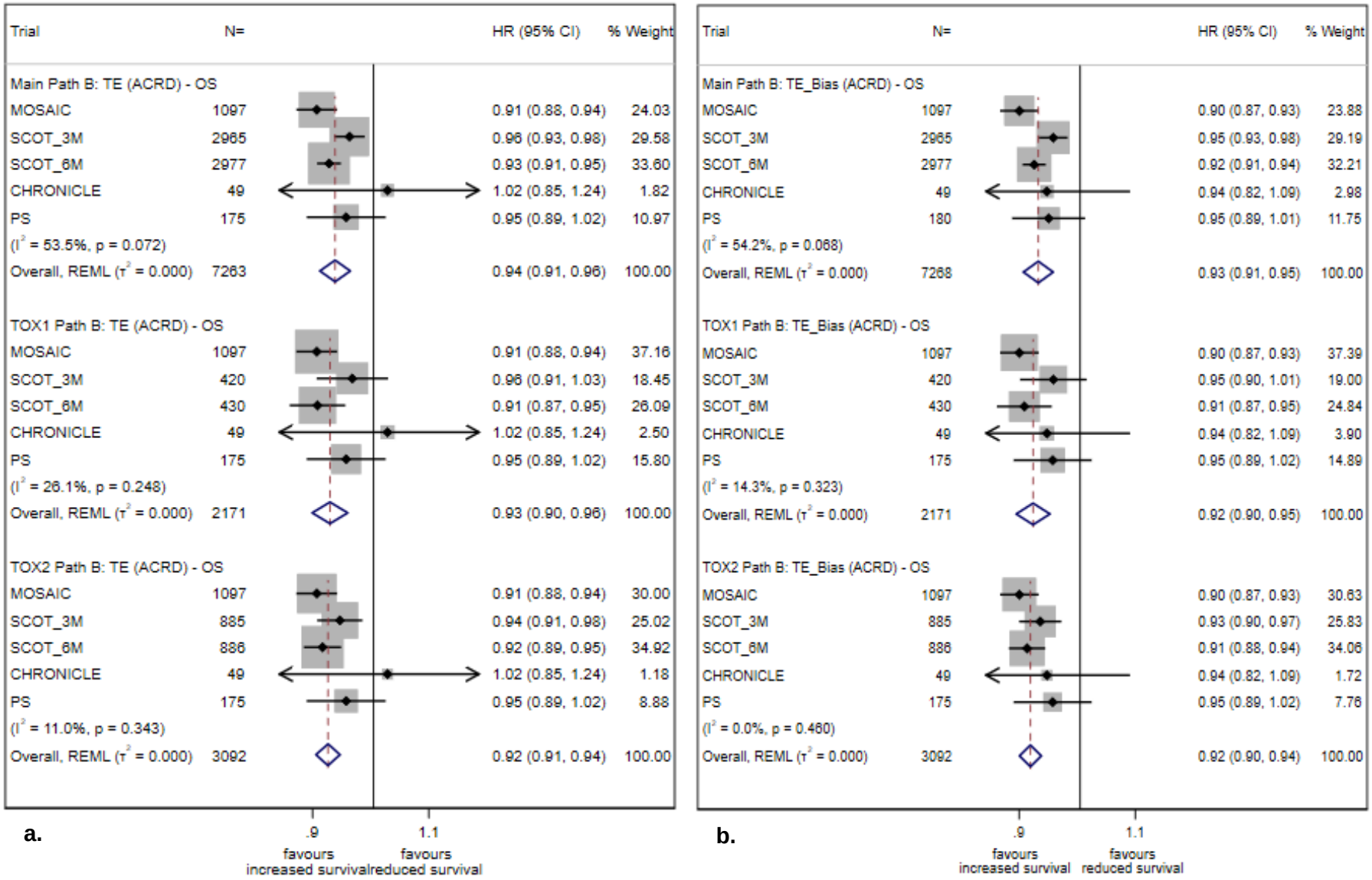


Figure 5.25 | Path *b* – ACRD effect on disease-free survival
Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ACRD increments on disease-free survival

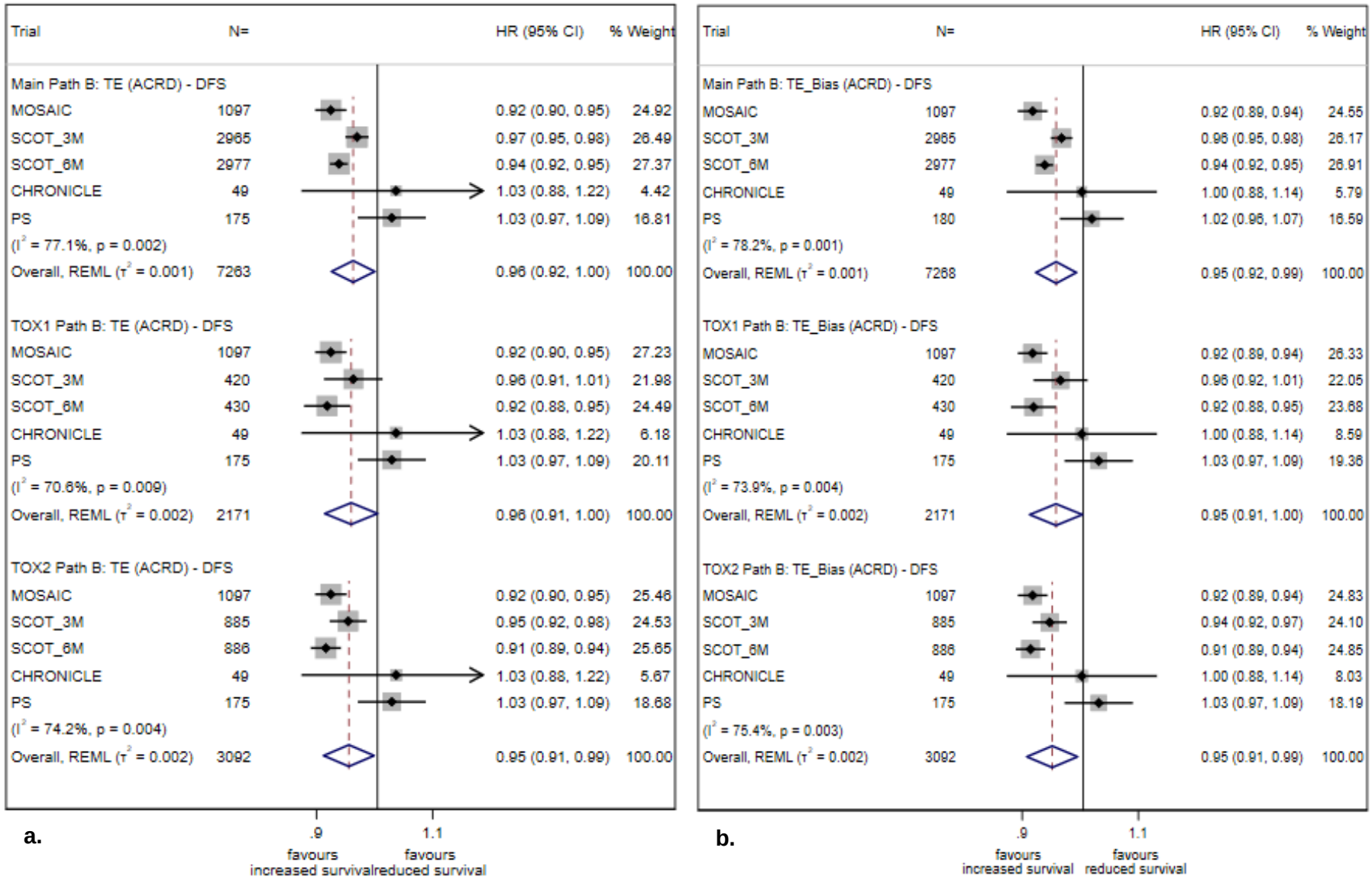


Figure 5.26 | Path *b* – ACRD effect on cancer-specific survival

Forest plots demonstrating **a.** the total effect (TE) and **b**. the biased total effect (not adjusted for toxicity) of 5% ACRD increments on cancer-specific survival.

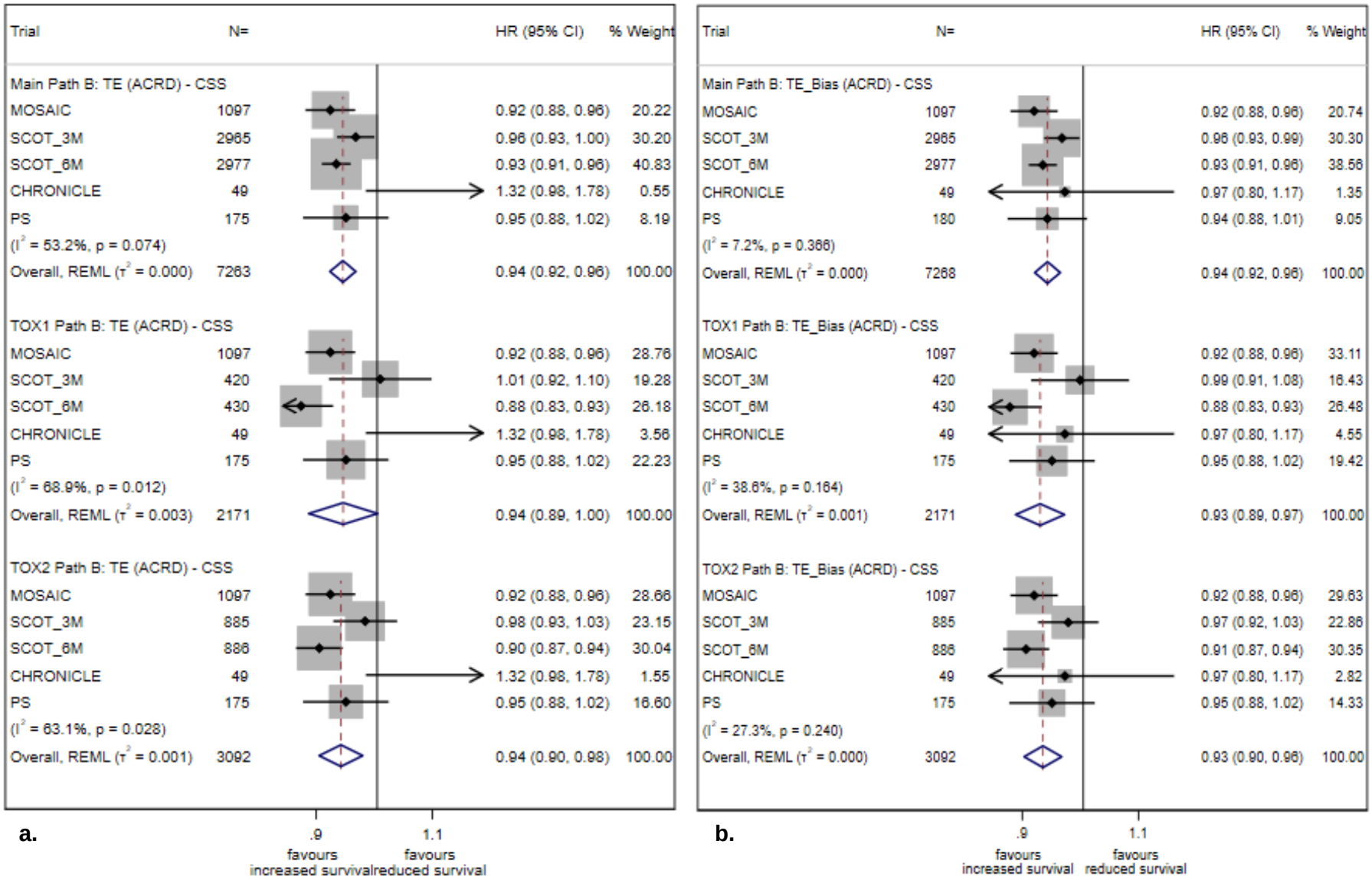


Figure 5.27 | Path *b* – Linearity (ARDI)
Graphs demonstrating the predicted log hazard ratio (logHR, line) and 95% confidence intervals (shaded area) plotted against ARDI from linear and spline (3, 4 or 5 knots) multivariate meta-analysis models for the total effect of path *b*. ARDI is centred at 100% (referent point). Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are presented for the respective models.

AIC and BIC values

			Spline model no. knots		
		Linear	**3**	**4**	**5**
OS	**AIC**	-17.29	**-28.45**	-18.02	2.06
	BIC	-18.07	**-30.41**	-21.54	-2.63
DFS	**AIC**	-14.59	**-27.44**	-19.31	1.16
	BIC	-15.38	**-29.40**	-22.83	-4.30
CSS	**AIC**	-15.83	**-21.70**	-8.48	21.11
	BIC	-16.61	**-23.65**	-11.99	15.64

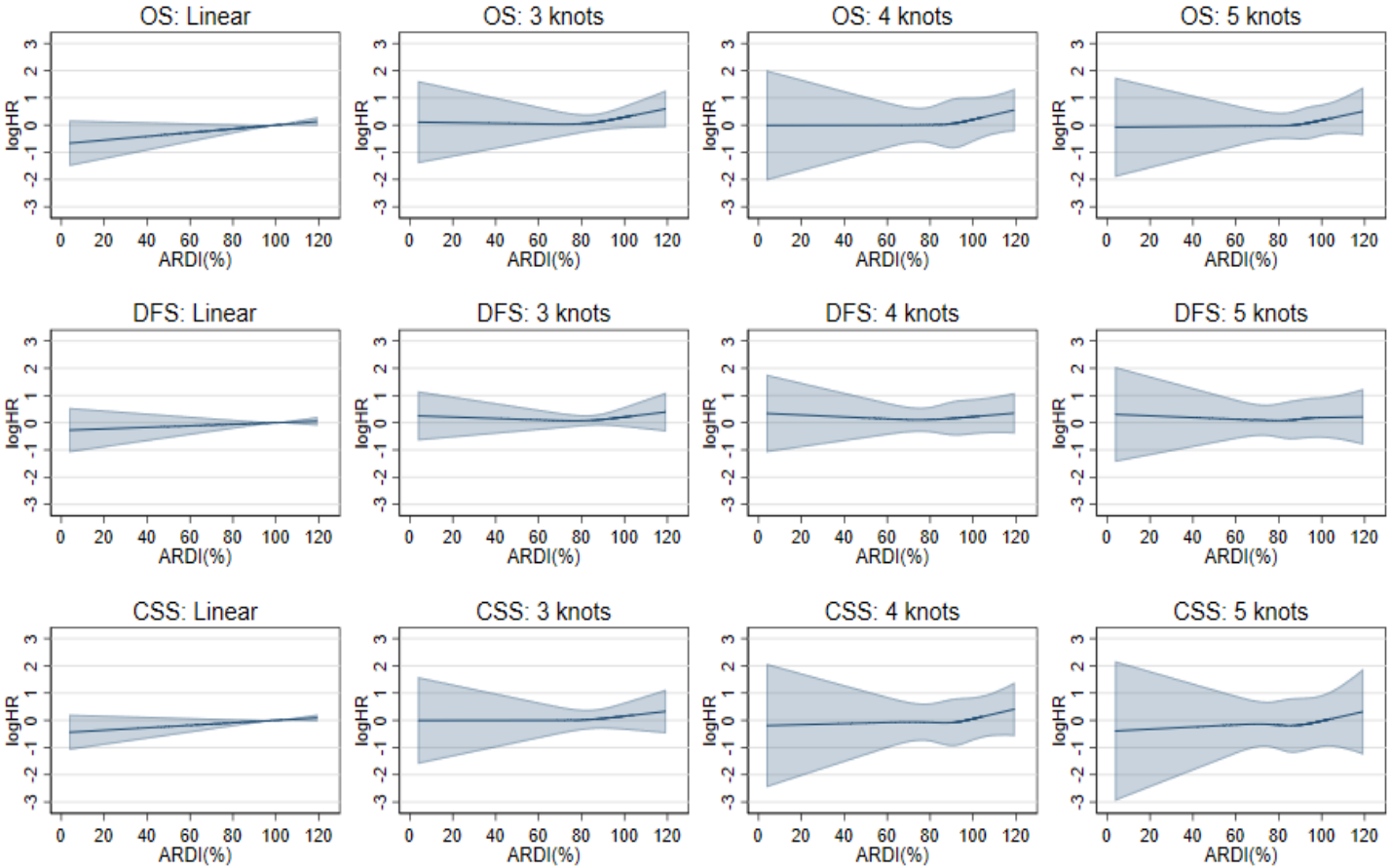
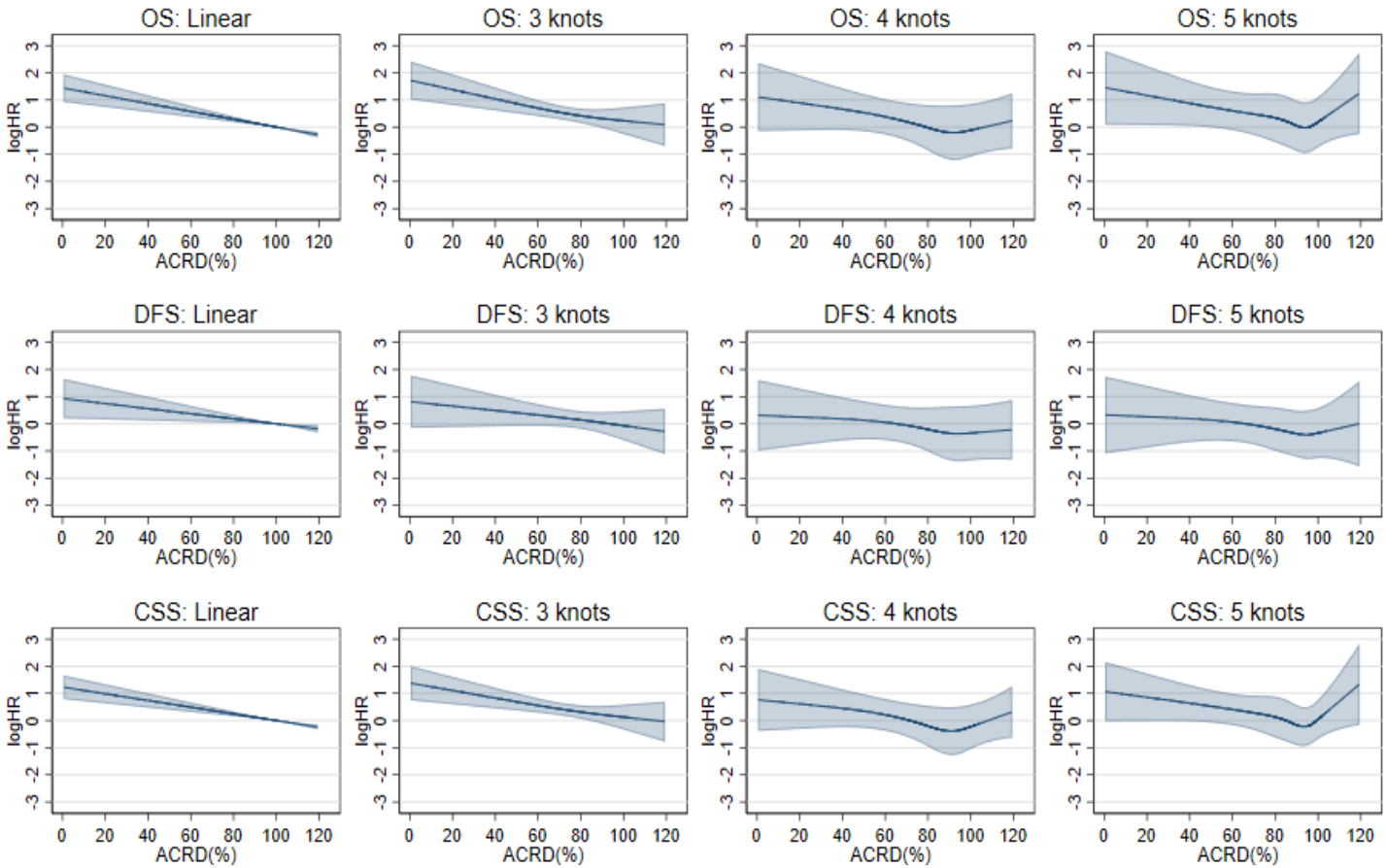


Figure 5.28 | Path *b* – Linearity (ACRD)
Graphs demonstrating the predicted log hazard ratio (logHR, line) and 95% confidence intervals (shaded area) plotted against ACRD from linear and spline (3, 4 or 5 knots) multivariate meta-analysis models for the total effect of path *b*. ACRD is centred at 100% (referent point). Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are presented for the respective models.



AIC and BIC values					
			Spline model no. knots		
		Linear	3	4	5
OS	**AIC**	-23.78	**-41.33**	-22.82	3.25
	BIC	-24.56	**-43.28**	-26.33	-2.22
DFS	**AIC**	-21.02	**-37.82**	-20.38	2.40
	BIC	-21.80	**-39.78**	-23.89	-3.07
CSS	**AIC**	-24.37	**-43.03**	-23.93	1.60
	BIC	-25.15	**-44.99**	-27.45	-3.86

Effect modification by sex and stage was examined for total effects. Addition of a BMI-sex interaction term did not result in any substantial changes to the effect estimates for the relationship between both ARDI and ACRD and all three survival outcomes (**Table A5.1**). Furthermore, there was no significant interaction demonstrated**.** Similarly, there was minimal change to effect estimates after BMI-stage interaction terms were added for both ARDI and ACRD and all three survival outcomes (**Table A5.2**), with no convincing evidence of a significant within-trial interaction. Heterogeneity was generally low across all analyses with low Tau^2 values.

Summary effect estimates of sensitivity analyses are presented in the appendix (**Figures A5.12 to A5.17**). None of the sensitivity analyses resulted in a substantial change to the effect estimates, with ARDI- or ACRD- survival relationships remaining similar. For ARDI, there was a general tendency for already borderline relationships to become less significant (**Figures A5.12 to A5.14**). However, for ACRD (**Figures A5.15 to A5.17**), exclusion of the SCOT_3M arm and of the capecitabine-containing regimen slightly strengthened OS and CSS effect estimates (by approximately 2-3%). Importantly, exclusion of early deaths resulted in only a slight reduction in the strength of OS, DFS and CSS effect estimates (by approximately 1-2%), suggesting minimal reverse causality (i.e., early deaths during chemotherapy resulting in reduced adherence did not substantially bias effect estimates [**Figures A5.12 to A5.17**]). Confidence intervals were generally wider for TOX1 and TOX2 populations as would be expected from smaller patient numbers. Overall, there remained substantial and convincing evidence of a relationship between increasing ACRD with improved survival, with a less convincing relationship for ARDI.

5.3.5 PATH *E*

The relationship between grade 3+ toxicity and ACT adherence is depicted as path *e* in the DAGs from **Figure 5.4a** and **5.4b**. IPD meta-analysis of path *e* was undertaken for both adherence measures to explore the effect of toxicity on adherence.

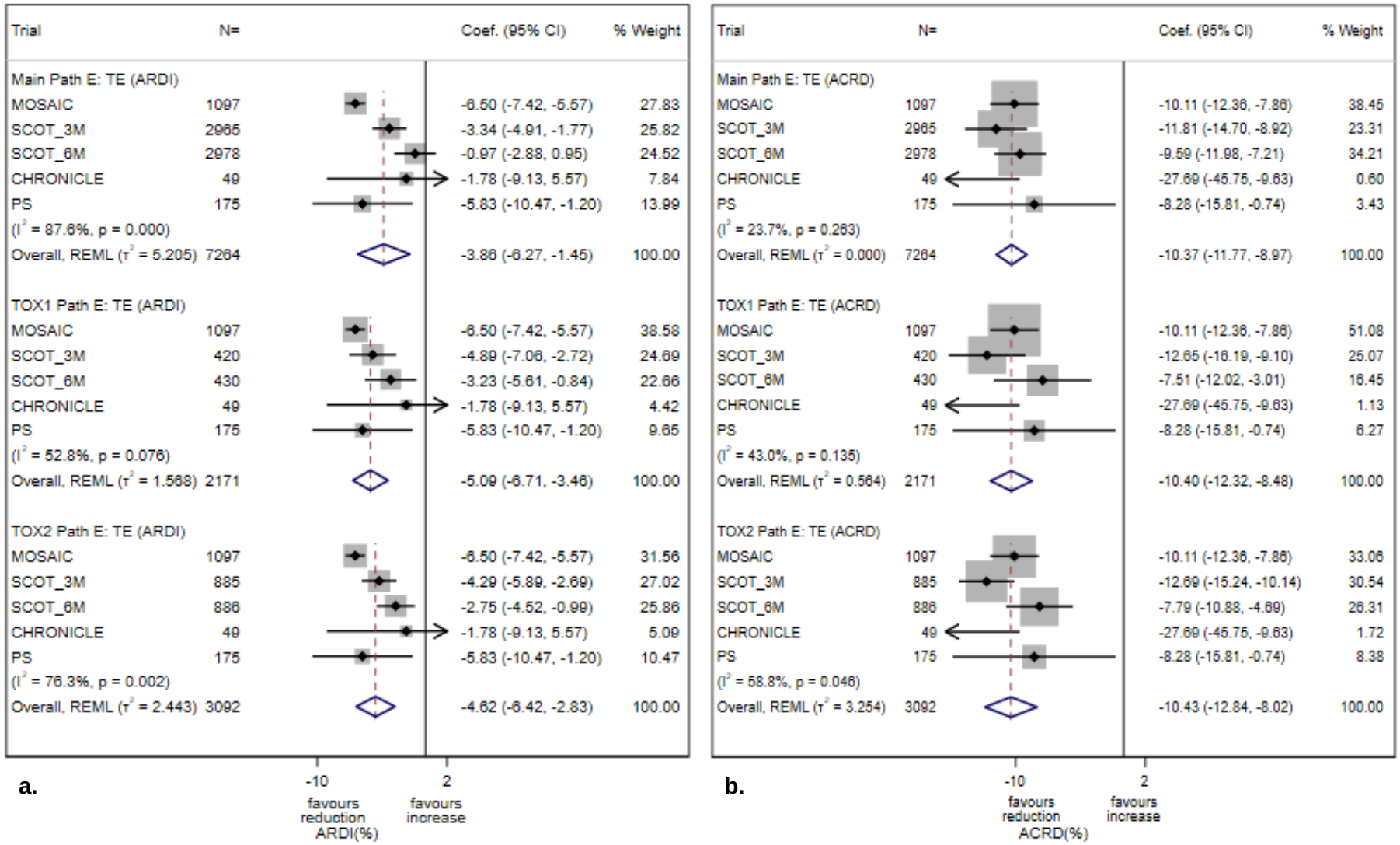
Grade 3+ toxicity was associated with a significant reduction of both ARDI (-3.86%; 95%CI -6.27, -1.45; **Figure 5.29a**) and ACRD (-10.37%; 95%CI -11.77, -8.97; **Figure 5.29b**), with substantial and low heterogeneity respectively (ARDI Tau^2 = 5.205 and ACRD Tau^2 = 0.000). Results were consistent across the toxicity populations, though a slightly larger effect estimate was demonstrated in the TOX1 and TOX2 populations for ARDI.

Effect modification by sex and stage was examined for path *e*. Addition of a toxicity-sex interaction term did not substantially alter effect estimates for ARDI or ACRD (**Table A5.1**) compared with the non-interaction model, and there was no significant within-trial interaction demonstrated for female vs. male for any population. Similarly, inclusion of toxicity-stage interactions within regression models did not substantially alter effect estimates for ARDI or ACRD (**Table A5.2**) compared with the non-interaction model, and there was no significant within-trial interaction demonstrated for stage II-HR or stage III-HR vs. stage III-LR.

Summary estimates of sensitivity analyses for path *e* are presented in **Figure A5.18**, within the appendix. There was a small increase in the strength of the effect estimate for ARDI (Coef. -5.35; 95%CI-7.26, -3.43) on exclusion of patients receiving capecitabine. Conversely, exclusion of patients receiving capecitabine resulted in a small reduction in the strength of the effect estimate (Coef. -8.12; 95%CI -10.84, -6.0) for ACRD, with wider confidence intervals. However, both toxicity-ARDI and toxicity-ACRD relationships remained consistent across sensitivity analyses and populations, with strong evidence for a reduction in both ARDI and ACRD due to grade 3+ toxicity, and a substantially larger effect for ACRD compared with ARDI.

Figure 5.29 | Path *e* – Toxicity effect on ARDI and ACRD

Forest plot demonstrating the relationship between grade 3+ toxicity and the **a.** average relative dose intensity (ARDI) and **b.** average cumulative relative dose (ACRD) for the three populations.



5.3.6 PATH *F*

The relationship between grade 3+ toxicity and survival represented as path *f* in the DAG from **Figure 5.4b**. Models were meta-analysed with and without the addition of both ARDI and ACRD, to obtain direct effect estimates and explore the potential mediating effects of ARDI and ACRD, in addition to modelling both Weibull and Cox survival models, as described above.

Kaplan Meier curves and risk tables are presented in the appendix (**Figures A5.19a** to **A5.19c**) for toxicity at the trial level for, TOX1 and TOX2 populations. The SCOT_3M TOX2 and CHRONICLE trials displayed some evidence of non-proportional hazards for (**Figures A5.20a** and **A5.20b**), however, only for some survival outcomes and deviations generally appeared to be small. The addition of exposure*time interactions into the models were explored, and resulted in a strengthening of path *f* relationships, with smaller effect estimates for the time varying effects, in the opposing direction. Again, the obtained hazard ratios should be considered as an average hazard ratio across a median follow-up of 3 years. Furthermore, it was assumed that the independent censoring assumption was held (see **Section 5.3.4** for more detail).

The total effect of grade 3+ toxicity was a significant reduction in overall survival (**Figure 5.30a**; HR 1.37, 95%CI 1.17, 1.61), a borderline non-significant reduction in disease-free (**Figure 5.31a**; DFS HR 1.19, 95%CI 1.00, 1.43) and non-significant tendency to reduced cancer-specific survival (**Figure 5.32a**, CSS HR 1.15, 95%CI 0.96, 1.38). The direct effect when adjusting for ARDI, demonstrated minimal change to the effect estimates, albeit with a tendency to slightly increase effect estimates. However, the direct effect (**Figures 5.30b, 5.31b** and **5.32b**) when adjusting for ACRD resulted in an approximate halving of effect estimates for OS and DFS, suggesting that the effect of toxicity was partially mediated via a reduction in ACRD (OS HR 1.20, 95%CI 1.02, 1.41; DFS HR 1.08, 95%CI 0.94, 1.22). Effect estimates for CSS were completely attenuated (HR 1.02, 95%CI 0.85, 1.24), suggesting no direct effect of toxicity on CSS. Effects were consistent across toxicity populations and for Cox models (**Figures A5.21a** and **A5.21b**).

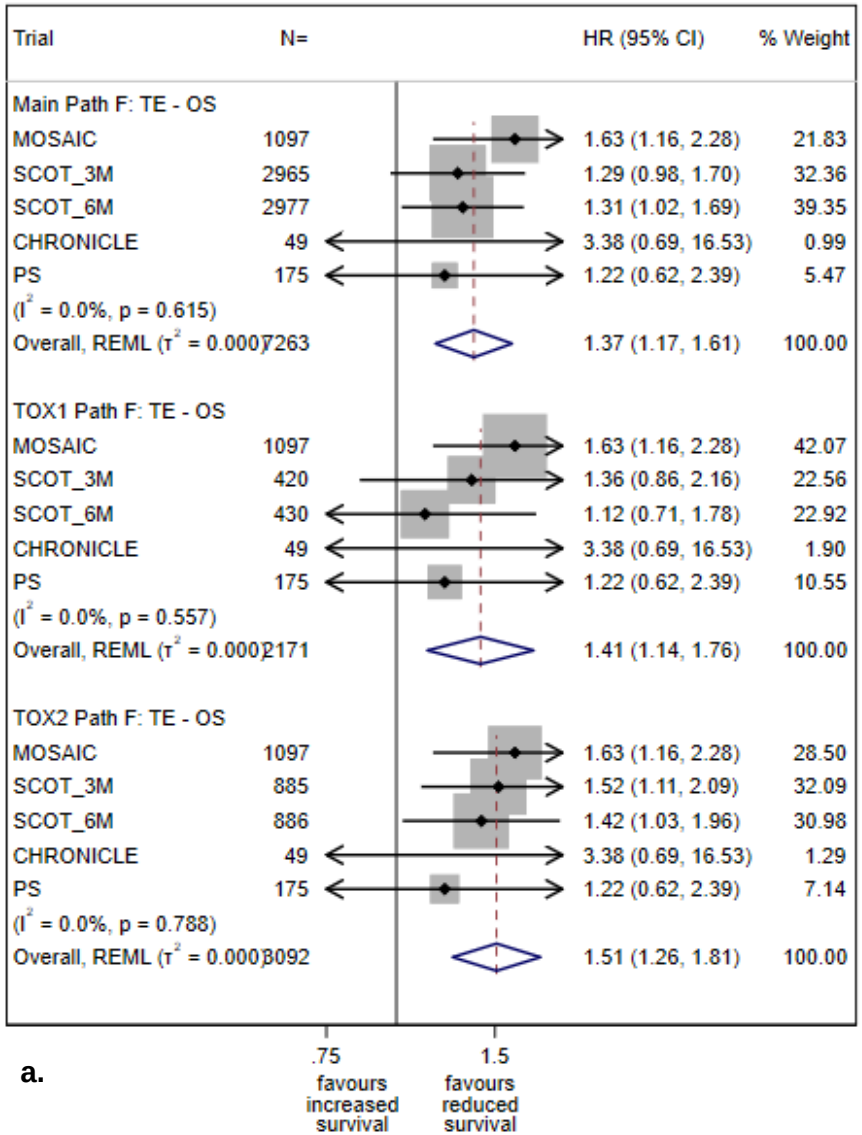
Effect modification by sex and stage was examined for total effects. Addition of a toxicity-sex interaction term did not result in any substantial changes to the effect estimates of path *f* total effects for all three survival outcomes (**Table A5.1**), with no significant interaction demonstrated**.** Similarly, there were small but inconsistent changes to effect estimates after a toxicity-stage interaction term was added (**Table A5.2**), with no convincing evidence of a significant within-trial interaction. Heterogeneity was generally low across all analyses with low Tau^2 values.

Summary effect estimates of sensitivity analyses are presented in the appendix (**Figures A5.22 to A5.24**). Only exclusion of deaths within the first 6 months substantially altered summary

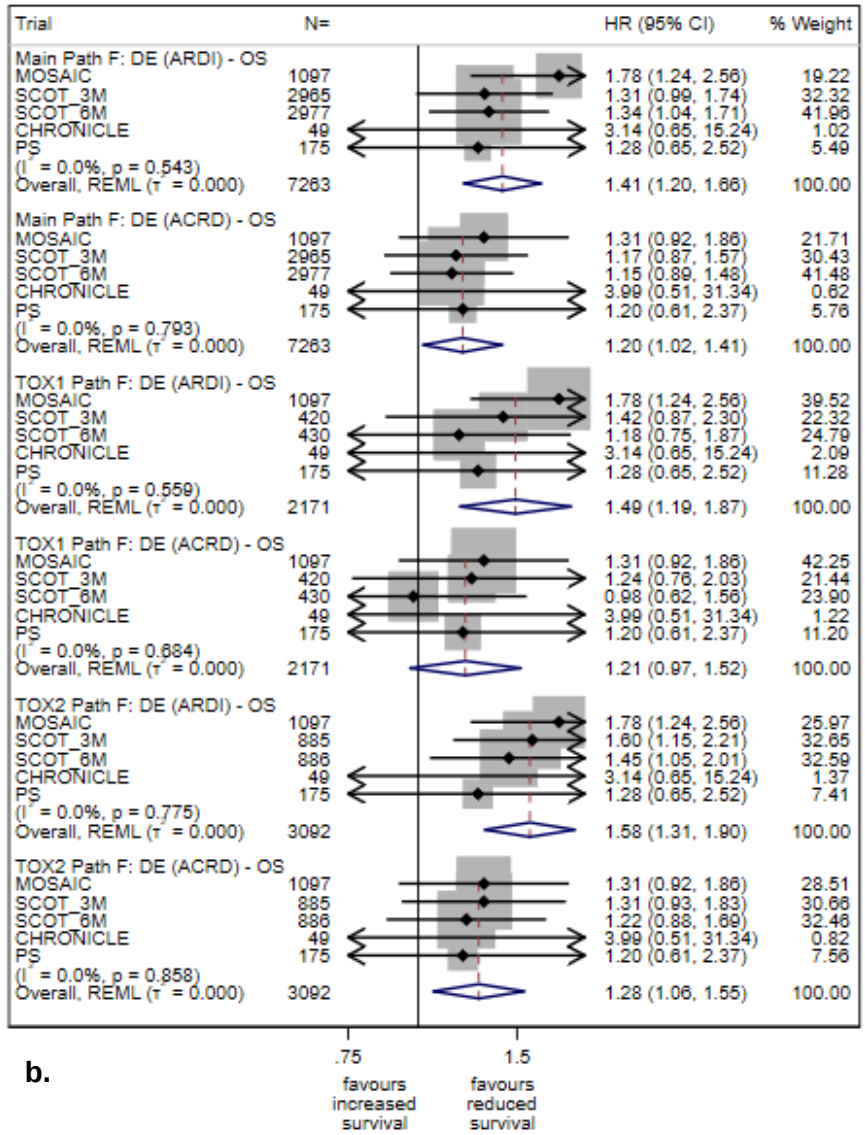
effect estimates for overall and disease-free (estimates approximately halved), but not cancer-specific survival, as would be expected given that a small proportion of deaths occurring during ACT regimens were directly attributable to chemotherapy-related toxicity. For overall survival, the total effect of toxicity remained significant (HR 1.19, 95%CI1.01, 1.40), and the direct effect lost significance, but still displayed a tendency towards worse survival (HR 1.09, 95%CI 0.96, 1.30). Results for other sensitivity analyses remained mostly consistent, with some widening of confidence intervals with patient exclusions. Furthermore, the more conservative confidence intervals from the HKSJ approach resulted in DFS and CSS confidence intervals crossing the null effect line. Overall, there was convincing evidence for a total and direct effect relationship for toxicity and overall survival, with a potentially mediated pathway via a reduction in ACRD.

Figure 5.30 | Path *f* – Toxicity effect on overall survival

Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of grade 3+ toxicity on overall survival, for the three populations



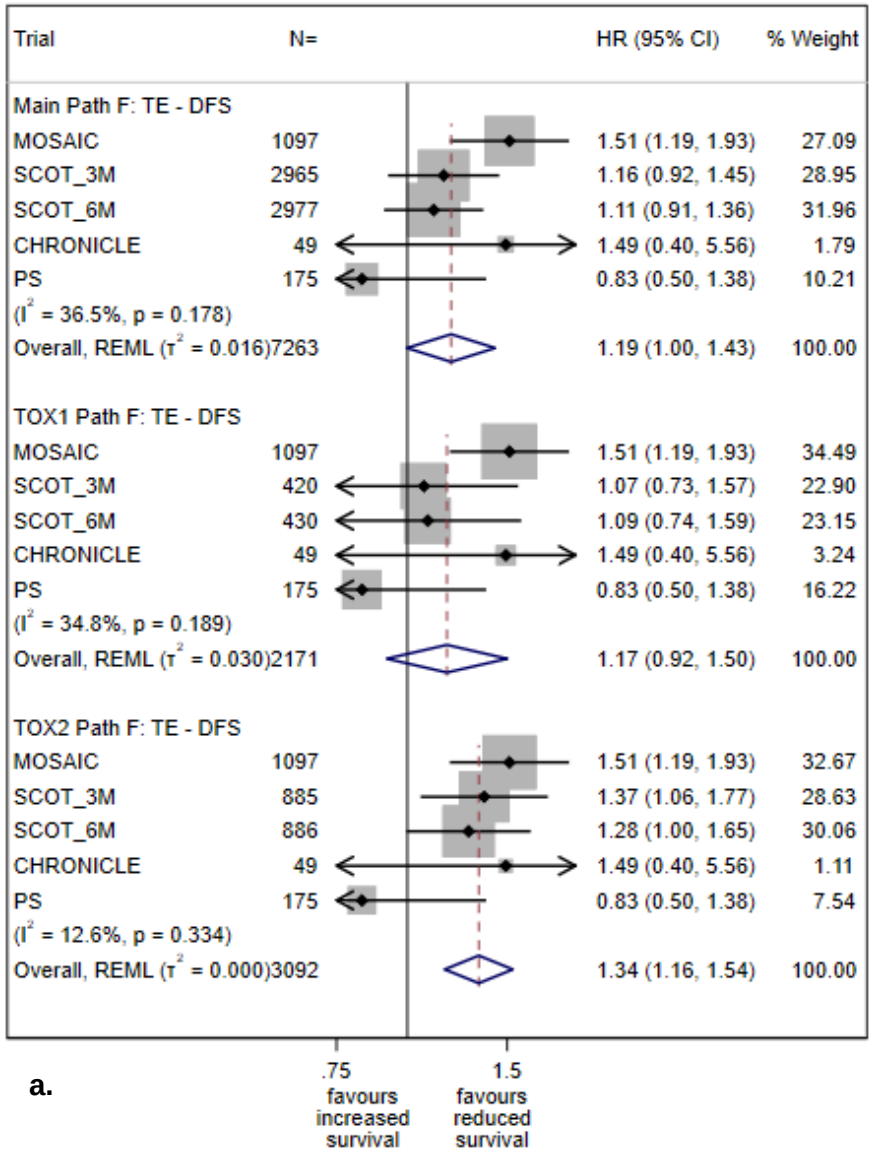
a.



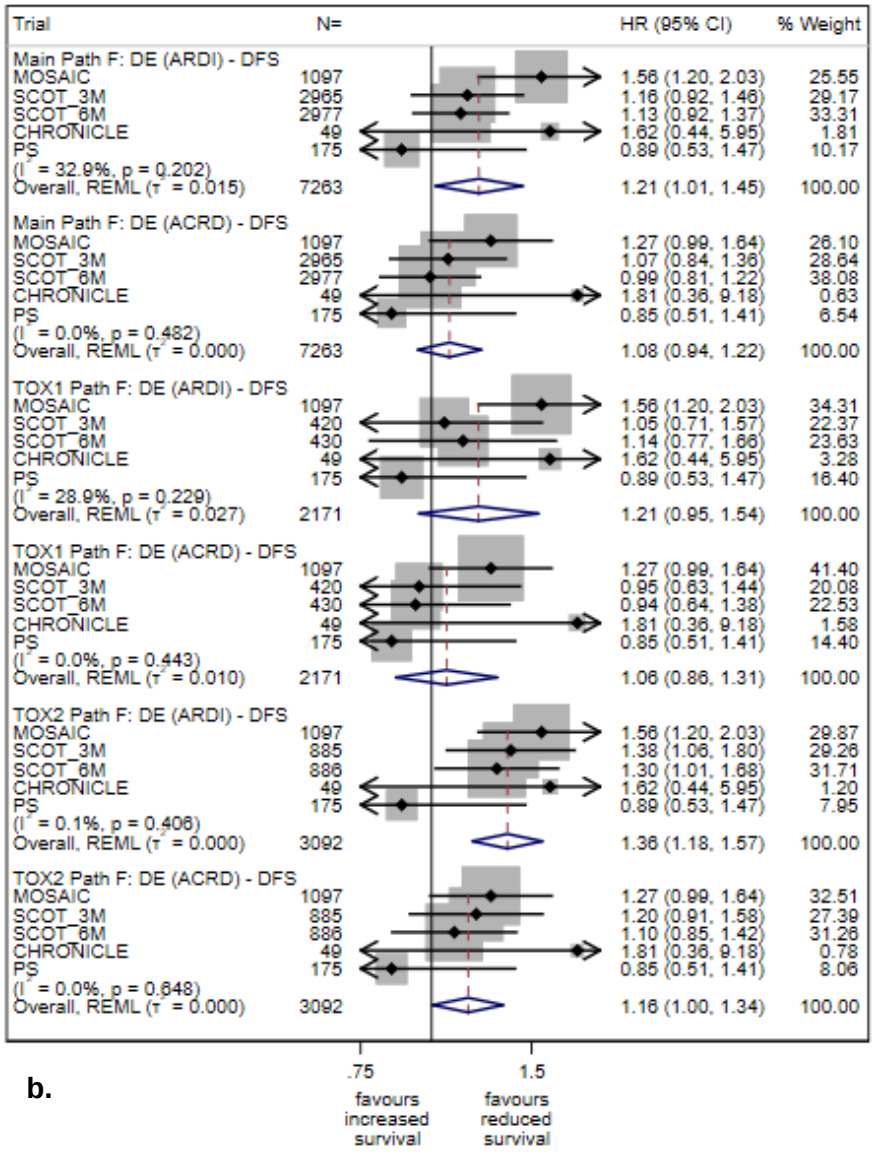
b.

Figure 5.31 | Path *f* – Toxicity effect on disease-free survival

Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of grade 3+ toxicity on disease-free survival, for the three populations.



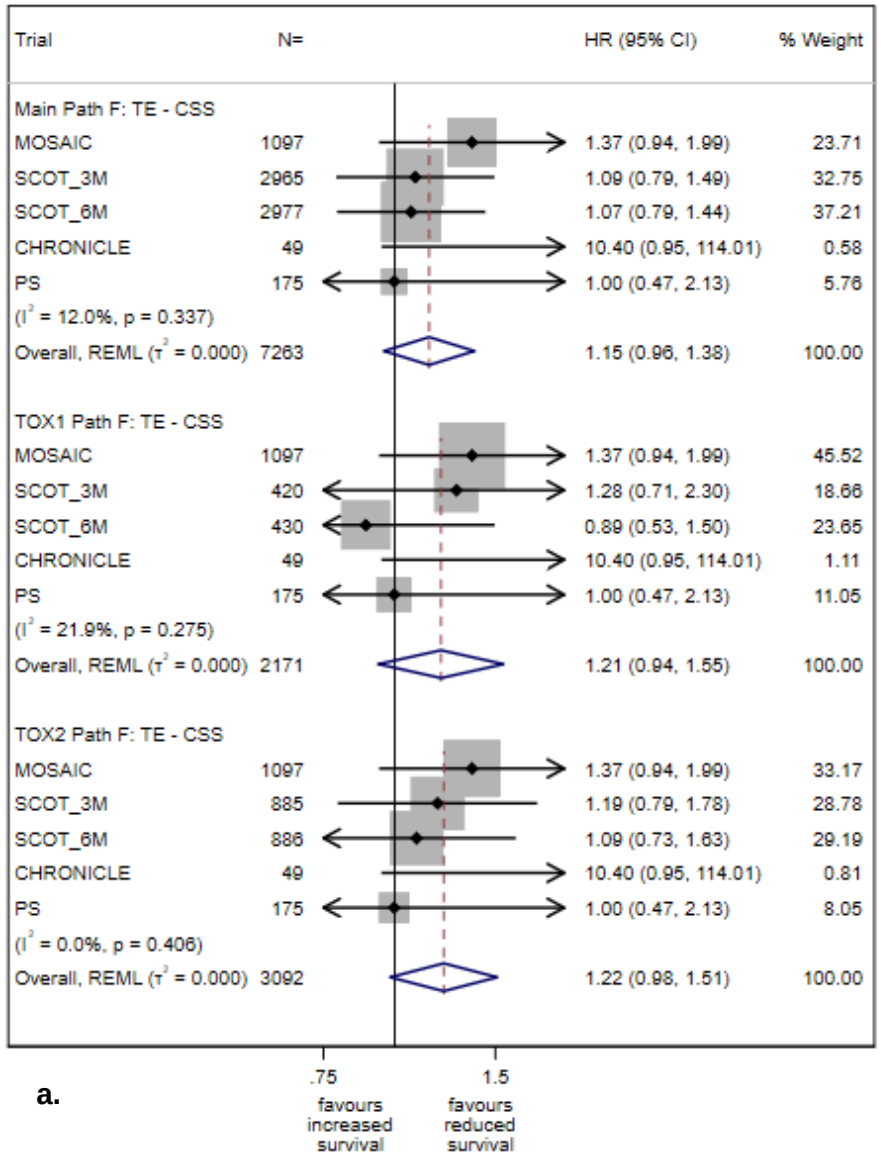
a.

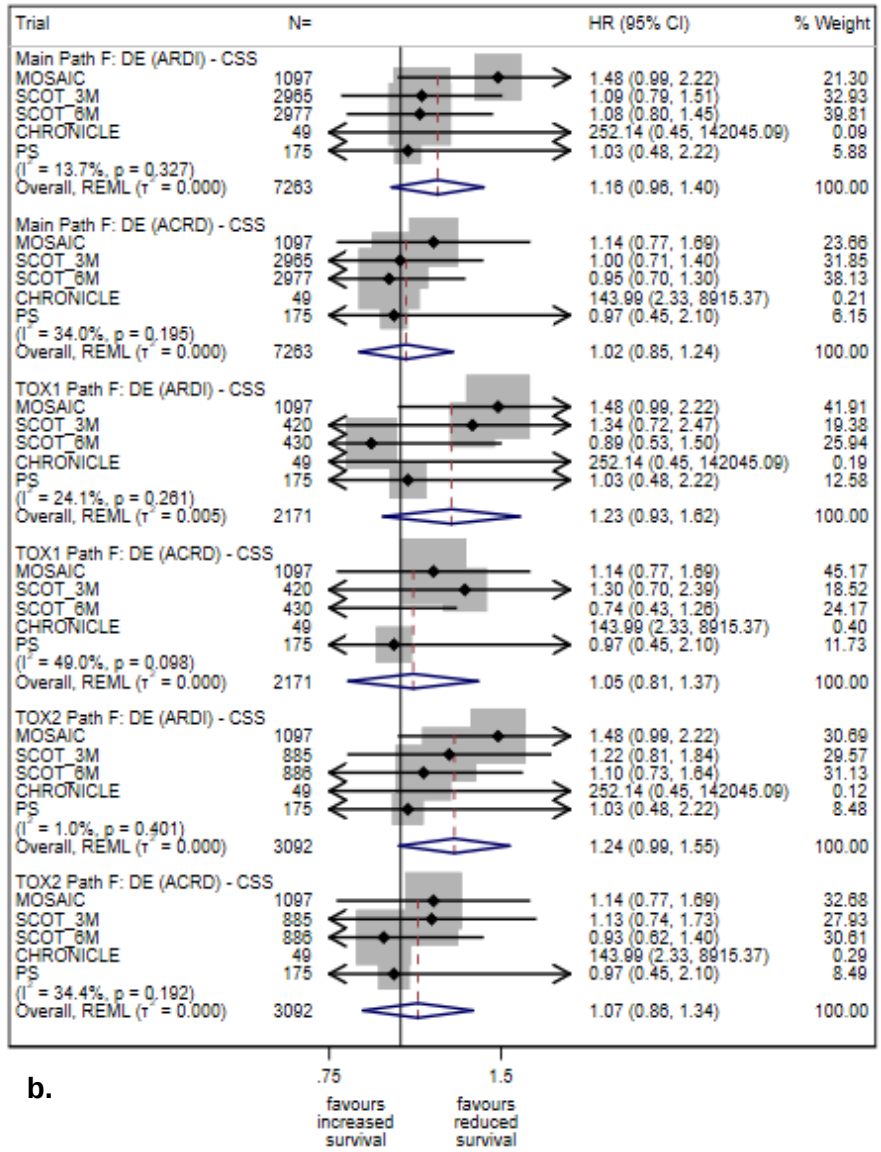


b.

Figure 5.32 | Path *f* – Toxicity effect on cancer-specific survival

Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of grade 3+ toxicity on cancer-specific survival, for the three populations.





5.3.7 PATH *C*

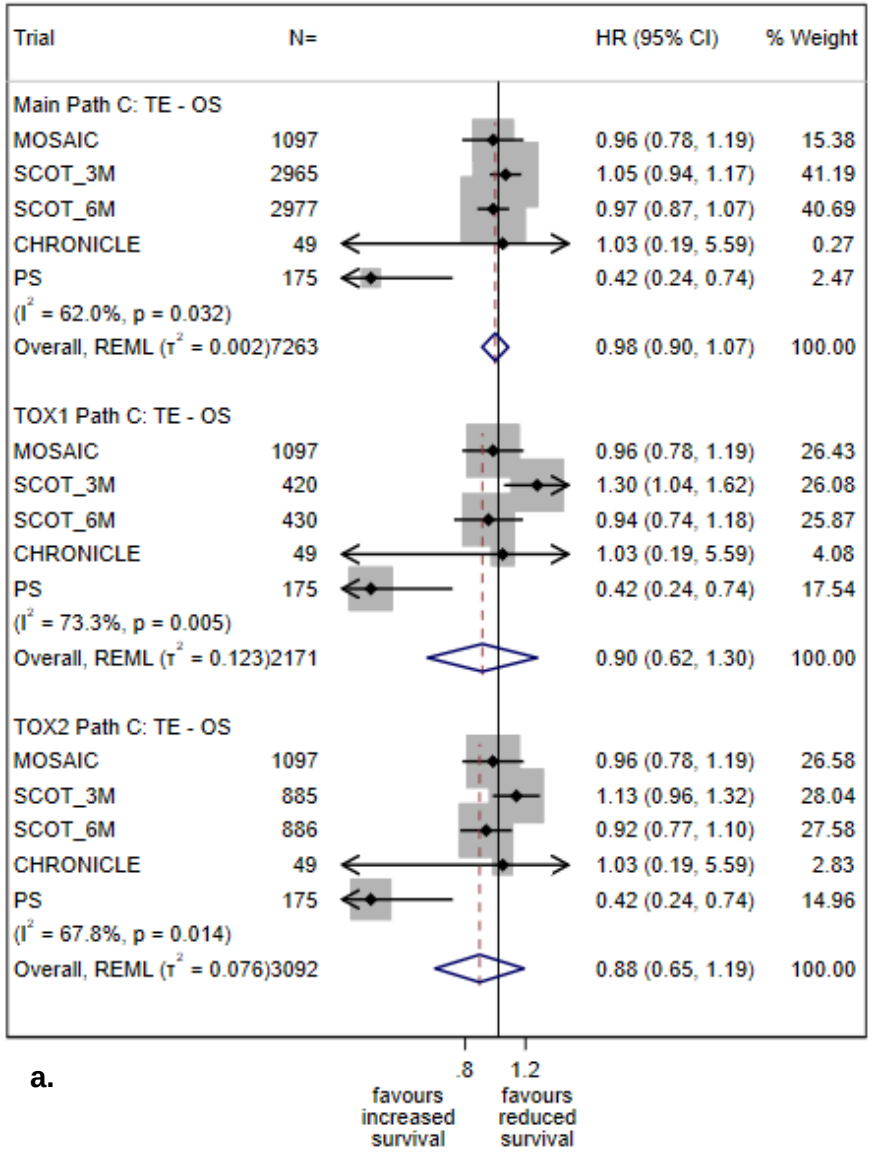
The relationship between BMI and survival is depicted as path *c* in the DAG from **Figure 5.4a**. IPD meta-analysis of path *c* was undertaken for both the total and direct effects (with and without both ARDI and ACRD), to explore both the effect of BMI and the potential for mediation via adherence. Furthermore, risk of residual confounding bias was assessed for both total and direct effects by excluding toxicity as a covariate from analyses.

Kaplan Meier curves and risk tables are presented in the appendix (**Figures A5.25a** and **A5.25b**) for toxicity at the trial level. Only the CHRONICLE trial displayed evidence of non-proportional hazards for (**Figure A5.26**), and only for some survival outcomes, with deviations generally appearing to be small, likely due to the small trial numbers and events. Hence models were generally felt to be valid. Again, it was assumed that the independent censoring assumption held (see **Section 5.3.4** for more detail).

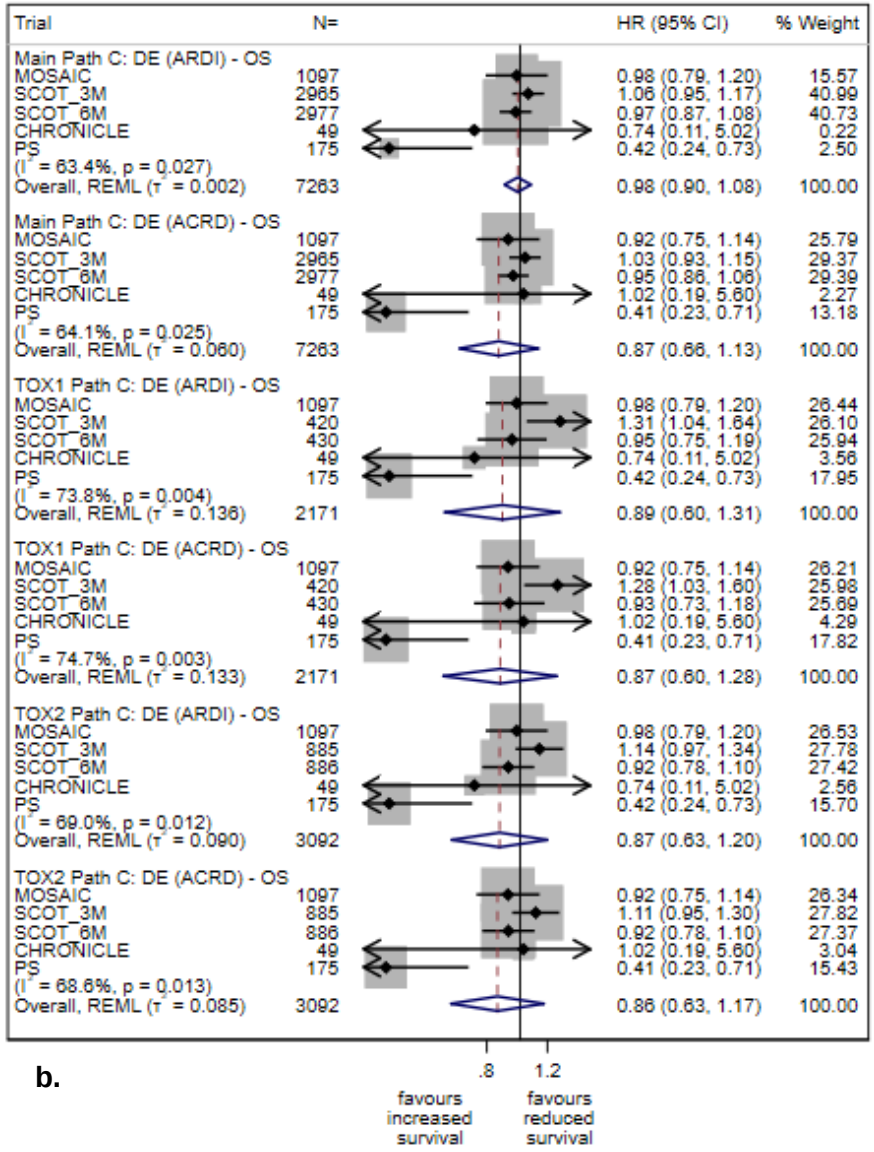
There was no significant total effect demonstrated for overall (**Figure 5.33a,** HR 0.98, 95%CI 0.90, 1.07), disease-free overall (**Figure 5.35a,** HR 0.98, 95%CI 0.90, 1.07) or cancer specific survival overall (**Figure 5.37a,** HR 0.98, 95%CI 0.90, 1.07), nor was there a significant direct effect after adjusting for ARDI (**Figures 5.33b, 5.35b** and **5.37b**). Adjusting for ACRD however appeared to result in an approximately 10% reduction in the risk of death for overall survival (HR 0.87, 95%CI 0.66, 1.13), though still not statistically significant (**Figure 5.33b)**. When examining individual trial effect estimates, it was evident that these each reduced by approximately 1-4%, which would not account for such a large improvement in the HR. However, the study weights differed substantially between the total effect and ACRD-adjusted direct effect models. Thus, such a substantial reduction in the effect estimate was more likely attributed to increased weighting of both MOSAIC and PS studies, resulting in a larger than expected reduction in the effect estimate. In comparison, the biased model, which demonstrated a more likely 3% change in the HR, was more consistent with path *a* and path *b* results, with study-weighting that did not substantially vary across total and direct effects. There was some variability across the toxicity populations for both total and biased effects on overall survival outcomes, with the TOX1 and TOX2 populations demonstrating larger effect estimates (**Figures 5.33a** and **5.34a**), though not significant. However, individual trial estimates were virtually identical to the Main population, with weighted proportions again differing and likely resulting in the observed differences.

The partially adjusted ("biased") models (**Figures 5.34, 5.36** and **5.38**) demonstrated almost identical results to the fully adjusted models, suggesting exclusion of toxicity as a covariate from the overall models resulted in minimal bias, with the advantage of not requiring multiple imputation. Furthermore, the Cox models also demonstrated virtually identical results to the Weibull models (**Figure A5.27a** and **A5.27b**).

Figure 5.33 | Path *c* – BMI effect on overall survival
Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of 5kg/m^2 increments of BMI on overall survival, for the three populations.

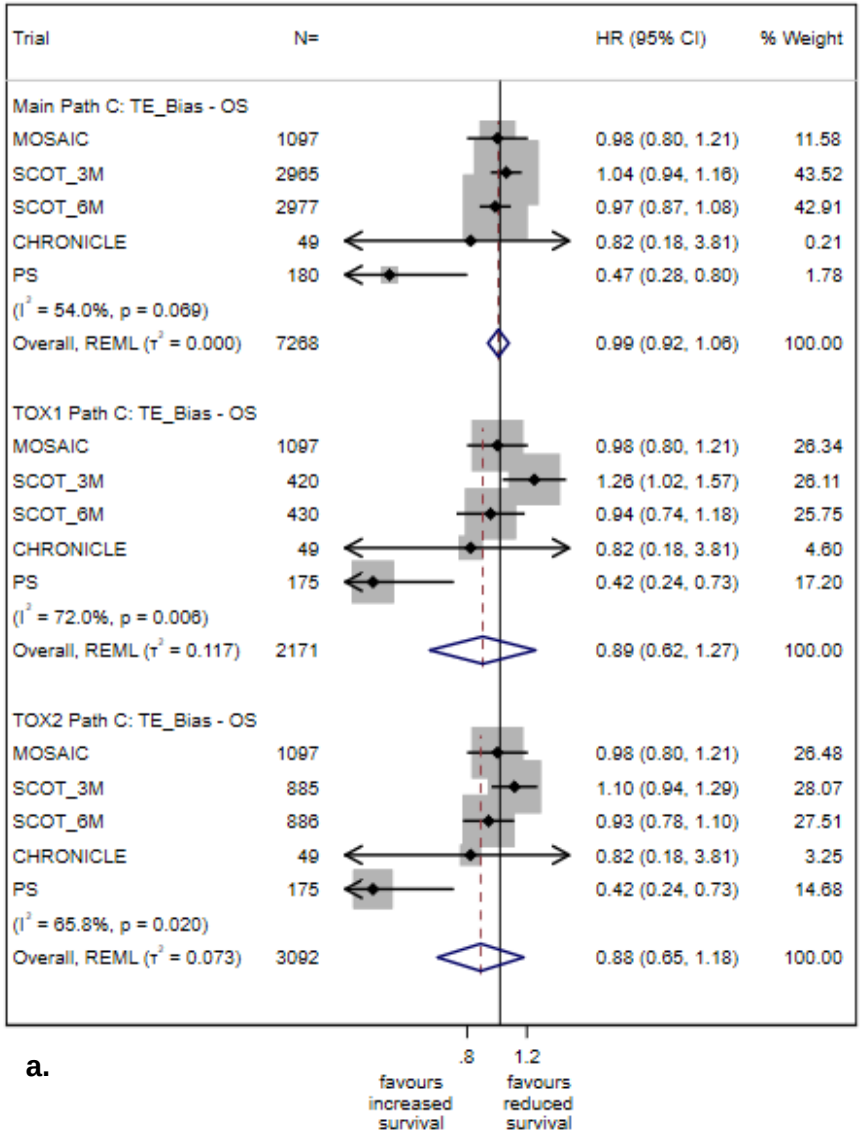


a.

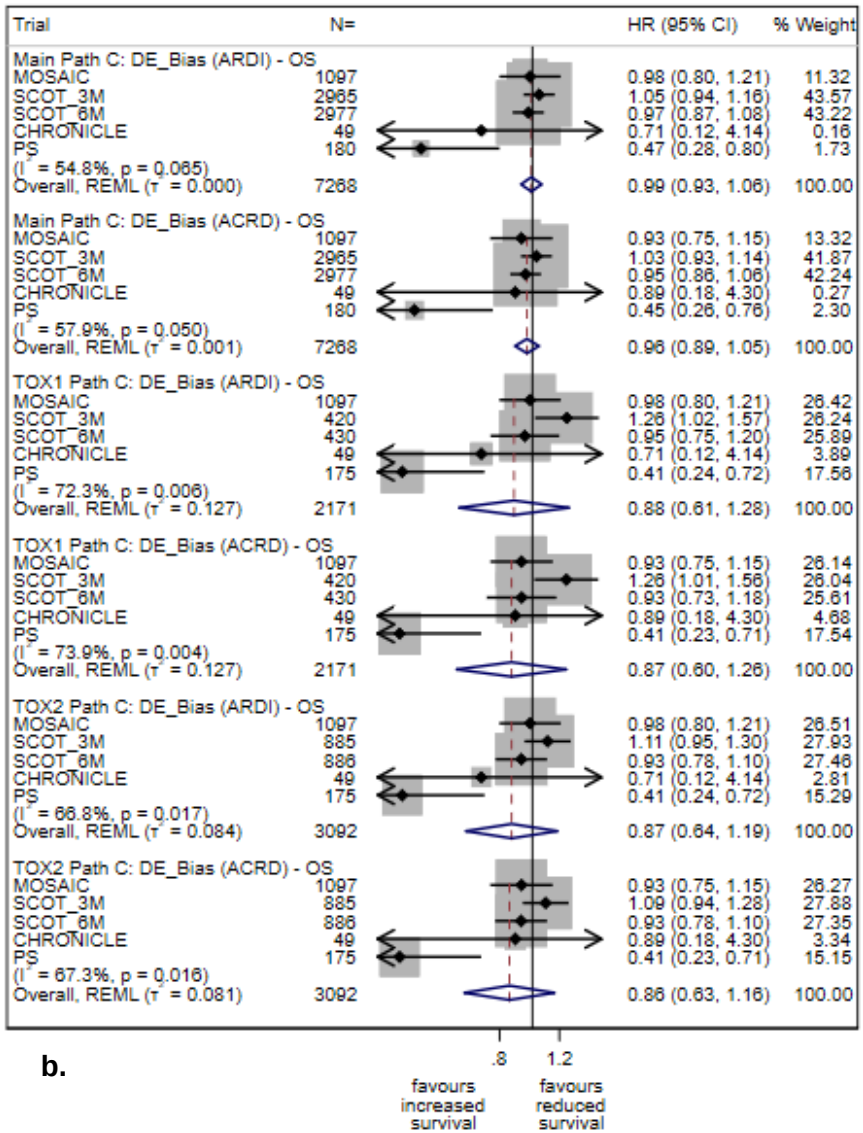


b.

Figure 5.34 | Path *c* – BMI effect on overall survival *(biased)* Forest plot demonstrating biased **a.** total effect and **b.** direct effects (adjusted for ARDI or ACRD) of 5kg/m^{2}increments of BMI on overall survival, for the three populations



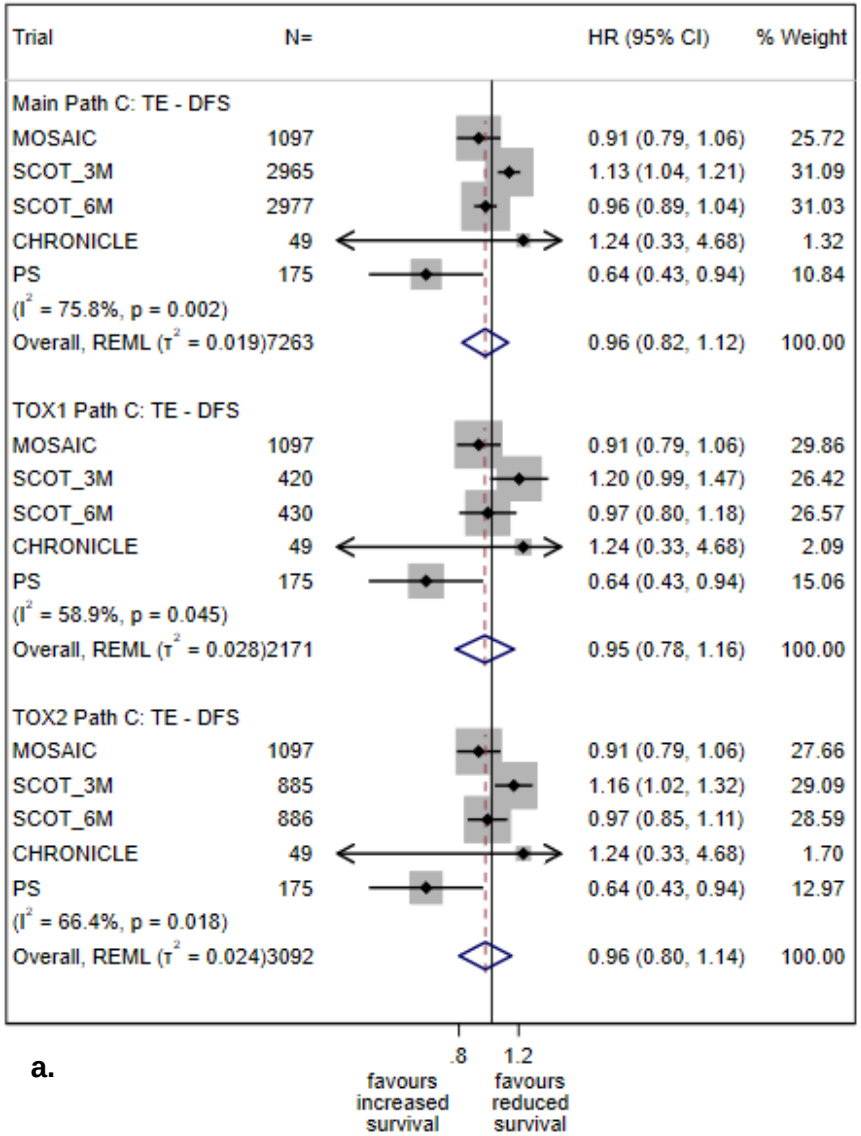
a.



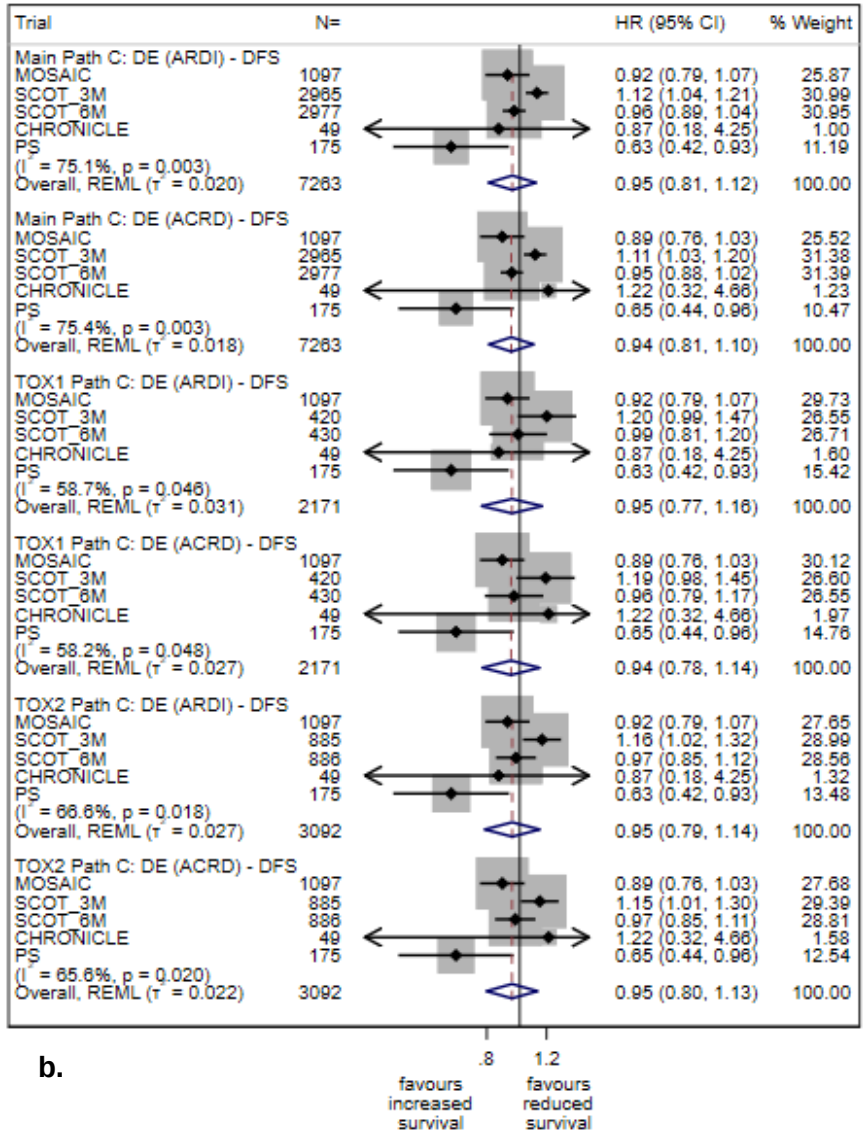
b.

Figure 5.35 | Path *c* – BMI effect on disease-free survival

Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of 5kg/m^{2}increments of BMI on disease-free survival, for the three populations.

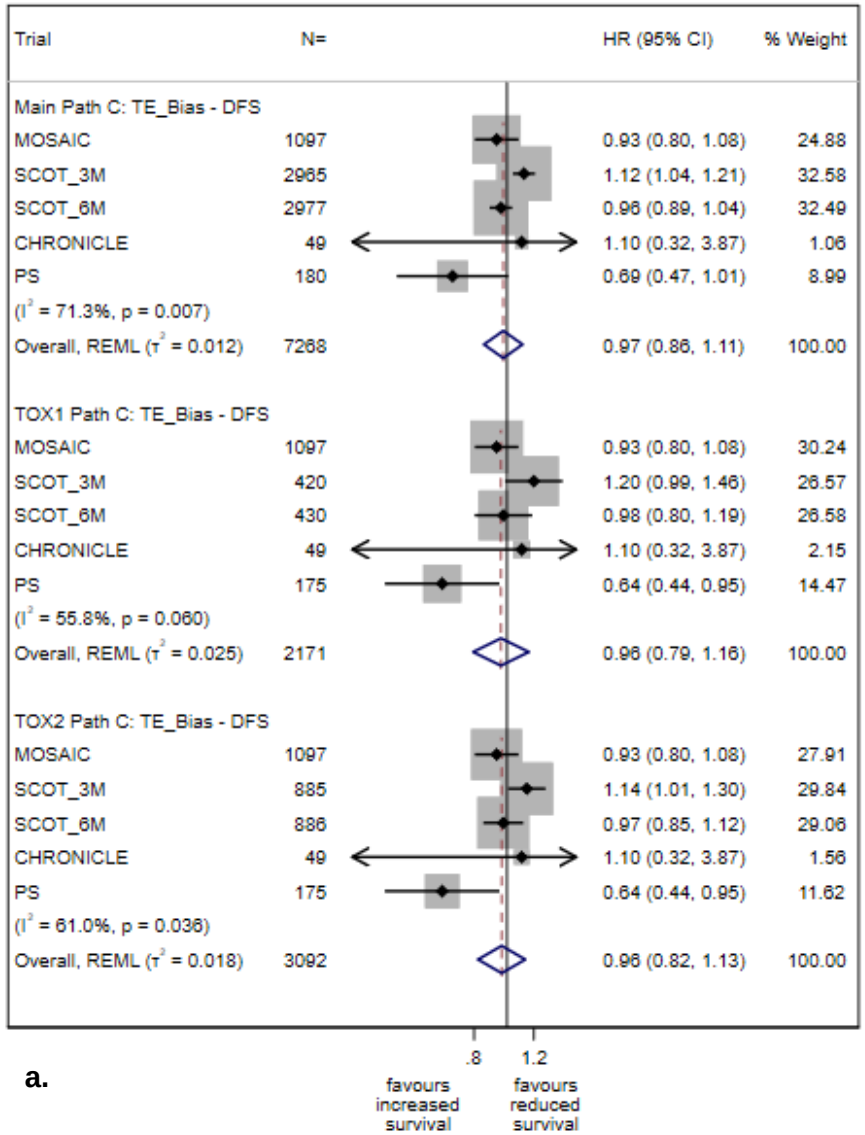


a.

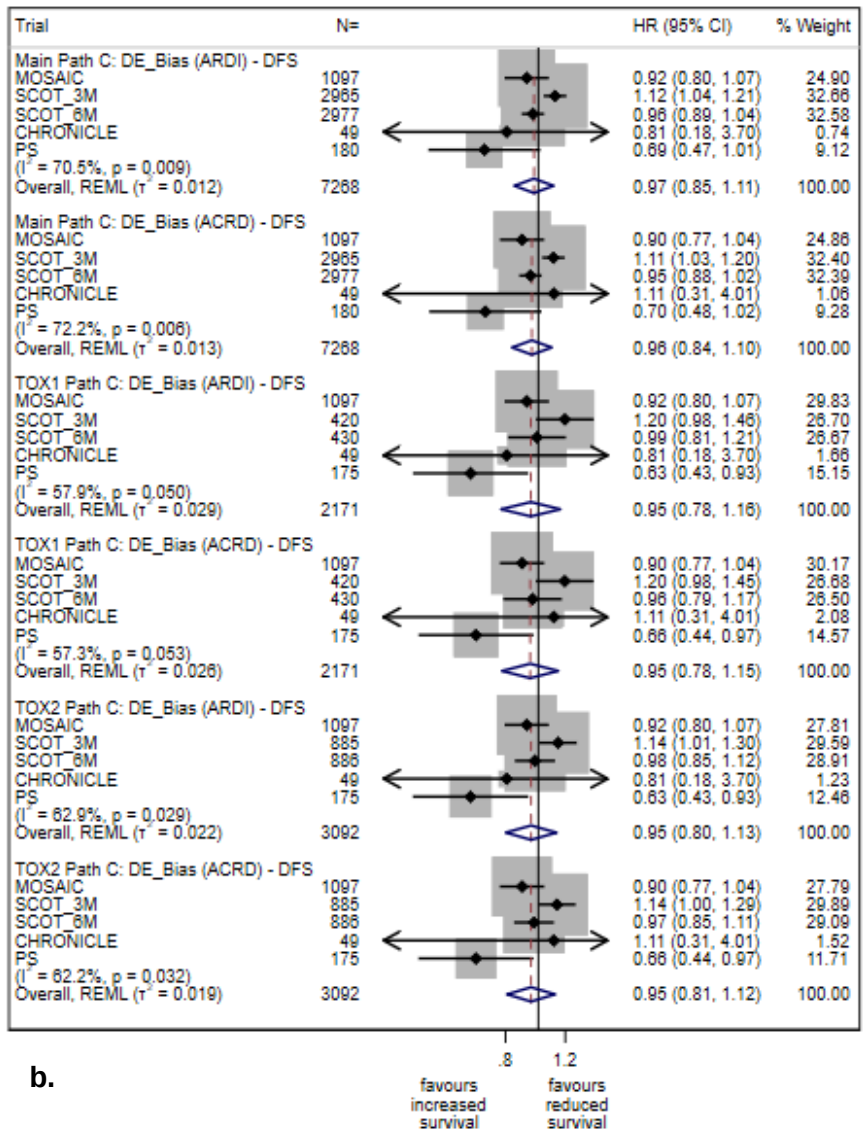


b.

Figure 5.36 | Path *c* – BMI effect on disease-free survival*(biased)*
Forest plot demonstrating biased **a.** total effect and **b.** direct effects (adjusted for ARDI or ACRD) of 5kg/m^{2}increments of BMI on disease-free survival, for the three populations.



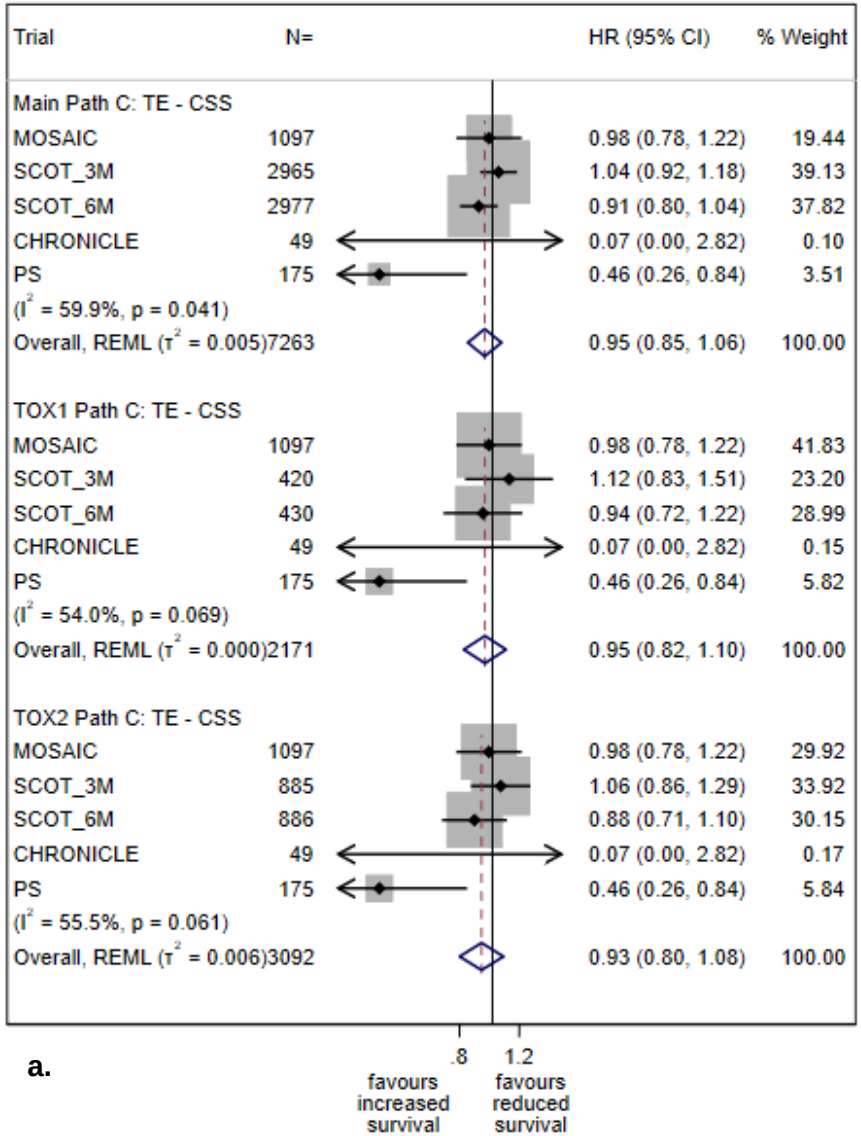
a.



b.

Figure 5.37 | Path *c* – BMI effect on cancer-specific survival

Forest plot demonstrating **a.** total effect and **b.** the direct effect (adjusted for ARDI or ACRD) of 5kg/m^{2}increments of BMI on cancer-specific survival, for the three populations.



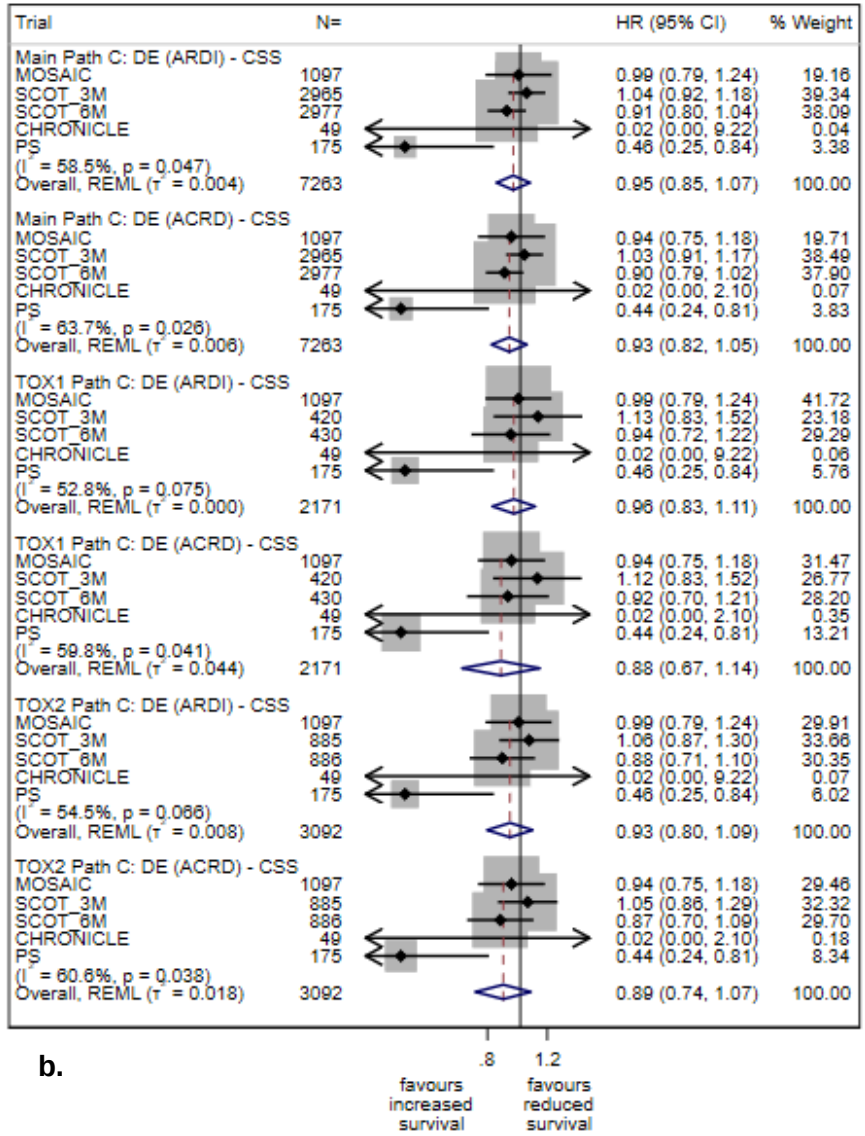
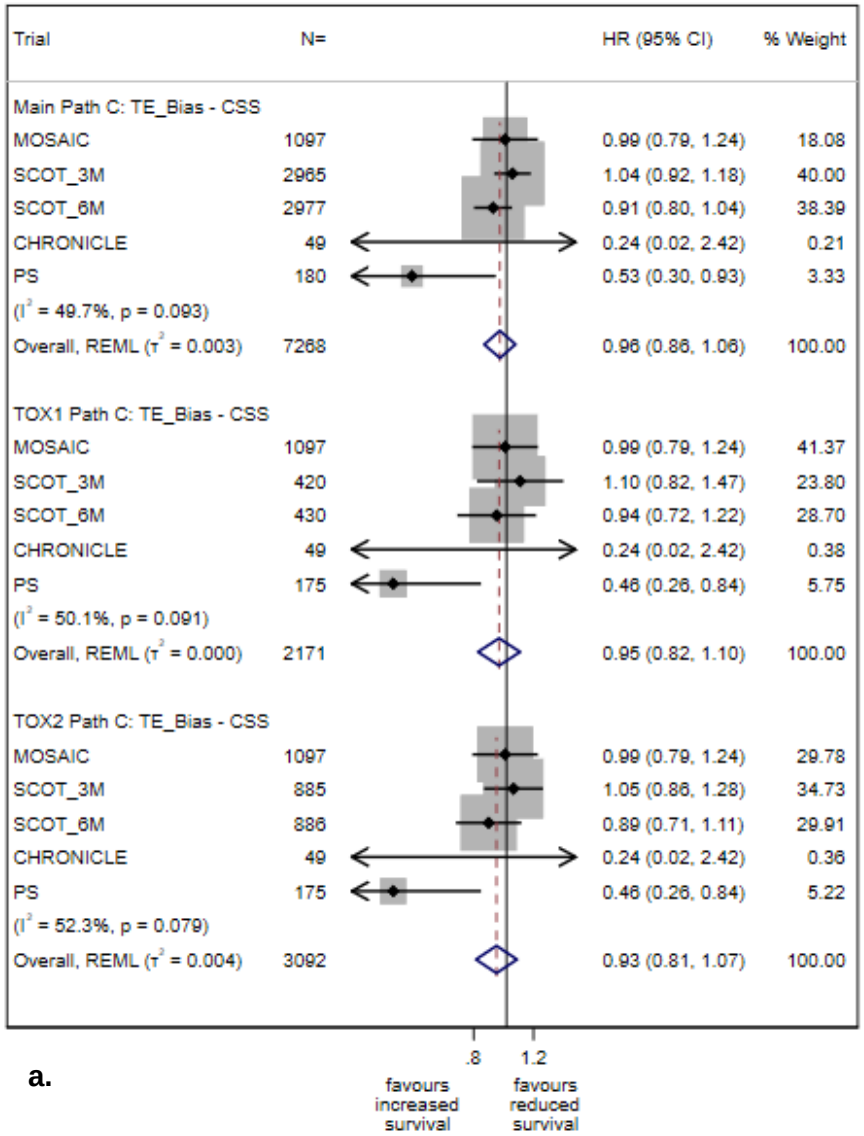
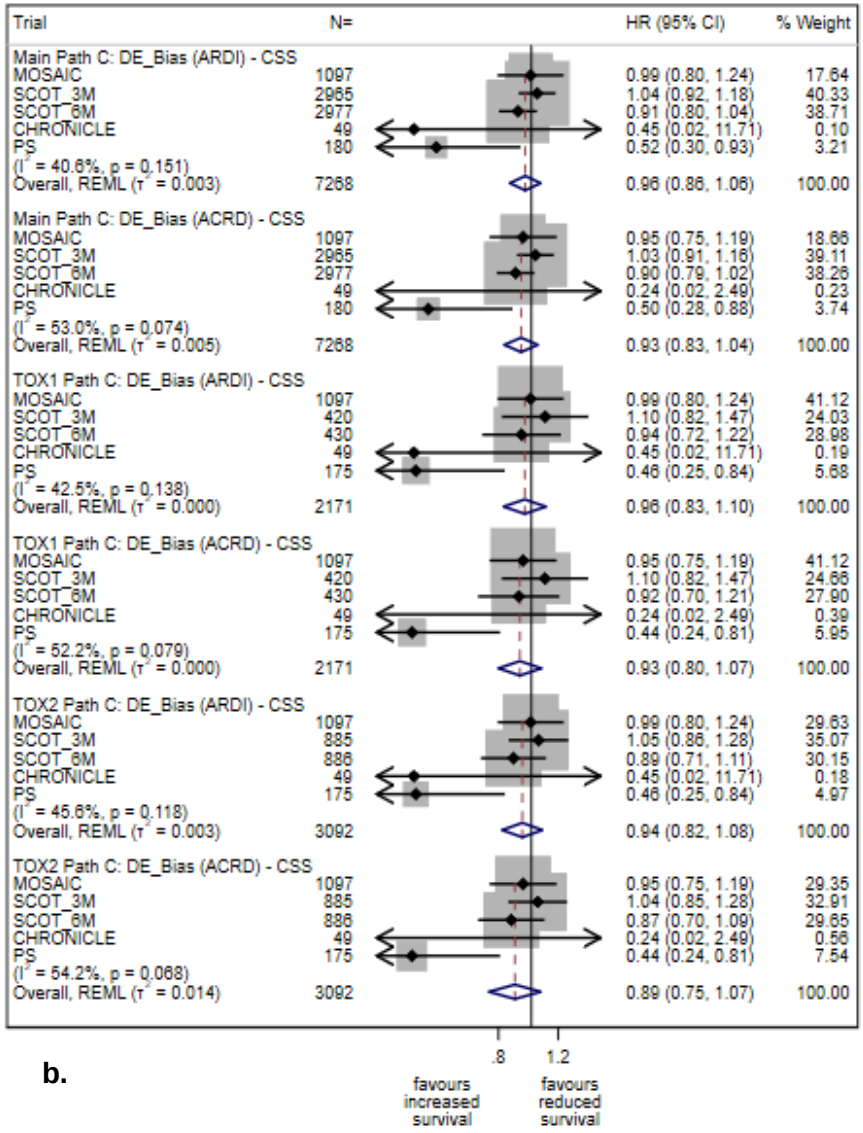


Figure 5.38 | Path *c* – BMI effect on cancer-specific survival *(biased)* Forest plot demonstrating the biased **a.** total effect and **b.** direct effects (adjusted for ARDI or ACRD) of 5kg/m^{2}increments of BMI on cancer-specific survival, for the three populations.



a.



b.

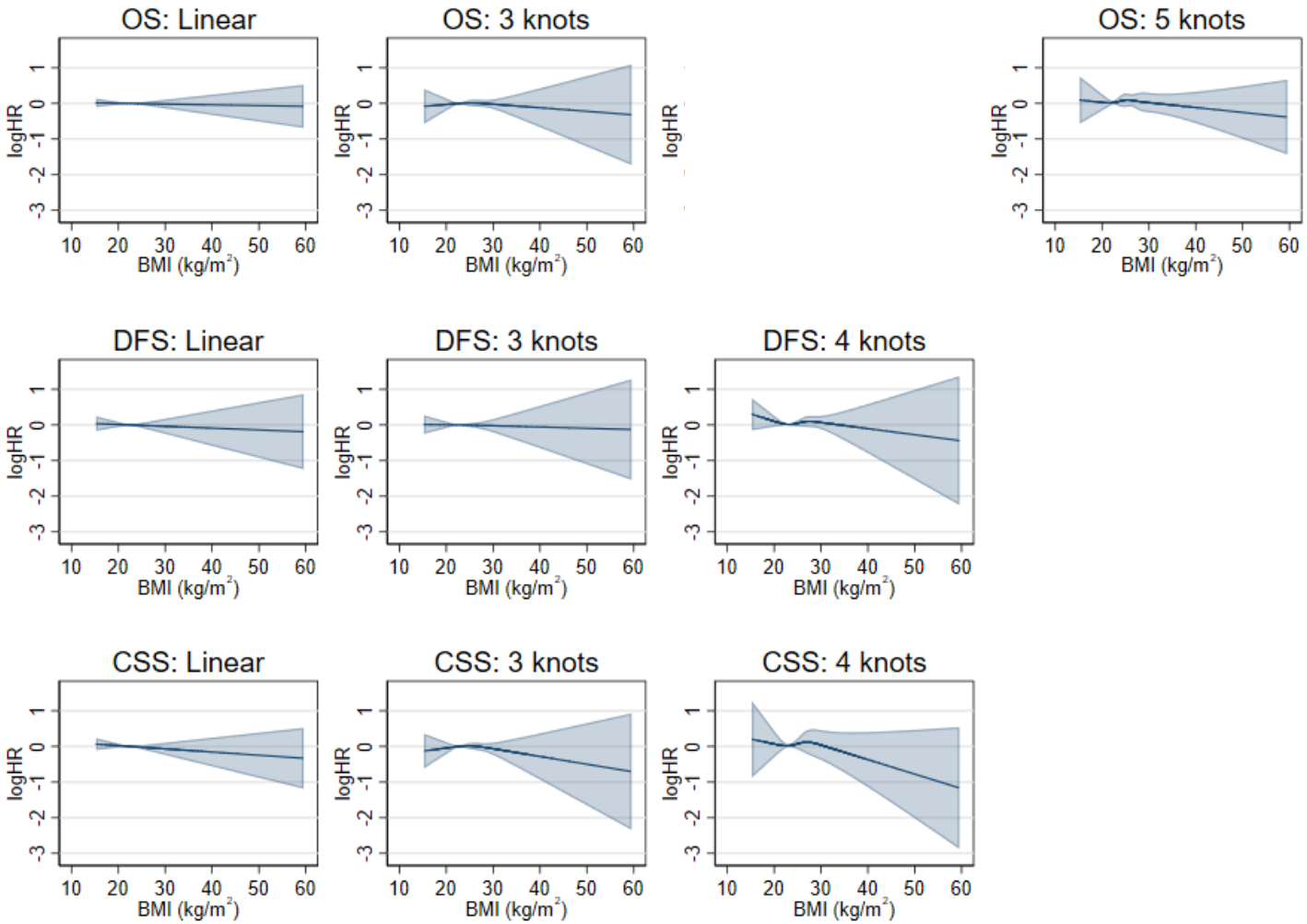
Linearity was assessed using multivariate meta-analysis of restricted cubic splines of BMI with three to five knots for the total effect of path *c* but was only possible for partially adjusted models (i.e., excluding toxicity). **Figure 5.39** demonstrates meta-analysed linear and spline models with varying numbers of knots, and the corresponding AIC and BIC values. Best fitting models according to AIC and BIC values were the 3 knot spline models, followed by the linear models. The 3 knot OS and CSS models demonstrated a small degree on non-linearity with a shallow inverse-U relationship, peaking at an approximate BMI of 25kg/m^2 and with improved survival at the lower and higher spectrums of the BMI scale. However, 95% confidence intervals encompassed zero (on the logHR scale) for all models, confirming no significant relationship between BMI and survival. Hence, linear models provided a reasonable approximation of the relationship.

Effect modification by sex and stage was examined for total effects. Addition of a BMI-sex interaction term did not result in any substantial changes to the effect estimates of path *c* total effects for all three survival outcomes (**Table A5.1**), with no significant interaction demonstrated**.** Similarly, no substantial changes occurred to effect estimates after the addition of a BMI-stage interaction term after it was added to models (**Table A5.2**), with no evidence of within-trial interaction. Heterogeneity was generally low across all analyses with low Tau^2 values.

Summary effect estimates of sensitivity analyses are presented in the appendix (**Figures A5.28 to A5.30**). Only exclusion of the 3-month arm substantially altered effect estimates for overall (**Figure A5.28a**; Main TE HR 0.81 (95%CI 0.53, 1.22)) and cancer-specific survival (**Figure A5.30a**; Main TE HR 0.81, (0.58, 1.13)), with an increased tendency towards improved survival. However, confidence intervals also widened markedly, and results remained non-significant. Overall, there was no convincing evidence for a relationship between BMI and survival, but there remained the possibility of a small indirect effect mediated through ACRD.

Figure 5.39 | Path *c* – linearity
Graphs demonstrating the predicted log hazard ratio (logHR, line) and 95% confidence intervals (shaded area) plotted against BMI from linear and spline (3, 4 or 5 knots) multivariate meta-analysis models for the total effect of path *c* (biased). BMI is centred at 22.5kg/m^2 (referent point). Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) values are presented for the respective models. 4-knot OS, 5-knot DFS and 5-knot CSS models not estimable.

AIC and BIC values					
			Spline model no. knots		
		Linear	3	4	5
OS	**AIC**	7.38	**-1.37**		44.69
	BIC	6.60	**-3.33**		39.22
DFS	**AIC**	4.27	**-11.59**	4.49	
	BIC	3.49	**-13.54**	0.97	
CSS	**AIC**	7.50	**2.10**	24.36	
	BIC	6.72	**0.15**	20.85	



5.4 DISCUSSION

5.4.1 SUMMARY AND INTERPRETATION OF RESULTS

The hypothesised causal relationships have been formally defined and explored through individual analysis of each path, generating a number of key findings, and confirming several of the observations from Chapters one and two.

First, a relationship between 5kg/m^2 BMI increments and almost three times the odds of cycle 1 dose capping was established, corresponding to an approximate 2% reduction in cycle 1 average relative dose received. These relationships displayed a degree of non-linearity with the odds of under-dosing and reduction of cycle 1 ARDR beginning at a BMI of approximately 25kg/m^2.

Second, 5kg/m^2 increments of BMI were associated with a modest reduction (approximately 1%) of both ARDI and ACRD. The halving of the effect on adherence measures, in comparison with cycle 1 dosing, is likely due to the trends seen in Chapter three, where a gradual convergence of cycle-level dosing was displayed, most likely resulting from toxicity. Again, there was some evidence of a significant non-linear relationship for ARDI, with no-relationship demonstrated until a BMI of approximately 25kg/m^2, followed by a significant reduction in adherence with increasing BMI with a steeper slope than that identified in linear models. For ACRD however, the linear model appeared to be the best fitting. BMI-adherence relationships did not appear to be mediated by toxicity, with virtually no difference in effect estimates on adjusting for grade 3+ toxicity. Furthermore, a small, significant interaction was demonstrated for sex for ARDI only, suggesting the potential for sex-differences in adherence, with the reduction in ARDI less pronounced for females compared with males.

Third, there was no significant relationship identified between BMI and grade 3+ toxicity, further implying that the BMI-adherence relationship was unlikely to be mediated by toxicity. Non-linear models tended to display a reduction in the odds of toxicity with BMI above approximately 30kg/m^2, however these were non-significant, with wide confidence intervals and potentially underpowered and biased due to complete case-analysis. When models were additionally adjusted for dose capping and a BMI-dose capping interaction, though there was a tendency for the odds of toxicity to increase (by 7%) with increasing BMI, these results were not statistically significant, and nor was there a within-trial BMI-dose-capping interaction identified. Individual toxicity data was less reliable due to the degree of missing data, and for the majority of toxicities, no significant relationship was identified. However, BMI did appear to be associated with a 29% reduction in the odds of neutropenia, and a tendency towards an increase in the odds of neuropathy. Furthermore, there was some evidence to suggest that toxicity was more likely to be a later event as BMI increased. However, results for individual and timing of toxicity

were likely to be both under-powered and potentially biased by missing data and consequent complete case analysis.

Fourth, a relationship between reduced ACRD and adverse survival was established, wherein 5% increments of ACRD resulted in a 6% increase in OS, a 4% increase in DFS and a 6% increase for CSS. These relationships were consistent across toxicity populations, with minimal bias resulting from partially adjusted models. Furthermore, the relationship appeared to be mostly linear, with convincing evidence of a significant effect on linear and multivariate spline meta-analyses. Conversely, and unexpectedly, 5% increments of ARDI were associated with a borderline significant 5% reduction of OS, with non-significant tendency to reduced DFS (3%) and borderline-significant reduction in CSS (3%). The results for ARDI were less convincing, with linear and multivariate spline meta-analysis models confidence intervals spanning zero on the logHR scale. The differences in results for ARDI and ACRD are likely to be the result of the nature in which they are both calculated, as discussed in Chapter three. For example, a patient dying as a result of toxicity after half their cycles (fully dosed), would have an ARDI of 100% and an ACRD of 50%. This demonstrates the discriminative limitation of using ARDI where patients do not receive all cycles and might be the result of opposing ARDI and ACRD effects. Optimal ACRD, however, appeared to be important for improved survival outcomes, and was mostly robust to reverse causality from treatment-related and early deaths. Furthermore, models that excluded toxicity resulted in minimal change to effect estimates, and together with no demonstrable BMI-toxicity relationship, demonstrated toxicity to be unlikely to cause substantial bias as an intermediate confounder.

Fifth, grade 3+ toxicity was associated with a reduction in both ARDI and ACRD, the latter displaying a larger effect. Furthermore, toxicity was associated with a significant reduction in overall survival, which was potentially, at least partially, mediated through a reduction in ACRD.

Sixth, there was no significant relationship demonstrated between BMI and survival. However, adjustment for ACRD did result in a (non-significant) improvement in survival estimates. Though, the Main population fully adjusted results for OS were potentially overestimated due to differences in the weighting of trials. Results obtained from the partially adjusted models (excluding toxicity) were more likely to be closer to the true effect, as effect sizes obtained from path *a* and *b* analyses would suggest that the indirect effect would be in the order of approximately 1-2% reduction in OS for each 5kg/m^2 BMI increment.

Finally, some differences were observed in BMI-dose capping/cycle 1 RDR/adherence relationships between SCOT toxicity populations, demonstrating the importance of utilising complete data to reduce bias, though meta-analysed effects appeared mostly consistent across TOX1, TOX2 and Main (including MI) populations. Though it would not be possible to completely exclude residual bias related to assumptions surrounding missingness mechanisms,

meta-analysed effects for BMI-toxicity, toxicity-adherence and toxicity-survival relationships were also reassuringly consistent across TOX1, TOX2 and Main (MI) population, with MAR assumptions seeming reasonable (see **Sections 2.4.4, 2.5.2, 4.4,** and **5.2.8**). Overall, risks of bias using complete case analysis with the TOX1 dataset alone were felt to have been greater than risks of residual bias related to unidentified MNAR mechanisms.

CHAPTER SIX

RESULTS PART IV

Meta-Mediation

CHAPTER SIX PREFACE

Chapter six progressed the work from Chapter five, taking the hypothesised mediated pathways within the BMI-Chemotherapy Adherence-Toxicity-Survival relationships, and formally testing for mediation at the trial level. This allowed selection of a mediation approach to be taken forwards to explore meta-analysis methods for mediation modelling. The concepts of mediation analysis, introduced in Chapter two are discussed in more detail within the counterfactual framework, further defining total, direct and indirect effects, and these principles are applied in practice.

6.1 INTRODUCTION

Chapter five explored the individual causal pathways making up the overall hypothesised BMI-adherence-toxicity-survival relationships. A possible indirect effect of BMI acting through average cumulative relative dose (ACRD) was identified, whereby a significant inverse relationship between BMI and ACRD was demonstrated, in addition to a proportional relationship between ACRD and overall survival. Though BMI was also associated with a significant reduction in average relative dose intensity (ARDI), the relationship between ARDI and survival seemed less convincing. Furthermore, there appeared to be no relationship between BMI and grade 3+ toxicity, suggesting the latter did not mediate BMI-adherence relationships. However, grade 3+ toxicity was associated with a reduction in both adherence measures and reduced overall survival and was therefore a possible confounder of the adherence-survival relationship, though lack of adjustment for toxicity did not substantially affect estimates. Furthermore, the relationship between grade 3+ toxicity and adverse overall survival appeared to be at least partly mediated by a reduction in ACRD, but not by ARDI. Chapter six examines these relationships formally using counterfactual mediation analysis approaches.

6.1.1 LIMITATIONS OF THE TRADITIONAL MEDIATION ANALYSIS APPROACHES

A number of limitations to the traditional mediation analysis approaches exist. For continuous outcomes and continuous mediators, the indirect effect calculated through the difference of coefficients method will equate to that calculated by the product of coefficients method (described in Chapter five). Problems arise, however, with a binary outcome that is common (>10%) and modelled using logistic regression.[256] Within the context of the difference methods, the non-collapsibility of the odds ratios (leading to an increase in size of the OR as a result of adding covariates) means that with a common binary outcome, the odds ratios from the two outcome models (with and without the mediator) are not directly comparable.[257] With a rare outcome, however, the OR will approximate the relative risk, and these issues do not apply. The counterfactual framework has allowed extension of mediation to model survival outcomes, with the use of accelerated failure time models (Weibull or exponential distributions) producing valid estimates of effect decomposition, including within the setting of common outcomes.[244,258–260] Hence the counterfactual approach lends itself to mediation analysis in the context of the current clinical question.

6.1.2 COUNTERFACTUAL APPROACHES TO MEDIATION ANALYSIS

The counterfactual (or ‘potential outcomes’) framework, provides a general approach to disentangle direct and indirect effects from total effects. It considers that for any one individual, it is only possible to observe one outcome based on their observed exposure at a given point in time, whereas that individual’s ‘counterfactual’ outcome (that which would occur under an

alternative exposure) cannot be observed, and vice versa.[261] Taking the example of a binary exposure (X) and a binary outcome (Y), for an individual *i*, their potential outcome would be $Y_i(x)$, depending on the value of the exposure X. Hence, there are two potential outcomes:

Y(0) – the observed outcome when X = 0 (unexposed)

Y(1) – the observed outcome when X = 1 (exposed)

However, for that individual only one outcome (either Y(0) or Y(1)) can be observed, the other outcome being counterfactual. The individual treatment effect is a comparison between Y(0) and Y(1) for each individual, such as the difference or odds ratio. This is unobservable at the individual level but can be estimated as the average treatment effect at the population-level.[209] Equally, within the mediation analysis setting, the effects of the exposure on the mediator and of the mediator on the outcome may also be estimated. The counterfactual framework also allows for exposure-mediator interactions, permitting estimation of the impact of such an interaction on the direct effect.

Counterfactual notation can be used to define the potential outcomes for exposure (X) and mediator (M) values, in addition to the various effects resulting from mediation analysis:[209,213,262,263]

Y(x) – the value of Y when X = x

M(x) – the value of M when X = x

Y(x,m) – the value of Y when X = x and M = m

Y(x,M(x*)) – the value of Y when X = x and M takes the value it would when X = x*

Controlled direct effect (CDE)

The CDE estimates the effect of the exposure on Y, when M is controlled at a given level m, and is a measure of the unmediated effect if the mediator were intervened on and set at m. For a binary exposure, the CDE, conditional on covariates, C, can be defined as the difference in potential outcomes between exposed (Y(1)) and unexposed (Y(0)), when M is held fixed for both outcomes at a given value of M = m:[209,262,264]

$$CDE = E[Y(1,m) - Y(0,m)|C]$$

Where there is no X-M interaction, the CDE will equal the natural direct effect. However, where there is an interaction, the CDE will vary across values of M. Hence, it is often most useful within public health decision-making, where intervention on a mediator might be feasible for a population.[209,263,265]

Natural direct effect (NDE)

The NDE is the measure of the unmediated effect of X on Y, when M takes the value it would take for each individual if they were unexposed. Here, the mediator takes the distribution that it would, if everyone were unexposed (i.e., it's "natural level"), rather than being set to a fixed level. For a binary exposure, the NDE is defined as the difference in potential outcomes between the exposed population (Y(1)) with unexposed mediator (M(0)), and the unexposed population (Y(0)) with unexposed mediator (M(0)), conditional on covariates, C: [209,263,265]

$$NDE = E[Y(1,M(0)) – Y(0,M(0)) \mid C]$$

The NDE is also referred to as the pure natural direct effect (differing from the total natural direct effect $E[Y(1,M(1))-Y(0,M(1)) \mid C]$.[209,262,264]

Natural indirect effect (NIE)

The NIE is the effect of the exposure that occurs solely though the mediator. It is defined as the difference in the potential outcomes for the exposure (X=1) that is seen by changing the mediator from exposed (M(x=1)) to unexposed (M(x=0)), conditional on covariates, C:[209,262,265]

$$NIE = E[Y(1,M(1)) – Y(1,M(0)) \mid C]$$

The NIE is also known as the total natural indirect effect which differs from the pure natural indirect effect (defined as $E [Y(0, M (1)) - Y (0, M(0)) \mid C]$).[262,265] Furthermore, for the indirect effect, there is no equivalent to the CDE, i.e., no controlled indirect effect, unless complete mediation exists.[266]

Where an understanding of mechanisms and hence effect decomposition are sought, the NDE and NIE are thought to be more useful.[265,267]

Total Causal Effect (TCE)

Finally, the total causal effect is total effect of the exposure on the outcome that includes the mediated effect and is either the sum of the NIE and NDE (for outcomes on the additive scale [TCE = NIE + NDE]), or their product (for outcomes on the multiplicative scale [TCE = NIE*NDE]).[266] For a binary exposure, it can be defined as the difference in potential outcomes for the exposure, where the mediator takes its exposed value (Y(1,M(1)), compared with unexposed, where the mediator takes its unexposed value (Y(0,M(0)), conditional on covariates, C:[209,266]

$$TCE = E[Y(1,M(1)) – Y(0,M(0) \mid C]$$

For a continuous exposure, the CDE, NDE, NIE and TE can be defined as comparing exposure levels x and x*, rather than 1 and 0, respectively, and the above definitions can be substituted accordingly.

Assumptions

For causality to be inferred from observational data in the mediation setting a number of assumptions must be met. The majority of these assumptions are conceptual rather than being formally testable utilising observed data.

1) No interference assumption: one individual's outcome is not influenced by another's exposure.[268,269] Under certain circumstances the no interference assumption might not be met. Such circumstances often relate to social interaction across populations, that might, for example influence behaviours. Though it is unlikely that one patient's BMI would directly interfere with the outcome of another patient, in the context of this study, there may be instances where social interactions could influence behaviours. Examples might include whether a patient takes their prescribed capecitabine tablets, reports adverse events as a result of talking to other patients about their treatment, or prescribing tendencies of a clinician based on past experience, which might influence both mediators and outcomes. Unfortunately, such behaviours were not captured within the trial data, and any association with the exposure is unlikely to be testable.

2) Consistency assumption: states that for individuals with observed exposure X = x, and observed mediator M = m, their observed outcome (Y) is equal to the potential outcome should X have been set to x and M to m (i.e., Y(x,m) = Y, when X = x and M=m). That is, it is assumed that the observed outcome Y in the subgroup of patients with observed exposure X = x and observed mediator M = m equals the potential outcome if X were intervened on and set to x, and M set to m. Hence, this assumption cannot be tested formally using observed data.[209]

3) Composition assumption: which is important for effect decomposition, in particular for natural direct effects, states that for exposure X = x, the potential outcome Y(x) equals the potential outcome when intervening to set exposure X = x and M the value it would take for X=x (i.e., Y(x) = Y(x,M(x)). Hence, when X is set to unexposed, interventions on M to set it to its "naturally occurring level" have no further effect on the outcome. Again, this assumption cannot be tested formally. [209]

4) Conditional exchangeability: there is no unmeasured confounding of X-M, M-Y or X-Y relationships: [209]

   For valid inference of the total effect, there must be:

   a) no unmeasured confounding of the exposure-outcome (X-Y) relationship
   b) no unmeasured confounding of the exposure-mediator (X-M) relationship

   Additionally, for valid inference of direct and indirect effects, there must be:

   c) no unmeasured confounding of the mediator-outcome (M-Y) relationship

d) no unmeasured confounding of the mediator-outcome (M-Y) relationship, that is itself affected by the exposure (X) (i.e., no intermediate confounder).

Use of DAGs and careful consideration of potential confounders is important to ascertain potential unmeasured confounding. Following which, it may be possible to conduct sensitivity analyses to assess the extent to which such unmeasured confounders may influence effect estimates, or assess the strength of association required to attenuate effects.[270,271] Though some methods exist for survival analyses on the hazard ratio scale, it is unclear whether such methods are currently validated for mediation analysis on the mean survival ratio scale (see **Section 6.2.7**).

6.1.3 APPLIED MEDIATION ANALYSIS

Several statistical packages have been developed for mediation analysis, falling into two broad categories: those using regression-based approaches, and those using simulation-based approaches. Two Stata user-written commands, `paramed`[272] and `gformula` [273] allow decomposition of total effects into the CDE, NDE and NIE. However, neither supports time-to-event mediation analyses. More recently, the R package `regmedint`[274] became available, extending mediation analysis to time-to-event outcomes.

Paramed (Stata)

`Paramed` is a regression-based approach written by Liu, Emsley, and Dunn [272] based on the SAS `mediation` macro from Valeri and VanderWeele.[259] It estimates a model for the mediator (regressed on X and C), and for the outcome (regressed on X, M and C), performing mediation analysis using the counterfactual definitions of direct, indirect, and total effects. `Paramed`, allows for continuous, binary or count outcomes, and continuous or binary mediators, in addition to bootstrapping of confidence intervals, but does not facilitate multiple imputation approaches within the command itself. Additionally, `paramed` allows the user to set comparative values of the exposure (particularly useful for continuous variables), in addition to the mediator level (important when specifying an X-M interaction, to obtain the CDE), and levels at which to evaluate confounders for conditional effects.

Gformula (Stata)

`Gformula` is a simulation-based approach written by Daniel, De Stavola and Cousens,[273] based on the g-computation procedure introduced by Robins.[275] It can be used for mediation analysis in the presence of intermediate confounding, in order to yield accurate direct and indirect effects. The definitions for CDE, NDE, NIE and TE are the same as those above. However, though the user may define a referent value of X, (and set levels of M to explore the CDE), the comparison for the exposure is then taken from the distribution of X arising naturally from the observed data (see **Section 6.2.7** for further explanation).[273]

Regmedint (R)

`Regmedint`, written by Yoshida, Li and Mathur[274] for R, is similar to `paramed`, but allows mediation analysis of time-to-event outcomes. It implements the SAS `mediation` macro that was updated in 2015, to allow for survival mediation analysis,[260] based on the work of VanderWeele.[244] Like `paramed`, it allows for specification of referent and comparative exposure values, mediator values, and also confounder values to produce conditional effects.

Additional Stata commands and R packages are also available such as the Stata `med4way`[276] command which produces four-way decomposition of effects where an exposure-mediator interaction is present; and `mediation` in R which is a simulation-based approach developed by Tingley and colleagues.[277]

6.2 METHODS

6.2.1 AIMS

The main aim of Chapter six was threefold, first, to explore approaches for mediation modelling, and in particular for survival outcomes, second, to select one of these approaches to develop meta-analysis strategies for the mediated effects (meta-mediation), and finally to undertake meta-mediation to formally test for mediated effects in the previously defined relationships.

6.2.2 DATA SOURCE & POPULATION

Again, all three datasets (the Main dataset and the two additional toxicity datasets, TOX1 and TOX2), were utilised.

6.2.3 DIRECTED ACYCLIC GRAPHS

The pre-defined hypothesised causal pathways depicted in DAGs3, 4a and 4b (**Chapter 5, Figures 5.3, 5.4a** and **5.4b**, respectively) were formally tested. DAG 3 describes the overarching hypotheses, that is, the relationship between BMI and survival, mediated through adherence (referred to subsequently as path *c*) and encompasses DAG 4a (the hypothesised BMI-adherence relationship mediated by toxicity, referred to subsequently as path *a*) and DAG 4b (the hypothesised toxicity-survival relationship, mediated by adherence and referred to as path *f*).

6.2.4 EXPOSURE

The primary exposure throughout this Chapter was BMI, modelled continuously to reduce loss of information. However, during analysis of DAG 4b toxicity was treated as a binary exposure.

6.2.5 MEDIATORS

Both the average relative dose intensity (ARDI) and average cumulative relative dose (ACRD) were explored as continuous mediators for paths *c* and *f*, in addition to toxicity as a binary mediator for path *a*.

6.2.6 OUTCOMES

The primary outcome was overall survival (OS), and secondary outcomes were disease-free survival (DFS) and cancer-specific survival (CSS). Additional secondary outcomes for DAG 4a were ARDI and ACRD.

Additional outcome definitions

`Paramed` and `gformula`, as described above, do not support time-to-event analysis. Hence, a binary 3-year overall survival variable was generated:

3-year overall survival

Defined as an overall survival event (death from any cause) occurring within 3 years of randomisation.

During the process of generating the 3-year OS variable, an important limitation of the available data was encountered. The data available from the MOSAIC trial did not appear to contain the full published follow-up data for 5- or 10-years follow-up,[163,278] but rather what appeared to be the data from the first publication,[183] meaning that full 3-year survival data was only available for 664 patients, with 458 patients censored prior to 3 years. The risk table from the OS Kaplan-Meier graphs from a subsequent publication,[278] however, confirmed that at 3 years (36 months), there were 949 patients remaining at risk with 150 overall survival events. On generating a binary indicator variable for the MOSAIC dataset (pre-exclusions), there were 133 events. Assigning all 458 patients with less than 3 years follow-up as "alive" therefore incorrectly assigned 17 patients with an event by 3 years, as alive. Following exclusions (see Chapters two and three), there were a total of 129 3-year overall survival events from 1097 patients. Similar event data at 3 years was not available for DFS or CSS within the MOSAIC publications and hence, analyses were restricted to overall survival only, due to lack of ability to assess for potential bias.

For SCOT, the authors' described a requirement for extension of the recruitment period by 6 months, which increased completion of 3-year follow-up to 88%, allowing for a 2-month deviation from the assessment time.[185] Accordingly, the same 2-month deviation was allowed for, and following patient exclusions (see Chapters two and three), there were 290 3-year OS events for 2786 patients in the SCOT_3M arm, and 301 3-year OS events from 2763 patients in the SCOT_6M arm. No assumptions were made for the 249 (8.20%) SCOT_3M patients or the 267 (8.81%) SCOT_6M patients not completing at least 34 months of follow-up, and hence they were excluded. Similarly, CHRONICLE lacked completed 3-year follow-up data for 14 (28.6%) of 49 patients, and PROCTOR-SCRIPT (PS) 8 (4.44%) out of 180 patients, again, assumptions were not made of these patients, as no additional data was available through the respective publications.[171] Though analysis of 3-year overall survival variables generated in this way would potentially introduce a degree of bias, for exploration of the `paramed` and `gformula` mediation approaches, this was accepted as a limitation of the available data and highlighted the potential advantage of time-to-event approaches.

6.2.7 Statistical Analysis: Trial Level Mediation Analysis

Patient inclusion, baseline characteristics and survival data were previously summarised within Chapters three, four and five, and hence data are not repeated here.

Mediation analysis was first undertaken at the trial-level using `paramed`, `gformula` and `regmedint` for Path *c* overall survival. `Paramed` and `gformula` packages were used to explore 3-year overall survival outcomes as a binary outcome within Stata and outcomes are reported on the odds ratio scale (OR). `Regmedint` was used to model OS as a time-to-event outcome using the accelerated failure time model with the Weibull distribution. Here, outcomes are modelled on the mean survival ratio scale (MSR), meaning that they refer to a change in mean survival time compared with the referent, such that values of <1 indicate comparatively reduced mean survival time (worse survival) and values of >1 indicate comparatively increased mean survival time (improved survival).[244] Both `paramed` and `regmedint` analyses were specified to model a 5kg/m^2 change in BMI as the exposure. However, when modelling a continuous exposure using `gformula,` though it allows specification of a referent BMI (selected as 22.5kg/m^2, in keeping with Chapter five non-linear models and representing a "normal" BMI), it does not allow user-specification of the comparative level of BMI. Instead, this is defined by the underlying population distribution, as determined by the command itself. Hence, `gformula` estimates the effect of a change in the mean population exposure (in this case, the mean BMI for the trial), compared with a referent exposure (here defined as a BMI of 22.5kg/m^2).

Intermediate confounding has the potential to bias estimates for the natural direct and indirect effects, meaning that the true NDE and NIE cannot be identified.[279] This is due to its dual role as mediator and confounder. To obtain unbiased estimates of the effect of the M-Y relationship, the intermediate confounder would require adjusting for within analyses. However, adjustment for an intermediate confounder will influence the indirect and direct effects (due to its role as a mediator of both mediator and outcome). Hence, to explore the possible impact of different assumptions regarding the role of toxicity, separate mediation models were run including toxicity a normal confounder (`paramed`, `gformula`, `regmedint`) and as intermediate confounder (`gformula` only). Furthermore, though Chapter five results suggested that exclusion of toxicity as a confounder resulted in minimal bias of path *b* and path *c,* models were repeated excluding toxicity as a confounder (`paramed`, `gformula`, `regmedint`), to confirm these findings in the mediation setting. Similar to Chapter five, these partially adjusted models are referred to as "biased" models throughout the Chapter to distinguish them from models including toxicity.

Confounders for all analyses were those previously defined: splines of age (3 knots), sex, performance status, (y)pT stage, (y)pN stage (and regimen for SCOT and PS trials). Additionally, BMI was included as a confounder for path *f* (see **Section 6.2.8** below).

Bootstrapping Confidence intervals

Confidence intervals were bootstrapped for all analysis. The `paramed` and `gformula` commands both have inbuilt bootstrapping methods, and confidence intervals were generated using 1000 bootstrapped samples. `Paramed` supports bootstrapping confidence intervals using the percentile method, whereas the `gformula` approach used the normal-based method. Code for user-defined bootstrapping of the `regmedint` package was available from the author of the `regmedint` package and was utilised to bootstrap confidence intervals using the percentile method.[280] However, within R, this required at least the same number of bootstrap samples as the number of individuals and hence 3000 bootstrapped samples were used for all trials.

Missing toxicity data and multiple imputation

Chapter five demonstrated the potential bias introduced by complete case analysis, particularly for the path *a* relationship within the SCOT trial, which could impact on indirect effect estimates. Due to the requirement to bootstrap confidence intervals, methods for combining multiple imputation and bootstrapping were necessary. Broadly, there exist two approaches: bootstrap followed by imputation (Boot-Impute [BIM]) of each bootstrapped dataset, then analysis within each boot-impute dataset prior to combining results; or impute first, then analyse and bootstrap (Impute-Boot) each imputed datasets to obtain confidence intervals, and finally combine the results from imputed datasets using e.g., Rubin's rules. Von Hippel and Bartlett[281] proposed an approach to combining point estimates and standard errors which was computationally less expensive, requiring at least 200 bootstraps with 2 imputations for each bootstrap (generating 400 Boot-Impute datasets) in datasets with high missingness (>90%)). They demonstrated the superiority of Boot-Impute von Hippel approach[281] for confidence interval coverage, particularly in the settings of uncongeniality and misspecification. Furthermore, the authors created a user defined package available in R.[282] Hence analyses requiring multiple imputation for `regmedint` in R, namely the SCOT trial, utilised the Boot-Impute (BIM) von Hippel approach for the advantages of both efficiency and accuracy. Again, and as previously discussed data were assumed MAR (see **Sections 2.4.4, 2.5.2, 4.4.1,** and **5.2.8** for rationale of such assumptions). Mice with random forest was used, in keeping with Chapter five, with 500 bootstraps and 2 imputations (totalling 1000 boot-impute datasets), with 10 trees and 10 iterations, and the same predictor variables as previously described (see **Section 5.2.8**). User-defined code for combining multiple imputation with `regmedint` was available from the author of the `regmedint` package, this was modified to incorporate the BIM code.[283]

A similar user-defined command to reproduce the same approach was not available for Stata and hence an Impute-Boot-Rubin approach was undertaken, utilising the same imputed SCOT

datasets from Chapter five. `Paramed` was run for each of the 10 imputed datasets (each bootstrapped 1000 times), and the results combined using Rubin's rules via the Stata `mi estimate` command, with the `cmdok` option, which allows for combining results from user defined analyses that are posted to Stata 'e(b)' and 'e(V)' matrices, outside of those supported within the `mi estimate` command.

`Gformula` has inbuilt imputation methods which consist of single stochastic imputation using chained equations, because of the simulation approach whereby standard errors and confidence intervals are estimated via bootstrapping.[273] Furthermore, because `gformula` does not post beta coefficients and variances to the e(b) or e(V) matrices, which are required for the `mi estimate` command, it was not possible to utilise the same approach as for `paramed`. Hence, the built-in `gformula` imputation method was utilised, again using the same previously defined predictors.

Consequently, having established that exclusion of toxicity as a covariate resulted in minimal bias in Chapter five, the validity of these approaches to obtain effect estimates was assessed by running models for path *c* with and without toxicity (again, the latter termed 'biased' pathways).

6.2.8 Statistical Analysis: Meta-Mediation Analysis

There appear to be no standard methods for meta-analysis of mediation effects from causal inference models at present. Meta-analysis methods for structural equation modelling (SEM) exist, which have been extended to the mediation analysis setting.[284] Furthermore, Zhu and colleagues[285] have previously approached the meta-mediation problem by first performing meta-analysis of the separate mediator model and outcome model regression analyses and then calculating the causal effects using the meta-analysed regression model effect estimates and error terms. However, the effect of applying post-meta-analysis calculations, particularly in the setting of modelling interactions, on the risk of ecological bias was not explored or discussed, and remains unclear.

Hence, in attempt to reduce the potential risk of ecological bias, in addition to retaining the bootstrapped standard errors, an alternate approach to meta-mediation was taken, utilising two-stage meta-analysis approaches. Stage one involved fitting the individual mediation models. Stage two was undertaken using both univariate and multivariate meta-analysis approaches.

Mediation model selection

The `regmedint` approach was selected for meta-mediation, to reduce the potential bias as a result of generating binary 3-year OS variables. Meta-mediation modelling of time-to-event survival outcomes was likely to introduce less bias than that from potential time-varying

confounding by toxicity, with results that were more interpretable (than with `gformula`). The fully adjusted path *c* (including toxicity as a normal confounder) mediation analysis effect estimates were meta-analysed. In addition, `regmedint` mediation models were run at the trial level for paths *a* and *f.* Hence, the final meta-mediation analyses consisted of the Main population and utilised the BIM approach for missing toxicity data.

Univariate meta-analysis

For univariate (UV) analyses the effect estimates and bootstrapped confidence intervals from the `regmedint` results in R were exported to Stata, and the trials were meta-analysed using the `metan` command. In keeping with Chapter five, random effects were assumed, to account for the more likely situation of between-study heterogeneity, and models were estimated using restricted maximum likelihood (REML).

Multivariate meta-analysis

Since the NDE and NIE for each trial are correlated, the multivariate (MV) meta-analysis approach was also utilised, which allows for joint synthesis of correlated outcomes, specifically allowing for their correlation. The user-defined multivariate meta-analysis `mvmeta` package, is available in both Stata and R. They require variances and covariances in addition to effect estimates for the outcomes, which were not generated automatically in R for the bootstrapping and boot-impute methods employed. Hence, the following steps were undertaken prior to running the multivariate meta-analysis:

1. The individual models were run in R and the point estimates and standard errors were exported to Stata (for results on the ratio scale, estimates and standard errors (SE) were taken on (or transformed to) the log scale.
2. The variance was calculated (utilising the bootstrapped standard error on the log scale):[286]

$$variance = SE^2$$

2.1. Where the bootstrapped SE was not generated, this was calculated from the upper and lower confidence intervals.[286]

$$SE = \frac{\text{upper confidence interval} - \text{ lower confidence interval}}{2 * 1.96}$$

3. The bootstrapped effect estimates (beta-coefficients) for all of the mediation effects were exported to Stata, to estimate the within-trial correlations between the NDE and NIE, using the Stata `correlate` command.
4. Correlations and standard errors were then used to calculate co-variances for the natural direct effect and natural indirect effects:

$$covariance_{nde\_nie} = correlation_{nde\_nie} * SE_{nde} * SE_{nie}$$

5. Finally, the effect estimates, variances, and covariance for the NDE and NIE were utilised to perform multivariate meta-analysis using the `mvmeta` command in Stata. Furthermore, univariate meta-analysis of the TE was also undertaken using the `mvmeta` command.[252]

Though complicated by switching between statistical software, the advantage of using the Stata `mvmeta` command over the R `mvmeta` package is that the Stata version can provide study weights and borrowing of strength (BoS) estimates which are not currently implemented in the R package.

Study-weights

Definition of the total effect as the sum (or product, if on the ratio scale) of the direct and indirect effects is a central concept to effect decomposition. It was expected, that across trials, the proportion of the direct and indirect effects making up the total effect might differ as a result of between-study heterogeneity. Though allowing the weights to vary naturally according to the standard random-effects inverse-variance approach is advantageous, in that heterogeneity is better accounted for, it could lead to different study-weights being applied to direct and indirect effects. This would result in meta-analysed effect estimates for the NDE and NIE that do not sum to the TE, if within- and across-trial variance differs between effect estimates (which is likely). Therefore, univariate meta-analysis models were also run, assigning the trial-specific weights for the NDE and NIE to be those from the univariate total effect weights (referred to as univariate-forced weight (UVFW) models), to assess how these issues might affect interpretation of results.

Borrowing of strength

The correlation between outcomes that is taken into account through multivariate meta-analysis, may improve the precision of estimation, compared with univariate meta-analysis. This occurs through a process of borrowing strength. The borrowing of strength (BoS) statistic (calculated as a percentage) refers to the gain in information as a result of correlated outcomes. It is “the percentage reduction in the variance of a summary result that is due to correlated or indirect evidence”.[287] BoS is most useful for situations where outcomes are highly correlated and there is a high proportion of studies with missing outcome data, allowing strength to be borrowed from the studies with non-missing outcomes (e.g., a set of studies with DFS and OS outcomes (highly correlated), where some studies lack DFS outcomes, and information can be gained about DFS from OS within a multi-variate meta-analysis). Where outcome data is complete for all studies, such as in this case, it is expected that BoS would be small or zero.[287,288] Jackson and colleagues have derived methods for calculating study weights, which inherently encompass borrowing of strength statistics, and are implemented within the mvmeta command.[288]

Because effect sizes are small for key analyses, results within this Chapter are presented to three decimal places. Statistical analyses were performed in Stata version 17 (StataCorp LLC, 2021, College Station, TX, USA), R version 3.6.2. and R Studio (version 1.4.11).

6.3 RESULTS

6.3.1 PATH C OVERALL SURVIVAL – TRIAL-LEVEL

The three packages for mediation analysis were explored for the overall pathway (path *c*), with both ARDI and ACRD as mediators. As discussed above, toxicity was included in the models as either a normal confounder (`paramed`, `gformula`, `regmedint`), an intermediate confounder (`gformula` only) or was excluded as a confounder (`paramed`, `gformula`, `regmedint`). The latter, partially adjusted models, are referred to as "biased" throughout the Chapter to distinguish them from those including toxicity.

Paramed

Results for `paramed` are presented in **Table 6.1** with ARDI and ACRD as mediators, for both fully adjusted (including toxicity) and partially adjusted (["biased"] excluding toxicity) models, for each trial. In fully adjusted models, with ARDI as the mediator, there was no evidence of a significant total, natural direct or natural indirect effect for 5kg/m^2 increments of BMI on 3-year overall survival. However, a small significant NIE mediated via ACRD was demonstrated for MOSAIC and SCOT_3M, meaning that for each 5kg/m^2 increment of BMI, there was a 3% increase in the odds of death from any cause at 3 years for MOSAIC (OR 1.03; 95%CI 1.00, 1.06), and a 1% increase in the odds for SCOT_3M (OR 1.01; 95%CI 1.00, 1.03). There was also a tendency for the NIEs in the SCOT_6M and PS trials to be in the same direction. For MOSAIC, the NDE was in the opposing direction of the NIE, and for SCOT_3M it was in the same direction, though NDEs were not statistically significant. CHRONICLE displayed unlikely effect estimates and confidence intervals, which was most likely the result of small numbers of patients and events, in addition to a large number of covariates and resulting in problems during bootstrapping estimates (probably due to resampling). Effect estimates for fully adjusted and partially adjusted path *c* estimates were very similar, suggesting minimal bias introduced as a result of not adjusting for toxicity.

Results for TOX1 and TOX2 populations are presented in the appendix (**Table A6.1**) and demonstrated similar NIE results, with a tendency towards a small increased OR for SCOT_3M, but a small reduction in the NIE OR for SCOT_6M. However natural direct and total effects, though remaining non-significant, were substantially different from the Main populations for both ARDI and ACRD, again highlighting the potential for introducing bias thought complete-case analysis.

Table 6.1 | Path *c* 3-year overall survival – `Paramed`

Results of path *c* mediation analyses with `paramed` demonstrating the total (TE) and natural direct (NDE) effects of 5kg/m^2 BMI on 3-year overall survival, and the natural indirect effect (NIE) mediated either through ARDI or ACRD for the Main population. Results are presented for models including toxicity as a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the mean survival time ratio (MSR); confidence intervals are calculated with bootstrapping methods. Statistically significant results in **bold.**

		ARDI				**ACRD**			
		Path C[a]		**Path C biased[b]**		**Path C[a]**		**Path C biased[b]**	
		OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
MOSAIC	**NDE**	0.971	(0.772, 1.214)	0.980	(0.797, 1.222)	0.930	(0.744, 1.166)	0.936	(0.744, 1.169)
	NIE	0.982	(0.934, 1.015)	0.997	(0.950, 1.034)	**1.025**	**(1.004, 1.055)**	**1.034**	**(1.009, 1.066)**
	TE	0.954	(0.761, 1.190)	0.977	(0.780, 1.212)	0.954	(0.759, 1.194)	0.968	(0.767, 1.212)
SCOT_3M	**NDE**	1.049	(0.895, 1.204)	1.042	(0.897, 1.203)	1.021	(0.873, 1.169)	1.016	(0.876, 1.171)
	NIE	0.990	(0.976, 1.004)	0.992	(0.980, 1.005)	**1.015**	**(1.002, 1.028)**	**1.015**	**(1.004, 1.031)**
	TE	1.039	(0.886, 1.191)	1.034	(0.892, 1.197)	1.036	(0.886, 1.186)	1.032	(0.889, 1.186)
SCOT_6M	**NDE**	0.974	(0.853, 1.095)	0.977	(0.865, 1.102)	0.955	(0.835, 1.074)	0.956	(0.843, 1.084)
	NIE	**0.987**	**(0.975, 0.999)**	**0.988**	**(0.972, 0.997)**	1.007	(0.989, 1.025)	1.008	(0.979, 1.020)
	TE	0.961	(0.842, 1.081)	0.965	(0.852, 1.088)	0.961	(0.841, 1.081)	0.963	(0.852, 1.089)
CHRONICLE	**NDE**	$2.97\text{x}10^{282}$	*	3.448	(0.000, 7.87E+^{28})	337.679	(0.000, $7.84\text{x}10^{37}$)	1.925	(0.000, $6.90\ \text{x}10^{30}$)
	NIE	$1.78\text{x}10^{-05}$	(0.000, 0.035)	0.928	(0.000, 2.34E+^{16})	0.990	(0.000, $3.17\text{x}10^{06}$)	0.942	(0.000, $3.84\ \text{x}10^{16}$)
	TE	$5.29\text{x}10^{277}$	*	3.199	(0.000, 1.00E+^{31})	334.142	(0.000, $4.98\text{x}10^{37}$)	1.814	(0.000, $1.17\ \text{x}10^{32}$)
PS	**NDE**	0.530	(0.022, 2.543)	0.676	(0.097, 2.280)	0.442	(0.065, 2.121)	0.535	(0.086, 1.956)
	NIE	0.918	(0.196, 1.079)	0.900	(0.200, 1.044)	1.180	(0.994, 1.926)	1.133	(0.993, 1.595)
	TE	0.487	(0.013, 2.474)	0.609	(0.081, 2.289)	0.522	(0.078, 2.984)	0.606	(0.110, 2.141)

Abbreviations: ARDI, average relative dose intensity; **ACRD**, average cumulative relative dose; **NDE** Natural direct effect; **NIE**, Natural indirect effect; **OR,** Odds ratio; **TE,** Total Effect; **TVC,** Time-varying confounding

[a] Path C – including toxicity modelled as a standard confounder.

[b] Path C biased – modelled excluding toxicity as a confounder.

* Not estimable.

Gformula

Results for `gformula` are presented in **Table 6.2** for both ARDI and ACRD as mediators. The aim of utilising `gformula` was to assess for potential intermediate confounding effects by comparing fully adjusted models with toxicity as an intermediate confounder with fully adjusted models treating toxicity as a standard confounder, and partially adjusted models (excluding toxicity), for each trial.

However, clinical interpretation of `gformula` results was challenging. As discussed in the methods, when modelling a continuous exposure such as BMI, `gformula` compares a referent BMI (in this case a BMI of 22.5) with the distribution of BMI within the trial. Therefore, the interpretation of the effect of the exposure here is for a change in the exposure to the mean population BMI, compared with a BMI of 22.5kg/m^2. For a continuous exposure, without a plausible "zero" level (which is the default comparison level and would enable comparison of no exposure vs. the population average exposure), not only does this approach make it more difficult to interpret the meaning of direct and indirect effects within each trial, but it also prevents standardised comparison of effects across the different trials, given different within-trial BMI distributions.

Results for the NDE, NIE and TE were generally not statistically significant and closer to a null effect, than with `parmed` and `regmedint` results, with minimal difference between partially adjusted models (excluding toxicity) and fully adjusted models treating toxicity as a time-varying or a standard confounder, probably the result of the underlying BMI distributions used for comparison.

Results for TOX1 and TOX2 populations are presented in the appendix (**Table A6.2**) and demonstrated similar NIE results. However, similar to `paramed` models, natural direct and total effects for the TOX1 and TOX2 populations tended to differ from those of the Main population.

Finally, worth noting, however, is the potential advantage of `gformula` in the setting of small studies such as CHRONICLE, where multiple confounders and small event numbers may be problematic for estimation and bootstrapping. `Gformula` produced more plausible estimates and confidence intervals, likely as a result of the simulation-based approach, compared with the regression-based approach of `parmed` and `regmedint`.

Table 6.2 | Path *c* 3-year overall survival - `gformula`

Results of path *c* mediation analyses with `gformula` demonstrating the total (TE) and natural direct (NDE) effects of 5kg/m^2 BMI on 3-year overall survival, and the natural indirect effect (NIE) mediated either through ARDI or ACRD for the Main population. Results are presented for models including toxicity as a time-varying confounder (path *c* - TVC), a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the mean survival time ratio (MSR); confidence intervals are calculated with bootstrapping methods. Statistically significant results in **bold.**

		ARDI						ACRD					
		Path C – TVC[a]		Path C[b]		Path C biased[c]		Path C – TVC[a]		Path C[b]		Path C biased[c]	
Trial	**Effect**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
MOSAIC	**NDE**	0.987	(0.954, 1.021)	1.018	(0.986, 1.052)	1.011	(0.978, 1.018)	0.986	(0.953, 1.019)	0.997	(0.966, 1.029)	0.998	(0.967, 1.030)
	NIE	**1.029**	**(1.003, 1.055)**	0.980	(0.955, 1.006)	0.991	(0.966, 1.016)	1.022	(0.997, 1.047)	0.993	(0.969, 1.017)	0.994	(0.970, 1.018)
	TE	1.016	(0.983, 1.050)	0.998	(0.967, 1.031)	1.002	(0.971, 1.035)	1.007	(0.975, 1.041)	0.990	(0.959, 1.022)	0.992	(0.961, 1.025)
SCOT_3M	**NDE**	0.999	(0.979, 1.020)	0.994	(0.974, 1.014)	1.011	(0.992, 1.031)	1.000	(0.980, 1.020)	0.993	(0.974, 1.012)	1.007	(0.988, 1.027)
	NIE	1.005	(0.990, 1.021)	1.011	(0.995, 1.026)	0.994	(0.979, 1.010)	1.010	(0.994, 1.026)	1.011	(0.995, 1.027)	0.992	(0.977, 1.008)
	TE	1.004	(0.984, 1.025)	1.004	(0.985, 1.025)	1.005	(0.986, 1.026)	1.009	(0.989, 1.030)	1.004	(0.989, 1.024)	1.000	(0.980, 1.019)
SCOT_6M	**NDE**	1.000	(0.981, 1.019)	0.993	(0.975, 1.011)	1.006	(0.988, 1.025)	0.996	(0.977, 1.014)	0.992	(0.974, 1.010)	1.011	(0.993, 1.031)
	NIE	0.998	(0.983, 1.014)	0.996	(0.981, 1.011)	0.991	(0.976, 1.006)	1.006	(0.991, 1.022)	1.002	(0.986, 1.018)	0.989	(0.974, 1.004)
	TE	0.998	(0.979, 1.018)	0.989	(0.971, 1.007)	0.997	(0.979, 1.016)	1.002	(0.983, 1.022)	0.994	(0.975, 1.013)	1.001	(0.982, 1.020)
CHRONICLE	**NDE**	1.063	(0.802, 1.409)	1.130	(0.843, 1.515)	1.021	(0.769, 1.354)	1.042	(0.760, 1.428)	1.130	(0.817, 1.564)	0.960	(0.705, 1.307)
	NIE	1.000	(0.900, 1.111)	1.000	(0.909, 1.100)	0.941	(0.853, 1.038)	1.000	(0.908, 1.101)	0.980	(0.898, 1.069)	0.960	(0.866, 1.064)
	TE	1.063	(0.810, 1.395)	1.130	(0.850, 1.503)	0.960	(0.731, 1.262)	1.042	(0.763, 1.422)	1.107	(0.803, 1.527)	0.922	(0.681, 1.247)
PS	**NDE**	0.972	(0.895, 1.055)	0.983	(0.906, 1.067)	0.983	(0.907, 1.065)	0.983	(0.913, 1.058)	0.994	(0.925, 1.069)	0.994	(0.926, 1.067)
	NIE	0.989	(0.942, 1.038)	1.017	(0.971, 1.066)	1.029	(0.980, 1.081)	1.006	(0.962, 1.051)	1.006	(0.962, 1.052)	0.994	(0.951, 1.039)
	TE	0.961	(0.889, 1.038)	1.000	(0.923, 1.083)	1.011	(0.937, 1.092)	0.989	(0.915, 1.068)	1.000	(0.927, 1.078)	0.989	(0.918, 1.065)

Abbreviations: ARDI, average relative dose intensity; **ACRD**, average cumulative relative dose; **NDE** Natural direct effect; **NIE**, Natural indirect effect; **OR,** Odds ratio; **TE,** Total Effect; **TVC,** Time-varying confounding

[a] Path C TVC – including toxicity modelled as a time-varying confounder.

[b] Path C – including toxicity modelled as a standard confounder.

[c] Path C biased – modelled excluding toxicity as a confounder.

Regmedint

Trial-level results for `regmedint` are presented in **Table 6.3** for both ARDI and ACRD as mediators. For SCOT_3M and SCOT_6M Main populations, results from the BIM approach are presented in addition to standard bootstrapping alone (only possible for partially adjusted analysis) for comparison, to assess the reliability of the BIM approach.

Models examining ARDI as a potential mediator demonstrated no significant TE, NDE or NIE for any trial, except for a small significant NIE for SCOT_6M. However, for fully adjusted models for ACRD, there was a small significant NIE mediated via ACRD for both MOSAIC and SCOT_3M. That is, for each 5kg/m^2 increment of BMI, there was a 2% reduction in the mean overall survival time for MOSAIC (MSR 0.98, 95%CI 0.96, 1.00), and a 1% reduction for SCOT_3M (MSR 0.99, 95%CI 0.98, 1.00). Similar to `paramed`, the NIE was in the opposing direction of the NDE for MOSAIC and in the same direction for SCOT_3M, though NDEs were not statistically significant. There was also a tendency for the NIE in PS to demonstrate a reduction in mean survival time (MSR 0.96, 95%CI 0.98, 1.03). Bootstrapping of models for CHRONICLE, similarly, had difficulty converging, and hence bootstrapped confidence intervals could not be calculated.

Effect estimates for fully and partially adjusted path *c* models were very similar, suggesting minimal bias introduced as a result of not adjusting for toxicity. Furthermore, the results obtained with boot-impute methods (both fully and partially adjusted models) and the partially adjusted bootstrapped model demonstrated very similar effect estimates and confidence intervals, suggesting that the BIM method produced reliable results.

Results for TOX1 and TOX2 populations are presented in the appendix (**Table A6.3**) and demonstrated similar NIE results but tended to be non-significant for all trials. Again, NDE and TE estimates for TOX1 and TOX2 populations, though remaining non-significant, were substantially different from the Main population, for SCOT_3M with both ARDI and ACRD as mediators. Overall, results were in keeping with those demonstrated from `paramed`.

Table 6.3 | Path *c* overall survival – `Regmedint`

Results of path *c* mediation analyses with `regmedint` demonstrating the total (TE) and natural direct (NDE) effects of 5kg/m^2 BMI on 3-year overall survival, and the natural indirect effect (NIE) mediated either through ARDI or ACRD for the Main population. Results are presented for models including toxicity as a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the mean survival time ratio (MSR); confidence intervals are calculated with bootstrapping or boot-impute methods. Statistically significant results in **bold.**

			ARDI				ACRD			
			Path C[a]		Path C Biased[b]		Path C[a]		Path C Biased[b]	
Trial	**Method**	**Effect**	**MSR**	**95%CI**	**MSR**	**95%CI**	**MSR**	**95%CI**	**MSR**	**95%CI**
MOSAIC	**Boot**	**NDE**	1.016	(0.892, 1.175)	1.011	(0.891, 1.168)	1.055	(0.926, 1.226)	1.050	(0.923, 1.222)
		NIE	1.012	(0.992, 1.040)	1.001	(0.979, 1.028)	**0.982**	**(0.964, 0.997)**	**0.976**	**(0.956, 0.993)**
		TE	1.028	(0.903, 1.190)	1.012	(0.891, 1.169)	1.037	(0.910, 1.208)	1.026	(0.899, 1.195)
SCOT_3M	**Boot**	**NDE**	NA	NA	0.967	(0.893, 1.049)	NA	NA	0.980	(0.907, 1.062)
		NIE	NA	NA	1.002	(0.995, 1.011)	NA	NA	**0.991**	**(0.983, 0.997)**
		TE	NA	NA	0.969	(0.896, 1.052)	NA	NA	0.971	(0.898, 1.054)
	BIM	**NDE**	0.959	(0.884, 1.040)	0.966	(0.892, 1.047)	0.975	(0.900, 1.057)	0.980	(0.905, 1.061)
		NIE	1.005	(0.996, 1.013)	1.002	(0.995, 1.010)	**0.992**	**(0.984, 0.999)**	**0.991**	**(0.984, 0.999)**
		TE	0.963	(0.888, 1.045)	0.969	(0.894, 1.049)	0.967	(0.893, 1.047)	0.971	(0.897, 1.051)
SCOT_6M	**Boot**	**NDE**	NA	NA	1.022	(0.945, 1.111)	NA	NA	1.037	(0.960, 1.127)
		NIE	NA	NA	**1.008**	**(1.002, 1.018)**	NA	NA	0.995	(0.984, 1.006)
		TE	NA	NA	1.030	(0.953, 1.122)	NA	NA	1.033	(0.955, 1.120)
	BIM	**NDE**	1.025	(0.945, 1.112)	1.024	(0.944, 1.110)	1.039	(0.960, 1.125)	1.039	(0.960, 1.124)
		NIE	**1.009**	**(1.001, 1.016)**	**1.008**	**(1.001, 1.016)**	0.995	(0.985, 1.006)	0.995	(0.984, 1.007)
		TE	1.034	(0.953, 1.122)	1.032	(0.952, 1.120)	1.034	(0.955, 1.119)	1.034	(0.955, 1.119)
CHRONICLE	**Boot**	**NDE**	1.007	*	1.074	*	0.922	*	1.007	*
		NIE	1.026	*	1.035	*	1.016	*	1.008	*
		TE	1.033	*	1.111	*	0.937	*	1.015	*
PS	**Boot**	**NDE**	1.795	(1.163, 2.818)	1.681	(1.098, 2.538)	1.801	(1.209, 2.861)	1.709	(1.148, 2.572)
		NIE	1.018	(0.964, 1.125)	1.012	(0.964, 1.103)	0.960	(0.864, 1.031)	0.955	(0.865, 1.017)
		TE	1.827	(1.185, 2.888)	1.700	(1.125, 2.571)	1.728	(1.146, 2.720)	1.633	(1.096, 2.471)

Abbreviations: ARDI, average relative dose intensity; **ACRD**, average cumulative relative dose; **Boot,** Bootstrapped; **BIM,** Boot-Impute; **MSR,** Mean Survival ratio; **NDE** Natural direct effect; **NIE**, Natural indirect effect; **TE,** Total Effect.

[a] Path C – including toxicity modelled as a standard confounder.

[b] Path C Biased – modelled excluding toxicity as a confounder

* CHRONICLE model effect estimates from non-bootstrapped models, bootstrapping of confidence intervals not estimable.

6.3.2 PATH C – META-MEDIATION

Path C models for overall, disease-free, and cancer-specific survival were run at the trial level using the `regmedint` package, followed by meta-analysis using univariate (UV), univariate forced weights (UVFW) and multivariate (MV) methods as described above.

Overall Survival

The results for overall survival are presented in **Figures 6.1a** and **6.1b** for ARDI and ACRD as mediators respectively. For both models there was no evidence of a total or natural direct effect of 5kg/m^2 increments of BMI on OS. However, there was a significant NIE resulting via ARDI for all three meta-analysis approaches, where each 5kg/m^2 BMI increment was associated with approximately a 1% increase in the mean survival time (UV MSR: 1.007 (95%CI 1.002, 1.013); UVFW MSR: 1.008 (95%CI 1.001, 1.014); MV MSR 0.007 (95%CI 1.001, 1.014)). Conversely, there was a significant NIE in the opposing direction via ACRD, with an MSR: 0.991 for all three meta-analysis approaches, meaning an approximate 1% reduction in mean survival time with 5kg/m^2 BMI increments (UV MSR 0.991 [95%CI: 0.986, 0.997]; UVFW MSR 0.991 [95%CI: 0.985, 0.997]; MV MSR 0.991 [95%CI 0.985, 0.998]).

Univariate and multivariate total weights were similar, with minimal borrowing of strength. Furthermore, NDE weights tended to be similar to TE weights in univariate and multivariate meta-analysis, whereas NIE weights tended to differ from both.

Disease-Free Survival

The results for disease-free survival are presented in **Figures 6.2a** and **6.2b** for ARDI and ACRD as mediators respectively. There was no evidence of a total or natural direct effect of 5kg/m^2 increments of BMI on disease-free survival, and no evidence of a natural indirect effect via ARDI. However, there was a significant natural indirect effect for ACRD. The NIE via ACRD was an MSR of 0.990 for both UV (95%CI: 0.984,0.996) and MV (95%CI: 0.982, 0.999) models, and 0.992 for UVFW (95%CI: 0.982, 1.002) for the three meta-analysis approaches, meaning approximately a 1% reduction in the mean survival time for each 5kg/m^2 increment in BMI. The univariate forced weights approach was borderline non-significant. Again, univariate, and multivariate total weights were similar, with minimal BoS. Furthermore, NDE weights tended to be similar to TE weights in univariate and multivariate meta-analysis, whereas NIE weights tended to differ substantially.

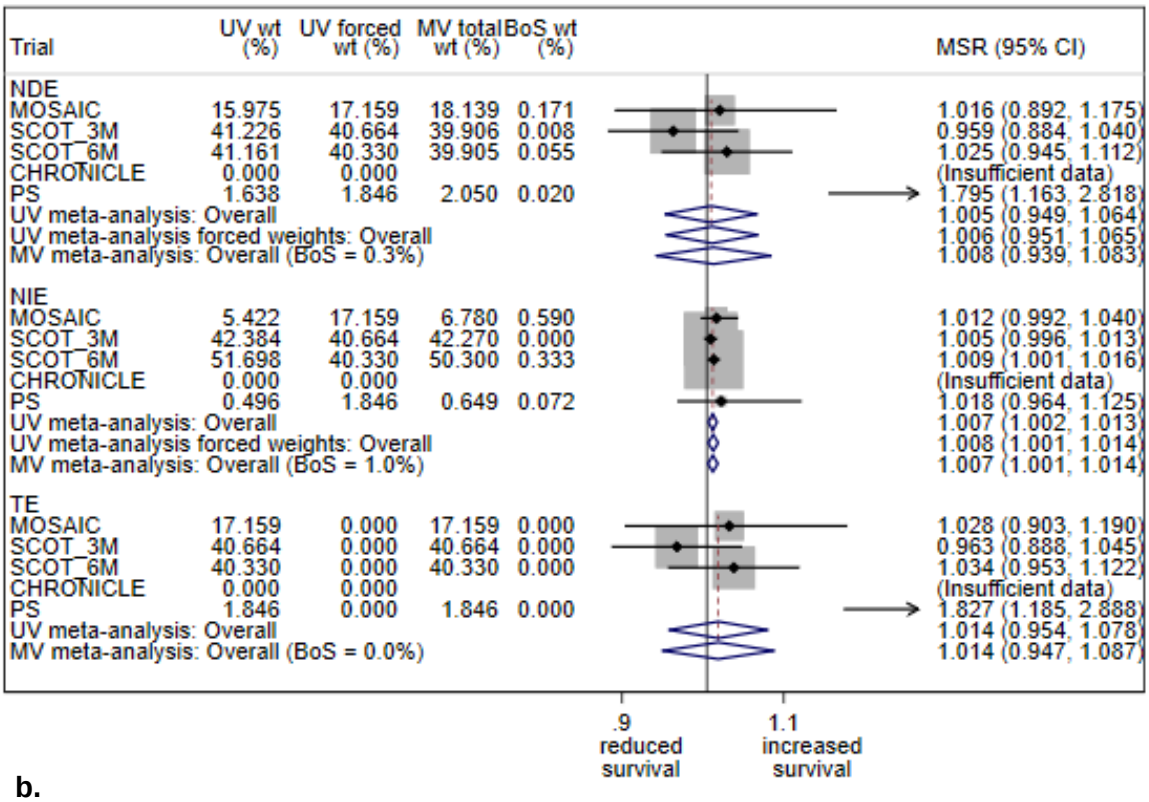
Cancer-Specific Survival

Convergence issues were encountered with some of the CSS models during bootstrapping and boot-impute analyses, producing seemingly unreliable estimates, possibly due to the smaller number of events combined with the number of covariates included in the models, and the resampling during bootstrapping, and hence these were not meta-analysed.

Figure 6.1 | Path *c* meta-mediation for overall survival

Forest plots demonstrating the results of meta-analysed mediation models for the effect of 5kg/m^2 increments of BMI on overall survival, mediated by **a** ARDI and **b** ACRD. Univariate (UV) and multivariate (MV) meta-analysis of the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) are presented together with their respective weights, in addition to UV models for the NDE and NIE with weights (wt) forced to those of the TE. Also presented are borrowing of strength (BoS) weights for the multivariate analyses.

a.



b.

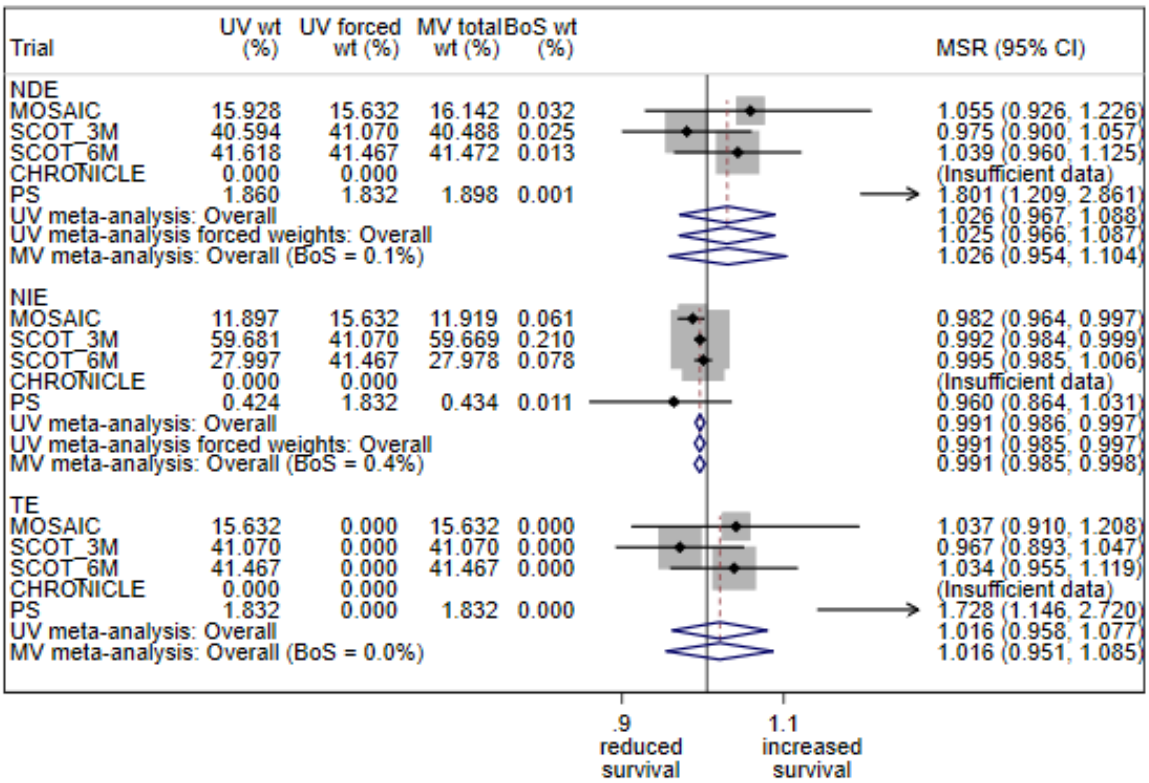
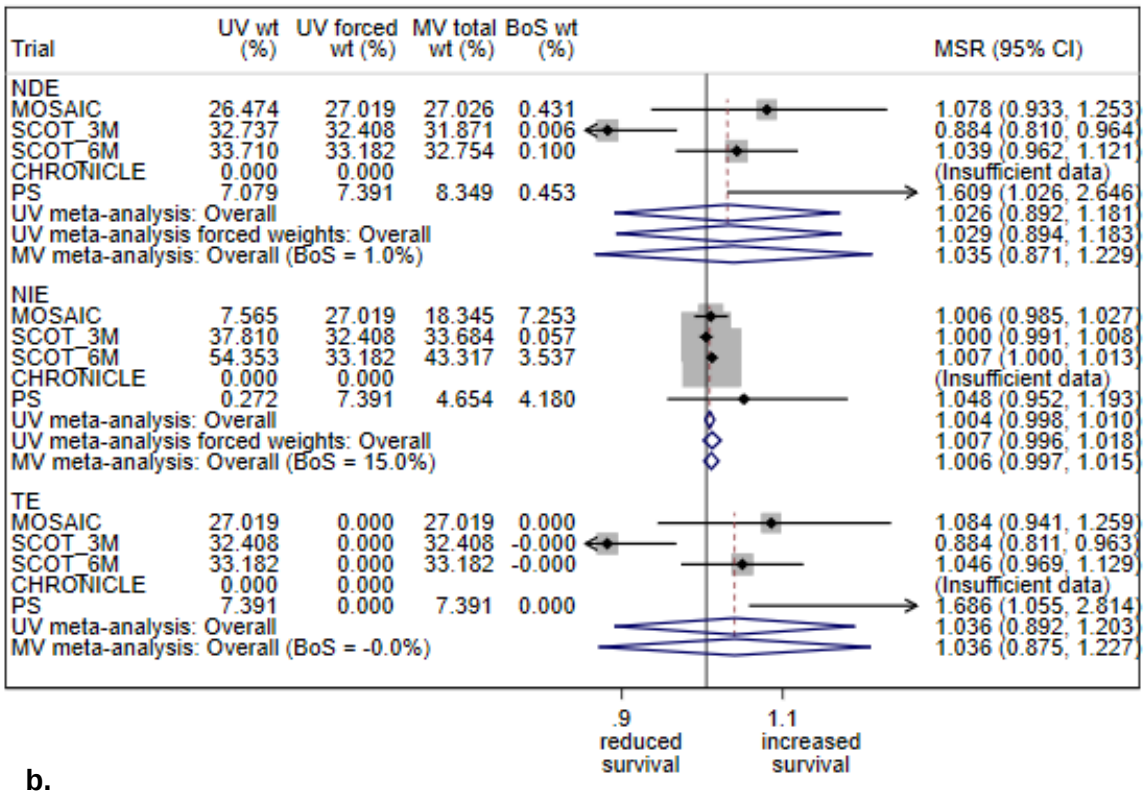


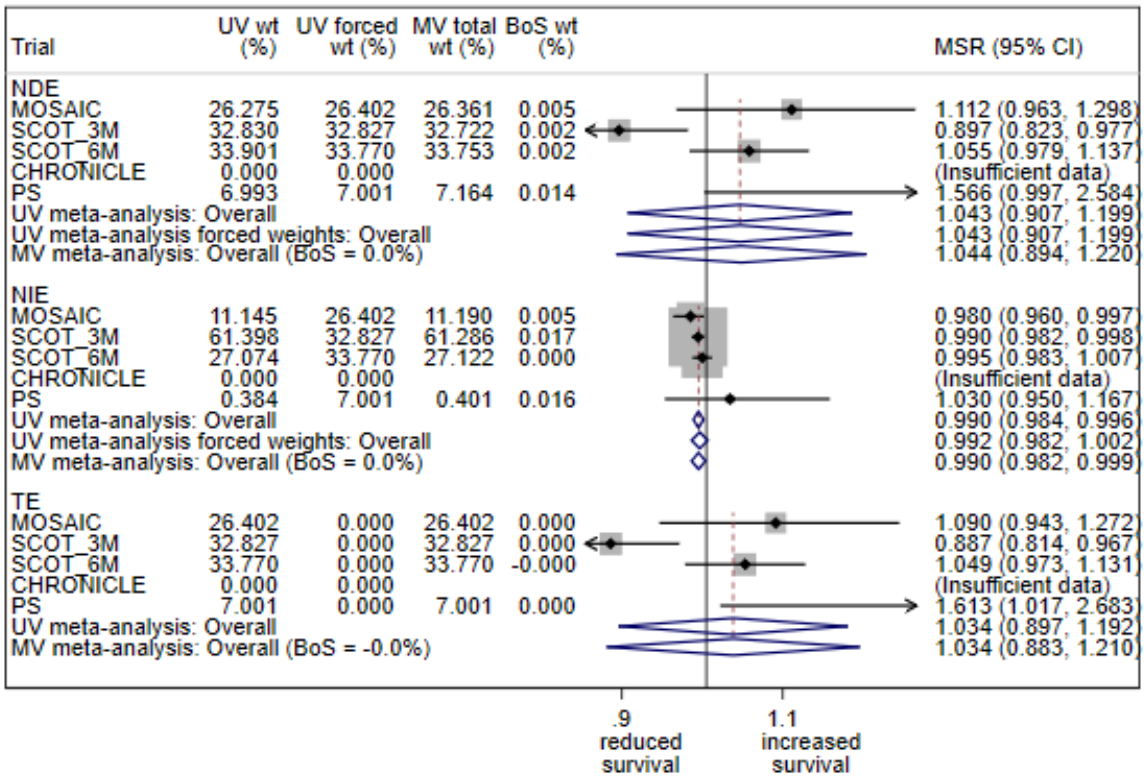
Figure 6.2 | Path *c* meta-mediation for disease-free survival

Forest plots demonstrating the results of meta-analysed mediation models for the effect of 5kg/m^2 increments of BMI on disease-free survival, mediated by **a** ARDI and **b** ACRD. Univariate (UV) and multivariate (MV) meta-analysis of the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) are presented together with their respective weights, in addition to UV models for the NDE and NIE with weights (wt) forced to those of the TE. Also presented are borrowing of strength (BoS) weights for the multivariate analyses.

a.



b.



6.3.3 PATH A – META-MEDIATION

Meta-mediation of path *a* was undertaken to confirm the lack of mediation of BMI-ARDI and BMI-ACRD relationships by grade 3+ toxicity, demonstrated in Chapter five, as a result of no significant BMI-toxicity association.

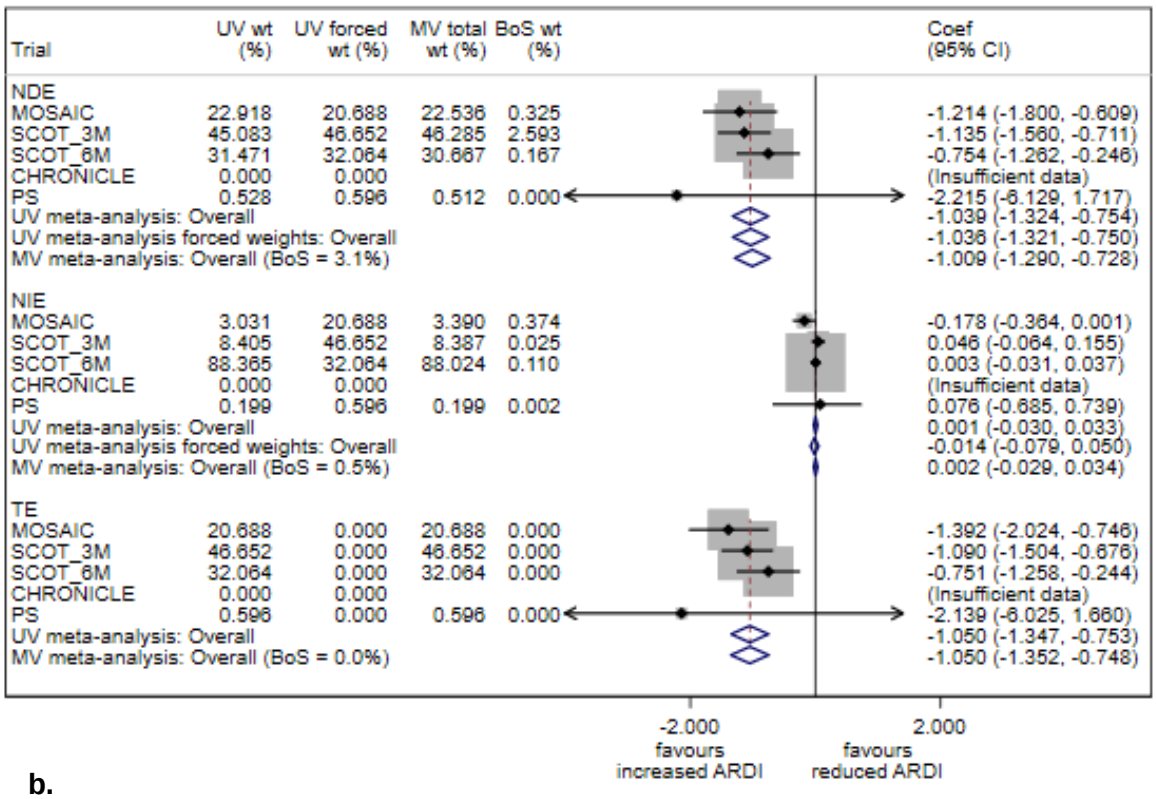
The results for ARDI and ACRD are presented in **Figures 6.3a** and **6.3b** respectively. For both outcomes, the there was no evidence of a natural indirect effect via toxicity. There was a significant total and natural direct effect of 5kg/m^2 increments of BMI on ARDI of approximately -1% (in keeping with Chapter five results). Univariate and multivariate approaches produced similar effect estimates with similar weights for NDE compared with TE, with minimal borrowing of strength for the MV models. These differed substantially from the NIE weights, and hence the univariate forced weights approach, substantially altered the NIE weights. Though this had the potential to influence the pooled NIE result for the forced-weights approach, it did not substantially alter the NIE or its interpretation.

Similarly, for ACRD there was a significant TE and NDE, with approximately a 1% reduction of ACRD for each 5kg/m^2 increment of BMI. Again, univariate, and multivariate approaches produced similar effect estimates with similar weights for NDE and TE, with no borrowing of strength. The univariate and multivariate NIE weights were also reasonably similar to the TE weights and use of forced weights did not substantially alter results.

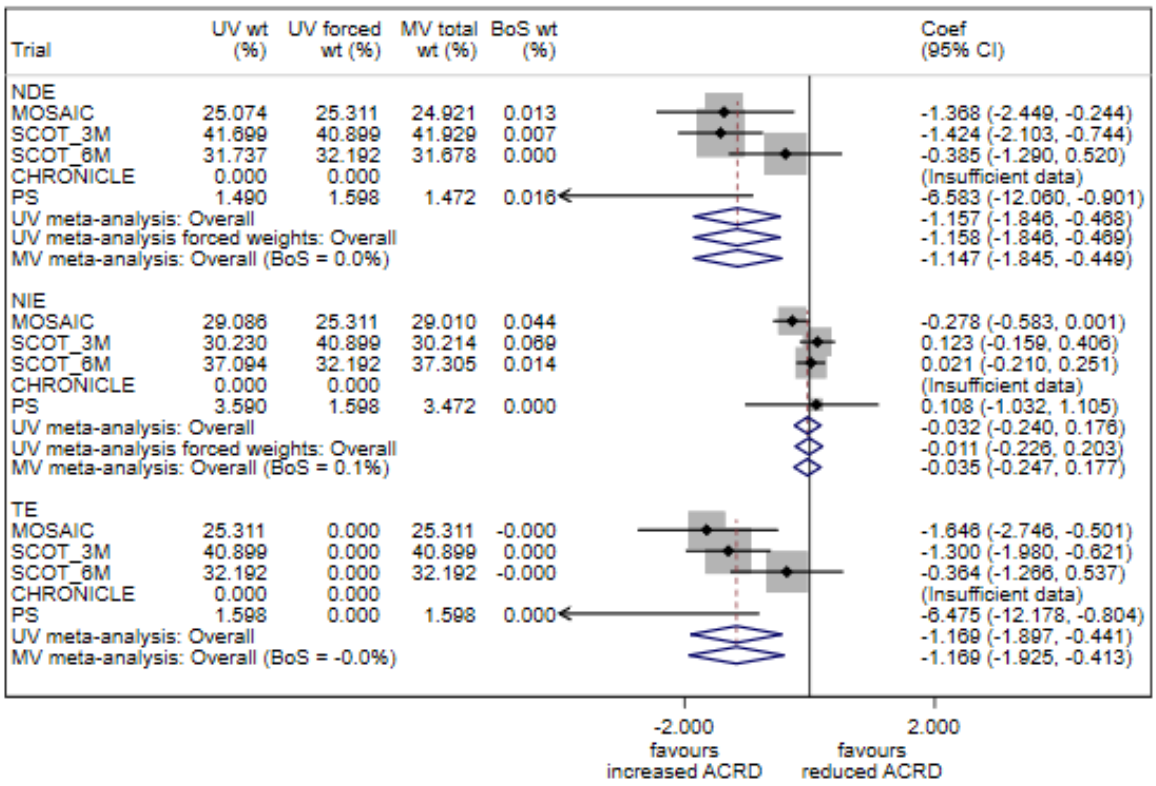
Figure 6.3 | Path *a* meta-mediation

Forest plots demonstrating the results of meta-analysed mediation models for the effect of 5kg/m^2 increments of BMI on **a** ARDI and **b** ACRD, mediated by grade 3+ toxicity. Univariate (UV) and multivariate (MV) meta-analysis of the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) are presented together with their respective weights, in addition to UV models for the NDE and NIE with weights (wt) forced to those of the TE. Also presented are borrowing of strength (BoS) weights for the multivariate analyses.

a.



b.



6.3.4 PATH F – META-MEDIATION

Overall Survival

The results for overall survival are presented in **Figures 6.4a** and **6.4b** for ARDI and ACRD as mediators respectively. The ARDI model demonstrated a significant total effect of toxicity on overall survival, with approximately a 19% reduction in mean survival time and identical results for UV and MV methods (MSR 0.811, 95%CI: 0.735, 0.895). There was no significant NIE, meaning that the effect of toxicity on overall survival occurred via pathways other than that through ARDI, with a significant NDE demonstrating a reduction in mean survival time of 20%.

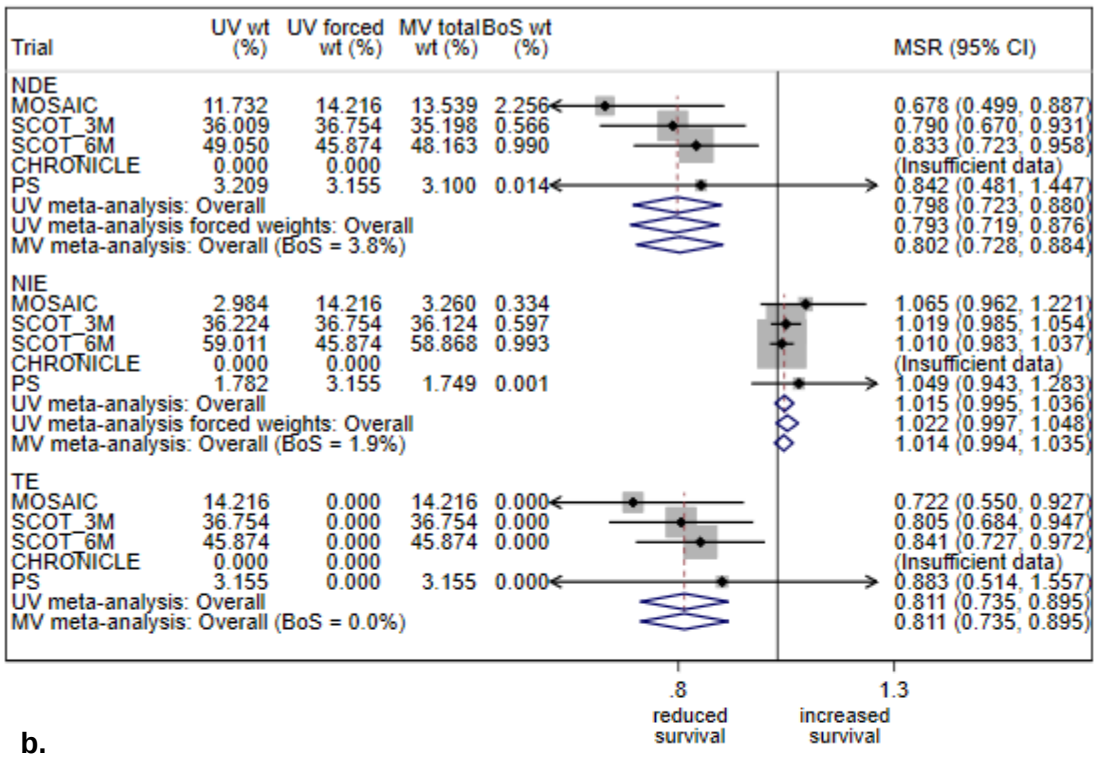
Conversely, where ACRD was included as the mediator, there was evidence of approximately half of the effect being mediated via the natural indirect effect: the effect of toxicity on overall survival acting via ACRD was a reduction in the mean survival time of approximately 9% (UV and MV MSR 0.907 [95%CI: 0.876, 0.939]; UVFW MSR 0.906 [95%CI: 0.874, 0.939]) and the effect acting though other pathways (the NDE) was a 10% reduction in the mean survival time (UV MSR 0.900 [95%CI: 0.824, 0.983]; MV MSR 0.901 [95%CI: 0.825, 0.984]; UVFW MSR 0.899 [95%CI: 0.823, 0.982]). The NIE and NDE combined to a total effect of approximately 19% reduction in the mean survival time (UV and MV MSR 0.814 [95%CI 0.740, 0.896]).

Again, univariate, and multivariate total weights were similar, with minimal borrowing of strength, and NDE weights tended to be similar to TE weights in univariate and multivariate meta-analysis, whereas NIE weights tended to differ from those of the NDE and TE. However, forcing the weights to take the value of the TE weights did not substantially alter effect estimates or confidence intervals for either model.

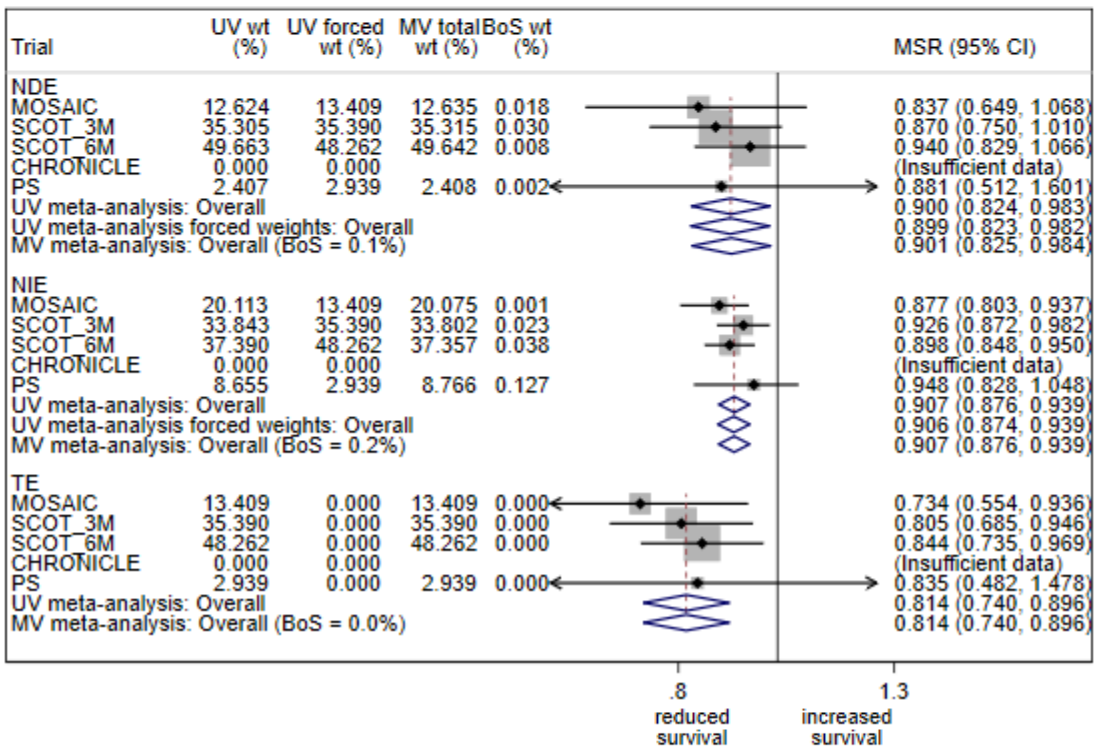
Figure 6.4 | Path *f* meta-mediation for overall survival

Forest plots demonstrating the results of meta-analysed mediation models for the effect of grade 3+ toxicity on overall survival, mediated by **a** ARDI and **b** ACRD. Univariate (UV) and multivariate (MV) meta-analysis of the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) are presented together with their respective weights, in addition to UV models for the NDE and NIE with weights (wt) forced to those of the TE. Also presented are borrowing of strength

a.



b.



Disease-Free Survival

The results for disease-free survival are presented in **Figures 6.5a** and **6.5b** for ARDI and ACRD as mediators respectively. Where ARDI was included as the mediator, there was a significant total effect of toxicity on DFS, with approximately a 15% reduction in mean survival time (UV MSR 0.846 (95%CI 0.744, 0.963); MV MSR 0.846 (95%CI: 0.742, 0.964)). Similar to overall survival results, there was no significant NIE, meaning that the effect of toxicity on DFS occurred via pathways other than that through ARDI, with the NDE demonstrating a significant reduction in mean survival time of 16%-17%.

Conversely, where ACRD was included as the mediator, there was evidence of approximately two-thirds of the effect being mediated via the natural indirect effect: the effect of toxicity on DFS acting indirectly via ACRD was approximately a 10% reduction in the mean survival time (UV MSR 0.898 (95%CI 0.866, 0.931); UVFW MSR 0.895 (95%CI: 0.863, 0.929); MV MSR 0.904 (95%CI: 0.849, 0.962)), and the effect acting though other pathways (the NDE) was a non-significant reduction of the mean survival time of approximately 3-5% (model-dependent). Thus, the total effect was an approximate 15% reduction in the mean survival time (UV MSR 0.848 (95%CI 0.755, 0.952); MV MSR 0.848 (95%CI: 0.751, 0.957).

For the ARDI model, univariate and multivariate total weights were similar, with only a small amount of borrowing of strength, and NDE weights tended to be similar to TE weights in univariate and multivariate meta-analysis. The NIE weights were substantially different to the NDE and TE weights, however, forcing weights did not substantially alter the NIE effect estimates, and only slightly altered their confidence intervals, increasing uncertainty.

Conversely, for the ACRD model, although the univariate and multivariate TE weights were similar, they differed slightly for the NDE, with a larger borrowing of strength (7%). The NIE univariate and multivariate weights differed to the total effect weights, with less borrowing of strength. However, forcing the weights to take the values of those from the TE did not substantially alter effect estimates.

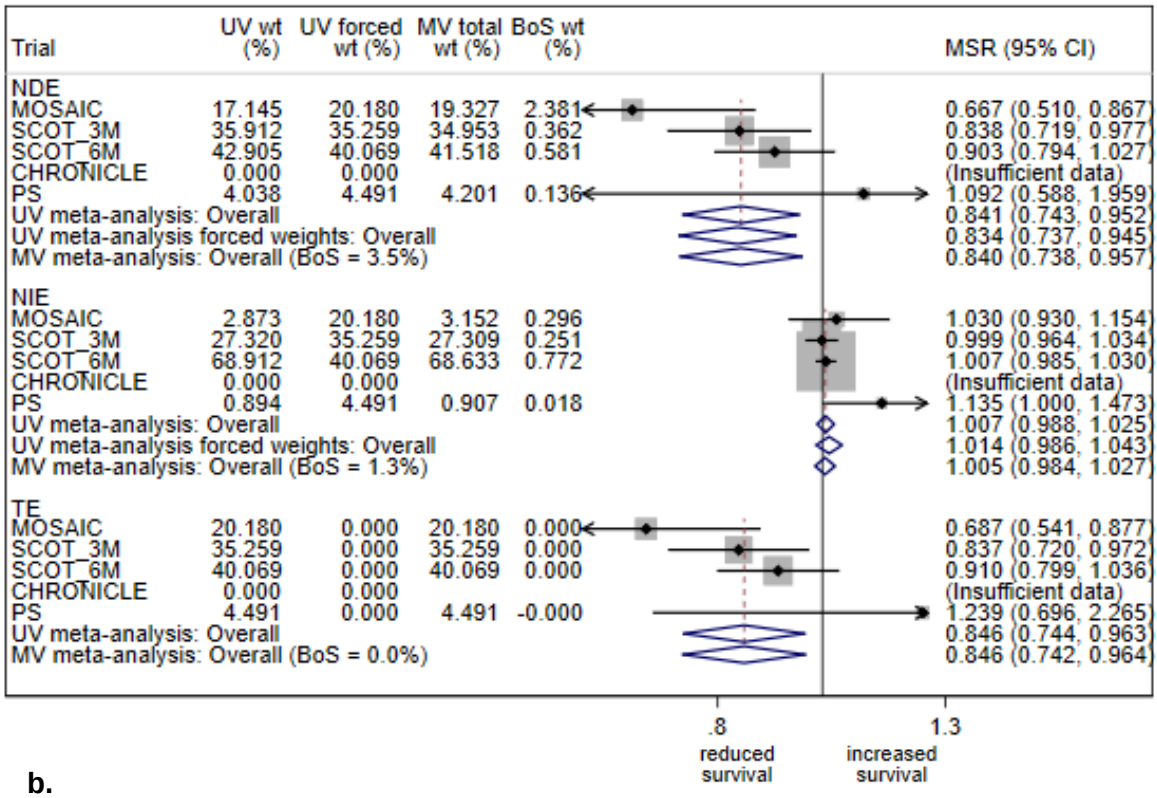
Cancer-Specific Survival

Similar to path *c*, there were problems with some of the CSS models not converging during bootstrapping and boot-impute analyses, hence meta-analysis was not performed.

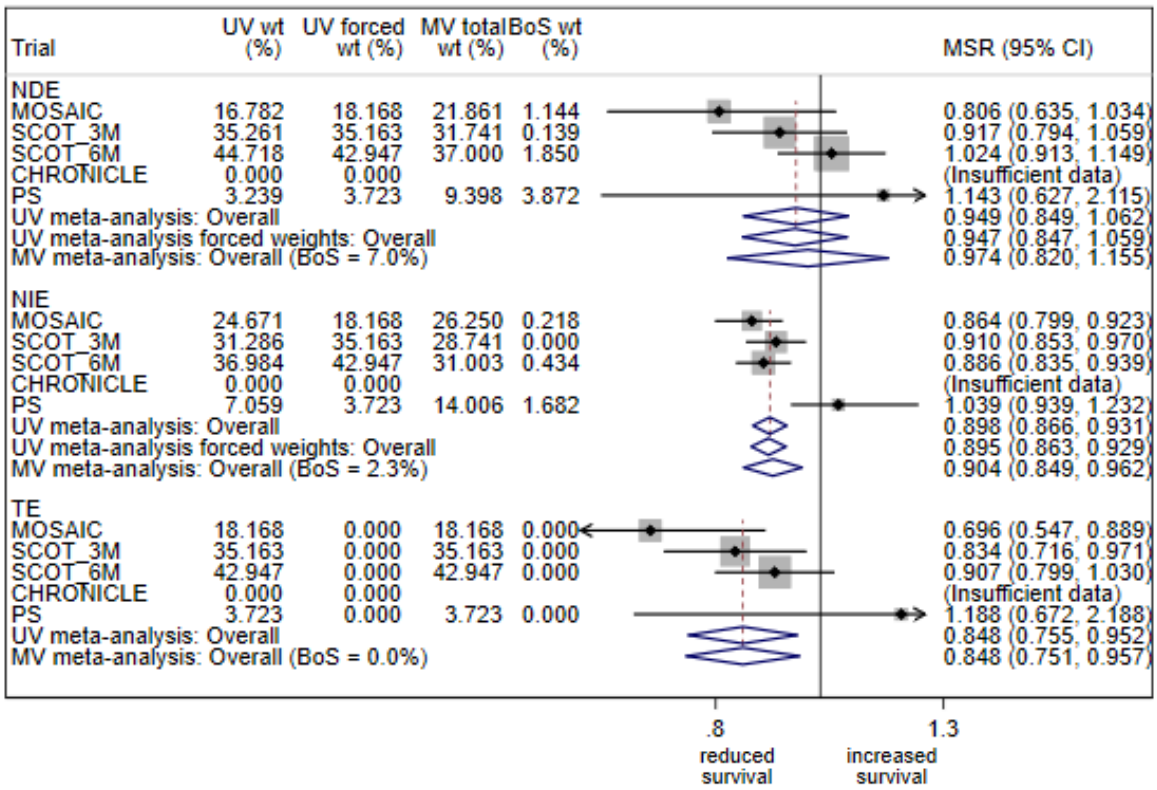
Figure 6.5 | Path *f* meta-mediation for disease-free survival

Forest plots demonstrating the results of meta-analysed mediation models for the effect of grade 3+ toxicity on overall survival, mediated by **a** ARDI and **b** ACRD. Univariate (UV) and multivariate (MV) meta-analysis of the natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) are presented together with their respective weights, in addition to UV models for the NDE and NIE with weights (wt) forced to those of the TE. Also presented are borrowing of strength (BoS) weights for the multivariate analyses.

a.



b.



6.3.5 TOTAL EFFECTS

Given that the total effect is the sum (or product) of the NDE and NIE, it would be expected that addition (or multiplication, for the ratio scale) of the meta-analysed NDE and NIE estimates would equal the meta-analysed TE estimate. As discussed in the methods, it was expected that should the trial-weights for the NDE differ from the NIE, then this would not be the case. **Table 6.4** demonstrates the estimated total effect (TE-Est) and those calculated (TE-Calc) by simply combining the NDE and NIE estimate (either adding or multiplying them depending on the scale). Though TE-Est and TE-Calc were generally very similar for the majority of analyses, only the univariate forced weight models resulted in estimated TEs that equalled the calculated TEs.

Table 6.4 | Comparison of estimated and calculated total effects

Table demonstrating the total effects estimated (TE-Est) from the meta-analysis models and the total effect calculated (TE-Calc) by summing the meta-analysed natural direct effect (NDE-Est) and natural indirect effect (NIE-Est) estimates. Note that on the ratio scale the NDE is multiplied by the NIE (multiplicative scale rather than additive). Where the TE-Est and TE-Calc agree, this is highlighted in **bold**.

Path	Adherence measure	Meta-analysis method	NDE-Est	NIE-Est	TE-Est	TE-Calc
			MSR	**MSR**	**MSR**	**MSR**
Path *c* (OS)	**ARDI**	**UV**	1.005	1.007	1.014	1.012
		UVFW	1.006	1.008	**1.014**	**1.014**
		MV	1.008	1.007	1.014	1.016
	ACRD	**UV**	1.026	0.991	1.016	1.017
		UVFW	1.025	0.991	**1.016**	**1.016**
		MV	1.026	0.991	1.016	1.017
Path *c* (DFS)	**ARDI**	**UV**	1.026	1.004	1.036	1.031
		UVFW	1.029	1.007	**1.036**	**1.036**
		MV	1.035	1.006	1.036	1.041
	ACRD	**UV**	1.043	0.990	1.034	1.032
		UVFW	1.043	0.992	**1.034**	**1.034**
		MV	1.044	0.99	**1.034**	**1.034**
			Coef.	**Coef.**	**Coef.**	**Coef.**
Path *a*	**ARDI**	**UV**	-1.039	0.001	-1.050	-1.038
		UVFW	-1.036	-0.014	**-1.050**	**-1.050**
		MV	-1.009	0.002	-1.050	-1.006
	ACRD	**UV**	-1.157	-0.032	-1.169	-1.189
		UVFW	-1.158	-0.011	**-1.169**	**-1.169**
		MV	-1.147	-0.035	-1.169	-1.182
			MSR	**MSR**	**MSR**	**MSR**
Path *f* (OS)	**ARDI**	**UV**	0.798	1.015	0.811	0.810
		UVFW	0.793	1.022	**0.811**	**0.811**
		MV	0.802	1.014	0.811	0.814
	ACRD	**UV**	0.900	0.907	0.814	0.816
		UVFW	0.899	0.906	**0.814**	**0.814**
		MV	0.901	0.907	0.814	0.817
Path *f* (DFS)	**ARDI**	**UV**	0.841	1.007	0.846	0.847
		UVFW	0.834	1.014	**0.846**	**0.846**
		MV	0.840	1.005	0.846	0.845
	ACRD	**UV**	0.949	0.898	0.848	0.852
		UVFW	0.947	0.895	**0.848**	**0.848**
		MV	0.974	0.904	0.848	0.880

Abbreviations: ACRD, average cumulative relative dose; **ARDI**, average relative dose intensity**; DFS**, disease-free survival; **MV**, multivariate; **NDE-Est**, natural direct effect – estimated; **NIE-Est**, natural indirect effect – estimated; **OS**, overall survival; **UV**, univariate; **UVFW**, univariate forced weights; **TE-Est**, total effect – estimated; **TE-Calc**, Total effect – calculated;

6.4 DISCUSSION

6.4.1 SUMMARY AND INTERPRETATION OF RESULTS

Overall, the results from the meta-mediation demonstrated a number of key findings, consistent with those demonstrated in Chapter five.

First, meta-mediation resulted in a significant natural indirect effect of BMI on both overall survival and disease-free survival, mediated through ACRD. Increments of 5kg/m^2 of BMI were associated with a 1% reduction in the mean survival time. However, there was no significant natural direct effect of BMI on either OS or DFS, and the NIE effect size was likely too small to induce a significant total effect. There was furthermore, a significant NIE effect on BMI on overall survival through ARDI, with a 1% increase in the mean survival time, but not for DFS.

Second, there was no mediation of either BMI-ARDI or BMI-ACRD relationships by grade 3+ toxicity, most likely due to the lack of BMI-toxicity relationship, suggesting that adjusting for toxicity would not substantially bias NDE and NIE effect estimates as a result of intermediate confounding.

Third, grade 3+ toxicity was associated with a reduced overall and disease-free mean survival time of 19% and 15% respectively (total effect). There was partial mediation of toxicity effects on OS by ACRD, with approximately 50% of the TE going via the NIE (9% reduction of mean survival time) and the NDE (10% reduction). Similarly, there was partial mediation of toxicity effects on DFS via ACRD, with the NIE demonstrating a 10% reduction in the mean survival time, whereas the NDE was smaller and non-significant, suggesting the majority of the toxicity effect on survival was due to the indirect reduction in the ACRD.

In addition to these clinical findings, the practical application of counterfactual mediation analysis approaches, and of methods combining bootstrapping and multiple imputation were demonstrated.

First, despite the potential bias from the 3-year OS outcome models, `paramed` and `regmedint` produced similar results at the trial level. Whereas the `gformula` results were more difficult to interpret clinically, and were close to the null effect, this was likely the result of the different model specification.

Second, analysis of the partially adjusted path *c* models (excluding toxicity) allowed direct comparison of the Boot-Impute method with the standard bootstrapped models. Results from both were very similar for the two arms of SCOT, suggesting that BIM methods produced valid effect estimates and confidence intervals. Furthermore, results from the partially adjusted BIM

and fully adjusted BIM models were also very similar, suggesting minimal bias would be introduced by excluding toxicity as a confounder, in keeping with results from Chapter five. Again, residual bias related to missingness being MNAR rather than MAR could not be completely excluded, though the consistency of outcomes across the BIM and standard bootstrapped models provided a degree of reassurance.

Third, there were convergence issues with models for cancer specific survival outcomes, and for CHRONICLE during bootstrapping. This was probably the result of the small number of events and substantial number of covariates (several of which were binary or categorical), likely producing estimation difficulties as a result of increased risk of perfect prediction within strata of covariates during bootstrap sampling. This highlights the challenges of ensuring sufficient adjustment of confounding, with smaller studies and event rates, when utilising bootstrapping methods.

Fourth, meta-mediation using a two-stage approach was demonstrated to be feasible, using both the univariate and multi-variate approaches, which yielded similar (often identical) effect estimates.

Finally, the issue of weighting in relation to calculation of the total effect was highlighted. Whilst, forcing weights for direct and indirect effects to be the same does not allow for the natural between-trial heterogeneity of the proportion mediated, it does allow the NDE and NIE to combine to equal the TE. Conversely, allowing the weights to vary naturally according to the inverse variance, may give a better understanding of the true population average NDE and NIE effects, but may not sum to the TE. Thus, presentation of both approaches may be useful in drawing conclusions.

CHAPTER SEVEN
DISCUSSION

CHAPTER SEVEN PREFACE

The overarching hypotheses for this thesis were four-fold. First, that there is a relationship between increasing BMI and sub-optimal dosing of adjuvant chemotherapy (ACT). Second, that there is no relationship between BMI and toxicity from ACT. Third that elevated BMI is associated with adverse outcomes. And finally, that this association is mediated at least partly through hypothesis number one. Furthermore, additional aims were to explore and develop these hypotheses using methodology to limit biases and attempt to infer causality.

The results from Chapters three to six, supported hypotheses one, two and four, however no evidence of a BMI-survival relationship was established. This final Chapter explores the thesis results in the context of the current literature, the clinical implications of the findings, and provides critique on the work undertaken, with discussion of unanswered questions and suggestions for future work.

7.1 – FINDINGS IN CONTEXT

7.1.1 BMI AND ADJUVANT CHEMOTHERAPY DOSING

Findings from Chapters three, five and six, supported the first hypothesis, outlined in Chapter one, demonstrating evidence for a relationship between increasing BMI and sub-optimal dosing of adjuvant chemotherapy.

Dose capping

The majority of the literature exploring BMI-dosing relationships in the colorectal cancer (CRC) setting focuses on the relationship between BMI and cycle 1 dose capping. Two large secondary analyses of adjuvant and metastatic CRC randomised trial data, by Dignam et al. (4288 patients). [117] and Chambers et al. (4781 patients)[104] respectively, found increasing incidence of dose capping as BMI increased, with 32-73% of those with a BMI of ≥30kg/m^2 being dose capped (**Chapter 1**, **Table 1.8a**). Findings of a relationship between increasing BMI and increasing dose capping incidence have also previously been reported for breast cancer.[129,132,141,142] Conversely, two earlier studies by Meyerhardt et al. in colon (3438 patients) [120] and rectal (1688 patients)[116] cancer, reported low overall dose capping rates with no significant trends across BMI categories, suggesting the existence of variation in dose capping practices (**Chapter 1, Table 1.8a**).

Results from Chapter three supported the findings of the Dignam[117] and Chambers[104] studies, demonstrating increasing BMI categories were associated with increasing proportions of patients receiving capped cycle 1 doses. Indeed, across the included trials, dose capping ranged 29.6% to 62.2% amongst obese patients, compared with 2.2 to 29.6% amongst patients with normal BMI. Chapter five confirmed these findings, demonstrating the odds of being dose capped more than doubled for each 5kg/m^2 BMI, and further demonstrated a slightly non-linear relationship with increased risk beginning at BMIs of approximately ≥25kg/m^2. These risks are comparable to those from the study published by Griggs et al. within the breast cancer literature, where the odds ratio for dose capping, approximately doubled for each increment in BMI category (**Chapter 1, Table 1.8b**). Furthermore, Chapters three and five demonstrated that dose capping corresponded to a reduction in the relative dose received (RDR) at cycle 1, with the pooled meta-analysed results from Chapter five displaying a 2% reduction in RDR per 5kg/m^2 increment of BMI (Coef. -2.12; 95%CI -2.55, -1.68).

Adherence

The relationship between BMI and adherence measures in colorectal cancer is lacking, converse to the breast and ovarian cancer literature where BMI-dosing relationships often report adherence. Relative dose intensity (RDI) is commonly utilised, often being dichotomised

at a threshold of 85%. Studies from breast and ovarian cancers, on the whole demonstrate increased odds of receiving an RDI of <85% with increasing BMI categories.[133–135,141] Whilst an RDI of <85% is often cited as a clinically significant threshold for potentially adversely impacting on survival outcomes, this data comes mainly from the breast cancer literature.[130,289] and categorising adherence measures is likely to result in substantial loss of information. Griggs et al., explored BMI-RDI relationships utilising linear regression, and published a large retrospective multi-centre cohort study of 9672 patients with stage I-III breast cancer treated with ACT. The authors demonstrated a significant change in the relative dose intensity (RDI) compared with normal BMI: 1.7% for overweight; -3.4% for grade 1 obese; and -7.1% for grade II obese (95%CI not reported), but did not go on to relate this to survival outcomes.[129] Comparatively, the meta-analysis reported in Chapter five, found a significant 1% reduction in ARDI (Coef. -1.08; 95%CI -1.44, -0.72) for each 5kg/m^2 increase in BMI (Chapter five).

The discriminative ability of ARDI to represent overall dosing, in the context of early discontinuation, was questioned early on in the thesis. For example, a patient receiving only one fully BSA-dosed cycle could have an ARDI of 100%, as could a fully BSA-dosed patient receiving all cycles. Hence, the average cumulative relative dose (ACRD) was explored in addition to ARDI. Similar to results for ARDI, the Chapter five meta-analysis reported a significant 1% reduction in the ACRD for each 5kg/m^2 BMI increment (Coef. -1.14; 95%CI-1.91, -0.38). In comparison to cycle 1 RDR, these effects were attenuated, likely the result of longitudinal cycle-level dose reductions reducing differences across BMI, as described in Chapter three. Though a recently published study similarly using data from MOSAIC, identified the potential disadvantages ARDI and advocated for use of a longitudinal cumulative dose measure similar to ACRD, their analysis did not explore the relationship with BMI.[290] Hence, results appeared novel, and no similar literature exploring the relationship between BMI and cumulative dose was identified.

7.1.2 BMI AND TOXICITY

The rationale for dose capping results from concerns over the potential for increased toxicity. The second hypothesis outlined in Chapter one was a lack of association between BMI and toxicity, meaning such justifications might be unfounded. Results from Chapters four and five supported this hypothesis, demonstrating no evidence of a significant relationship between BMI and the occurrence of any grade 3+ toxicity. Furthermore, this lack of association suggested that BMI-ARDI and BMI-ACRD relationships were not mediated through the occurrence of grade 3+ toxicity, which was confirmed in the meta-mediation results from Chapter six.

These results were comparable to those published within the ACT-CRC literature (**Chapter 1, Table 1.11a)**. Two studies from Meyerhardt et al., demonstrated a reduced incidence of grade

3+ toxicity with increasing BMI, both in populations of patients receiving adjuvant chemotherapy with minimal dose capping across all BMI categories.[116,120] Chambers et al., similarly demonstrated a significant trend to reducing grade 3+ toxicity incidence with increasing BMI categories in fully dosed individuals, within their pooled analysis of chemotherapy trial data for metastatic CRC.[104] A number of additional trials presented data without stratifying according to dose-capping status, and therefore made it difficult to identify BMI effects on toxicity across fully dosed patients. These included results from Dignam et al., (demonstrating no significant association in the adjuvant CRC setting) [117] in addition to Simkens et al., (again demonstrating no relationship in the metastatic CRC setting).[115] These studies were additionally limited by either pooling results across different trials (not accounting for random effects) or analysing them separately (thereby reducing their power) in addition to categorising BMI.

Given that stratification and meta-regression has the potential to introduce ecological bias,[247] meta-analysis of the interaction term between BMI and dose capping status was undertaken. Results from meta-analyses models with added dose capping and a BMI-dose capping interaction terms, remained non-significant, though displayed tendency for the odds of toxicity to increase with increasing BMI. However, no significant within-trial BMI-dose-capping interaction was identified, indicating that BMI effects on toxicity did not differ according to dose capping status. Furthermore, to ensure non-linear relationships were accounted for properly between BMI and toxicity outcomes, spline multivariate meta-analysis was undertaken, finding a non-significant tendency towards a reduction in the odds of toxicity with BMI above approximately 30kg/m^2.

Individual common toxicities were also explored, and for the majority, demonstrated no significant relationship with BMI (Chapters four and five). However, BMI did appear to be associated with a 29% reduction in the odds of neutropenia, and a non-significant tendency to an increase in the odds of neuropathy. The latter might be explained by the increased risk of neuropathy resulting from altered glycaemic control, such as occurs in diabetes mellitus which is a well-recognised complication of obesity. Hence an elevated baseline risk, may further increase the risk of neuropathy with oxaliplatin use.[291,292] The majority of BMI-toxicity data from the breast cancer literature focuses on neutropenia or febrile neutropenia. In general, studies have demonstrated either no significant relationship or a reduction in neutropenic complications with increasing BMI.[129,132,140,142,293] Finally, some interesting hypothesis-generating findings were observed with the first onset of grade 3+ toxicity occurring during later cycles (>3 months), displaying a tendency increase as BMI increased. However, results for non-linearities, individual toxicities and timing of toxicity were likely to be both under-powered and potentially biased by missing data and consequent complete case analysis.

7.1.3 ADJUVANT CHEMOTHERAPY AND SURVIVAL

The prognostic benefits of maintaining a high dose, relative dose intensity or dose density have mainly been demonstrated within the breast cancer literature.[130,145,146,151,289] Whilst similar relationships in the colorectal cancer setting might seem logical, as a comparatively less chemo-sensitive malignancy, there is some evidence that dose reductions, delays and modifications might not adversely affect survival outcomes in the context adjuvant chemotherapy trials for non-metastatic CRC.[162] Within the obesity literature, much of the colorectal cancer data simply explores the effects of dose capping as a binary indicator, as opposed to adherence measures, which are more commonly reported for breast[141,142] and ovarian cancers.[133–135] In the adjuvant[131] and metastatic [104] CRC settings, two studies have demonstrated that reduced dosing in obese patients was associated with poorer outcomes but are limited in that analyses were only undertaken in obese patients and did not compare across the BMI spectrum. Conversely, dose capping has tended not to display a significant relationship with survival outcomes, including not altering BMI-survival relationships when included as a covariate, but may not be sufficiently discriminative as a binary variable. [116,117,120]

Results from Chapter five demonstrated a seemingly novel observation of the relative importance of optimising ACRD for improving survival outcomes in CRC, in comparison with ARDI. Increments of 5% of ARDI were associated with a borderline significant 5% reduction in overall (HR 1.05; 95CI 1.01, 1.09) and 3% reduction (HR 1.03, 95%CI 1.00, 1.06) in cancer-specific survival, with a non-significant tendency for a 3% reduction in disease-free survival (HR 1.03, 95%CI 0.99, 1.07). These findings were less convincing than those for ACRD, and in the opposite direction to the hypothesised relationship. This begs the question whether the lack of published data pertaining to (A)RDI in the colorectal cancer setting is the result of publication bias resulting from null associations. Conversely, a significant relationship was established between ACRD and survival, wherein 5% increments of ACRD resulted in a 6% increase in overall (HR 0.94, 95%CI 0.91, 0.96), a 4% increase in disease-free (HR 0.96; 95%CI 0.92, 1.00) and 6% increase in cancer-specific survival (HR 0.94; 95%CI 0.92, 0.96). Whilst it is possible that the intensity of chemotherapy is less important than the cumulative dose, these differences in outcomes highlight important distinctions in the nature of ARDI and ACRD measurements (Chapters three and five) and are more likely the result of the discriminative limitations of using ARDI in the context of ACT early discontinuation. Importantly the results for ACRD appeared to be robust to adjustment for toxicity, and to reverse causation (demonstrated in a sensitivity analysis which excluded deaths within the first 6 months).

Interestingly, a recently published large population-based study utilising UK registry data from the National Bowel Cancer Audit (NBOCA) and including 4147 patients with stage III CRC receiving oxaliplatin-based chemotherapy, assessed completion of the number of chemotherapy cycles in relation to CRC-specific survival.[294] The authors demonstrated that

cumulative incidence of mortality increased as the number of completed chemotherapy cycles decreased for both FOLFOX and CAPOX, and furthermore demonstrated up to a doubling in the risk of death in adjusted competing risk regression analyses for patients receiving fewer than 12 FOLFOX cycles and 8 CAPOX cycles. These results were limited by not being able to take into account cycle-level and cumulative dosing, and furthermore, treatment modification was only explored as a binary indicator in the subgroup of individuals receiving all cycles. Whilst results are not directly comparable, as ACRD was calculated based on protocolled expected numbers of cycles, they are likely to crudely mirror results reported in Chapter five, as the number of cycles received will correlate with cumulative relative dose.

The suggestion of a possible indirect effect of BMI on survival via dose capping or reduced adherence has, for the most part, been inferred through independent analyses of BMI-adherence and adherence-survival relationships. A single publication, by Cespedes Feliciano et al., has included a sub-analysis to formally assess mediation of the relationship between adiposity (quantified by CT) and survival by RDI in the ACT setting for breast cancer.[295] The authors demonstrated that RDI explained 22% of the association with overall survival and 20% of the association with breast cancer-specific mortality. However, this study was limited by the use of Cox proportional hazards models for the outcome combined with the traditional difference of coefficients method with a common binary outcome (22.8% event rate for overall survival) and hence cannot produce valid estimates of mediation according to Vanderweele.[244] Furthermore, their use of a binary mediator (RDI threshold of 85%) will have resulted in loss of information. The work presented within this thesis is the first study to formally demonstrate an indirect effect of BMI mediated through adherence on survival outcomes in patients receiving ACT for colorectal cancer (Chapters five and six), partially supporting hypothesis four. Furthermore, the natural indirect effects (NIE) were quantified (through accelerated failure time models which are demonstrated to be robust to a common outcome) as an approximate 1% reduction in the mean overall survival time for each 5kg/m^2 of BMI increments mediated via a reduction in ACRD (UV MSR 0.991 [95%CI: 0.986, 0.997]; UVFW MSR 0.991 [95%CI: 0.985, 0.997]; MV MSR 0.991 [95%CI 0.985, 0.998]).

7.1.4 Toxicity and survival

Given that toxicity often results in protocol-mandated dose reductions and delays, the results from Chapter five, demonstrating that the occurrence of grade 3+ toxicity was associated with reduced ARDI and ACRD measures, were anticipated. The effect on ACRD was larger, with a 10% reduction (Coef. -10.37; 95%CI -11.71, -8.97) compared with 4% (Coef. -3.86%; 95%CI -6.27, -1.45) reduction in ARDI. Again, these differences in adherence outcomes are likely the result of reduced discriminative ability of ARDI to capture cumulative dose changes within the context of early discontinuation.

Accordingly, it would seem intuitive to hypothesise that toxicity might adversely affect survival both directly as a result of severe toxicity (grade 5 toxicity is defined as toxicity-related death) and indirectly as a result of reduced adherence. Indeed, results from Chapters five and six demonstrated this to be the case for ACRD. Grade 3+ toxicity was associated with a 37% increased risk of death for OS (HR 1.37, 95%CI 1.17, 1.61), with results attenuating on adjusting for ACRD (reducing the increased risk to 20% [OS HR 1.20; 95%CI 1.02, 1.41]), but not ARDI. Mediation via ACRD was subsequently confirmed in Chapter six. Almost half of the total effect of Grade 3+ toxicity on overall survival, a 19% reduction in mean survival time (UV and MV MSR 0.814 [95%CI 0.740, 0.896]), was via the NIE, demonstrating a significant 9% reduction in mean OS time (UV and MV MSR 0.907 [95%CI: 0.876, 0.939]; UVFW MSR 0.906 [95%CI: 0.874, 0.939]). The reminder was through the natural direct effect (NDE]), with a significant 10% reduction in mean OS time (UV MSR 0.900 [95%CI: 0.824, 0.983]; MV MSR 0.901 [95%CI: 0.825, 0.984]; UVFW MSR 0.899 [95%CI: 0.823, 0.982]). Furthermore, there was mediation of approximately two thirds of the total effect of toxicity on DFS by ACRD, with a smaller non-significant NDE.

Converse to the presented findings, some data exist supporting the alternative hypothesis that toxicity might be a surrogate of more optimal dosing, where chemotherapy-related myelosuppressive toxicity is associated with improved outcomes in, for example, non-small cell lung cancer[157] and epithelial ovarian cancer.[134] Furthermore, in patients treated with capecitabine, some evidence suggests there may be an association between occurrence of hand-foot syndrome and improved survival outcomes in metastatic[296,297] and non-metastatic CRC,[298] in the setting of clinical trial data. Though these studies are limited to small patient numbers,[296,297] lack of time-to-event modelling[297] and by small event numbers of higher-grade toxicities, [296–298] and therefore such findings may be more applicable to lower grade toxicity. Furthermore, secondary analysis of 1033 patients pooled from two ACT-CRC trials of fluorouracil singlet therapy demonstrated that any grade (I-IV) neutropenia, nausea/vomiting, mucositis, and a composite measure of non-haematological toxicities were associated with improved overall survival. However, grade 4 neutropenia tended to increase the risk of adverse OS, though again, numbers of higher-grade toxicities were too small to draw concrete conclusions.[299] All of these studies lack data on the relationship between toxicity and cumulative dosing or relative dose intensity, thus hindering mechanistic understanding. It is possible that certain toxicities might indicate better pharmacokinetic distribution and higher serum levels, and hence be associated with improved survival, particularly where toxicity is of lesser severity and where cumulative dosing can be maintained. These hypotheses warrant further investigation but were not feasible due to the level missing data.

Additional consideration should be given to the well-known problem of marked pharmacokinetic (PK) variability of fluorouracil chemotherapy between patients treated at the same dose/dose

bands based on BSA, and the consequent risks of either over- or under-dosing. Previous studies in patients receiving IV 5FU dosed according to BSA have demonstrated that approximately 20-30% of patients reach serum levels that are within the therapeutic range, with 10-20% being overdosed, and 40-60% being underdosed.[156] Hence, dose banding and dose capping may further contribute to such pharmacokinetic-related underdosing. Equally, even dose capped patients may be pharmacokinetically over-dosed. Here, body composition might play an important role, with low lean body mass and sarcopenia being associated with increased risk of toxicity[300,301] and correlated with reduced 5FU clearance.[302] Measurement of 5FU serum levels and PK-guided dose adjustment of continuous IV 5FU are not currently recommended in routine clinical practice, and further evidence is required.[303] However, such methods may help to personalise dosing, reduce toxicity and may further optimise outcomes across all patients in future.

7.1.5 BMI-Survival

Presented within this thesis are the results for the first IPD meta-analysis of studies examining the relationship between BMI and CRC survival, whilst taking into account the potential effects of differential chemotherapy dosing. Despite its significance, the small natural indirect effect of BMI mediated via ACRD on survival was not sufficient to adversely influence the total effect. Hence, contrary to the third hypothesis, no significant total, or natural direct effects of BMI on overall, disease-free, or cancer-specific survival were found (Chapters five and six). Though obesity increases CRC incident risk,[5,6] these results reassuringly suggest that survival from colorectal cancer, once developed, is not influenced by elevated BMI, at least in the setting of randomised clinical trials for adjuvant chemotherapy.

Three previous meta-analyses have been published examining BMI-CRC relationships, the results of which are summarised in **Chapter 1, Table 1.5.**[71–73] On the whole there appeared to be a U-shaped association between BMI and overall survival/mortality with underweight and obese patients at risk of adverse outcomes. These studies were likely to be limited by bias e.g., from variation between BMI categories utilised across included studies, differential adjustment for prognostic factors, and variable BMI measurement timing. However, they highlight the importance of BMI measurement timing and distinguishing between studies of mortality and survival.[72,73] In the study by Lee et al., pre-diagnosis obesity was associated with a significant increased risk of mortality from any cause (HR1.25; 95%CI 1.03, 1.68) compared with normal BMI, whereas risks were attenuated in the meta-analysis for post-diagnosis obesity vs. normal BMI (HR 1.08; 95%CI 1.03, 1.13). Similar differences were seen in the study by Wu and colleagues.[72,73] Mortality studies are often population cohorts measuring pre- or peri-diagnosis BMI, where outcomes are inextricably linked to cancer incidence, and hence, increased mortality risk may represent increased incidence within the population of interest. Survival studies often take a selected colorectal cancer population, utilising peri-diagnosis, or peri-

treatment BMI, but may consequently be subject to selection bias. Combining both types of studies inappropriately may confound and attenuate results. The study by Parkin et al., importantly recognised these distinctions, grouping and meta-analysing different types of studies accordingly, and on the whole, demonstrated insufficient evidence for a relationship between BMI and survival.[69] However, all these studies were limited by the inability to account for chemotherapy dosing in their outcomes.

Within the context of patients receiving adjuvant chemotherapy for colon and rectal cancers, three large studies overall demonstrate a modest increased risk of adverse outcomes with increasing BMI, particularly BMI ≥35 kg/m^2.[111,117,118] Dignam et al. demonstrated the very obese to be at a substantially increased risk of adverse OS, DFS and CSS. However, despite reporting a high proportion of patients being dose capped, there was insufficient adjustment for potential differences in dosing.[117] A secondary analysis of 4,381 patients from seven RCTs of adjuvant chemotherapy for CRC demonstrated a tendency towards improved OS for overweight patients but worse OS and DFS for grade I and grade II-III obesity.[118] This study was later updated by a pooled analysis of >25,000 patients from 21 RCTs of adjuvant chemotherapy, and demonstrated that obesity was associated with adverse overall and to a lesser extent disease-free survival.[111] Furthermore, a non-linear relationship was demonstrated, with increased mortality risk for underweight and obese patients. Though spline terms were reported significant, the plotted confidence intervals crossed the null effect for BMI's above 20kg/m^2, reducing confidence in the reported outcomes. Both studies were limited by inclusion of patients not receiving chemotherapy (or ineffective ACT), lack of reporting on missing data, not modelling random effects at the study level to account for between study heterogeneity, and a lack of chemotherapy dosing and toxicity data.[111,118]

Conversely, Meyerhardt et al., demonstrated no significant relationship between BMI and survival outcomes in rectal cancer, in the context of minimal dose-capping.[116] Furthermore, a later study by the same authors displayed a tendency for OS to improve with increasing BMI categories, whilst DFS and recurrence-free survival tended to be worse for obese patients, but did not comment of the practice of dose-capping.[119]

The implications of obesity on the biological characteristics of colon and rectal tumours are not well understood. It is possible that obesity might not influence development of adverse phenotypic characteristics, despite the increased incident risk, and hence elevated BMI might not be associated with adverse survival once developed. There is little evidence in the obesity literature exploring the relationships between obesity and, for example, adverse pathological features, tumour sidedness, BRAF status, KRAS and DNA mismatch repair (MMR) status. The 2010 study by Sinicrope et al., found obesity was associated with a mixture of comparatively protective (higher rate of distal tumours)[304,305] and adversely prognostic features (higher rate of

T3 and N2 disease, fewer tumours with defective MMR). Unfortunately, data were not available to explore such relationships within the available trials.

Given the higher risk of obesity related CRC incidence in men compared with women, effect modification by sex was explored. Results from Chapter 5 demonstrated no significant meta-analysed within-trial BMI-sex interaction. These results were in keeping with studies by Meyerhardt et al.[116,120] and Dignam et al.,[117] but were converse to other published studies. The 2003 study by Meyerhardt et al. demonstrated a significant BMI-sex interaction for both overall survival and disease recurrence for colon cancer, with worse BMI-related outcomes for females.[120] Similarly, the two meta-analyses by Wu et al. and Lee et al. demonstrated a larger adverse effect on overall survival/mortality for obese women compared with a smaller[73] or no effect[72] for obese men. Conversely, Sinicrope and colleagues found a significant BMI-sex interaction in both linear and spline models, with worse BMI-related outcomes in men.[111] Finally, the meta-analysis from Doleman et al. demonstrated larger adverse effects for obese women for overall survival, whereas both cancer-specific and disease-free mortality were worse in obese men.[71] These meta-analyses and pooled studies were again limited by stratification of results, risking ecological bias.

7.1.6 METHODOLOGICAL ACHIEVEMENTS

Several methodological achievements should be noted. The thesis has demonstrated the utility and practical applicability of causal inference, in approaching complex clinical oncology questions. Specifically, mediation analysis was successfully implemented utilising clinical trial data. Few studies within the oncology literature have adopted mediation analysis, where uptake has tended to be in the psychological and social sciences literature. Only a single study adopting mediation analysis in a similar context was identified, that by Cespedes Feliciano et al. (described above), and even so, the mediation analysis made up a minority of the study.[295] However, such studies aid in demonstrating the value of this approach, improve mechanistic understanding, and are expected to become increasingly common within the oncology literature.

Though multiple imputation has been implemented for mediation analysis (e.g., within the `gformula` command itself), Chapter six demonstrated the first known use of the Boot-Impute von Hippel approach within the mediation analysis setting to deal with the combination of requiring multiple imputation and bootstrapping of confidence intervals, which appeared to be a valid method for dealing with such scenarios. Furthermore, the feasibility of meta-mediation using a two-stage approach was demonstrated, adopting both univariate and multivariate approaches, and the issues in relation to weighting were highlighted. These methods were not without challenges and the work presented here has certainly tested the bounds of current understanding, in addition to the available statistical packages.

7.2 STRENGTHS AND LIMITATIONS

7.2.1 STRENGTHS

There are several strengths to the present thesis. First, data were obtained from randomised clinical trials, which are on the whole, high quality in nature, with low missingness, and reduced bias from protocol-directed treatment and follow-up, and prospective data collection.

Second, and specifically, important to this thesis, was the availability of detailed cycle-level dosing and toxicity data, in addition to adequate clinical and pathological covariates which allowed for a thorough examination of chemotherapy adherence and toxicity in relation to BMI and furthermore their relationships with survival, whilst adjusting for important confounders.

Third, the quality of height and weight variables appeared high, with only a small proportion of patients identified as having potential data entry errors. Furthermore, there were reasonable proportions of patients with elevated BMI, particularly within the SCOT trial, providing an adequate range of BMI to explore its effects.

Fourth, the causal inference approach and use of DAGs not only facilitated confounder selection but allowed explicit graphical presentation of assumptions for these complex relationships. Care was taken to consider and minimise sources of bias, and to examine the potential effects of such though, for example, sensitivity analysis (Chapter five) and use of multiple imputation (Chapters five and six).

Fifth, adopting IPD meta-analysis approaches addressed many of the limitations described within the literature review and above, and hence inherently strengthened the presented work, as it was possible to standardise all aspects across the trials, from data harmonisation to individual analyses, including adjustment for the same set of confounders.

Sixth, the use of individual participant data meant that modelling of BMI did not rely on pre-categorised thresholds, (often variable within the literature, and a source of heterogeneity and bias), but rather allowed modelling continuously, additionally reducing loss of information. Furthermore, utilising continuous data combined with meta-analytic methods facilitated exploration of non-linearities, (which have the potential to attenuated results), and would not have been possible with aggregate data. Additionally, analyses were not limited to those previously published (as would be the case using aggregate data), producing greater insight into mechanistic pathways.

Seventh, the two-stage IPD meta-analysis approach facilitated trial-level assessment of model specification, and importantly, careful consideration of the functional form of age, which is

argued to be one of the most important confounders, often not adequately modelled, and requiring “special attention”.[306]

Finally, this was a large study, and it could be argued that this, together with the volume of analysis might increase the risk of detecting small unimportant differences. However, as described by the recently updated ASCO guidance (see **Section 7.4** below), the impact of relatively small reductions in adherence would require large samples sizes for sufficient power to assess long-term outcomes.[190] Hence, the meta-analysis approach is more likely to have facilitated avoiding a type II error with a small indirect effect size, whilst accounting for within and across trial heterogeneity.

7.2.2 LIMITATIONS

A number of limitations of the presented work were identified. First, BMI is an imperfect measure of adiposity. The height and weight measures on which BMI was calculated, contained at least a small proportion of patients who may additionally be at risk of data-entry or measurement error which may bias effect decomposition.[87,307] Furthermore, lean muscle mass in relation to adiposity may be more important for determining risks of toxicity and consequently influencing overall adherence and survival.[295] However other anthropometric measures and imaging data were not available to explore such concepts further, thus assumptions regarding body composition cannot be made.

Second, the timing of BMI measures is important, BMI at trial entry may not accurately represent life-time BMI, and in the ACT setting will be influenced by disease severity, pre-existing bowel obstruction or perforation and preceding surgery with any associated complications. Indeed, the tendency demonstrated in Chapter three for BMI to increase, suggests a risk of misclassification bias of the exposure, in addition to possible time-varying exposure effects and reverse causality. However, an attempt to assess the impact of reverse causality was made, and similar results were seen for models excluding early deaths, though this in itself might introduce selection bias, making it difficult to completely reject. Additional, methods such as marginal-structural-modelling[308] or g-formula for a time-varying exposure and confounder,[273] may have helped to determine risk of bias from time-varying exposure, but do not, however, allow for effect decomposition.

Third, despite the high-quality clinical trial data, potential sources of residual bias pertaining to the data itself, such as the high degree of missing toxicity data and the survival follow-up data issues. However, such limitations were made explicit throughout, with exploration and discussion of potential causes missingness and adopted assumptions. Missingness was managed with a focus on approaches to reduce risk of bias (e.g., comparison of complete case and full datasets, sensitivity analyses, and in particular multiple imputation). Distinguishing

between MAR and MNAR is not possible within observational data,[198] and hence bias resulting from MNAR mechanisms cannot be excluded. However, overall MAR assumptions were felt to be reasonable and most likely related to date of randomisation. The use of time-to-event analysis was chosen to allow appropriate modelling right censoring of data. Additionally, use of summary variables such as grade 3+ toxicity, ARDI and ACRD, may have resulted in some degree of loss of information compared with methods for longitudinal analysis.

Fourth, oral anti-neoplastic agent compliance could not be taken into consideration in the majority of trials, and it is possible that capecitabine doses were overestimated. However, patient-related adherence was included in the adherence measures where data were available (PROCTOR-SCRIPT), furthermore, as stated by the SCOT trial authors, compliance with oral anti-neoplastic treatment tends to be high.[309] Furthermore, though sensitivity analysis excluded capecitabine-containing regimens, it was not possible to assess effect modification by regimen.

Fifth, a substantial proportion of data came from a single trial (SCOT) and hence may disproportionately affect outcomes. Furthermore, the choice of the chemotherapy regimen in the SCOT trial was not randomised and might bias estimates. It is arguable, however, that SCOT was a pragmatic trial which was more likely to emulate modern day and realistic dosing practices, given the large number of patients recruited from several centres and countries and that treatment involved standard and current chemotherapy regimens.[309] Hence, conversely, results may be more applicable to current clinical settings, than previously explored ACT-CRC trial data. Furthermore, there was no evidence of BMI influencing the regimen choice, which was also adjusted for within analyses. That being said, data from clinical trials may, in general, not fully represent the full range of adiposity in wider oncology populations due to selection into trials.[90] Consequently the effects of selection bias in relation to BMI are unclear, and a degree of selection bias from inclusion of a “fitter” obese population (particularly in the rectal cancer trials) is possible. The trials eligible for inclusion were taken from the OCTOPUS consortium, which specifically included trials with BMI data and survival outcomes, and furthermore required detailed cycle-level dosing and toxicity data. Therefore, these were highly selected trials. Additionally, other ethnicities were not well represented, and precluded analysis of potentially important effect modification.[310]

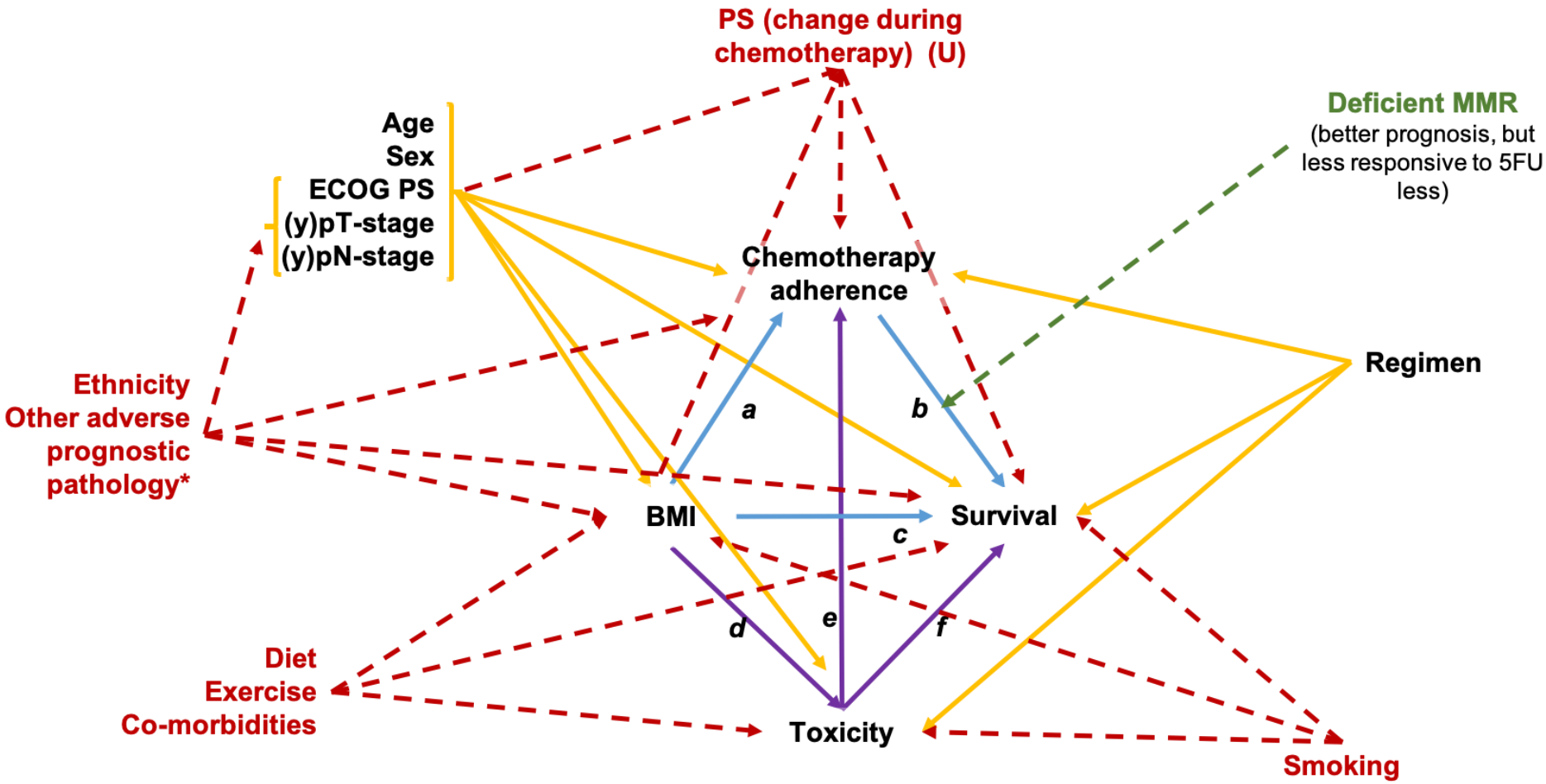
Sixth, the four trials included differed from one another in, for example, their populations, treatments (including both singlet and doublet ACT), and follow-up time, and arguably may not have been suitable to aggregate. However, results were largely consistent across the trials, demonstrating that the identified relationships might indeed apply to the wider ACT-CRC setting, and hence be appropriate to meta-analyse.

Finally, mediation analysis requires the no-unmeasured confounding assumptions to be met. Despite efforts to identify and adjust for all confounders, most studies, notwithstanding the

present thesis, are at risk of residual bias. In this case, unmeasured residual confounding might include factors such as smoking, comorbidities (particularly renal function), diet[311] and exercise[312] in addition to changing performance status (which might act as an additional intermediate confounder) as exemplified in **Figure 7.1**. Unmeasured residual confounding of X-M or M-Y relationships would additionally risk collider bias being introduced into outcome regression models (where the mediator is adjusted for), potentially opening backdoor pathways and biasing mediation results.[92,93] Sensitivity analysis through simulation might have allowed exploration of these risks, should time have allowed.[94,95] However, it is also unclear whether current methods are currently validated for mediation analysis on the mean survival ratio scale.

In the context of the limitations described, the inference of true causality may not be possible. However, the causal inference approaches undertaken throughout have strengthened the interpretation of the results presented, reinforced much of the existing literature, and gone beyond to provide a better understanding of underlying mechanisms, within the context of the outlined assumptions.

Figure 7.1 | DAG 5
Directed acyclic graph demonstrating additional sources of potential unmeasured confounding (**red**), collider bias (where two arrows point to the same variable, e.g., chemotherapy adherence or toxicity) and effect modification (**green**). The main mediation pathway is also demonstrated (**blue**) in addition to measured confounders adjusted for throughout analyses (**yellow**), and intermediate confounder (**purple**). Note that change in performance status may be an unmeasured intermediate confounder.



* Poorly-/un-differentiated; perineural invasion; lymphatic invasion; vascular invasion; Perforation/Obstruction; Reduced LNH

7.4 CLINICAL IMPLICATIONS

Obesity prevalence continues to rise, and with colorectal cancer a well-recognised obesity-related disease, the proportion of patients requiring adjuvant chemotherapy following primary tumour resection who are obese is likely to grow. Hence, improved understanding of the nuances of treating the obese patient is vital and can be gained through improved mechanistic knowledge.

The main implication of the presented thesis results is providing additional evidence supporting the updated American Society of Clinical Oncology (ASCO) guidance, published in 2021. The guidance overall supports full body-size-based dosing of cytotoxic chemotherapy in obese and non-obese patients, stating:[190]

"There is little evidence to suggest that obese patients dosed on the basis of their actual body weight have increased toxicity, while there are data from retrospective studies that underdosing is associated with inferior outcomes."[190]

With recommendation 1 stating:

"Full weight-based dosing of cytotoxic chemotherapy should be offered regardless of obesity status" [190]

Specifically, the work presented here, provides additional evidence that elevated BMI is associated with comparatively reduced dosing, that reduced cumulative relative dosing adversely impacts on efficacy, and that justification for such reductions based on assumptions of increased toxicity are not confirmed.

ASCO recommendations were generally based on low quality evidence, hence, within the context of colorectal cancer, the presented analyses improve on the limitations of existing studies and may contribute to strengthening the evidence for such recommendations.

One criticism might be that a small indirect effect (1% reduction in the relative overall survival time for each 5kg/m^2 BMI increment), may not be clinically significant. Furthermore, the indirect effect was not large enough to adversely influence the total effect of BMI on overall survival. However, the following should also be noted. First, the higher the BMI, the more clinically relevant these effects may become. For example, a patient with an overweight BMI of 27.5kg/m^2 might have approximately a 2% reduction in the cycle one relative dose received, with an overall 1% reduction in their survival time relative to a BMI of 22.5kg/m^2. However, for a patient with a BMI of 42.5kg/m^2 falling into the obese III category, such an effect would increase

to approximately an 8% reduction in cycle 1 RDR and a 4% reduction in their mean survival time. Second, with the widespread adoption of a reduced duration of 3 months chemotherapy for patients with low-risk stage III disease, recommended as a result of the IDEA collaborative,[242] maintaining optimal dosing may be increasingly important.

Ultimately, there may be additional factors that require dose reductions for well-established safety reasons, such as reduced renal function or dihydropyrimidine dehydrogenase (DPD) deficiency (routine testing for the latter post-dates the included trials and has only been implemented in the UK only since 2020).[313] Hence, treatment dosing decisions in practice will always come down to an evaluation of each individual patient's risk-benefit profile. However, as a result of meta-analysing the effects of cumulative doses on survival, the work undertaken within this thesis provides an additional layer of understanding to allow such decisions to be made, and for informed discussions with patients pertaining to dosing where appropriate.

Finally, additional relevance may be seen in planning prospective studies or clinical trials in the wider oncology setting, and within the context of cancer outcome databases. First, future studies should consider the importance of understanding treatment effects for obese patients with cancer, particularly where treatment relates directly to weight. Hence, efforts should be made to ensure adequate representation of obese patients within trial settings, in addition to consideration of collecting adiposity measurements and planned secondary outcome reporting of adiposity-specific effects. Second, highlighted here are the potential issues with reliance on relative dose intensity for assessing adherence where early discontinuation rates are high. Thus, prospective studies might need to consider whether relative cumulative dosing provides better contextualisation of study findings. Also, important to note is that (A)RDI in the clinical trial setting may be alternatively calculated based on the prescribed cycle 1 dose, rather than based on standard dosing, as was undertaken throughout, and care should be taken to make this explicit within methods. Finally, the utility of mediation analysis has been demonstrated in a clinical oncology setting, and future studies should consider whether such an approach might reveal important relationships. For example, mediation analysis may be useful in the clinical trial setting to explore reasons for results confirming the null hypothesis, where opposing direct and indirect effects might "cancel out" a total effect.[314] By contemplating potential mechanisms *a priori*, including mediators and post-randomisation confounders (particularly mediator-outcome confounders) it may also be possible to identify additional targets for intervention.

Within this context, there are opportunities for collaboration with ongoing and future studies within the clinical oncology setting. For example, the Add Aspirin trial[315] is a large phase III multi-centre, double-blinded, placebo-controlled randomised trial assessing the addition of aspirin vs. placebo on cancer outcomes across four parallel tumour-specific cohorts. These cohorts include patients who have undergone curative treatment for colorectal (n=2600), breast (n=3100), gastro-oesophageal (n =2100) and prostate (n = 2120) cancers. The study will collect

active follow-up data for 5 years, including baseline height and weight, followed by repeated weight measurements. Additional computed tomography imaging data will also be collected as part of the colorectal cancer follow-up. Further passive follow-up is planned for 10 years using routinely collected health care data, after planned validation. Such a study would provide a valuable opportunity to examine relationships between adiposity and long-term survivorship outcomes in colorectal and other cancers, making use of repeated measures, imaging, and treatment data. Indeed, the study investigators suggest that the “size and diversity of the Add-Aspirin cohort provides opportunity to address other secondary research questions”.[315]

7.5 UNANSWERED QUESTIONS AND FUTURE RESEARCH

7.5.1 CLINICAL RESEARCH QUESTIONS

Results from the trial setting may not be directly representative to the wider oncology population as a result of strict inclusion and exclusion criteria.[316] Hence a large and well conducted prospective observational study, or analysis of robust registry data, may be required to better represent “real life” oncological practice and supplement the results of this thesis.

How subcutaneous adipose tissue, visceral adipose tissue and lean muscle mass relate to dosing, toxicity and outcomes within the colorectal cancer setting, remains unclear. Additional studies using imaging to quantify such measures of adiposity may be useful to understand how body composition relates to dosing and toxicity, and the relative importance of sarcopenic obesity. Furthermore, studies are required to improve understanding of pharmacokinetics within the context of the obese colorectal cancer patient, to elucidate whether drug distribution differs across various compositions of adiposity and lean mass. Fundamentally, BSA may not be the most effective method for chemotherapy dosing, thus, combined with imaging studies, it might be possible to elucidate new approaches for drug dosing that can improve the efficacy of current treatments, and answer the question “is there a better way of dosing adjuvant chemotherapy?”

7.5.2 METHODOLOGICAL RESEARCH QUESTIONS

Meta-mediation approaches, outside of the structural equation modelling setting, are emerging within the literature and require more exploration and validation. For example, comparison of the univariate and multivariate two-stage IPD meta-analysis methods undertaken here (meta-analysis of mediation effect estimates), with the approach undertaken by Zhu et al. (meta-analysis of regression models then post-estimation calculation of mediation effects [see Chapter six]) is required, particularly within the context of ecological bias and modelling interactions.[285]

An alternate approach that would facilitate one-stage meta-mediation is joint modelling. This would allow for chemotherapy dosing to be modelled longitudinally, with a link function (association structure) from the longitudinal model then utilised within the survival model. Commands are available in Stata,[317] and would allow the principles of one-stage meta-analysis with random effects to be followed, additionally, variance from the longitudinal model is introduced to the survival model through the association structure and may account better for uncertainty and measurement error. Such models are computationally intensive, however, and require careful selection of a meaningful association structure, to ensure outcomes are interpretable and clinically relevant. However post-analysis combination of estimates is required to calculate indirect and total effects, and hence might still be at risk of ecological bias.

7.6 CONCLUSION

In conclusion, elevated BMI was not found to be associated with colorectal cancer survival outcomes for patients receiving adjuvant chemotherapy within the context of randomised trials. However, a small adverse indirect effect of BMI acting through average cumulative dose on overall and disease-free survival was demonstrated. There was no evidence of an association between BMI and toxicity to justify dose capping, and hence data from this thesis supports the American Society of Clinical Oncology guidelines, which advocates against dose capping, on both safety and efficacy grounds. These results support optimisation of chemotherapy and may aid clinical decision-making, to ensure the indications for dosing modifications are justified, and to reduce variability in dosing practices.

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LIST OF APPENDICES

Item A0.1 | Research outputs resulting from this PhD

1. **Publications:**
   1.1. Slawinski CGV, Barriuso J, Guo H, Renehan AG. Obesity and Cancer Treatment Outcomes: Interpreting the Complex Evidence. *Clinical Oncology* 2020; 32:591–608. doi:10.1016/j.clon.2020.05.004.

2. **Manuscripts in preparation:**
   2.1. C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A Harkin, T Iveson, R Glynne-Jones, C Van de Velde, A. G. Renehan. Body mass index, adjuvant chemotherapy, toxicity and survival in colorectal cancer: and individual participant data meta-analysis (OCTOPUS). *Planned for submission to Lancet Oncology and based on the work from Chapter Five.*

3. **Published Abstracts:**
   3.1. C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A. G. Renehan on behalf of The OCTOPUS Consortium. P297 - Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for survival in colorectal cancer, with potential implications for treating patients with an elevated body mass index (BMI): an individual participant data (IPD) meta-analysis within the OCTOPUS consortium. *Colorectal disease*, 2021. 32(S3): 24 (See 4.1 below)

   3.2. C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A Harkin, T Iveson, R Glynne-Jones, C Van de Velde, A. G. Renehan. O-4 - Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for colorectal cancer survival, with implications for treating obese patients: The OCTOPUS consortium. *Annals of Oncology*, 2021. 32 (S3): S618 (See items 4.2 and 7.1 below)

   3.3. C. Slawinski, L. Malcomson, H. Guo, J. Barriuso, A Harkin, T Iveson, R Glynne-Jones, C Van de Velde, A. G. Renehan. P260 - Elevated BMI is associated with reduced average relative dose intensity (ARDI) of adjuvant chemotherapy regimens in two randomised trials of colorectal cancer: the OCTOPUS consortium. *Colorectal disease*, 2020; 22 (S1): 53 (See item 5.1 below)

   3.4. C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A. G. Renehan. P157 - The potential for nodal stage misclassification with increasing BMI in patients undergoing curative resection for colorectal cancer: the OCTOPUS study. *Colorectal disease*, 2019; 21 (suppl 3): 61 (See item 5.2 below)

4. **Oral presentations:**
   4.1. “Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for survival in colorectal cancer, with potential implications for treating patients with an elevated body mass index (BMI): an individual participant data (IPD) meta-analysis within the OCTOPUS consortium.”
   C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A. G. Renehan on behalf of The OCTOPUS Consortium.
   Association of Coloproctology Great Britain and Ireland (ACPGBI) annual meeting, 07.07.2021. (ORAL POSTER PRESENTAION - PRIZE SECTION WINNER)

   4.2. “Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for colorectal cancer survival, with implications for treating obese patients: The OCTOPUS consortium.”
   C. Slawinski, L. Malcomson, J. Barriuso, H. Guo, A Harkin, T Iveson, R Glynne-Jones, C Van de Velde, A. G. Renehan.

European Society of Medical Oncology (ESMO) World Gastrointestinal conference, 02.07.21. (ORAL VIRTUAL PRESENTATION - SELECTED FOR PRESS RELEASE PROGRAMME*)*

4.3. Body mass index, adjuvant chemotherapy, toxicity and survival in colorectal cancer: and IPD meta-analysis [OCTOPUS]
C. Slawinski*, L. Malcomson, J. Barriuso, H. Guo, A. G. Renehan on behalf of The OCTOPUS Consortium.
Royal Society of Medicine Coloproctology Section Joint Northern Meeting, Manchester, UK, 11.03.22 (ORAL PRESENTATION)

4.4. Average cumulative relative dose of adjuvant chemotherapy is more important than average relative dose intensity for survival in colorectal cancer, with implications for treating obese patients: an IPD meta-analysis within the OCTOPUS consortium
C. Slawinski*, L. Malcomson, J. Barriuso, H. Guo, A. G. Renehan on behalf of The OCTOPUS Consortium.
Manchester Regional Association of surgeons Trainee Prize session, 09.03.21. (ORAL VIRTUAL PRESENTATION – RUNNER UP)

4.5. Elevated BMI predicts receipt of reduced average relative dose intensity (ARDI) of adjuvant chemotherapy regimens in two randomised trials of colorectal cancer: the OCTOPUS consortium
C Slawinski*, J Barriuso, H Guo, AG Renehan
Manchester Regional Association of surgeons Trainee Prize session, The Chill Factore, Manchester, 10.03.20 (ORAL PRESENTATION)

5. Poster presentations:

5.1. "Elevated BMI is associated with reduced average relative dose intensity (ARDI) of adjuvant chemotherapy regimens in two randomised trials of colorectal cancer: the OCTOPUS consortium."
C. Slawinski*, L. Malcomson, H. Guo, J. Barriuso, A Harkin, T Iveson, R Glynne-Jones, C Van de Velde, A. G. Renehan.
Accepted for poster presentation at ACPGBI Annual Meeting 2020 – Meeting Cancelled due to COVID-19 Pandemic, but abstracts were published.

5.2. "The potential for nodal stage misclassification with increasing BMI in patients undergoing curative resection for colorectal cancer: the OCTOPUS study"
C Slawinski*, L Malcolmson, J Barriuso, H Guo, AG Renehan
European Society of Coloproctology Annual Meeting, Vienna, Austria, 25.09.2019

6. Prizes:

6.1. Winner - Colorectal Disease 2021 'Quickfire' best poster presentation. Association of Coloproctology Great Britain & Ireland Annual Meeting 2021, 07.07.2021. (See item 4.1 above).

6.2. Runner up - Manchester Regional Association of Surgeons Trainee Prize Session, 09.03.21 (See item 4.4 above).

7. Press releases:

7.1. "Poorer survival in obese colorectal cancer patients possibly linked to lower chemotherapy doses." ESMO World GI 2021 Press Release. (See item 4.2 above) [Accessed at: https://www.esmo.org/newsroom/press-releases/poorer-survival-in-obese-colorectal-cancer-patients-possibly-linked-to-lower-chemotherapy-doses]

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Overview

Obesity and Cancer Treatment Outcomes: Interpreting the Complex Evidence

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Abstract

A wealth of epidemiological evidence, combined with plausible biological mechanisms, present a convincing argument for a causal relationship between excess adiposity, commonly approximated as body mass index (BMI, kg/m^2), and incident cancer risk. Beyond this relationship, there are a number of challenges posed in the context of interpreting whether being overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI $\geq$ 30.0 kg/m^2) adversely influences disease progression, cancer mortality and survival. Elevated BMI ($\geq$ 25.0 kg/m^2) may influence treatment selection of, for example, the approach to surgery; the choice of chemotherapy dosing; the inclusion of patients into randomised clinical trials. Furthermore, the technical challenges posed by an elevated BMI may adversely affect surgical outcomes, for example, morbidity (increasing the risk of surgical site infections), reduced lymph node harvest (and subsequent risk of under-staging and under-treatment) and increased risk of margin positivity. Suboptimal chemotherapy dosing, associated with capping chemotherapy in obese patients as an attempt to avoid excess toxicity, might be a driver of poor prognostic outcomes. By contrast, the efficacy of immune checkpoint inhibition may be enhanced in patients who are obese, although in turn, this observation might be due to reverse causality. So, a central research question is whether being overweight or obese adversely affects outcomes either directly through effects of cancer biology or whether adverse outcomes are mediated through indirect pathways. A further dimension to this complex relationship is the obesity paradox, a phenomenon where being overweight or obese is associated with improved survival where the reverse is expected. In this overview, we describe a framework for evaluating methodological problems such as selection bias, confounding and reverse causality, which may contribute to spurious interpretations. Future studies will need to focus on prospective studies with well-considered methodology in order to improve the interpretation of causality.

Key words: Cancer; chemotherapy; immunotherapy; obesity; radiotherapy; surgery

Statement of Search Strategies Used and Sources of Information

A systematic review was beyond the scope of this paper. PubMed was searched (up to 6 October 2019) using terms related to adiposity (e.g. 'obesity', 'BMI', 'body mass index', 'adiposity') and cancer (e.g. 'cancer', 'neoplasia', 'malignancy') combined with search terms relating to treatment selection (e.g. 'selection', 'treatment', 'surgery', 'chemotherapy', 'immunotherapy', 'randomised clinical trial', 'RCT'), surgery (e.g. 'conversion', 'approach', 'complication', 'morbidity', 'mortality', 'lymph node harvest', 'lymph node yield', 'positive margin', 'positive surgical margin'), chemotherapy (e.g. 'chemotherapy', 'dosing', 'dose capping', 'dose reduction', 'relative dose intensity', 'dose delay', 'toxicity'), immunotherapy (e.g. 'immunotherapy', 'checkpoint inhibitor', 'PD-1', 'PD-L1', 'CDLA-4'), radiotherapy (e.g. 'radiotherapy', 'radiation therapy', 'interfraction displacement', 'set-up error'), outcomes (e.g. 'survival', 'mortality', 'prognosis', 'recurrence') and the 'obesity paradox'. Reference lists of pertinent papers were also screened for further

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relevant papers, in addition to expert knowledge of existing evidence.

Introduction

Excess adiposity is commonly measured by body mass index (BMI; weight in kilograms divided by height in metres squared, kg/m^2) as a proxy for nutritional state (Table 1) [1]. An excess adiposity–incident cancer relationship is now well-established and despite few clinical trials evaluating long-term weight gain avoidance or weight loss, a wealth of epidemiological data and plausible biological mechanisms (hyperinsulinaemia and increased insulin-like growth factor-1 bioavailability, altered sex-hormone metabolism, adipokine dysregulation and inflammation and the tumour environment [2,3]) provide a convincing argument for causality. Hence, in 2016, following several meta-analyses based mainly on observational data [4–6], the International Association for Research on Cancer recognised the existence of 'sufficient evidence' for 13 obesity-related cancers (endometrial; oesophageal [adenocarcinoma]; gastric [cardia]; liver; kidney [renal cell]; thyroid; multiple myeloma; meningioma; pancreas; colorectal; gallbladder; breast [postmenopausal; female]; ovarian) [7].

Worldwide, there is an overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI $\geq$ 30.0 kg/m^2) pandemic, with an estimated 1.9 billion overweight adults, of which 650 million are obese, equating to 39% of the world's adult population [1]. In the UK, obesity figures for 2017 increased to 29%, with 67% of adult females and 62% of adult males being obese or overweight. Globally, an estimated 481 000 (3.6%) new cancers (in $\geq$30 year olds) were attributable to elevated BMI ($\geq$25.0 kg/m^2) in 2012 [8]. In the UK, with over 360 000 new cancer cases per year [9], obesity is the second most common overall cause of cancer, behind smoking [10]. As global childhood obesity rates continue to rise, implying continued upward adult trends [11], exposure to excess adiposity as an incident cancer risk factor will continue. Thus, the adiposity–cancer relationship is a substantial and concerning global health problem.

Here we discuss the implications of obesity on cancer treatments and outcomes, providing context of methodological concepts that make interpretation of the current evidence base challenging. Furthermore, we explore future directions for methodological approaches, in particular mediation analysis, which can facilitate improved understanding of causal mechanisms.

Table 1
World Health Organization definitions of adiposity based on body mass index [1]

Category	Body mass index (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obese	≥30.0
Class I	30.0–34.9
Class II	35–39.9
Class III	≥40.0

Methods

A full systematic review was beyond the scope of this paper. Hence, our strategy for inclusion of evidence was four-fold. First, we discuss evidence mainly relating to BMI as the most extensively investigated approximation of adiposity. Second, as most evidence comes from observational data, we draw mainly from this literature, including secondary analyses of trial data and meta-analyses, where available. Third, where possible, large-scale, high-quality studies were selected in an attempt to reduce the interpretation of type II statistical errors. Fourth, our aim throughout was to present a balanced review and critical appraisal of the literature.

To contextualise the evidence presented, we start by discussing methodological problems that may lead to spurious results and limit interpretation. Many of these issues, grounded in causal inference theory, are encountered within the obesity paradox paradigm, described for several cancers, including, for example, colorectal [12], renal [13] and B-cell lymphoma [14]. This is a phenomenon where being overweight or obese is associated with improved survival where the reverse is expected. As a consequence, the risk effects often normalise or reverse at the extreme ranges of BMI, resulting in reverse J- or U-shaped risk distributions. Lennon *et al.* [15] presented a comprehensive review of these concepts, which are summarised in Figure 1 and briefly explored below.

Although BMI is the most commonly used adiposity measure, it is by no means the most accurate. It may introduce measurement error [6]; be associated with treatment selection bias [37]; and may not reflect metabolic function [38]. Other anthropometric measures (e.g. imaging-quantified adipose compartments or skeletal muscle mass) may be more accurate [39–41].

Confounding is common in observational data, where the true outcome effect of an exposure is obscured by the presence of additional variables. A confounder is associated with exposure and outcome, but not affected by the exposure, thus not lying within the causal pathway [42]. Adjustment for all confounding (e.g. smoking) [23–28] may not be possible if some factors are unobserved, or may not be adequate, resulting in residual confounding [29,30]. One specific form of confounding frequently encountered in obesity research is reverse causality, where an exposure (BMI) itself is influenced by the disease (cancer), which in turn influences outcome (survival), creating false associations [17,43].

A specific form of selection bias, known as collider stratification bias, results in an association between an exposure and a confounder, which can alter the exposure–outcome association, remaining after adjustment [22,44,45]. This occurs during statistical analysis, when adjusting for a 'collider' variable (a variable caused by

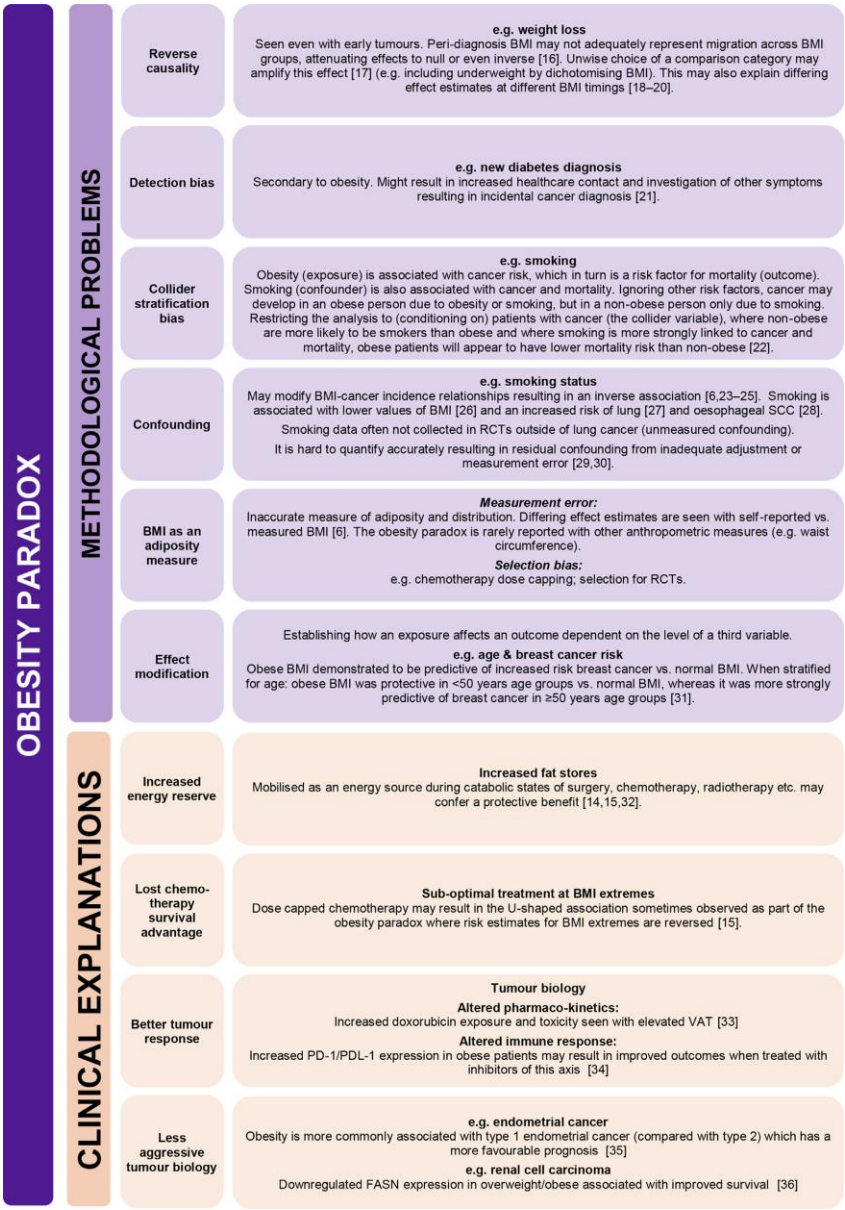

Fig 1. The obesity paradox. A summary of the methodological issues and clinical explanations for the obesity paradox described by Lennon *et al.* [15].

both exposure and confounder), resulting in a falsely strengthened [46] or reversed [29] effect estimate.

Detection bias may occur when diagnosis of one condition (e.g. diabetes) due to an exposure (e.g. obesity) results in further investigations and detection of incidental diseases (e.g. cancer) [21], creating 'opportunistic screening' and detection of earlier staged disease with improved outcomes [15].

Effect modification, which occurs when one exposure alters the relationship of another on an outcome, may result

in biased effect estimates if not properly accounted for in statistical modelling [31,47]. Therefore, interaction terms should be carefully considered (ideally *a priori*) and fitted within statistical models to ensure robust analysis.

Several arguments for the true occurrence of the obesity paradox, clinical and/or biological explanations, have been postulated and are summarised in Figure 1 [15,33,34,36].

Results

Treatment Selection

BMI may influence treatment selection, which can in turn affect oncological outcomes or introduce selection bias into observational studies. In randomised trials, the selection process may occur as part of eligibility pre-randomisation or as selection to treatments that are not part of the trial question post-randomisation. Pestine *et al.* [37] showed that 95% of clinical trials for obesity-related cancers did not report proportions of obese subgroups. Less than a third of trials provided this information when asked, and from this data a median of 18% of trial participants were found to be obese. Although not conclusive due to the volume of missing data, and with proportions of obese patients in obesity-related cancers reaching up to 47% [48], these results are suggestive of obese patient under-representation in clinical trials, i.e. selection bias. Furthermore, the commonly used inclusion criteria of World Health Organization performance status of $\leq$2 in, e.g. most adjuvant chemotherapy trials, is likely to result in selection of the 'fitter proportion' of the obese patient population. There is some evidence of possible changing trends for selection into clinical trials over time. Table 2 presents secondary analyses of breast and colon cancer trials, showing an increasing proportion of obese patients with time, reflecting perhaps not only changes in population trends, but also in approach to trial recruitment [49–54].

Elevated BMI may influence the selection of surgical approach, e.g. balancing reduced morbidity associated with laparoscopic techniques with the technical challenges posed by excess adiposity, which may increase operative and thus anaesthetic times. A large retrospective analysis (n = 1465) of patients undergoing colorectal resection for malignancy, found that obese patients (BMI $\geq$ 30 kg/m^2) were less likely to be offered laparoscopic surgery and more likely to be offered open surgery, conceivably reflecting the technical challenges of operating on obese patients [55]. Furthermore, treatment selection occurs in the context of chemotherapy through selecting-out those receiving chemotherapy, due to competing risks from comorbidities and reduced functional status [56]. Although previously shown not to be the case for obese patients with breast cancer [57], evidence exploring BMI as a predictive factor for receipt of chemotherapy is lacking. Moreover, obesity has been associated with reduced chemotherapy doses, through the practice of dose capping [58] or through differential adherence to treatment [59].

Surgery in the Obese Patient

Technical Challenges

Increased visceral adiposity often results in a shortened fatty mesentery (which may easily tear and additionally makes adequate exposure difficult) and a smaller intra-abdominal working space (especially during laparoscopic surgery) [32]. Indeed, taking laparoscopic colorectal cancer resections as an example, meta-analyses have shown obesity to be associated with a significantly increased risk of conversion to open (potentially reflecting technical difficulties) [60,61], which in turn has been associated with worse overall survival [62], Moreover, in breast cancer, two large observational studies have shown obesity to be associated with a reduced likelihood of successful sentinel lymph node mapping [63,64].

Complications

Obesity has been consistently associated with an increased risk of surgical site infection following surgery for

Table 2
Secondary analyses of adjuvant chemotherapy trials presenting the proportion of patients per body mass index category

Reference (country)	Trial(s)	Recruitment years	n	Cancer site and trial setting	Proportion (%) per body mass index (kg/m^2) category			
					–	<25	25–29.9	≥30
[49] (international)	International Breast Cancer Study Group (4 trials)	1978–1993	2140	Adjuvant breast, premenopausal, node positive	–	60	28	12
					<21	21–24.9	25–29.9	≥30
[50] (USA)	Intergroup INT-0089	1988–1992	3438	Adjuvant colon stage II/III	14.2	33.9	34.4	17.7
					<20	20–24.9	25–29.9	≥30
[54] (USA)	Intergroup INT-0014	1990–1992	1688	Adjuvant rectal stage II/III	6.5	36.2	39.2	18.1
					<18.5	18.5–24.9	25–29.9	≥30
[51] (USA)	NSABP C-04 and C-05	1989–1994	4288	Adjuvant colon Dukes B & C	3.3	42.0	35.8	18.9
					<21	21–24.9	25–29.9	≥30
[52] (USA)	CALGB 89803	1999–2001	1264	Adjuvant colon stage III	6.5	24.5	35.0	33.9
					–	<25	25–29.9	≥30
[53] (USA)	CALGB 49907	2001–2006	615	Adjuvant breast stage I–IIIb	–	26	32.5	41.5

both benign and cancerous indications. This is highlighted in several analyses of large datasets from the American College of Surgeons' (ACS) National Surgical Quality Improvement Program (NSQIP), among other observational studies and meta-analyses across a range of cancers [60,61,65–68].

Beyond surgical site infection, the association with other morbidity and perioperative mortality seems to be less consistent, as exemplified by several analyses of the ACS-NSQIP dataset. Two large studies (7207 women undergoing unilateral mastectomy for breast cancer [66]; 15 937 patients undergoing breast reconstruction [69]) showed an increased risk of bleeding [66], major surgical complications, medical complications and return to the operating theatre with increasing BMI [69]. Conversely, three further large studies showed that significant relationships between obesity and other morbidities (outside of surgical site infections) did not remain in adjusted analyses, in patients undergoing liver surgery for benign and malignant indications [[67], abdominal surgery for an assortment of gastrointestinal cancers [68] and laparoscopic colorectal resections (benign and malignant indications) [70]. Disease indication may be an effect modifier, whereby obesity is associated with increased morbidity within malignant but not benign indications. In this setting, surgeons may opt to avoid surgery for benign disease in obese patients perceived to be at high risk for complications [71].

Surgical Outcomes

Furthermore, excess adiposity is thought to influence surgical outcomes, often due to the associated technical challenges. Lymph node harvest (LNH) is one example, where a reduced LNH is a poor prognostic factor due to the risk of nodal downstaging (i.e. not examining a metastatic node that is present) and hence nodal-stage misclassification. In colorectal cancer, a LNH of 12 is thought to represent an adequate surgical and pathological specimen for accurate staging and prognostication in multiple guidelines [72–74]. The evidence for an association between adiposity and a reduced LNH is, however, conflicting, with some studies suggesting a reduction in LNH with increasing BMI [75,76] and conversely others finding no association [77,78].

Margin positivity, another poor prognostic factor, may be influenced by BMI. In a large cohort study of 1434 men treated with radical prostatectomy, increasing BMI was predictive for positive surgical margins [79]. Similarly, in a multicentre study of 4118 patients undergoing radical cystectomy, obese patients were more likely to have positive surgical margins [80]. Conversely, in colorectal cancer, no difference in positive surgical margins (proximal, distal or circumferential) was shown in a meta-analysis of nine studies [76].

Obesity and Chemotherapy

There is growing evidence of suboptimal chemotherapy dosing for overweight and obese patients, the details of which are frequently under-reported. First, concerns over increased toxicity when dosing according to body surface area derived from actual bodyweight, have resulted in the practice of capping chemotherapy at maximum doses corresponding to a body surface area of 2 m^2 or 2.2 m^2, creatinine clearance of 125 ml/min (e.g. carboplatin) and an ideal or adjusted ideal bodyweight. Second, empirical first dose reductions (e.g. up to 25%) are frequently used, dependent on factors such as significant comorbidities, increased performance status, age, palliative intent and certain chemotherapy types [81]. Third, toxicity or exacerbation of patient comorbidities may result in sequential dose reductions and/or delays between cycles, thus reducing treatment adherence [82]. Fourth, such toxicities may result in early discontinuation of chemotherapy.

Dose capping (Table 3) occurs across a range of cancers (including those of the colon [50,51,54,58], rectum [54,58], breast [49,84,86,91,92] and ovaries [87–89]) within clinical trials and cohort studies and frequently displays a proportional relationship with BMI, as exemplified in Table 4. Clearly this may carry prognostic implications.

Historically, chemotherapy drug concentrations and dose intensity, particularly in the setting of chemo-sensitive malignancies (e.g. lymphoma and leukaemia) were shown to correlate with efficacy and toxicity, with steep dose–response relationships [94,95]. Prognostic benefits have been shown with higher doses and dose-intense regimens in, for example, breast [96,97], haematological [98] and germ cell tumours [99]. Dose-dense regimens (consisting of reduced dosing intervals) have been associated with improved survival in lymphoma [100,101] and breast cancer [102].

To put the effect of dose capping into context, there is a relationship between the reduced first cycle relative dose or relative dose intensity (Table 3) and adverse prognostic outcomes for adjuvant and metastatic chemotherapy studies in colorectal [58,85,103,104], breast [49,92] and ovarian cancer [83,87–89] (Table 5).

Although the concern of toxicity has historically been the driving influence of these dosing practices, the literature increasingly does not support a proportional relationship between BMI and toxicity in fully dosed chemotherapy. Indeed, elevated BMI has been associated with equivalent or reducing levels of toxicity among fully dosed obese patients, in comparison with those with normal BMI in, for example, colorectal [50,51,54,58,85,105], breast [84,86,90,91] and small cell lung cancer [106]. Furthermore, the pharmacokinetic effects of obesity on hepatic and renal drug clearance are not understood. Hence, there is a general lack of evidence to justify reducing chemotherapy doses on such grounds [93]. However, an interesting avenue warranting further exploration is that of pharmacokinetic-guided dose adjustments (e.g. 5-fluorouracil serum testing) [107].

In attempt to understand whether dose capping is justified and to improve and standardise care for patients receiving chemotherapy, in 2012 the American Society of Clinical Oncology published a comprehensive review of dosing in relation to toxicity and outcomes. They concluded: 'there is no evidence that short- or long-term toxicity is increased among obese patients receiving full weight-based chemotherapy doses' [93] and published a

Table 3
Key definitions

Relative dose	A ratio of the dose delivered to the standard dose based on actual bodyweight-derived body surface area (BSA). Commonly explored based on first cycle dosing. Thresholds of 85% [83], 90% [84] or, more commonly, 95% [50,54,85] of the standard dose are often used to define dose capping (see below).
Dose capping	A maximum dose assigned to a chemotherapy agent based on the dose corresponding to a certain BSA or creatinine clearance value. Commonly, capping is undertaken for a BSA $\geq$2 m^2 or $\geq$2.2 m^2 and defined in studies exploring dose capping as a relative dose below a certain threshold.
Actual dose intensity	Total cumulative dose delivered divided by the duration of treatment in weeks, expressed as mg/m^2/week.
Expected dose intensity	Total cumulative expected dose according to the study protocol or dosing guidelines based on actual bodyweight divided by the expected duration of treatment in weeks, expressed as mg/m^2/week.
Relative dose intensity	A ratio (or percentage) of the actual dose intensity to the expected dose intensity. Usually calculated for the entire course of chemotherapy and accounts for both cumulative dosing and dose delays, hence also reflecting adherence to planned/protocol-driven chemotherapy dosing. A reduced relative dose intensity is often assigned a threshold of <85% [83,89–96].

number of key dosing recommendations (Table 6), acknowledging the lack of available randomised trials on which to base recommendations.

There are a number of limitations to the evidence concerning chemotherapy dosing and toxicity in obese patients. First, many studies (particularly of breast and ovarian cancer) are observational and thus subject to substantial confounding and bias. Second, trial data are frequently 'lumped' together without performing an individual participant data meta-analysis, retaining trial clustering [51,58,108] Third, dose capping is often explored as a dichotomous variable that may not be sensitive enough to assess the impact of dose reductions, rather it may be more appropriate to model relative dose or relative dose intensity as a continuous variable. Fourth, a lack of detailed dosing analyses and standardised outcome reporting in studies exploring complex BMI–dose–toxicity–survival relationships hinder interpretation [109]. Fifth, several of these studies are likely to be underpowered to detect differences between BMI subgroups [50,54].

Immunotherapy Effects in Obesity

Immunotherapy innovations are transforming cancer therapy and represent the strive towards personalised treatment [110]. Improved mechanistic understanding of the obesity–cancer relationship has determined that excess adiposity is associated with chronic low-grade systemic and local inflammatory states [3], generating interest in the effects of immunotherapy in this context.

Inhibitory immune checkpoints, predominantly associated with T cells, can be utilised by tumours to down-regulate T-cell anti-tumour immune responses and may be exploited by immunotherapy to counteract these effects [111]. To this end, immunotherapeutic agents targeting programmed death 1 (PD-1), PD-1 ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitory checkpoints have been developed for a range cancers (e.g. metastatic melanoma, lung, kidney, colorectal, breast, oesophageal, liver) [112–121]. Although their use is increasing, it seems that such immunotherapy agents are only effective in generating sustained clinical responses for a limited proportion of patients, hence the search for predictive biomarkers [122]. Within this context, there is some evidence of a prognostic benefit of immunotherapy in overweight and obese patients — an obesity paradox — emerging (Table 7).

Recently, Wang and colleagues [34] showed that obesity is associated with chronic inflammatory states that result in suppressed immune responses; T-cell exhaustion (aging) was increased, demonstrated by upregulated PD-1 expression in mouse, primate and human models. Furthermore, obesity increased tumour proliferation and infiltration of PD-1-expressing T-cells and PD-1-mediated T-cell dysfunction, doing so at least partly via leptin pathways. Treatment with antibodies against the PD-1 inhibitory checkpoint resulted in increased tumour shrinkage and prevention of metastasis formation, with no observed toxic effects in obese versus control murine models. These results seemed to translate clinically with prognostic benefits (improved progression-free and overall survival) demonstrated in obese individuals. Table 7 presents the results of three studies of checkpoint blockade [34,123,124], showing an apparent overall survival improvement with elevated BMI.

Although obesity might be a 'mediator of immune dysfunction and tumour progression that can be successfully reversed by PD-(L)1 checkpoint inhibition resulting in heightened efficacy', rather than a prognostic factor, as stated by Wang *et al.* [34], we urge caution when interpreting these clinical results as evidence of definite prognostic benefit of checkpoint inhibitors in overweight/obese patients over those with normal BMI. First, these patient groups in general include those with advanced or metastatic disease and are, therefore, inherently subject to a higher degree of reverse causation and BMI downward

Table 4
Summary of selected studies reporting dose reduction by body mass index (BMI) category

Reference (country)	Study name/type	Setting and cancer type	Setting	*n*	Chemotherapy regimen	Dose reduction	BMI category (kg/m^2)	Dose reduction outcome		*P*
								Proportion (%)		*P*
[58] (UK)	FOCUS FOCUS 2 COIN	Colorectal cancer	Metastatic	4781	FOCUS – 5 arm trial: 5-FU ± IR or Ox FOCUS 2–2 × 2: 5-FU or Cap ± Ox COIN - 3 arms: intermittent versus continuous 5-FU + Ox (or OxCAP) ± cetuximab	<95% standard dose*	<25.0 25.0–29.9 ≥30.0	4% 16% 54%		<0.001‡
[51] (USA)	NSABP C04 and C05	Colon Dukes B & C	Adjuvant	4288	NSABP C-04: 5-FU ± LV ± LEV NSABP C-05: 5-FU/LV ± IFN-α	'Dose capping'†	<18.5 18.5–24.9 25.0–29.9 30–34.9 >35.0	NR 7% NR 55% 73%		NR
								Proportion (%)	OR (95%CI)§	*P*§
[84] (USA)	Retrospective multicentre cohort	Breast stage I, II, III	Adjuvant	9672	Doxorubicin + cyclophosphamide	<90% standard dose* (averaged for the two drugs)	<25.0 25.0–29.9 30–34.9 ≥35.0	9% 11% 20% 37%	1 (Ref) 1.21 (1.02, 2.42) 2.34 (1.92, 2.85) 5.97 (4.90, 7.27)	0.03 <0.001 <0.001
						Dose proportion		Change in dose proportion‖		*P*‖
							18.5–25 25.0–29.9 30–34.9 ≥35.0	1.00 (reference) −0.014 −0.018 −0.025		<0.001 <0.001 <0.001
								OR (95%CI)¶		*P*
[87] (USA)	KP-ROCS	Epithelial ovarian cancer FIGO I-IV	Adjuvant	806	Carboplatin + paclitaxel	ARDI <85%	<18.50 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥40.0	1.08 (0.38, 3.04) 1.00 (reference) 1.60 (1.09, 2.35) 2.85 (1.79, 4.55) 5.65 (3.01, 10.62) 19.85 (7.21, 54.65)		NR

5-FU, 5-fluorouracil; ARDI, average relative dose intensity (across all drugs in regimen); Cap, capecitabine; CI, confidence interval; IR, irinotecan; OR, odds ratio; Ox, oxaliplatin; LEV, levamisole; IFN- α, interferon alpha; NR, not reported; RDI, relative dose intensity (calculated across all cycles unless otherwise stated).

* Dose at first cycle.

† Dose capping at body surface are ≥ 2.0 m^2.

‡ Test for trend across BMI groups.

§ Logistic regression with BMI as a predictor of first cycle dose reduction. Adjusted for age, menopausal status, comorbid illness, white cell count, neutrophil count, lymph node status, treatment year.

‖ Multivariable linear regression with BMI as a predictor for dose proportion. Adjusted for first cycle dose reduction, age, menopausal status, comorbid illness, white cell count, neutrophil count, lymph node status, treatment year.

¶ Multivariable logistic regression model with BMI as predictor for reduced ARDI: age, race, ethnicity, stage, histology, differentiation grade, toxicities, granulocyte colony stimulating factor use, comorbidities.

Table 5
Summary of selected studies reporting prognostic outcomes in relation to dose reductions (±body mass index [BMI])

Reference (country)	Cancer type	Cohort	*n*	Treatment type	Chemotherapy regimen	Follow-up (years)	Dose-reduction measurement ± BMI categories	Outcomes			
								OS HR (95%CI)	*P*[‖]	RFS HR (95%CI)	*P*[‖]
[85] (Germany)	Colon cancer stage III	PETACC 3 Trial	280	Adjuvant	Irinotecan and 5-FU	5.5	BMI ≥ 30 + BSA ≥ 2 FD BMI ≥ 30 + BSA ≥ 2 RD	0.53 (0.28, 1.01) 1.00 (reference)	0.092	0.48 (0.27, 0.85) 1.00 (reference)	0.018
[104] (France)	Colorectal cancer	NCCTG N9741	1340	Metastatic	5-FU-based	7.8	'Dose Burden'[*]	Spearman correlation for dose burden and BMI $r = 0.41$ BMI effects no longer prognostic with a loss of protective effect of elevated BMI, when Cox models additionally adjusted for 'dose burden'			
								2-year OS HR (95%CI)	*P*	1-year PFS HR (95% CI)	*P*
[58] (UK)	Colorectal cancer	FOCUS FOCUS 2 COIN	4781	Metastatic	FOCUS – 5 arms 5-FU ± IR or OX FOCUS 2–2 × 2: 5-FU or CAP ± OX COIN - 3 arms: intermittent versus continuous 5-FU + OX (or CAPOX) ± cetiximab	NR	BMI ≥ 30 FD BMI ≥ 30 RD[†]	1.00 (reference) 1.12 (0.96, 1.30)	0.152	1.00 (reference) 1.21 (1.06, 1.39)	0.006
[51] (USA)	Colon Dukes B & C	NSABP C04 & C05	4288	Adjuvant	NSABP C-04: 5-FU ± LV ± LEV NSABP C-05: 5-FU/LV ± IFN-α	11.2	Dose capping indicator variable	No change in association between BMI and overall survival in Cox proportional hazards model			
								5-year OS HR (95%CI)	*P*	3-year DFS HR (95% CI)	*P*
[103] (USA)	Colon stage III	Retrospective cohort	367	Adjuvant	5-FU + LV ± OX CAP ± OX	NR	RDI ≤70%[‡] RDI >70%	1.00 (reference) NA[‖]	<0.001[¶]	1.00 (reference) 0.75 (0.50, 1.11)	0.009[¶]
[54] (USA)	Rectum stage II/III	Intergroup Trial 0014	1688	Adjuvant chemoradiotherapy	4 arms – various dosing/ combinations of RT + 5-FU ± LV	9.9	<95% standard dose	No change in association between obesity and overall survival after adjustment for dose reduction in proportional hazards models. Furthermore, numbers of patients under-dosed are too small to stratify analysis			
[50] (USA)	Colon stage II/III	Intergroup Trial 089	3438	Adjuvant	5-FU + LDLV or HDLV LEV + 5-FU ± LDLV	9.4	<95% standard dose	Not predictive of overall or recurrence-free survival (HR, 95%CI and *P* values not reported) in multivariate model			
								OS HR (95%CI)	*P*	DFS HR (95%CI)	*P*
[49] (international)	Premenopausal Node-positive breast cancer	International Breast Cancer Study Group (4 trials)	739	Adjuvant	CMF	22.0 22.0 18.0	ER-negative BMI ≥ 30 + RDI ≥ 85% BMI ≥ 30 + RDI < 85%	0.50 (0.28, 0.88) 1.00 (reference)	0.0158	0.55 (0.33, 0.93) 1.00 (reference)	0.0261
			1401			12.0	ER-positive BMI ≥ 30 + RDI ≥ 85% BMI ≥ 30 + RDI < 85%	1.26 (0.78, 2.06) 1.00 (reference)	0.3492	1.20 (0.80, 1.81) 1.00 (reference)	0.3687
								Failures (death/relapse) HR (95%CI)	*P*		
[92] (USA)	Breast cancer stage II	CALGB 8541	1435	Adjuvant	CAF 300/30/3000	NR	BMI ≥ 30 FD BMI ≥ 30 RD[†]	0.54 (0.31, 0.96) 1.0 (reference)	NR	–	–
					CAF 400/40/400	NR	BMI ≥ 30 FD BMI ≥ 30 RD[†]	0.91 (0.51, 1.61) 1.0 (reference)	NR	–	–
					CAF 600/60/6000	NR	BMI ≥ 30 + FD BMI ≥ 30 + RD[†]	0.67 (0.38, 1.20) 1.0 (reference)	NR	–	–
								OS HR (95%CI)	*P*	CSS HR (95%CI)	*P*
[87] USA	Epithelial ovarian cancer FIGO I-IV	KP-ROCS	806	Adjuvant	Carboplatin + paclitaxel	4.4	RDI >100% RDI 100–85% RDI <85–70% RDI <70%	0.84 (0.57, 1.25) 1.00 (reference) 1.16 (0.88, 1.52) 1.62 (1.10, 2.37)	0.05[**]	0.78 (0.51, 1.20) 1.00 (reference) 1.21 (0.90, 1.62) 1.69 (1.12, 2.55)	0.03[‡]
								OS HR (95%CI)	*P*	PFS HR (95%CI)	*P*

[88] (Australia)	Serous ovarian cancer FIGO III/IV	AOCS retrospective population-based	333	FIGO stage III/IV	Carboplatin-based chemotherapy	NR	Carboplatin RDI <85% RDI >85% Paclitaxel RDI <85% RDI >85% Combined RDI <85% RDI >85%	1.17 (0.90, 1.51) 1.00 (reference) 1.16 (0.89, 1.52) 1.00 (reference) 1.18 (0.90, 1.54) 1.00 (reference)	0.25†† 0.28†† 0.24††	1.29 (1.02, 1.63) 1.00 (reference) 1.02 (0.80, 1.30) 1.00 (reference) 1.15 (0.90, 1.46) 1.00 (reference)	0.004†† 0.87†† 0.28††
[89] (USA)	Epithelial ovarian cancer FIGO III/IV	Retrospective multi-centre	325	FIGO stage III/IV	Combination of: carboplatin + paclitaxel and/or doxorubicin, gemcitabine, topotecan, doxetacel, OX	34 months	RDI <85%	1.71 (1.19–2.45)	0.003‡‡	1.15 (0.64, 2.06)	0.650‡‡

5-FU, 5-fluorouracil; BSA, body surface area; CAF, cyclophosphamide, doxorubicin, fluorouracil; CAP, capecitabine; CAPOX, capecitabine + oxaliplatin; CI, confidence interval; CMF, cyclophosphamide, methotrexate and 5-FU; CSS, cancer-specific survival; DFS, disease-free survival; ER, oestrogen receptor; FD, full dose; HR, hazard ratio; IR, irinotecan; HDLV, high dose leucovorin; IFN-α, interferon alpha; LDLV, low dose leucovorin; NR, not reported; LEV, levamisole; OS, overall survival; OX, oxaliplatin; PFS, progression-free survival; RD, reduced dose; RDI, relative dose intensity calculated across all cycles unless otherwise stated; RFS, recurrence-free survival.

* Proportion of the maximum standard dose at first cycle.

† Dose at first cycle <95% standard.

‡ Calculated as the proportion of the standard regimen dose intensity for each drug averaged across each drug used within a given regimen, irrespective of BMI.

§ Proportional hazards assumption violated for RDI in overall survival model.

‖ Cox proportional hazards multivariate analysis.

¶ Log rank tests for Kaplan–Meier survival curves.

** *P* for trend; Cox proportional hazards adjusted for age, race, BMI at diagnosis, stage, grade, histological type, toxicity, granulocyte colony stimulating factor use, diabetes mellitus, hypertension, cardiovascular disease, renal disease, post-treatment Ca125 levels.

†† Unadjusted Cox models. After adjustment, there was no longer a significant difference for PFS in the carboplatin subgroup ($P = 0.06$). Adjusted models not presented.

‡‡ Multivariable Cox proportional hazards. Adjusted for stage, race, elevated Ca125, age, suboptimal debulking, histology.

Table 6
American Society of Clinical Oncology guidance key dosing recommendations for obese patients [93]

- Full weight-based chemotherapy doses should be used in obese patients, especially where cure is the primary aim.
- Toxicities should be managed in the same way regardless of body mass index.
- Consideration of resuming full weight-based dosing should be made in subsequent treatment cycles following a toxicity-related dose reduction (particularly where possible contributory factors have resolved).
- Evidence does not support increased dose reductions in obese versus non-obese patients.
- Fixed dosing of chemotherapy is only justified for a select few agents.

migration through weight loss [16], made worse by dichotomising BMI (and including underweight patients into the comparator group). Second, without normal, overweight and obese non-immunotherapy comparator groups it is difficult to tease out what might be reverse causality from what is truly a biological difference in treatment response. Third, these cohorts are reasonably small, observational, super-selected subsets, probably representing patients who have withstood multiple lines of chemotherapy and are likely to reflect the fitter end of the obese patient group. Fourth, these are also, in general, cohorts of mixed cancers that are unbalanced for this and other baseline characteristics and thus subject to confounding. Fifth, although gender effect differences have been shown for immune checkpoint blockade [125,126], conflicting effect estimates between the two studies reporting these subgroup analyses further suggest the possibility of residual confounding.

Obesity and Radiotherapy

A concern when administering radiotherapy to obese patients is the potential for increased risk of daily set-up errors, resulting in interfractional displacement, due to increased movement of skin and subcutaneous adiposity. Elevated BMI has been shown to be correlated with increased interfractional displacement in a number of small studies of radiotherapy for prostate [127], abdominal [128] and endometrial [129] cancer. Consequently, it has been postulated that such interfractional displacement might result in a reduced delivered radiation dose to target tissues, which might in turn account for the adverse outcomes associated with elevated BMI seen in some retrospective series, and that image-guided radiotherapy may help to overcome these issues [127].

The evidence examining the relationship between BMI and radiotherapy is limited and comes mainly from retrospective (mostly prostate cancer) cohorts, showing conflicting results. A retrospective series of 1868 patients with prostate cancer undergoing external beam radiotherapy showed a significant relationship between increasing BMI and biochemical recurrence (BCR) [130]. Conversely, a retrospective series of 1530 patients with localised prostate cancer undergoing brachytherapy failed to show an association between BMI and BCR, cancer-specific survival (CSS) or overall survival [131]. However, in the setting of localised prostate cancer treated with dose-escalated intensity-modulated radiotherapy with daily image-guided radiotherapy, a further retrospective series of 1442 patients showed a significant adverse relationship between increasing BMI and BCR, CSS and overall survival [132]. Within the context of radiotherapy for breast conservation in early breast cancer, a recent multicentre retrospective series of 2513 patients showed no significant relationship between BMI and locoregional relapse, disease-free, CSS or overall survival [133]. These studies remain at risk of many of the methodological issues previously discussed, including residual confounding and reverse causality, limiting the ability to draw any firm conclusions.

Obesity—Prognosis Evidence

Alongside probable causality for the BMI—incident cancer risk, it would seem logical that BMI similarly confers a causal association to cancer-related survival outcomes. In breast cancer, three meta-analyses have shown an inverse association between elevated BMI and CSS, as well as overall survival, implying that increased deaths are not solely the result of obesity-related comorbidities and metabolic disturbances [134–136]. Notably, the dose-response meta-analyses carried out by Chan *et al.* [136] included three BMI measurement timings (pre-, $<$12 months and $\geq$12 months of diagnosis), which maintained this relationship independent of timing.

Conversely, and despite the large excess BMI—incident endometrial cancer risk [6,7], a secondary analysis of the Medical Research Council ASTEC trial found no association between elevated BMI and overall survival or CSS (in the context of reduced biases within a standardised trial protocol) [35]. Two large observational cohort studies assessing mortality associated with BMI categories have previously reported the reverse [137,138]. These contrasting outcomes highlight important differences between studies of mortality risk (prospective population-based studies) and of prognostic survival risk. First, the timing of BMI measurement is increasingly thought to be important [18,139], where in the former BMI is measured several years before the development of cancer and in the latter peri-diagnosis or -treatment BMI is often utilised. Second, prospective population cohort studies are often not able to collect prognostic data and therefore are less likely to present fully adjusted models, but do, however, give better representation on a population level.

These features are exemplified by the systematic review and dose—response meta-analyses of the effects of 5 kg/m^2 increments of BMI on survival outcomes in colorectal cancer published by Parkin *et al.* [140], which was stratified according to study characteristics (timing of adiposity measurements and clinical setting), demonstrating conflicting outcomes [140]. Pre-diagnosis BMI and cancer-related

Table 7
Summary of selected studies of immunotherapy treatment outcomes by body mass index (BMI) category

Reference (country)	Study name/type	Setting and cancer type	Setting	*n*	Chemotherapy regimen	Outcome measure/subgroup	BMI category		
							18.5–24.9	25–30	≥30
[123] (USA)	Nested cohort			207	Ipilimumab + dacarbazine	OS HR* (95%CI) - all	1.00 (reference)	0.70 (0.53, 1.08)	0.54 (0.34, 0.86)
						OS HR* (95%CI) - men	1.00 (reference)	0.63 (0.39, 1.01)	0.40 (0.22, 0.72)
						OS HR* (95%CI) - women	1.00 (reference)	0.84 (0.43, 1.64)	1.16 (0.55, 2.46)
	Retrospective cohort	Melanoma	Metastatic	329	Pembrolizumab, nivolumab or atezolizumab	OS HR* (95%CI) - all	1.00 (reference)	0.78 (0.52, 1.17)	0.72 (0.48, 1.06)
						OS HR* (95%CI) - men	1.00 (reference)	0.71 (0.44, 1.17)	0.69 (0.42, 1.12)
						OS HR* (95%CI) - women	1.00 (reference)	1.00 (0.47, 2.10)	0.72 (0.36, 1.45)
	Meta-analysis of the above			339	Above combined	OS HR* (95%CI) - all	1.00 (reference)	NR	0.64 (0.47, 0.86)
						OS HR* (95%CI) - men	1.00 (reference)	NR	0.55 (0.32, 0.93)
						OS HR* (95%CI) - women	1.00 (reference)	NR	1.90 (0.54, 1.50)
							<30	≥30	
[34] (USA)	Single centre, retrospective cohort	Lung, melanoma, ovarian, other	NR	250	αPD-(L)1 checkpoint blockade	OS HR† (95%CI) - all	1.00 (reference)	0.594 (0.35, 0.99)	
							<25§	≥25	
[124] (Italy)	Retrospective cohort	NSCLC, melanoma, renal cell carcinoma	NR	976	Pembrolizumab, nivolumab, atezolizumab	OS HR‡ (95%CI) - all	1.00 (reference)	0.49 (0.38, 0.64)	
						OS HR‡ (95%CI) - men	1.00 (reference)	0.59 (0.43, 0.81)	
						OS HR‡ (95%CI) - women	1.00 (reference)	0.27 (0.15, 0.48)	

BMI, body mass index; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival.

* Adjusted for age, gender, stage, lactate dehydrogenase status, ECOG performance status.

† Adjusted for ECOG performance status, line of treatment, age, gender, cancer type.

‡ Adjusted for performance status, treatment line, number of metastatic sites, gender, primary tumour subtype and development of immune-related adverse events.

§ Includes underweight patients.

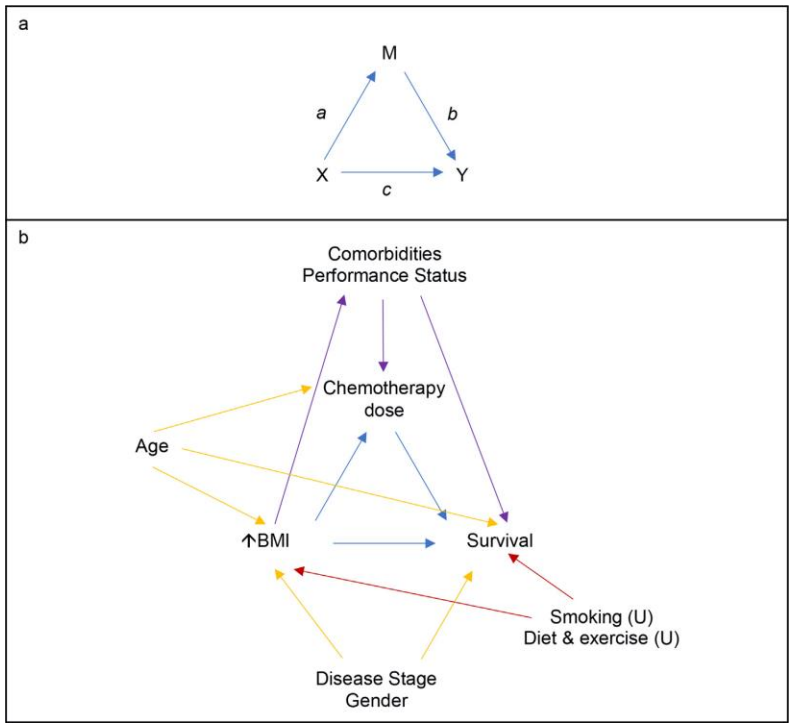

Fig 2. Directed acyclic graphs. (a) A causal association between X (exposure) and Y (outcome) may also occur through M (mediator). This forms the basis of the mediation model (blue arrows), whereby a total effect (paths ab + c) can be decomposed into a direct effect exerted by X on Y (path c) and an indirect effect exerted by X through M on Y (path ab). (b). Elevated body mass index (BMI; exposure) affects survival (outcome) directly, and indirectly through chemotherapy dose (mediator). These effects can be decomposed from the total effect of the exposure on the outcome. Adjustment for confounders of paths a, b and c (e.g. disease stage, gender, age; yellow arrows) is important for unbiased effect estimates. Careful consideration should be given to the effects of unmeasured (U) confounders (e.g. smoking, diet and exercise; red arrows), which can be explored using sensitivity analyses. Confounders such as comorbidity, which are caused by the exposure, result in intermediate confounding (purple arrows), and require approaches such as inverse probability weighting or g-estimation to produce accurate mediated effect estimates.

mortality (time zero at BMI measurement) showed a significant adverse dose–response relationship in men but not women. Conversely, pre-diagnosis elevated BMI (time zero at diagnosis) was associated with significantly increased summary overall survival and CSS risk estimates in women, but not men. Furthermore, secondary analyses of adjuvant chemotherapy trials in general showed increased peri-diagnosis/treatment BMI associated with slight (non-statistically significant) adverse survival (disease-free and overall) in men. Although three further meta-analyses showed an increased risk of mortality and recurrence in obesity with pre- and peri-diagnosis but not post-diagnosis BMI [19,20,141], significant limitations prevent causal interpretation.

Much of the current evidence exploring the BMI–survival relationship is subject to substantial heterogeneity and confounding, making interpretation of even meta-analyses challenging. Sources of heterogeneity include variation between BMI categories (often with dichotomised BMI); differential adjustment for prognostic or associated factors; variable BMI measurement timing; lack of assessment of BMI dose–response relationships. Of particular importance, contextualised in the discussions relating to chemotherapy, is the lack of careful consideration of possible suboptimal dosing effects on survival outcomes. Hence, the question remains: to what degree are the adverse outcomes shown directly associated with elevated BMI itself, rather than the indirect effects mediated through suboptimal chemotherapy dosing.

The relationship between elevated BMI and cancer outcome is undoubtedly complex for most obesity-related cancers, evidenced by the increasing body of conflicting evidence. Indeed, the International Association for Research on Cancer previously concluded that outside of breast cancer 'evidence …[of increased peri-diagnosis BMI and reduced survival]... for other cancers was sparse and less consistent' [7]. Although weight management strategies have been advocated in cancer survivors, this is as part of

encouragement to maintain a healthy lifestyle [139,142,143].

Future Directions

A causal relationship is hypothesised between excess adiposity and cancer prognosis, but cannot be inferred with confidence in the context of the current evidence [2]. Taking chemotherapy dosing as an example, to understand the true causal effect of excess adiposity on cancer survival, and accounting for suboptimal chemotherapy dosing and toxicity, statistical methodology is required that is able to decompose and quantify these effects, while appropriately dealing with confounding and bias. Mediation analysis is a strategy that allows one to answer, 'how does a relationship occur?' and not simply 'does it occur?'. It permits disentangling of a total effect of an exposure on an outcome into its direct effect and its indirect effect acting through a mediator [144]. This process involves the creation of directed acyclic graphs [145] to show associations (including causal relationships) between variables, to allow consideration of the pathways of interest on which to build statistical causal mediation models. The advantage of this approach is the ability to account for the possible effects of covariates, moderators, confounders and unknown confounders etc. (Figure 2). Mediation analysis as a methodological approach is emerging within the clinical literature, including within the context of oncology [146]. We anticipate that its use will be increasingly encountered, and that its ability to improve the understanding of mechanistic pathways will be a valuable addition to the statistical methodology used in a clinical oncology setting.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. J. Barriuso reports grants and non-financial support from Ipsen, non-financial support from Novartis, personal fees and non-financial support from Pfizer, non-financial support from AAA, non-financial support from Nanostring, outside the submitted work. All other authors declare no competing interests.

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Table A2.1 | OCTOPUS adjuvant chemotherapy randomised controlled trials summaries

Trial Name Author (year), Country	Setting / Disease	Intervention & Accrual	Eligibility	Exclusion	Randomisation	Outcomes	Toxicity
MOSAIC Andre *et al.* (2004)[183]	Adjuvant Phase III Colon stage II*/ III	5FU/LV + OX vs. 5FU/LV 1998 - 2001	≥ 18years Stage II (T3-4, N0, M0) Stage III (T1-4, N1-2, M0) CHT starting <7 weeks of surgery KPS ≥ 60 CEA < 10ng/ml Adequate blood counts Adequate liver/renal function	Previous CHT Previous IMT Previous DXT	Central Stratified: TNM stage Obstruction or perforation Centre	<u>Primary</u> DFS <u>Secondary</u> OS Safety Prognostic factors	CTCAE V.1
SCOT Iveson *et al* (2018)[185]	Adjuvant Phase III Colon & Rectum stage II*/ III	3 months vs. 6 months (CAPOX or FOLFOX) 2008 – 2013 Closed early	≥ 18years Curative resection (TME R0) Colon or rectal adenocarcinoma Stage III or HR Stage II* WHO PS 0-1 Adequate organ function Expected 5YS from co-morbidities Normal **CT-TAP** CEA <1.2x ULN Previous SCDXT allowed.	Previous CHT < 5yrs (or >5years + residual symptoms). Previous LC-CRT eGFR <30ml/min Hb <9g/dl / Neut <1.5 / Plts <100 AST/ALT >2.5x ULN Significant CVD disease Pregnancy/lactation Refusal of contraception Previous malignancy (excl. CIN, BCC, SCC) <5year disease free DPD deficiency	Central 1:1 – 3:6 months Minimisation: Centre Regimen Sex Site (colon v. rectum) N-stage T-stage Starting dose CAP	<u>Primary</u> DFS <u>Secondary</u> OS Safety QoL Cost-effectiveness	CTCAE V. 3
CHRONICLE Glynne Jones et al. (2014)[169]	Adjuvant Phase III Rectal - locally advanced (after NCRT + surgery)	Observation Vs. CAPOX 2004 – 2008 Closed early	≥ 18years Adenocarcinoma rectum (<15cm anal verge or below peritoneal reflection) ypT0-4, N0-N2 Pre-op NCRT WHO PS 0-1 Adequate renal/liver/ haematological function CRM >1mm	Metastatic disease R1/R2 resection Significant cardiac disease CNS disorders Known peripheral neuropathy Moderate/severe renal impairment Pregnancy/lactation	After surgery I:I Permuted blocks Stratified: Surgeon Nodal status	<u>Primary</u> DFS <u>Secondary</u> OS Toxicity Compliance to CHT	CTCAE V.3
PROCTOR-SCRIPT Breugom *et al.* (2015)[171]	Adjuvant Phase III RCT Rectal Stage II/III (after NCRT + surgery)	Adjuvant CHT vs. observation (5FU/LV or Capecitabine) 2000 – 2013 Closed early due to poor accrual.	≥ 18years Rectal adenocarcinoma Below S1/S2 on CT/MRI or <15cm from anal verge on sigmoidoscopy Pre-operative (chemo)-DXT + TME (y)pTNM stage II or III R0 (proctor) or R1 (Script)	FAP HNPCC Active IBD DPD Deficiency Current/Previous malignancy (exc. adequately treated BCC skin, insitu cervix/uterine) No previous cancer (Proctor) 10 years disease free (Script)	After surgery Central 1:1 Blocks (6) Stratified: Centre R0/R1 Time between last DXT & surgery Pre-op treatment	<u>Primary</u> 5yr OS <u>Secondary</u> DFS Any recurrence Locoregional recurrence Distant recurrence	Not defined

Table A2.1 | OCTOPUS adjuvant chemotherapy randomised controlled trials summaries

Trial Name Author (year), Country	Setting / Disease	Intervention & Accrual	Eligibility	Exclusion	Randomisation	Outcomes	Toxicity
NCCTG – N0147[187]	Adjuvant Phase III Colon Stage III	6 arm trial: mFOLFOX6+/- CET FOLFIRI +/- CET mFOLFOX+FOLFIRI +/- CET 2004 – 2009 Closed early	≥ 18years WHO PS 0-2 Stage III colon adenocarcinoma ≥12cm from anal verge Adequate blood counts & liver/kidney function Chemo < 10 weeks surgery	Previous CHT, IMT, DXT for colon cancer	Dynamic allocation procedure Stratified: T-stage No. positive nodes Differentiation	<u>Primary</u> DFS <u>Secondary</u> TTR OS Toxicity	CTCAE V.3

Abbreviations: **ALT/AST,** alanine/aspartate transaminase; **BCC**, basal cell carcinoma; **CEA**, carcinoembryonic antigen; **CHT**, chemotherapy; **CIN**, cervical intraepithelial neoplasia; **CNS**, central nervous system; **CT-TAP**, computed tomography of thorax, abdomen and pelvis; **CTCAE**, common terminology criteria for adverse events; **CVD**, cardiovascular disease; **DFS**, disease free survival; **DPD**, dihydropyrimidine dehydrogenase; **DXT**, radiotherapy; **EMVI**, extramural vascular invasion; **HR**, high risk; **IBD**, inflammatory bowel disease; **IMT**, immunotherapy; **KPS**, Karnofsky performance status; **LC-CRT,** long-course chemoradiotherapy; **LR**, low risk; **LNH**, lymph node harvest; **LVI**, lymphovascular invasion; **NCRT**, neoadjuvant chemo-radiotherapy; **MRI**, magnetic resonance imaging; **OS**, overall survival; **PNI**, perineural invasion; **PS**, performance status; **QoL**, quality of life; **SCC**, squamous cell carcinoma; **SCDXT**, short course radiotherapy; **TME**; total mesorectal excision; **TNM**, tumour, node, metastasis; **ULN**, upper limit of normal; **WHO**, world health organisation;

* High Risk Stage II disease (Stage II plus any of: T4, obstruction, <10 LNH, poorly diff, PNI, EMVI, LVI)

Table A2.2 | Key variables required for minimum dataset

Essential and desirable variables required (or calculable from other available variables).

	Baseline demographic	Pathology	Chemotherapy	Toxicity	Survival
Essential	• Height - at trial entry • Weight - at trial entry • BMI - calculable from height/weight • BSA - calculable from height/weight • Age (years) • Sex (male or female) • Performance status	• Tumour stage • Nodal stage	• Cycle 1 dose • Cumulative dose • Duration of chemotherapy (or calculable from dates for first and last cycles)	• Occurrence of any grade 3+ toxicity	• OS status • DFS status • CSS status • OS time from randomisation • DFS time from randomisation • CSS time from randomisation Or variables from which to calculate the above: • Inc. Time to last follow-up/death/recurrence • Survival status • Recurrence/ distant metastasis • New CRC tumour • Cause of death)
Desirable	• Race / Ethnicity • Randomisation centre • Repeated BMI cycle measures • Repeated performance status • Comorbidities	• Differentiation • Lymph node harvest • Perineural invasion • Lymphatic invasion • Vascular invasion • Perforation • Obstruction	• <u>Cycle-level:</u> • Cycle total dose • Cycle date • Cycle number	• <u>Cycle-level:</u> • Cycle toxicity type • Related toxicity grade (0-V) for all toxicities	• New non-CRC tumour • Recurrence/metastasis site

Table A2.3 | Summary of Risk of Bias assessment

Summary risk of bias judgements following use of the Risk of Bias - Version 2 (RoB2) assessment tool for meta-analysis of randomised trials from Sterne et al.[188] assessment of bias extended to include evaluation of exposure, confounders, and mediators in addition to outcomes, in addition to including judgement on data quality.

Bias arising from the randomisation process	
Low risk	*Randomisation not directly applicable to analyses as exposure cannot be randomised. All trials followed randomised allocation (open label), with no evidence of baseline imbalance. Therefore, randomisation was likely to reduce bias within study context, even though studied exposure cannot be randomised.*
Bias due to deviations from intended interventions	
	Section not applicable as study assesses deviation form protocolised treatment related to BMI, and these effects on outcomes.
Bias due to missing outcome data (extended to include exposure, confounders, and mediators)	
Low risk – Exposure	*Proportion of eligible patients with missing BMI data was low, and unlikely to substantially influence outcomes.*
Low/moderate risk - Confounders	*Minimal missing data for key confounders. Additional confounders such as poor prognostic features (e.g., lymph node harvest), race, smoking status mostly systematically missing.*
Low risk – Adherence measures	*Minimal missing chemotherapy data (11 patients excluded overall due to non-calculable adherence measures (either missing cycle dose or date data).*
Moderate risk – Toxicity	*Missingness relates mainly to toxicity data – potential bias resulting from missing toxicity data; however, this was protocol-related and therefore unlikely to be due to other study factors.*
Low risk – Survival	*There was evidence that survival outcomes were not biased by missing toxicity data.*
Bias in measurement of the outcome (extended to include exposure, confounders, and mediators)	
Low risk – Exposure	*Quality of BMI data appeared good overall, height and weight assumed to be directly measured and recorded as part of. Minor apparent data-entry errors identified, and sensitivity analysis planned to evaluate potential effects.*
Low risk - Confounders	*No significant issues identified of pertaining to measurement of confounders.*
Low risk – Adherence measures	*Quality of chemotherapy data overall good, minor proportion of patients with apparent data-entry errors and sensitivity analysis planned to evaluate potential effects.*
Low/moderate risk – Toxicity	*Trials graded toxicity according to standardised Common Terminology Criteria of Adverse Events (though unclear whether this was used for PROCTOR-SCRIPT).*
Low risk – Survival	*No concerns identified regarding survival outcome measurement. Issues regarding sufficient follow-up duration identified/attrition identified within all trials to a degree. Bias risk with composite 3-year survival outcome measure, reduced by time-to-event modelling.*
Bias in selection of the reported result	
	Not directly applicable as not an aggregate data meta-analysis. *All a priori defined analyses are presented within the thesis, including null results.* *Data for all a priori defined outcomes where available.*
Overall bias	
Low risk	*Overall, good quality of datasets, some concerns over missing toxicity data addressed through multiple imputation methods and sensitivity analyses.*

Table A2.4 Harmonisation of toxicity variables

Table demonstrating how data where harmonised. Green highlights the original variables that were pre-specified in datasets; Orange denotes free-text data (including spelling mistakes) usually found in "Other" variables. Red denotes not present (either in pre-specified variables or in "other" variables).

	MOSAIC	SCOT		CHRONICLE	PROCTOR		SCRIPT	
	Named	Named	"Other"	Named	Named	"Other"	Named	"Other"
Neutropenia	GRANULO-CYTOPENIA;	Neutropenia;	NA*	Granulocytes;	NA*	"neutropenia"; "neutropenie";	F06NEUTROGR;	NA*
Diarrhoea	DIARRHOEA;	Diarrhoea;	"Diarrhoea"	Diarrhoea;	P06DIARGR;	NA*	F06DIARGR;	NA*
Neuropathy	PARAESTHESIA; SENSORY DISTURBANCE; NEURITIS MOTOR; HYPERAESTHESIA	Neuropathy – Sensory;	"Neuropathy-sensory"; "Neuropathy-motor"	Neuropathy: sensory; Paraesthesia/ dysesthesia;	NA*	"neuropati sensory"; "neurosensory feet";	F06NEUROGR;	"neuropathy motory"
Nausea	NAUSEA;	Nausea	"Nausea	Nausea;	P06NAUGR;	NA*	F06NAUGR;	NA*
Vomiting	VOMITING;	Vomiting	"Vomiting	Vomiting;	P06VOMGR;	NA*	F06VOMGR;	NA*
Stomatitis/ mucositis	MUCOSITIS; STOMATITIS	MUCOSITIS (Functional/ Symptomatic); MUCOSITIS (clinical exam);	"Mucositis (clinical exam)"; "Mucositis (functional/ symptomatic)"; "Stomatitis"	NA*	P06MUCGR;	NA*	F06MUCGR; F06MUCSPEC (notes included cases of stomatitis);	NA*
Fatigue	FATIGUE;	Fatigue;	"Fatigue"	Fatigue;	NA*	"Fatigue"; "Fatique"; "faigue"; "fatgue"; "fatigue"; "fatique";	F06FATGR;	NA*

Table A2.4 Harmonisation of toxicity variables

Table demonstrating how data where harmonised. Green highlights the original variables that were pre-specified in datasets; Orange denotes free-text data (including spelling mistakes) usually found in "Other" variables. Red denotes not present (either in pre-specified variables or in "other" variables).

Skin	ACNE; BULLOUS ERUPTION; DERMATITIS HAEMORRHAGIC; ECZEMA; ERYTHEMA NODOSUM; HYPERKERATOSIS; PHOTOSENSITIVITY REACTION; RASH; RASH ERYTHEMATOUS; SKIN DISORDER; SKIN DRY; SKIN EXFOLIATION; SKIN ULCERATION; STEVENS JOHNSON SYNDROME;	Hand-foot syndrome; Rash;	Dermatitis; Dermatology – Other; Rash; Nail changes; Hand-foot;	Hand-Foot reaction;	NA*	"Hand foot syndrome"; "Dry skin"; "Hand foot syndrom"; "dry skin"; "dry skin hands"; "dry skin, nail disorders"; "dry skin/eczeem"; "exanthema upper body"; "hand foor syndrome"; "hand foot syndrome"; "rash"; "dru skin"; "nail change"	F06DERMGR; F06HANDGR;	"Dermatology: nail changes" "Dermatology: nail changing" "dry skin" "nail changes" "nail irritated" "nail-changes" "rash" "skin: thorax: rash" "dermatology/skin rash neck/face" "rash face" "Dermatoloog/skin: nailchanges." "hyperkeratosis (hands)"
Other	All other named toxicities.	Alopecia; Anaemia; Anorexia; Constipation; Photophobia; Taste alteration; Thrombocytopenia; Vomiting; Watery eye; Other named	All other specified toxicities not included in the named toxicities.	All other specified toxicities not included in the named toxicities. (Febrile neutropenia; Anorexia; Clumsiness; pain – abdomen)	P06EYESGR P06ALOGR	All other specified toxicities in "other" toxicity variables	F06HBGR; F06ANOGR; F06CONSTGR; F06DYSGR; F06EDEMAGR; F06BILGR; F06MOODGR; F06ABDGR; F06BACKGR; F06HEADGR; F06MUSCLEGR; F06DYSPGR; F06THROMGR; F06FEVERGR;	All other specified toxicities in "other" variables: F06OTH1SPEC F06OTH2SPEC F06OTH3SPEC With associated grades

*NA – not present in detail for other toxicities

N.B. spelling errors are intentional, denoting spelling within the original datasets.

Table A3.1 | Additional baseline characteristics by BMI and Trial					
		Underweight	Normal	Overweight	Obese
Race					
MOSAIC	**White**	31 (86.11%)	530 (97.79%)	382 (99.48%)	134 (99.26%)
	Other	5 (13.89%)	12 (2.21%)	2 (0.52%)	1 (0.74%)
	Missing	0 0.00%	0 0.00%	0 0.00%	0 0.00%
SCOT_3M	**White**	37 (88.10%)	858 (80.26%)	987 (81.50%)	545 (84.76%)
	Other	0 (0.00%)	50 (4.68%)	45 (3.72%)	14 (2.18%)
	Missing	5 (11.90%)	161 (15.06%)	179 (14.78%)	84 (13.06%)
SCOT_6M	**White**	31 (86.11%)	869 (81.14%)	1,005 (84.38%)	577 (84.85%)
	Other	0 (0.0%)	44 (4.11%)	20 (1.68%)	12 (1.76%)
	Missing	5 (13.89%)	158 (14.75%)	166 (13.94%)	91 (13.38%)
CHRONICLE	**White**		N R	N R	N R
	Other		N R	N R	N R
	Missing		N R	N R	N R
PS	**White**	N R	N R	N R	N R
	Other	N R	N R	N R	N R
	Missing	N R	N R	N R	N R
Differentiation					
MOSAIC	**PD or UD**	5 (13.89%)	77 (14.21%)	45 (11.72%)	17 (12.59%)
	WD or MD	30 (83.33%)	428 (78.97%)	320 (83.33%)	116 (85.93%)
	Missing	1 (2.78%)	37 (6.83%)	19 (4.95%)	2 (1.48%)
SCOT_3M	**PD or UD**	2 (4.76%)	49 (4.58%)	50 (4.13%)	22 (3.42%)
	WD or MD	7 (16.67%)	149 (13.94%)	160 (13.21%)	104 (16.17%)
	Missing	33 (78.57%)	871 (81.48%)	1,001 (82.66%)	517 (80.40%)
SCOT_6M	**PD or UD**	0 (0.00%)	59 (5.51%)	36 (3.02%)	21 (3.09%)
	WD or MD	7 (19.44%)	146 (13.63%)	173 (14.53%)	87 (12.79%)
	Missing	29 (80.56%)	866 (80.86%)	982 (82.45%)	572 (84.12%)
CHRONICLE	**PD or UD**		N R	N R	N R
	WD or MD		N R	N R	N R
	Missing		N R	N R	N R
PS	**PD or UD**	N R	N R	N R	N R
	WD or MD	N R	N R	N R	N R
	Missing	N R	N R	N R	N R
Perforation or obstruction					
MOSAIC	**No**	23 (63.89%)	397 (73.25%)	302 (78.65%)	114 (84.44%)
	Yes	13 (36.11%)	145 (26.75%)	82 (21.35%)	21 (15.56%)
	Missing				
SCOT_3M	**No**	7 (16.67%)	127 (11.88%)	158 (13.05%)	99 (15.40%)
	Yes	2 (4.76%)	70 (6.55%)	51 (4.21%)	27 (4.20%)
	Missing	33 (78.57%)	872 (81.57%)	1,002 (82.74%)	517 (80.40%)
SCOT_6M	**No**	6 (16.67%)	171 (15.97%)	190 (15.95%)	95 (13.97%)
	Yes	1 (2.78%)	24 (2.24%)	12 (1.01%)	11 (1.62%)
	Missing	29 (80.56%)	876 (81.79%)	989 (83.04%)	574 (84.41%)
CHRONICLE	**No**	6 (16.67%)	171 (15.97%)	190 (15.95%)	95 (13.97%)
	Yes	1 (2.78%)	24 (2.24%)	12 (1.01%)	11 (1.62%)
	Missing	29 (80.56%)	876 (81.79%)	989 (83.04%)	574 (84.41%)
PS	**No**	6 (16.67%)	171 (15.97%)	190 (15.95%)	95 (13.97%)
	Yes	1 (2.78%)	24 (2.24%)	12 (1.01%)	11 (1.62%)
	Missing	29 (80.56%)	876 (81.79%)	989 (83.04%)	574 (84.41%)
Perineural invasion					
MOSAIC	**No**	1 (2.78%)	24 (2.24%)	12 (1.01%)	11 (1.62%)
	Yes	29 (80.56%)	876 (81.79%)	989 (83.04%)	574 (84.41%)
	Missing	6 (16.67%)	171 (15.97%)	190 (15.95%)	95 (13.97%)
SCOT_3M	**No**	8 (19.05%)	176 (16.46%)	185 (15.28%)	116 (18.04%)
	Yes	1 (2.38%)	16 (1.50%)	16 (1.32%)	5 (0.78%)
	Missing	33 (78.57%)	877 (82.04%)	1,010 (83.40%)	522 (81.18%)
SCOT_6M	**No**	1 (2.78%)	24 (2.24%)	12 (1.01%)	11 (1.62%)
	Yes	29 (80.56%)	876 (81.79%)	989 (83.04%)	574 (84.41%)
	Missing	6 (16.67%)	171 (15.97%)	190 (15.95%)	95 (13.97%)

Table A3.1 | Additional baseline characteristics by BMI and Trial

		Underweight	Normal	Overweight	Obese
CHRONICLE	**No**	N A	N R	N R	N R
	Yes	N A	N R	N R	N R
	Missing	N A	N R	N R	N R
PS	**No**	N R	N R	N R	N R
	Yes	N R	N R	N R	N R
	Missing	N R	N R	N R	N R
Lymphovascular invasion					
MOSAIC	**No**	13 (36.11%)	211 (38.93%)	154 (40.10%)	57 (42.22%)
	Yes	7 (19.44%)	83 (15.31%)	50 (13.02%)	17 (12.59%)
	Missing	16 (44.44%)	248 (45.76%)	180 (46.88%)	61 (45.19%)
SCOT_3M	**No**	4 (9.52%)	105 (9.82%)	92 (7.60%)	49 (7.62%)
	Yes	5 (11.90%)	93 (8.70%)	117 (9.66%)	77 (11.98%)
	Missing	33 (78.57%)	871 (81.48%)	1,002 (82.74%)	517 (80.40%)
SCOT_6M	**No**	2 (5.56%)	103 (9.62%)	98 (8.23%)	35 (5.15%)
	Yes	5 (13.89%)	103 (9.62%)	113 (9.49%)	73 (10.74%)
	Missing	29 (80.56%)	865 (80.77%)	980 (82.28%)	572 (84.12%)
CHRONICLE	**No**	N A	N R	N R	N R
	Yes	N A	N R	N R	N R
	Missing	N A	N R	N R	N R
PS	**No**	0 (0.00%)	28 (28.57%)	29 (40.28%)	3 (33.33%)
	Yes	1 (100.00%)	22 (22.45%)	15 (20.83%)	1 (11.11%)
	Missing	0 (0.00%)	48 (48.98%)	28 (38.89%)	5 (55.56%)
Lymph node harvest					
MOSAIC		13.00 (7.50, 27.50)	13.50 (9.00, 20.00)	12.00 (8.00, 16.00)	12.00 (8.00, 18.00)
SCOT_3M		*	10.50 (7.50, 22.50) †	8.50 (7.00, 10.00) †	8.00 (6.00, 10.00) †
SCOT_6M		*	8.00 (5.00, 10.00) †	7.00 (5.00, 8.00) †	9.00 (6.00, 18.00) †
CHRONICLE		N A	N R	N R	N R
PS		13.00 (13.00, 13.00)	11.50 (7.00, 16.00)	11.00 (7.00, 15.00)	11.00 (10.00, 16.00)
Lymph node ≥ 10 nodes					
MOSAIC	**No**	14 (38.89%)	158 (29.15%)	134 (34.90%)	47 (34.81%)
	Yes	22 (61.11%)	384 (70.85%)	250 (65.10%)	88 (65.19%)
	Missing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
SCOT_3M	**No**	0 (0.00%)	10 (0.94%)	16 (1.32%)	13 (2.02%)
	Yes	8 (19.05%)	187 (17.49%)	194 (16.02%)	113 (17.57%)
	Missing	34 (80.95%)	872 (81.57%)	1,001 (82.66%)	517 (80.40%)
SCOT_6M	**No**	0 (0.00%)	13 (1.21%)	22 (1.85%)	9 (1.32%)
	Yes	7 (19.44%)	192 (17.93%)	189 (15.87%)	99 (14.56%)
	Missing	29 (80.56%)	866 (80.86%)	980 (82.28%)	572 (84.12%)
CHRONICLE	**No**	N A	N R	N R	N R
	Yes	N A	N R	N R	N R
	Missing	N A	N R	N R	N R
PS	**No**	0 (0.00%)	40 (40.82%)	25 (34.72%)	2 (22.22%)
	Yes	1 (100.00%)	58 (59.18%)	47 (65.28%)	7 (77.78%)
	Missing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Median post, op CEA (IQR), ng/ml					
MOSAIC		1.40 (0.75, 2.43)	1.37 (0.90, 2.20)	1.30 (0.96, 2.20)	1.18 (0.80, 2.00)
SCOT_3M		1.80 (1.10, 2.30)	1.70 (1.00, 2.40)	1.60 (1.00, 2.20)	1.40 (1.00, 2.00)
SCOT_6M		2.00 (1.30, 2.90)	1.70 (1.00, 2.60)	1.50 (1.00, 2.10)	1.60 (1.00, 2.05)
CHRONICLE		N A	N R	N R	N R
PS		*	1.65 (1.00, 2.40)	1.30 (1.00, 2.90)	1.10 (1.00, 3.40)

Abbreviations:
* All missing
† all missing within high-risk stage III cancers

Table A3.2 | Cycle 1 actual cycle doses and relative doses by drug

Table demonstrating the ACD and RDR by baseline BMI category for each drug within each regimen and trial.

Trial	Regimen		Underweight		Normal		Overweight		Obese	
Cycle 1 Actual total doses, median (IQR)										
MOSAIC	**5FU**	**5FU-B**	813.45	(804.36, 820.40)	796.24	(787.78, 802.93)	784.79	(777.28, 791.84)	770.79	(758.23, 779.91)
		5FU-I	1218.90	(1210.20, 1229.32)	1194.94	(1183.19, 1204.06)	1178.14	(1167.15, 1188.20)	1156.19	(1138.75, 1169.00)
SCOT 3M	**CAPOX**	**CAP**	27941.42	(27197.59, 28728.52)	27207.27	(23895.11, 28237.27)	26892.00	(23988.06, 27820.42)	25596.37	(22865.08, 27093.61)
		OX	131.96	(130.03, 132.76)	129.43	(127.59, 130.96)	127.56	(125.58, 129.39)	124.73	(119.73, 126.91)
	mFOLFOX	**5FU-B**	406.03	(399.53, 413.59)	397.22	(391.49, 401.89)	392.83	(386.35, 398.03)	383.08	(367.30, 390.78)
		5FU-I	2449.70	(2433.91, 2454.61)	2391.44	(2367.53, 2409.82)	2364.36	(2337.76, 2385.71)	2296.86	(2200.24, 2340.67)
		OX	86.67	(84.02, 87.62)	84.59	(83.60, 85.51)	83.56	(82.43, 84.58)	81.35	(78.05, 83.03)
SCOT 6M	**CAPOX**	**CAP**	27296.45	(25834.66, 28591.00)	27264.33	(23134.85, 28382.59)	26758.81	(23057.13, 27788.53)	25273.16	(22813.21, 26783.93)
		OX	131.96	(128.99, 132.87)	129.16	(127.30, 130.70)	127.40	(125.18, 129.16)	124.10	(118.41, 126.71)
	mFOLFOX	**5FU-B**	401.12	(398.14, 407.35)	398.18	(391.70, 403.08)	394.12	(386.95, 399.34)	385.16	(373.05, 392.00)
		5FU-I	2438.51	(2388.83, 2496.86)	2393.95	(2370.33, 2415.09)	2363.71	(2331.68, 2385.02)	2316.56	(2247.40, 2350.74)
		OX	85.76	(83.44, 87.10)	84.45	(83.25, 85.55)	83.62	(82.15, 84.50)	81.70	(79.09, 83.24)
CHRONIC LE	**CAPOX**	**CAP**	NA	NA	27977.12	(26324.89, 28658.23)	26405.17	(13616.75, 27620.06)	26509.34	(26481.53, 27107.35)
		OX	NA	NA	128.73	(126.65, 130.91)	127.69	(126.29, 128.64)	125.86	(123.97, 126.10)
PS	**MAYO**	**5FU-B**	NA	NA	2108.74	(2071.31, 2138.59)	2108.30	(2080.47, 2156.45)	2077.17	(2077.17, 2077.17)
	NORDIC	**5FU-B**	NA	NA	1003.43	(993.47, 1014.92)	986.94	(978.75, 992.11)	960.16	(901.57, 974.43)
	CAP	**CAP**	35548.70	(35548.70, 35548.70)	34158.57	(32394.67, 35418.14)	33580.84	(31878.79, 34635.13)	30527.90	(14803.63, 33245.50)
Cycle 1 relative dose, median (IQR)										
MOSAIC	**5FU**	**5FU-B**	101.68	(100.55, 102.55)	99.53	(98.47, 100.37)	98.10	(97.16, 98.98)	96.35	(94.78, 97.49)
		5FU-I	101.57	(100.85, 102.44)	99.58	(98.60, 100.34)	98.18	(97.26, 99.02)	96.35	(94.90, 97.42)
SCOT 3M	**CAPOX**	**CAP**	99.79	(97.13, 102.60)	97.17	(85.34, 100.85)	96.04	(85.67, 99.36)	91.42	(81.66, 96.76)
		OX	101.50	(100.02, 102.12)	99.56	(98.15, 100.74)	98.12	(96.60, 99.53)	95.94	(92.10, 97.62)
	mFOLFOX	**5FU-B**	101.51	(99.88, 103.40)	99.30	(97.87, 100.47)	98.21	(96.59, 99.51)	95.77	(91.83, 97.69)
		5FU-I	102.07	(101.41, 102.28)	99.64	(98.65, 100.41)	98.52	(97.41, 99.40)	95.70	(91.68, 97.53)
		OX	101.96	(98.85, 103.09)	99.52	(98.35, 100.60)	98.30	(96.98, 99.50)	95.70	(91.83, 97.68)
SCOT 6M	**CAPOX**	**CAP**	97.49	(92.27, 102.11)	97.37	(82.62, 101.37)	95.57	(82.35, 99.24)	90.26	(81.48, 95.66)
		OX	101.51	(99.22, 102.21)	99.36	(97.92, 100.54)	98.00	(96.29, 99.35)	95.46	(91.08, 97.47)
	mFOLFOX	**5FU-B**	100.28	(99.53, 101.84)	99.54	(97.93, 100.77)	98.53	(96.74, 99.83)	96.29	(93.26, 98.00)
		5FU-I	101.60	(99.53, 104.04)	99.75	(98.76, 100.63)	98.49	(97.15, 99.38)	96.52	(93.64, 97.95)
		OX	100.90	(98.16, 102.47)	99.35	(97.94, 100.65)	98.38	(96.64, 99.41)	96.11	(93.04, 97.93)
CHRONIC LE	**CAPOX**	**CAP**	NA	NA	99.92	(94.02, 102.35)	94.30	(48.63, 98.64)	94.68	(94.58, 96.81)
		OX	NA	NA	99.02	(97.42, 100.70)	98.22	(97.14, 98.95)	96.81	(95.36, 97.00)
PS	**MAYO**	**5FU-B**	NA	NA	96.95	(95.23, 98.33)	96.93	(95.65, 99.15)	95.50	(95.50, 95.50)
	NORDIC	**5FU-B**	NA	NA	100.34	(99.35, 101.49)	98.69	(97.88, 99.21)	96.02	(90.16, 97.44)
	CAP	**CAP**	101.57	(101.57, 101.57)	97.60	(92.56, 101.19)	95.95	(91.08, 98.96)	87.22	(42.30, 94.99)

Abbreviations: 5FU, 5-Flurouracil; **5FU-B** 5FU Bolus**; 5FU-I**, Infusion; **CAP,** capecitabine;

Table A3.3 | Cycle 1 dose capping by BMI for each drug

				Underweight	Normal	Overweight	Obese
Trial	**Regimen**	**Drug**	**Dose**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
MOSAIC	**5FU**	**5FU-B**	**Full**	36 (100.00%)	528 (97.42%)	366 (95.31%)	93 (68.89%)
			Capped	0 (0.00%)	14 (2.58%)	18 (4.69%)	42 (31.11%)
		5FU-I	**Full**	36 (100.00%)	529 (97.60%)	366 (95.31%)	97 (71.85%)
			Capped	0 (0.00%)	13 (2.40%)	18 (4.69%)	38 (28.15%)
SCOT 3M	**CAPOX**	**CAP**	**Full**	22 (75.86%)	463 (63.77%)	462 (56.34%)	143 (32.65%)
			Capped	7 (24.14%)	263 (36.23%)	358 (43.66%)	295 (67.35%)
		OX	**Full**	26 (89.66%)	690 (95.04%)	690 (84.15%)	253 (57.76%)
			Capped	3 (10.34%)	36 (4.96%)	130 (15.85%)	185 (42.24%)
	mFOLFOX	**5FU-B**	**Full**	13 (100.00%)	318 (92.71%)	352 (90.03%)	115 (56.10%)
			Capped	0 (0.00%)	25 (7.29%)	39 (9.97%)	90 (43.90%)
		5FU-I	**Full**	13 (100.00%)	324 (94.46%)	360 (92.07%)	118 (57.56%)
			Capped	0 (0.00%)	19 (5.54%)	31 (7.93%)	87 (42.44%)
		OX	**Full**	11 (84.62%)	329 (95.92%)	358 (91.56%)	108 (52.68%)
			Capped	2 (15.38%)	14 (4.08%)	33 (8.44%)	97 (47.32%)
SCOT 6M	**CAPOX**	**CAP**	**Full**	16 (66.67%)	455 (62.59%)	420 (53.44%)	136 (28.51%)
			Capped	8 (33.33%)	272 (37.41%)	366 (46.56%)	341 (71.49%)
		OX	**Full**	24 (100.00%)	675 (92.85%)	669 (85.11%)	263 (55.14%)
			Capped	0 (0.00%)	52 (7.15%)	117 (14.89%)	214 (44.86%)
	mFOLFOX	**5FU-B**	**Full**	12 (100.00%)	332 (96.51%)	348 (85.93%)	135 (66.50%)
			Capped	0 (0.00%)	12 (3.49%)	57 (14.07%)	68 (33.50%)
		5FU-I	**Full**	12 (100.00%)	331 (96.22%)	349 (86.17%)	137 (67.49%)
			Capped	0 (0.00%)	13 (3.78%)	56 (13.83%)	66 (32.51%)
		OX	**Full**	12 (100.00%)	325 (94.48%)	355 (87.65%)	132 (65.02%)
			Capped	0 (0.00%)	19 (5.52%)	50 (12.35%)	71 (34.98%)
CHRONICLE	**CAPOX**	**CAP**	**Full**	0	19 (70.37%)	7 (41.18%)	2 (40.00%)
			Capped	0	8 (29.63%)	10 (58.82%)	3 (60.00%)
		OX	**Full**	0	26 (96.30%)	13 (76.47%)	4 (80.00%)
			Capped	0	1 (3.70%)	4 (23.53%)	1 (20.00%)
PS	**MAYO**	**5FU-B**	**Full**	0	13 (81.25%)	8 (80.00%)	1 (100.00%)
			Capped	0	3 (18.75%)	2 (20.00%)	0 (0.00%)
	NORDIC	**5FU-B**	**Full**	0	20 (100.00%)	10 (83.33%)	2 (66.67%)
			Capped	0	0 (0.00%)	2 (16.67%)	1 (33.33%)
	CAP	**CAP**	**Full**	1 (100.00%)	41 (66.13%)	29 (58.00%)	1 (20.00%)
			Capped	0 (0.00%)	21 (33.87%)	21 (42.00%)	4 (80.00%)

Abbreviations: 5FU, 5-Flurouracil; **5FU-B** 5FU Bolus**; 5FU-I**, Infusion; **CAP,** capecitabine;

Figure A3.1 | Cycle-level relative dose received by drug

Dot and line graphs plotting median RDR values, with whiskers denoting IQR, for each cycle by baseline BMI category for each drug within each regimen and trial.

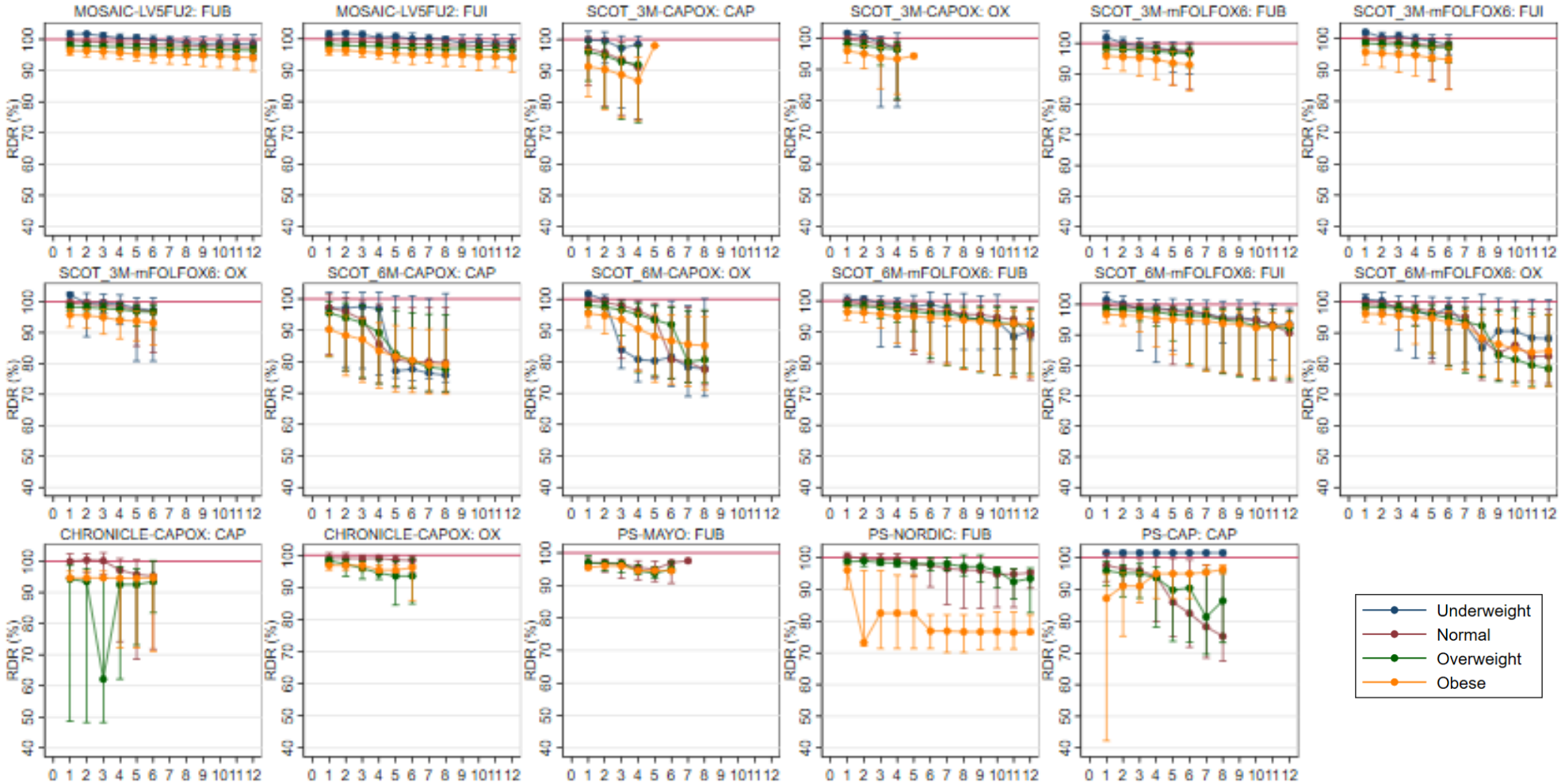


Figure A3.2 | Cycle-level relative under-dosing by drug

Dot and line graphs plotting the percentage of patients who were relatively under-dosed, for each cycle by baseline BMI category for each drug within each regimen and trial.

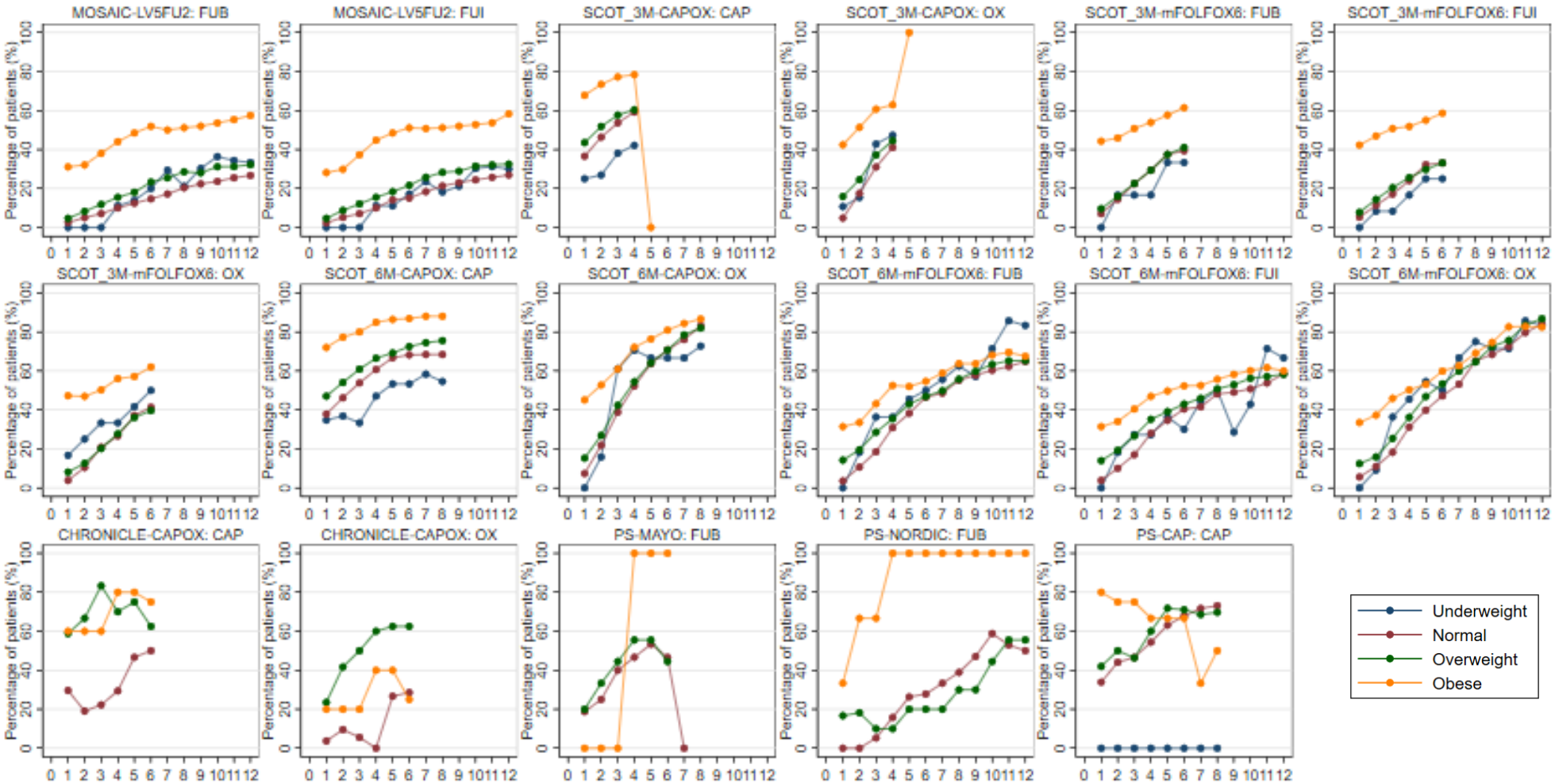


Figure A3.3 | Cycle-level dose reductions by drug

Dot and line graphs demonstrating the percentage of patents receiving a dose reduction at each cycle, by baseline BMI category for each drug. Dose reductions were defined as receipt of less than 95% of the preceding cycle dose.

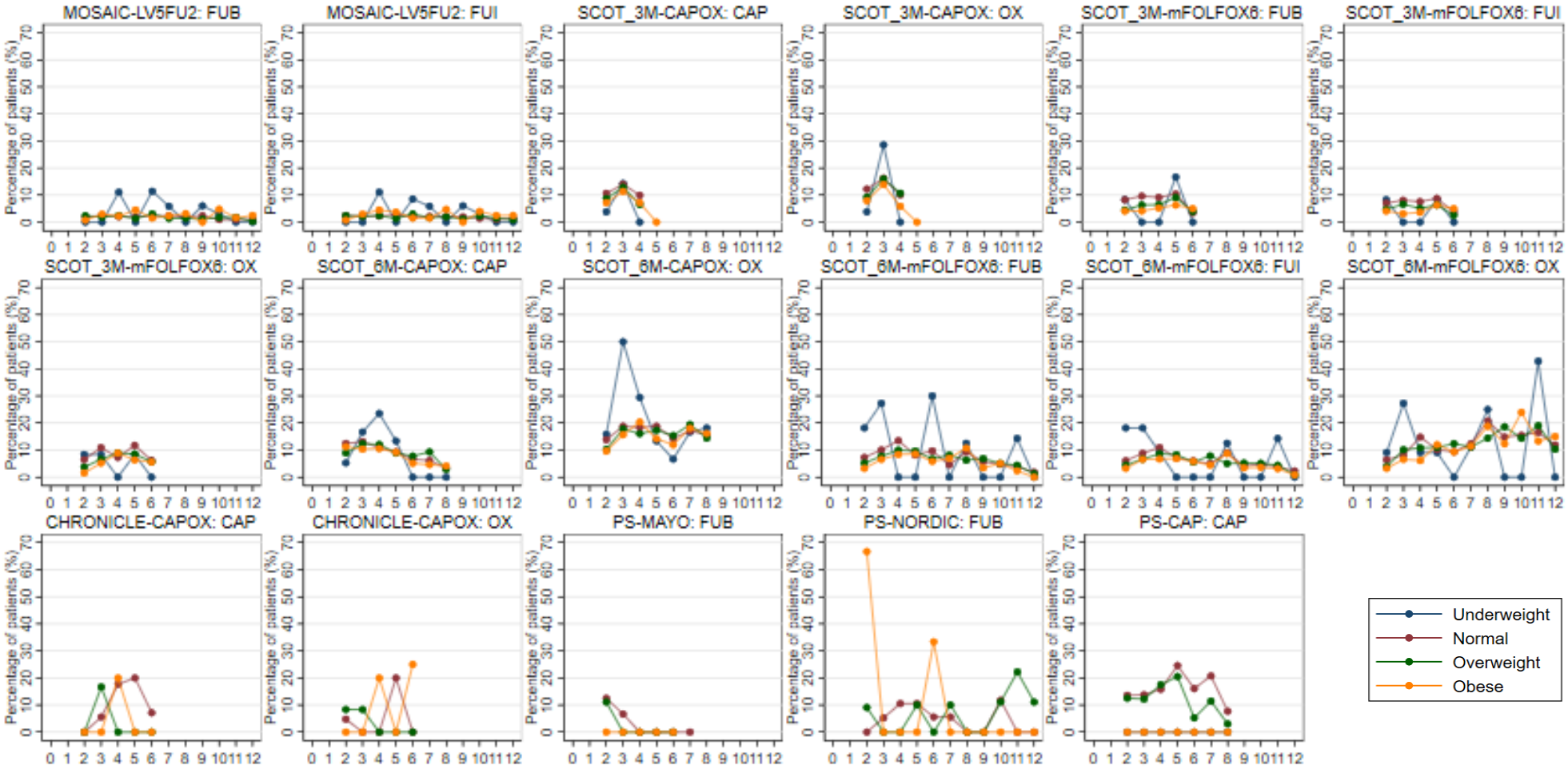


Figure A3.4 | Cycle-level cumulative attrition by drug
Dot and line graphs demonstrating the percentage of patients still receiving chemotherapy at each cycle.

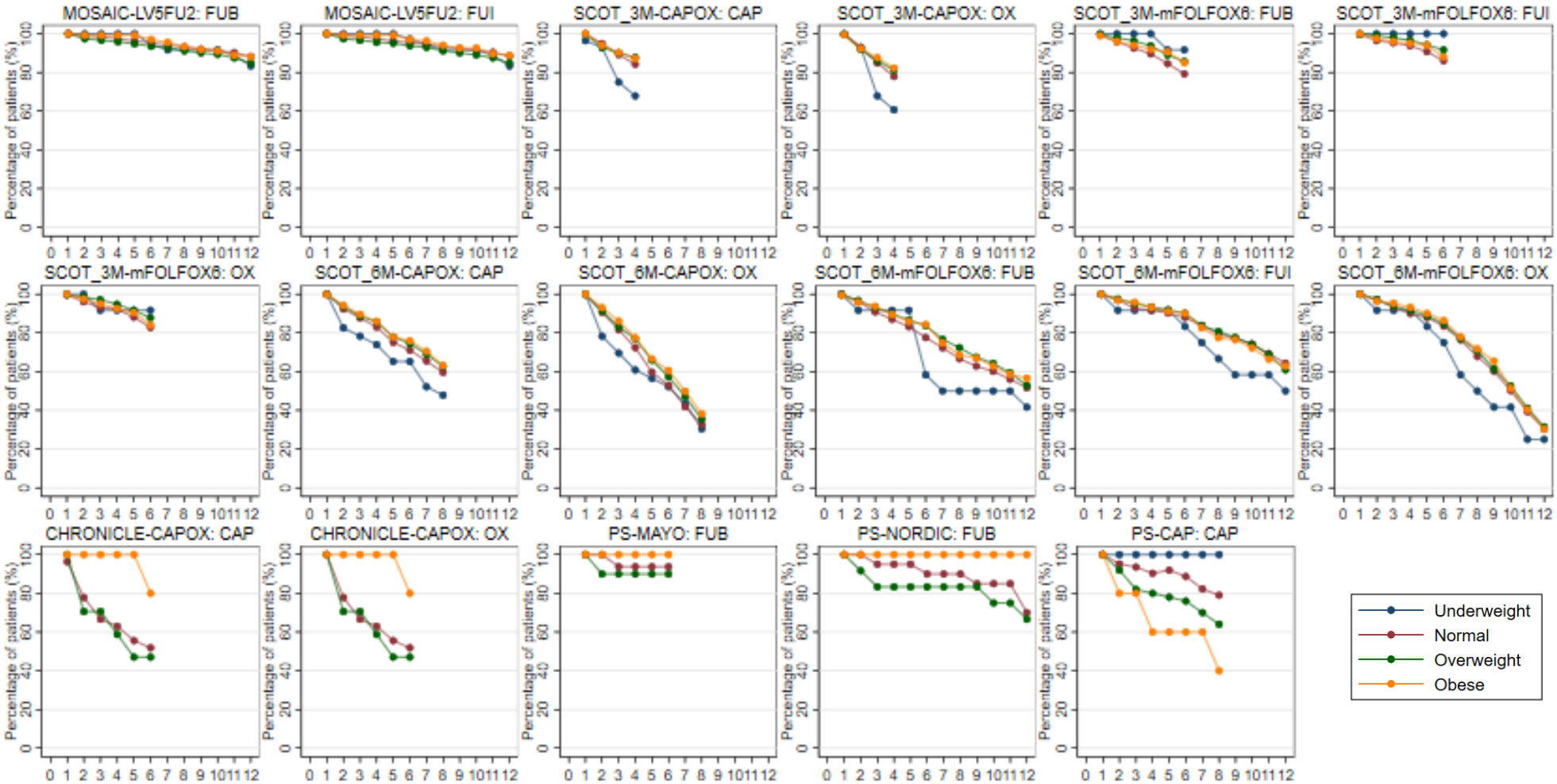


Table A3.4 | Early discontinuation of chemotherapy by each drug & regimen

				Underweight	Normal	Overweight	Obese
Trial	**Regimen**	**Drug**	**ED**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
MOSAIC	**5FU**	**FUB**	**Full**	30 (83.33%)	478 (88.19%)	325 (84.64%)	119 (88.15%)
			ED	6 (16.67%)	64 (11.81%)	59 (15.36%)	16 (11.85%)
		FUI	**Full**	30 (83.33%)	479 (88.38%)	324 (84.38%)	120 (88.89%)
			ED	6 (16.67%)	63 (11.62%)	60 (15.63%)	15 (11.11%)
SCOT 3M	**CAPOX**	**CAP**	**Full**	19 (67.86%)	590 (83.93%)	701 (87.73%)	373 (86.95%)
			ED	9 (32.14%)	113 (16.07%)	98 (12.27%)	56 (13.05%)
		OX	**Full**	17 (60.71%)	545 (77.52%)	645 (80.73%)	350 (81.59%)
			ED	11 (39.29%)	158 (22.48%)	154 (19.27%)	79 (18.41%)
	mFOLFOX6	**5FU-B**	**Full**	11 (91.67%)	265 (78.64%)	328 (85.42%)	171 (85.07%)
			ED	1 (8.33%)	72 (21.36%)	56 (14.58%)	30 (14.93%)
		5FU-I	**Full**	12 (100.00%)	286 (84.87%)	348 (90.63%)	177 (88.06%)
			ED	0 (0.00%)	51 (15.13%)	36 (9.38%)	24 (11.94%)
		OX	**Full**	11 (91.67%)	275 (81.60%)	336 (87.50%)	169 (84.08%)
			ED	1 (8.33%)	62 (18.40%)	48 (12.50%)	32 (15.92%)
SCOT 6M	**CAPOX**	**CAP**	**Full**	11 (47.83%)	413 (59.42%)	476 (62.55%)	287 (62.26%)
			ED	12 (52.17%)	282 (40.58%)	285 (37.45%)	174 (37.74%)
		OX	**Full**	7 (30.43%)	221 (31.80%)	263 (34.56%)	175 (37.96%)
			ED	16 (69.57%)	474 (68.20%)	498 (65.44%)	286 (62.04%)
	mFOLFOX6	**5FU-B**	**Full**	4 (33.33%)	169 (49.85%)	206 (52.28%)	102 (53.40%)
			ED	8 (66.67%)	170 (50.15%)	188 (47.72%)	89 (46.60%)
		5FU-I	**Full**	6 (50.00%)	213 (62.83%)	239 (60.66%)	115 (60.21%)
			ED	6 (50.00%)	126 (37.17%)	155 (39.34%)	76 (39.79%)
		OX	**Full**	3 (25.00%)	102 (30.09%)	122 (30.96%)	55 (28.80%)
			ED	9 (75.00%)	237 (69.91%)	272 (69.04%)	136 (71.20%)
CHRONICLE	**CAPOX**	**CAP**	**Full**	N A	14 (53.85%)	8 (47.06%)	4 (80.00%)
			ED	N A	12 (46.15%)	9 (52.94%)	1 (20.00%)
		OX	**Full**	N A	14 (51.85%)	8 (47.06%)	4 (80.00%)
			ED	N A	13 (48.15%)	9 (52.94%)	1 (20.00%)
PS	**MAYO**	**5FU-B**	**Full**	N A	15 (93.75%)	9 (90.00%)	1 (100.00%)
			ED	N A	1 (6.25%)	1 (10.00%)	0 (0.00%)
	NORDIC	**5FU-B**	**Full**	N A	14 (70.00%)	8 (66.67%)	3 (100.00%)
			ED	N A	6 (30.00%)	4 (33.33%)	0 (0.00%)
	CAP	**CAP**	**Full**	1 (100.00%)	46 (74.19%)	32 (64.00%)	2 (40.00%)
			ED	0 (0.00%)	16 (25.81%)	18 (36.00%)	3 (60.00%)

Abbreviations: ED, Early discontinuation

Table A3.5 | Relative dose intensity and cumulative relative dose by drug.

Table demonstrating the RDI and CRD by baseline BMI category for each drug within each trial's regimens

Trial	Regimen	Drug	Underweight		Normal		Overweight		Obese	
Relative Dose Intensity, median (IQR)										
MOSAIC	**LV5FU**	**5FU-B**	94.68	(84.93, 97.82)	95.71	(91.08, 98.50)	94.28	(88.55, 97.16)	91.99	(86.24, 95.76)
		5FU-I	94.98	(86.67, 98.68)	95.96	(91.01, 98.59)	94.31	(88.65, 97.32)	91.87	(86.24, 95.46)
SCOT_3M	**CAPOX**	**CAP**	96.96	(83.10, 101.08)	87.67	(74.55, 97.04)	89.12	(74.06, 96.82)	84.99	(74.32, 93.06)
		OX	93.82	(86.62, 101.54)	93.88	(81.29, 98.74)	92.49	(81.85, 97.85)	89.43	(81.74, 95.64)
	mFOLFOX6	**5FU-B**	91.36	(72.61, 101.36)	88.07	(76.54, 98.05)	89.90	(79.04, 96.76)	86.82	(77.17, 93.33)
		5FU-I	92.21	(78.45, 101.91)	89.57	(77.67, 98.30)	90.18	(80.45, 97.26)	86.96	(77.68, 93.38)
		OX	81.19	(68.98, 100.53)	88.56	(77.13, 97.52)	88.74	(80.11, 96.71)	86.42	(76.64, 93.38)
	mFOLFOX6/CAPOX	**FLUORO**	84.05	(75.75, 92.34)	71.07	(55.89, 85.10)	78.85	(68.51, 87.59)	72.25	(67.14, 81.83)
		OX	89.92	(88.71, 91.14)	74.55	(61.41, 89.58)	82.74	(73.09, 88.97)	79.95	(75.12, 87.69)
SCOT_6M	**CAPOX**	**CAP**	85.22	(71.35, 99.69)	82.82	(71.24, 95.09)	81.34	(70.98, 93.18)	79.73	(70.57, 88.78)
		OX	78.72	(58.80, 99.87)	80.86	(62.51, 94.59)	81.50	(64.39, 93.63)	81.05	(64.80, 90.34)
	mFOLFOX6	**5FU-B**	90.64	(63.42, 98.20)	80.01	(64.83, 91.88)	80.83	(69.89, 92.22)	79.72	(69.87, 91.39)
		5FU-I	93.57	(83.19, 96.82)	82.40	(72.55, 91.88)	83.85	(73.19, 92.44)	82.40	(72.02, 92.62)
		OX	79.80	(53.12, 91.00)	74.17	(60.18, 85.92)	74.81	(62.58, 87.28)	72.77	(63.53, 85.11)
	mFOLFOX6/CAPOX	**FLUORO**	72.52	(72.52, 72.52)	79.97	(72.29, 88.89)	74.51	(69.26, 86.55)	73.64	(66.84, 87.17)
		OX	73.49	(73.49, 73.49)	77.27	(53.70, 86.56)	73.71	(55.22, 84.74)	68.89	(48.24, 85.38)
CHRONICLE	**CAPOX**	**CAP**	-	-	94.02	(79.60, 99.64)	87.04	(59.53, 94.79)	89.04	(71.01, 93.83)
		PX	-	-	96.25	(91.67, 98.89)	93.56	(92.58, 98.64)	93.12	(89.04, 95.36)
PS	**MAYO**	**5FU-B**	-	-	91.33	(87.49, 99.31)	89.83	(83.12, 97.63)	100.78	(100.78, 100.78)
	NORDIC	**5FU-B**	-	-	90.68	(83.83, 95.56)	84.86	(80.60, 96.40)	76.86	(74.05, 81.51)
	CAP	**CAP**	101.57	(101.57, 101.57)	85.98	(75.96, 94.60)	89.63	(77.61, 94.51)	90.38	(63.44, 92.27)
Cumulative Relative Dose, median (IQR)										
MOSAIC	**LV5FU**	**5FU-B**	97.92	(88.45, 100.71)	97.89	(94.60, 99.29)	96.46	(89.90, 97.93)	94.35	(87.78, 96.63)
		5FU-I	98.98	(91.41, 100.83)	97.88	(94.59, 99.38)	96.54	(90.75, 98.00)	94.10	(88.47, 96.29)
SCOT_3M	**CAPOX**	**CAP**	84.25	(61.42, 100.05)	89.30	(73.66, 97.65)	90.50	(73.16, 97.15)	85.95	(72.32, 93.82)
		OX	88.08	(51.09, 100.34)	96.24	(77.98, 99.22)	95.33	(80.62, 98.37)	91.34	(78.15, 96.24)
	mFOLFOX6	**5FU-B**	98.48	(93.73, 99.83)	96.86	(82.66, 99.30)	96.39	(87.90, 98.73)	92.07	(83.14, 96.83)
		5FU-I	99.74	(96.89, 101.30)	97.40	(87.56, 99.63)	97.30	(90.09, 98.72)	92.68	(84.49, 96.89)
		OX	98.51	(89.14, 100.95)	96.41	(85.02, 99.23)	96.70	(88.51, 98.74)	92.30	(83.56, 96.40)
	mFOLFOX6/CAPOX	**FLUORO**	78.61	(39.04, 118.18)	79.60	(63.99, 101.73)	92.13	(82.80, 99.43)	78.93	(52.78, 84.48)
		OX	79.67	(43.51, 115.83)	86.64	(58.05, 101.81)	93.19	(84.70, 103.43)	88.22	(53.21, 102.03)

Table A3.5 | ***Continued***

Trial	Regimen	Drug	Underweight		Normal		Overweight		Obese	
SCOT_6M	CAPOX	CAP	67.83	(35.18, 87.26)	74.26	(48.69, 92.02)	76.56	(53.97, 91.29)	74.13	(53.64, 87.45)
		OX	63.70	(24.97, 83.25)	64.02	(37.32, 84.51)	69.14	(42.74, 86.85)	68.54	(42.94, 85.80)
	mFOLFOX6	5FU-B	62.35	(39.92, 95.36)	80.71	(48.29, 95.69)	81.83	(54.96, 94.73)	80.52	(49.90, 94.13)
		5FU-I	90.85	(46.57, 98.83)	86.29	(65.85, 97.05)	85.36	(66.12, 96.48)	82.72	(63.16, 95.40)
		OX	53.12	(39.37, 85.46)	70.56	(50.89, 87.56)	72.43	(51.73, 85.03)	71.38	(51.74, 83.62)
	mFOLFOX6/CAPOX	FLUORO	84.77	(84.77, 84.77)	71.03	(56.16, 89.22)	77.42	(60.61, 89.08)	75.48	(53.26, 91.46)
		OX	85.58	(85.58, 85.58)	71.71	(43.18, 81.82)	63.19	(51.85, 87.98)	68.27	(32.03, 81.28)
CHRONICLE	CAPOX	CAP	-	-	68.52	(25.03, 95.77)	57.33	(16.60, 73.92)	94.58	(73.82, 94.68)
		OX	-	-	91.27	(29.61, 98.54)	65.61	(16.77, 92.64)	95.36	(91.64, 96.81)
PS	MAYO	5FU-B	-	-	96.22	(92.44, 97.83)	94.53	(94.21, 96.63)	95.18	(95.18, 95.18)
	NORDIC	5FU-B	-	-	95.81	(80.23, 98.08)	94.91	(78.93, 96.98)	82.81	(73.17, 84.42)
	CAP	CAP	101.57	(101.57, 101.57)	82.41	(72.03, 94.83)	83.77	(60.81, 93.50)	83.48	(23.79 - 89.84)

Abbreviations: 5FU, 5-Flurouracil; **5FU-B** 5FU Bolus**; 5FU-I**, Infusion; **CAP,** capecitabine; **CRD,** Cumulative relative dose; **RDI,** relative dose intensity

Table A5.1 | Exposure-sex interaction models.

Meta-analysed summary effects for the effect of exposure (X) on outcome (Y) and the interaction terms, when including exposure-sex interaction within the total effect path models. Effect estimates presented as *Odds ratio; †Coef; or ‡Hazard ratios depending on the path

				Exposure effect			Interaction effect (Female vs. Male)		
Path	**Y**	**X**	**Pop**	**Est*†‡**	**(95%CI)**	**Tau2**	**Est*†‡**	**(95%CI)**	**Tau2**
NA	**Capping***	**BMI**	**Main**	1.26	(1.03 1.49)	0.030	**0.53**	**(0.46, 0.61)**	0.000
	Capping*	**BMI**	**TOX1**	1.39	(1.08 1.71)	0.040	**0.57**	**(0.41, 0.78)**	0.000
	Capping*	**BMI**	**TOX2**	1.27	(0.96 1.57)	0.055	**0.58**	**(0.46, 0.73)**	0.000
	ARDR†	**BMI**	**Main**	-2.73	(-3.52 -1.93)	0.488	**1.23**	**(0.31, 2.15)**	0.634
	ARDR†	**BMI**	**TOX1**	-2.59	(-3.40 -1.77)	0.405	**1.03**	**(0.08, 1.98)**	0.483
	ARDR†	**BMI**	**TOX2**	-2.66	(-3.44 -1.87)	0.434	**1.11**	**(0.27, 1.95)**	0.434
a	**ARDI†**	**BMI**	**Main**	-1.93	(-2.58, -1.27)	0.198	**1.63**	**(1.05, 2.20)**	0.000
	ARDI†	**BMI**	**TOX1**	-2.48	(-3.17, -1.78)	0.000	**1.92**	**(1.01, 2.83)**	0.000
	ARDI†	**BMI**	**TOX2**	-2.01	(-2.67, -1.35)	0.056	**1.77**	**(0.97, 2.57)**	0.000
	ACRD†	**BMI**	**Main**	-1.55	(-2.61, -0.49)	0.423	0.92	(-0.25, 2.08)	0.236
	ACRD†	**BMI**	**TOX1**	-1.57	(-3.01, -0.12)	0.000	0.84	(-1.23, 2.91)	0.431
	ACRD†	**BMI**	**TOX2**	-1.16	(-2.32, 0.00)	0.000	0.82	(-0.75, 2.39)	0.000
d	**G3 Tox***	**BMI**	**Main**	0.98	(0.88, 1.09)	0.000	1.04	(0.91, 1.19)	0.000
	G3 Tox*	**BMI**	**TOX1**	1.02	(0.86, 1.19)	0.000	1.07	(0.86, 1.32)	0.000
	G3 Tox*	**BMI**	**TOX2**	1.00	(0.88, 1.13)	0.000	1.03	(0.87, 1.23)	0.000
b	**OS‡**	**ARDI**	**Main**	1.04	(1.00, 1.09)	0.000	1.02	(0.97, 1.08)	0.000
	OS‡	**ARDI**	**TOX1**	1.06	(0.98, 1.14)	0.000	1.00	(0.90, 1.12)	0.000
	OS‡	**ARDI**	**TOX2**	1.06	(1.01, 1.13)	0.000	0.98	(0.90, 1.07)	0.001
	DFS‡	**ARDI**	**Main**	1.01	(0.96, 1.07)	0.002	1.04	(0.98, 1.10)	0.001
	DFS‡	**ARDI**	**TOX1**	1.01	(0.94, 1.08)	0.001	1.08	(1.00, 1.18)	0.000
	DFS‡	**ARDI**	**TOX2**	1.02	(0.97, 1.07)	0.001	1.03	(0.95, 1.11)	0.002
	CSS‡	**ARDI**	**Main**	1.01	(0.97, 1.06)	0.000	1.04	(0.98, 1.11)	0.000
	CSS‡	**ARDI**	**TOX1**	1.03	(0.95, 1.13)	0.000	0.99	(0.87, 1.11)	0.000
	CSS‡	**ARDI**	**TOX2**	1.03	(0.97, 1.11)	0.000	0.98	(0.89, 1.08)	0.000
	OS‡	**ACRD**	**Main**	0.93	(0.91, 0.96)	0.000	1.00	(0.97, 1.03)	0.000
	OS‡	**ACRD**	**TOX1**	0.93	(0.90, 0.96)	0.000	0.98	(0.94, 1.03)	0.000
	OS‡	**ACRD**	**TOX2**	0.92	(0.90, 0.94)	0.000	1.01	(0.97, 1.05)	0.000
	DFS‡	**ACRD**	**Main**	0.95	(0.92, 0.98)	0.001	0.99	(0.97, 1.02)	0.000
	DFS‡	**ACRD**	**TOX1**	0.96	(0.91, 1.01)	0.002	0.98	(0.95, 1.02)	0.000
	DFS‡	**ACRD**	**TOX2**	0.95	(0.91, 0.99)	0.001	0.99	(0.96, 1.02)	0.000
	CSS‡	**ACRD**	**Main**	0.95	(0.92, 0.98)	0.000	0.98	(0.94, 1.03)	0.000
	CSS‡	**ACRD**	**TOX1**	0.95	(0.90, 0.99)	0.001	0.95	(0.90, 1.01)	0.000
	CSS‡	**ACRD**	**TOX2**	0.94	(0.90, 0.99)	0.001	0.98	(0.94, 1.03)	0.000

Table A5.1 | *Continued*

				Exposure effect			Interaction effect Female vs. Male		
Path	**Y**	**X**	**Pop**	**Est*†‡**	**(95%CI)**	**Tau2**	**Est*†‡**	**(95%CI)**	**Tau2**
e	**ARDI†**	**G3 Tox**	**Main**	-3.41	(-5.40, -1.42)	2.500	-1.30	(-3.59, 0.99)	2.934
	ARDI†	**G3 Tox**	**TOX1**	-4.57	(-5.65, -3.49)	0.000	-0.39	(-5.82, 5.05)	23.969
	ARDI†	**G3 Tox**	**TOX2**	-4.31	(-5.29, -3.33)	0.000	-0.72	(-4.09, 2.66)	7.707
	ACRD†	**G3 Tox**	**Main**	-10.60	(-12.60, -8.60)	0.000	0.65	(-2.19, 3.48)	0.000
	ACRD†	**G3 Tox**	**TOX1**	-10.74	(-13.06, -8.43)	0.000	1.13	(-2.28, 4.55)	0.000
	ACRD†	**G3 Tox**	**TOX2**	-10.66	(-13.33, -7.99)	2.831	1.11	(-1.80, 4.03)	0.000
f	**OS‡**	**G3 Tox**	**Main**	1.43	(1.14, 1.78)	0.000	0.91	(0.66, 1.26)	0.000
	OS‡	**G3 Tox**	**TOX1**	1.52	(1.13, 2.06)	0.000	0.82	(0.53, 1.27)	0.000
	OS‡	**G3 Tox**	**TOX2**	1.56	(1.22, 2.00)	0.000	0.90	(0.63, 1.30)	0.000
	DFS‡	**G3 Tox**	**Main**	1.18	(0.92, 1.52)	0.032	0.99	(0.77, 1.27)	0.000
	DFS‡	**G3 Tox**	**TOX1**	1.15	(0.82, 1.61)	0.059	0.97	(0.69, 1.36)	0.000
	DFS‡	**G3 Tox**	**TOX2**	1.30	(1.05, 1.60)	0.010	1.03	(0.78, 1.37)	0.000
	CSS‡	**G3 Tox**	**Main**	1.17	(0.90, 1.53)	0.000	0.95	(0.63, 1.42)	0.000
	CSS‡	**G3 Tox**	**TOX1**	1.33	(0.94, 1.89)	0.000	0.76	(0.45, 1.27)	0.007
	CSS‡	**G3 Tox**	**TOX2**	1.20	(0.89, 1.62)	0.000	1.00	(0.63, 1.59)	0.026
c	**OS‡**	**BMI**	**Main**	0.96	(0.87, 1.07)	0.000	1.05	(0.92, 1.21)	0.000
	OS‡	**BMI**	**TOX1**	0.94	(0.62, 1.42)	0.134	0.94	(0.73, 1.22)	0.004
	OS‡	**BMI**	**TOX2**	0.91	(0.65, 1.27)	0.084	0.95	(0.73, 1.24)	0.026
	DFS‡	**BMI**	**Main**	0.99	(0.84, 1.16)	0.016	0.98	(0.88, 1.08)	0.001
	DFS‡	**BMI**	**TOX1**	0.94	(0.82, 1.09)	0.000	1.04	(0.85, 1.26)	0.000
	DFS‡	**BMI**	**TOX2**	0.97	(0.77, 1.22)	0.038	0.97	(0.76, 1.26)	0.035
	CSS‡	**BMI**	**Main**	0.94	(0.83, 1.07)	0.000	1.04	(0.88, 1.22)	0.000
	CSS‡	**BMI**	**TOX1**	1.01	(0.82, 1.25)	0.000	0.88	(0.66, 1.17)	0.000
	CSS‡	**BMI**	**TOX2**	0.98	(0.78, 1.25)	0.022	0.87	(0.69, 1.11)	0.000

Abbreviations: ACRD, Average cumulative relative dose**; ARDI,** Average relative dose intensity**; BMI,** Body mass index; **CSS,** Cancer-specific survival; **DFS,** Disease-free survival; **Est, E**stimate; **NA,** not applicable; **OS,** Overall survival; **Tox**, Toxicity.

Table A5.2 | Exposure-stage interaction models.

Meta-analysed summary effects for the effect of exposure (X) on outcome (Y) and the interaction terms, when including exposure-stage interaction within the total effect path models. Effect estimates presented as *Odds ratio; †Coef; or ‡Hazard ratios depending on the path

				Exposure effect			Interaction effect Stage II-HR vs. Stage III-LR			Interaction effect Stage III-HR vs. Stage III-LR		
Path	**Y**	**X**	**Pop**	**Est*†‡**	**(95%CI)**	**Tau2**	**Est*†‡**	**(95%CI)**	**Tau2**	**Est*†‡**	**(95%CI)**	**Tau2**
NA	**Capping***	**BMI**	**Main**	2.82	(2.09, 3.81)	0.059	0.96	(0.76, 1.22)	0.000	0.88	(0.77, 1.02)	0.000
	Capping*	**BMI**	**TOX1**	3.24	(2.38, 4.40)	0.025	1.06	(0.58, 1.94)	0.000	0.87	(0.62, 1.22)	0.000
	Capping*	**BMI**	**TOX2**	2.90	(2.00, 4.21)	0.089	0.83	(0.51, 1.37)	0.066	0.93	(0.68, 1.26)	0.026
	ARDR†	**BMI**	**Main**	-2.14	(-2.59, 1.69)	0.131	0.08	(-0.25, 0.40)	0.000	0.06	(-0.19, 0.32)	0.000
	ARDR†	**BMI**	**TOX1**	-1.80	(-2.13, 1.46)	0.018	0.11	(-0.26, 0.49)	0.000	-0.05	(-0.40, 0.30)	0.000
	ARDR†	**BMI**	**TOX2**	-1.89	(-2.26, 1.51)	0.050	0.08	(-0.29, 0.45)	0.000	-0.25	(-0.81, 0.31)	0.123
a	**ARDI†**	**BMI**	**Main**	-1.35	(-1.99, -0.71)	0.162	0.69	(-0.19, 1.58)	0.000	0.28	(-0.34, 0.90)	0.000
	ARDI†	**BMI**	**TOX1**	-2.00	(-2.75, -1.26)	0.000	1.54	(0.32, 2.77)	0.000	0.73	(-0.31, 1.76)	0.000
	ARDI†	**BMI**	**TOX2**	-1.43	(-2.31, -0.56)	0.271	1.29	(0.14, 2.44)	0.000	0.39	(-0.50, 1.29)	0.000
	ACRD†	**BMI**	**Main**	-0.76	(-1.52, 0.00)	0.000	0.40	(-1.22, 2.03)	0.000	-0.84	(-1.91, 0.23)	0.000
	ACRD†	**BMI**	**TOX1**	-0.38	(-2.03, 1.28)	0.283	0.43	(-2.25, 3.11)	0.000	-2.20	(-4.32, -0.08)	0.000
	ACRD†	**BMI**	**TOX2**	-0.22	(-2.05, 1.61)	1.496	1.55	(-1.24, 4.34)	1.387	-2.15	(-3.86, -0.45)	0.000
d	**G3 Tox***	**BMI**	**Main**	1.02	(0.89, 1.17)	0.005	0.93	(0.76, 1.15)	0.000	1.02	(0.88, 1.17)	0.000
	G3 Tox*	**BMI**	**TOX1**	1.07	(0.85, 1.35)	0.022	0.86	(0.63, 1.18)	0.000	0.95	(0.75, 1.21)	0.000
	G3 Tox*	**BMI**	**TOX2**	1.06	(0.91, 1.23)	0.004	0.88	(0.66, 1.16)	0.000	0.94	(0.78, 1.12)	0.000
b	**OS‡**	**ARDI**	**Main**	1.04	(0.99, 1.10)	0.000	1.04	(0.91, 1.18)	0.000	1.00	(0.94, 1.07)	0.000
	OS‡	**ARDI**	**TOX1**	1.05	(0.94, 1.17)	0.000	1.01	(0.82, 1.25)	0.000	1.00	(0.87, 1.14)	0.002
	OS‡	**ARDI**	**TOX2**	1.05	(0.97, 1.14)	0.000	0.95	(0.79, 1.15)	0.004	1.00	(0.91, 1.10)	0.000
	DFS‡	**ARDI**	**Main**	1.00	(0.97, 1.04)	0.000	1.09	(1.00, 1.19)	0.000	1.02	(0.97, 1.07)	0.000
	DFS‡	**ARDI**	**TOX1**	1.03	(0.95, 1.11)	0.000	1.04	(0.89, 1.21)	0.000	0.99	(0.90, 1.09)	0.000
	DFS‡	**ARDI**	**TOX2**	1.02	(0.96, 1.08)	0.000	1.05	(0.92, 1.20)	0.000	0.99	(0.91, 1.08)	0.002
	CSS‡	**ARDI**	**Main**	1.00	(0.93, 1.07)	0.000	1.09	(0.90, 1.32)	0.000	1.02	(0.95, 1.11)	0.000
	CSS‡	**ARDI**	**TOX1**	0.99	(0.87, 1.13)	0.000	1.05	(0.80, 1.38)	0.000	1.03	(0.88, 1.20)	0.000
	CSS‡	**ARDI**	**TOX2**	0.99	(0.89, 1.10)	0.000	1.06	(0.82, 1.37)	0.000	1.03	(0.91, 1.16)	0.000
	OS‡	**ACRD**	**Main**	0.92	(0.90, 0.95)	0.000	1.01	(0.93, 1.09)	0.003	0.99	(0.92, 1.08)	0.005
	OS‡	**ACRD**	**TOX1**	0.91	(0.86, 0.97)	0.002	0.94	(0.87, 1.03)	0.000	1.02	(0.89, 1.17)	0.017
	OS‡	**ACRD**	**TOX2**	0.90	(0.86, 0.96)	0.002	0.95	(0.88, 1.03)	0.000	1.02	(0.90, 1.15)	0.014
	DFS‡	**ACRD**	**Main**	0.95	(0.93, 0.98)	0.000	1.03	(0.95, 1.11)	0.003	1.00	(0.98, 1.02)	0.000
	DFS‡	**ACRD**	**TOX1**	0.94	(0.89, 1.00)	0.003	0.98	(0.89, 1.08)	0.002	0.99	(0.89, 1.10)	0.009
	DFS‡	**ACRD**	**TOX2**	0.94	(0.89, 1.00)	0.003	1.03	(0.92, 1.15)	0.007	0.99	(0.91, 1.09)	0.007
	CSS‡	**ACRD**	**Main**	0.93	(0.90, 0.96)	0.000	1.07	(0.97, 1.17)	0.000	0.99	(0.91, 1.08)	0.005
	CSS‡	**ACRD**	**TOX1**	0.89	(0.82, 0.97)	0.004	1.04	(0.92, 1.18)	0.000	1.05	(0.88, 1.26)	0.029
	CSS‡	**ACRD**	**TOX2**	0.90	(0.85, 0.96)	0.001	1.02	(0.91, 1.15)	0.000	1.02	(0.89, 1.17)	0.015

Table A5.2 | *Continued*

				Exposure effect				Interaction effect Stage II-HR vs. Stage III-LR				Interaction effect Stage III-HR vs. Stage III-LR			
Path	**Y**	**X**	**Pop**	**Est**	**(95%CI)**		**Tau2**	**Est**	**(95%CI)**		**Tau2**	**Est**	**(95%CI)**		**Tau2**
e	**ARDI†**	**G3 Tox**	**Main**	-4.03	(-6.47,	-1.58)	4.238	-0.31	(-2.26,	1.64)	0.128	-0.12	(-1.55,	1.31)	0.000
	ARDI†	**G3 Tox**	**TOX1**	-4.94	(-6.85,	-3.02)	1.346	-0.45	(-3.47,	2.58)	1.755	-0.58	(-2.40,	1.23)	0.000
	ARDI†	**G3 Tox**	**TOX2**	-4.76	(-6.59,	-2.93)	1.556	0.52	(-4.45,	5.49)	14.586	-0.20	(-1.83,	1.43)	0.000
	ACRD†	**G3 Tox**	**Main**	-9.49	(-12.57,	-6.40)	4.148	-2.83	(-6.84,	1.18)	0.000	-1.34	(-5.38,	2.70)	7.398
	ACRD†	**G3 Tox**	**TOX1**	-9.33	(-13.45,	-5.20)	8.262	-1.74	(-10.10,	6.62)	27.347	-1.48	(-6.79,	3.84)	11.043
	ACRD†	**G3 Tox**	**TOX2**	-9.07	(-13.05,	-5.09)	9.407	-2.20	(-11.30,	6.89)	51.405	-1.84	(-6.03,	2.36)	6.221
f	**OS‡**	**G3 Tox**	**Main**	1.40	(1.01,	1.95)	0.000	1.66	(0.83,	3.36)	0.000	0.89	(0.61,	1.31)	0.000
	OS‡	**G3 Tox**	**TOX1**	1.43	(0.92,	2.23)	0.000	2.16	(0.93,	5.01)	0.000	0.84	(0.49,	1.42)	0.001
	OS‡	**G3 Tox**	**TOX2**	1.64	(1.14,	2.37)	0.000	1.72	(0.80,	3.70)	0.000	0.79	(0.51,	1.21)	0.000
	DFS‡	**G3 Tox**	**Main**	1.19	(0.94,	1.50)	0.000	1.18	(0.72,	1.91)	0.000	1.00	(0.76,	1.31)	0.000
	DFS‡	**G3 Tox**	**TOX1**	1.15	(0.76,	1.75)	0.072	1.35	(0.75,	2.43)	0.000	1.00	(0.57,	1.77)	0.164
	DFS‡	**G3 Tox**	**TOX2**	1.38	(1.06,	1.80)	0.005	1.11	(0.65,	1.91)	0.000	0.93	(0.63,	1.36)	0.046
	CSS‡	**G3 Tox**	**Main**	1.06	(0.69,	1.62)	0.000	1.10	(0.38,	3.23)	0.000	1.09	(0.67,	1.75)	0.000
	CSS‡	**G3 Tox**	**TOX1**	1.31	(0.74,	2.29)	0.000	1.13	(0.32,	3.94)	0.000	0.81	(0.40,	1.66)	0.067
	CSS‡	**G3 Tox**	**TOX2**	1.25	(0.77,	2.03)	0.000	1.08	(0.35,	3.34)	0.000	0.93	(0.54,	1.63)	0.000
c	**OS‡**	**BMI**	**Main**	1.00	(0.87,	1.15)	0.000	0.86	(0.54,	1.39)	0.085	0.97	(0.83,	1.14)	0.000
	OS‡	**BMI**	**TOX1**	0.95	(0.60,	1.50)	0.140	0.98	(0.56,	1.74)	0.043	0.91	(0.68,	1.21)	0.000
	OS‡	**BMI**	**TOX2**	1.00	(0.78,	1.27)	0.020	0.91	(0.52,	1.59)	0.074	0.90	(0.72,	1.13)	0.000
	DFS‡	**BMI**	**Main**	0.90	(0.72,	1.14)	0.038	0.90	(0.71,	1.13)	0.000	1.05	(0.94,	1.17)	0.000
	DFS‡	**BMI**	**TOX1**	0.89	(0.61,	1.30)	0.105	0.92	(0.64,	1.33)	0.000	1.00	(0.80,	1.24)	0.000
	DFS‡	**BMI**	**TOX2**	0.91	(0.64,	1.28)	0.093	0.89	(0.64,	1.23)	0.000	0.96	(0.81,	1.13)	0.000
	CSS‡	**BMI**	**Main**	0.95	(0.79,	1.14)	0.000	1.05	(0.61,	1.78)	0.052	0.98	(0.80,	1.21)	0.000
	CSS‡	**BMI**	**TOX1**	0.81	(0.58,	1.12)	0.000	1.32	(0.68,	2.56)	0.012	1.10	(0.75,	1.60)	0.000
	CSS‡	**BMI**	**TOX2**	0.87	(0.66,	1.15)	0.000	1.17	(0.59,	2.33)	0.055	1.02	(0.75,	1.38)	0.000

Abbreviations: ACRD, Average cumulative relative dose**; ARDI,** Average relative dose intensity**; BMI,** Body mass index; **CSS,** Cancer-specific survival; **DFS,** Disease-free survival; **Est,** **E**stimate; **HR,** High risk; **LR**, Low risk; **NA,** not applicable; **OS,** Overall survival; **Tox**, Toxicity.

Figure A5.1 | Path *a* (ARDI) Sensitivity analysis
Forest plot demonstrating the overall effect estimates of each sensitivity analysis for **a.** the total effect of BMI on ARDI and **b.** the direct effect of BMI on ARDI.

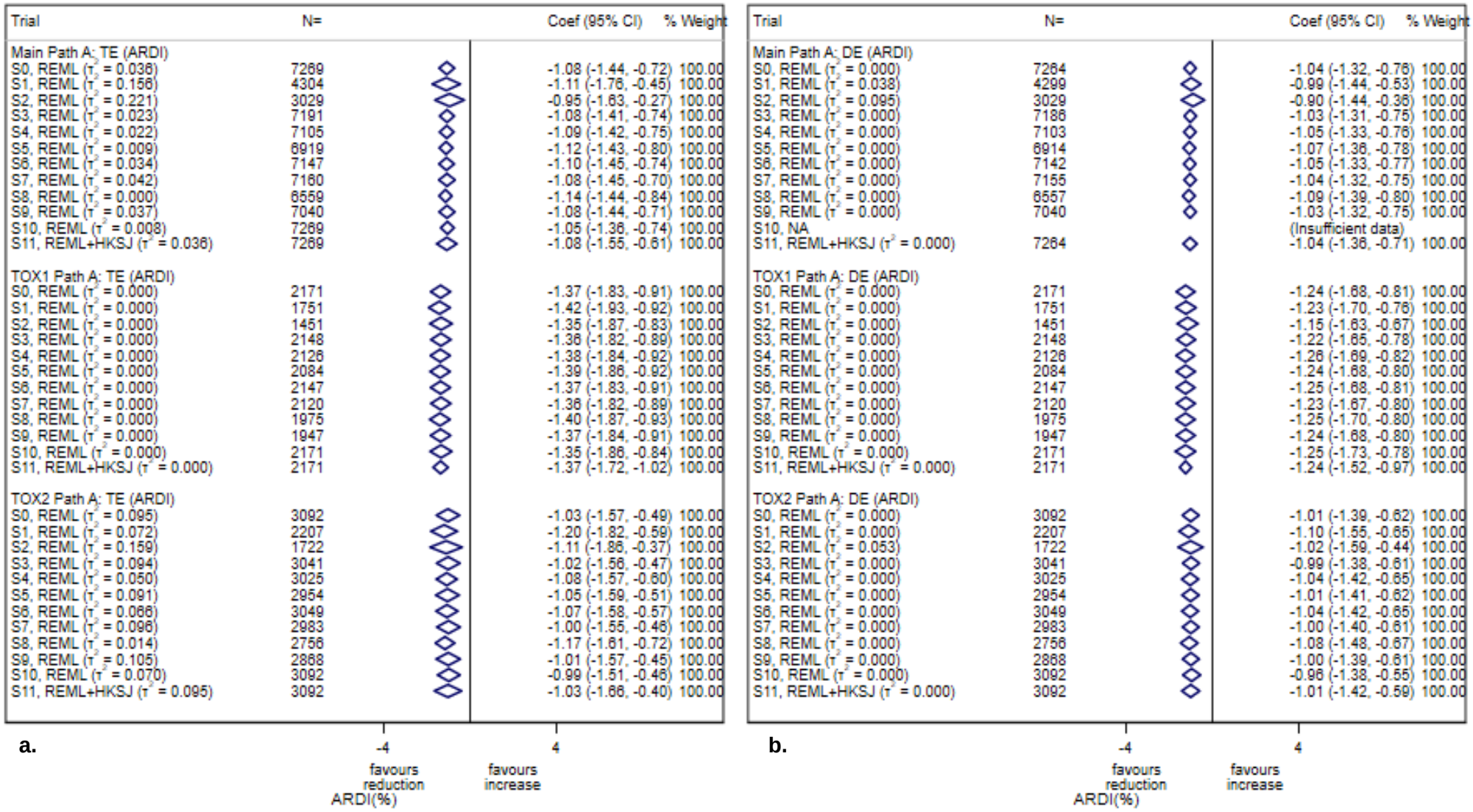
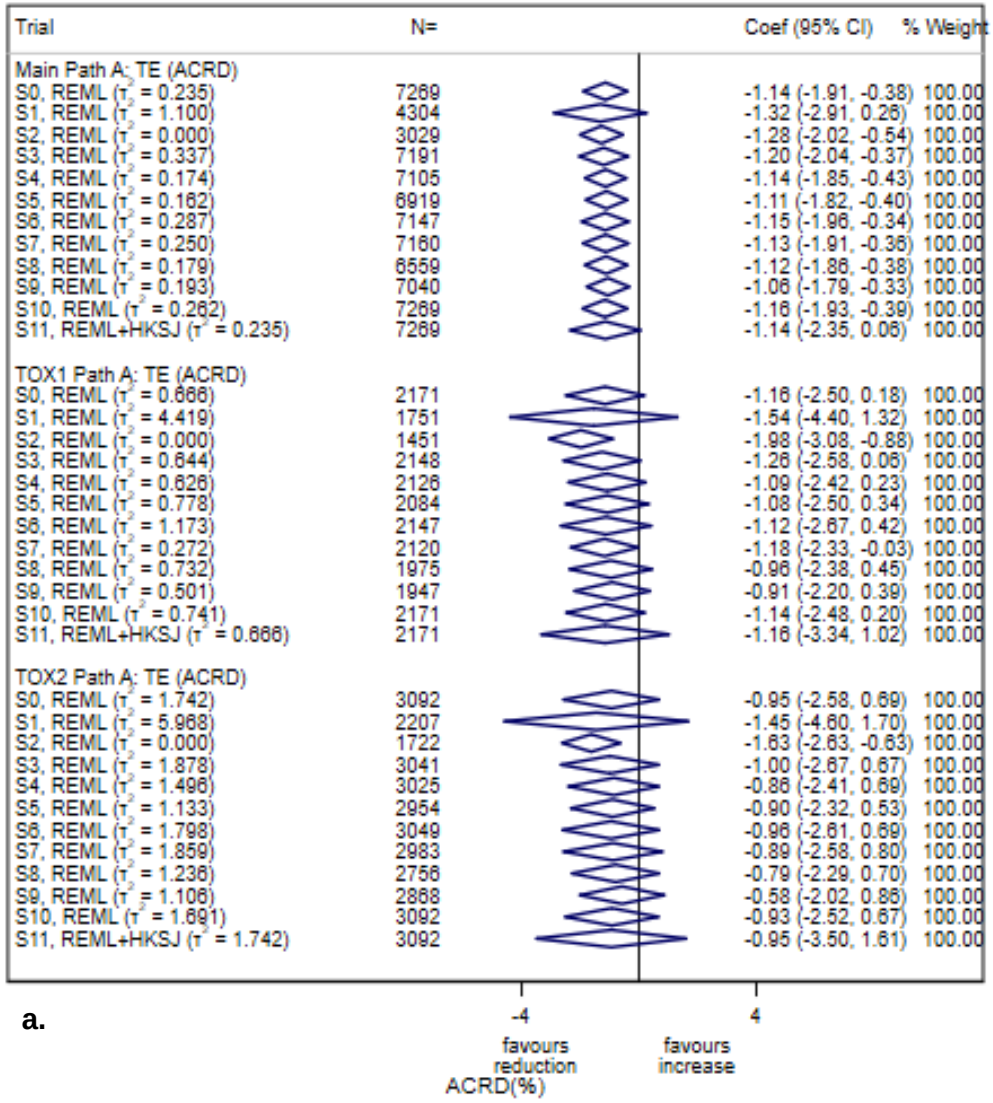
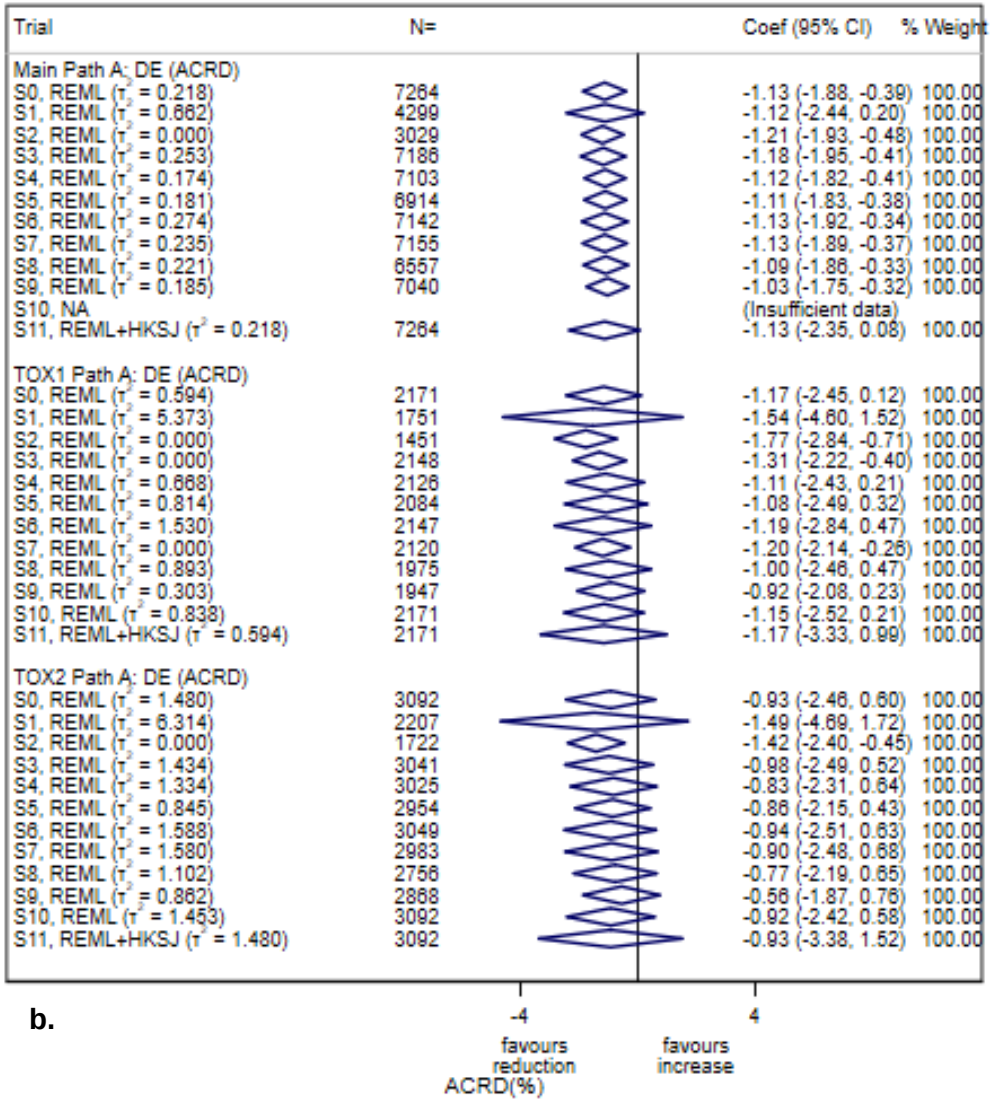


Figure A5.2 | Path *a* (ACRD) sensitivity analysis
Forest plot demonstrating the overall effect estimates of each sensitivity analysis for **a.** the total effect of BMI on ACRD and **b.** the direct effect of BMI on ACRD



a.



b.

Figure A5.3 | Path *d* sensitivity analysis
Forest plot demonstrating the summary effect estimates of each sensitivity analysis for the total effect of BMI on grade 3+ toxicity.

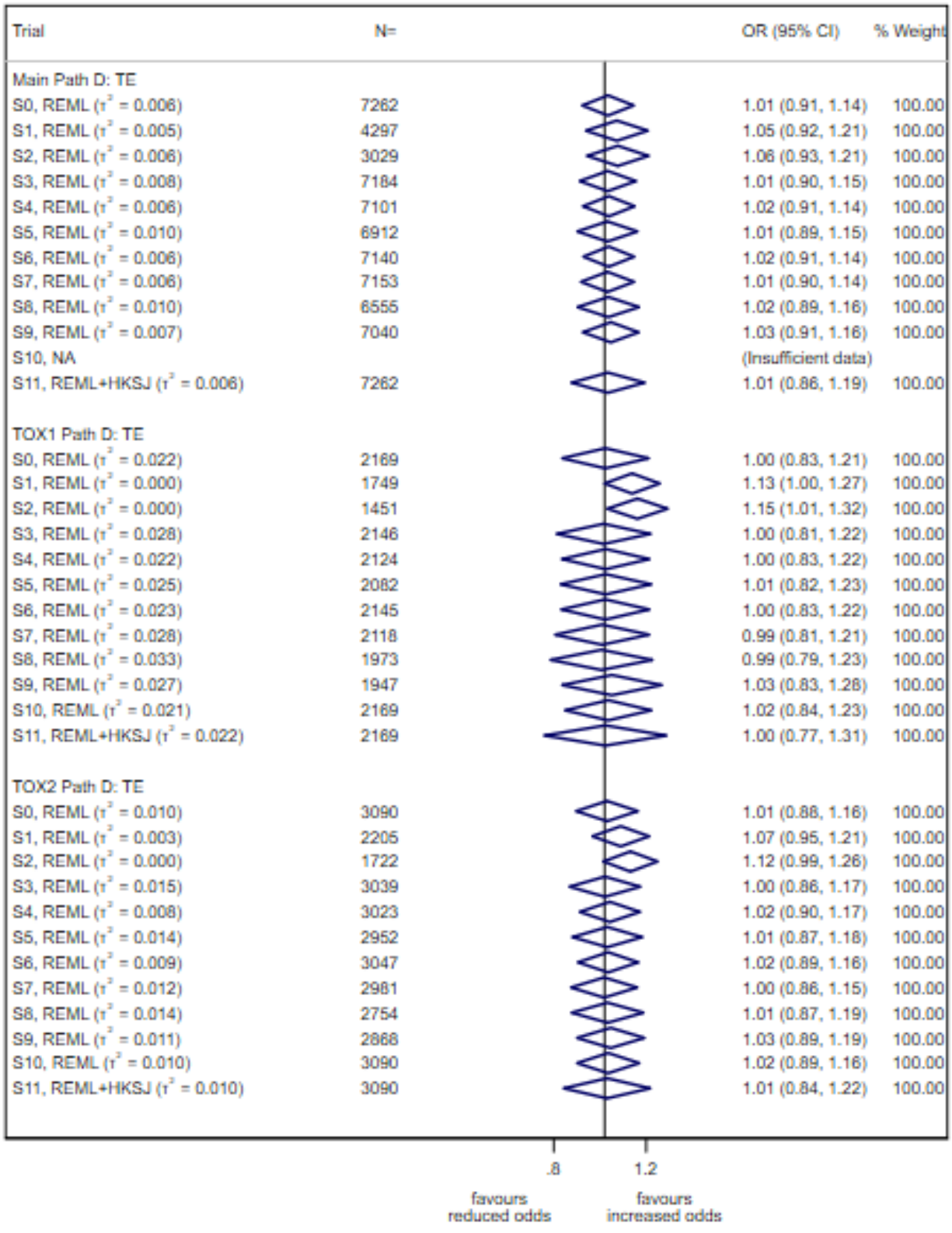


Figure A5.4 | Kaplan Meier curves for ARDI and ACRD (MOSAIC)
Kaplan Meier survival curves for the effects of ARDI and ACRD (categorised) on overall, disease-free, and cancer-specific survival.

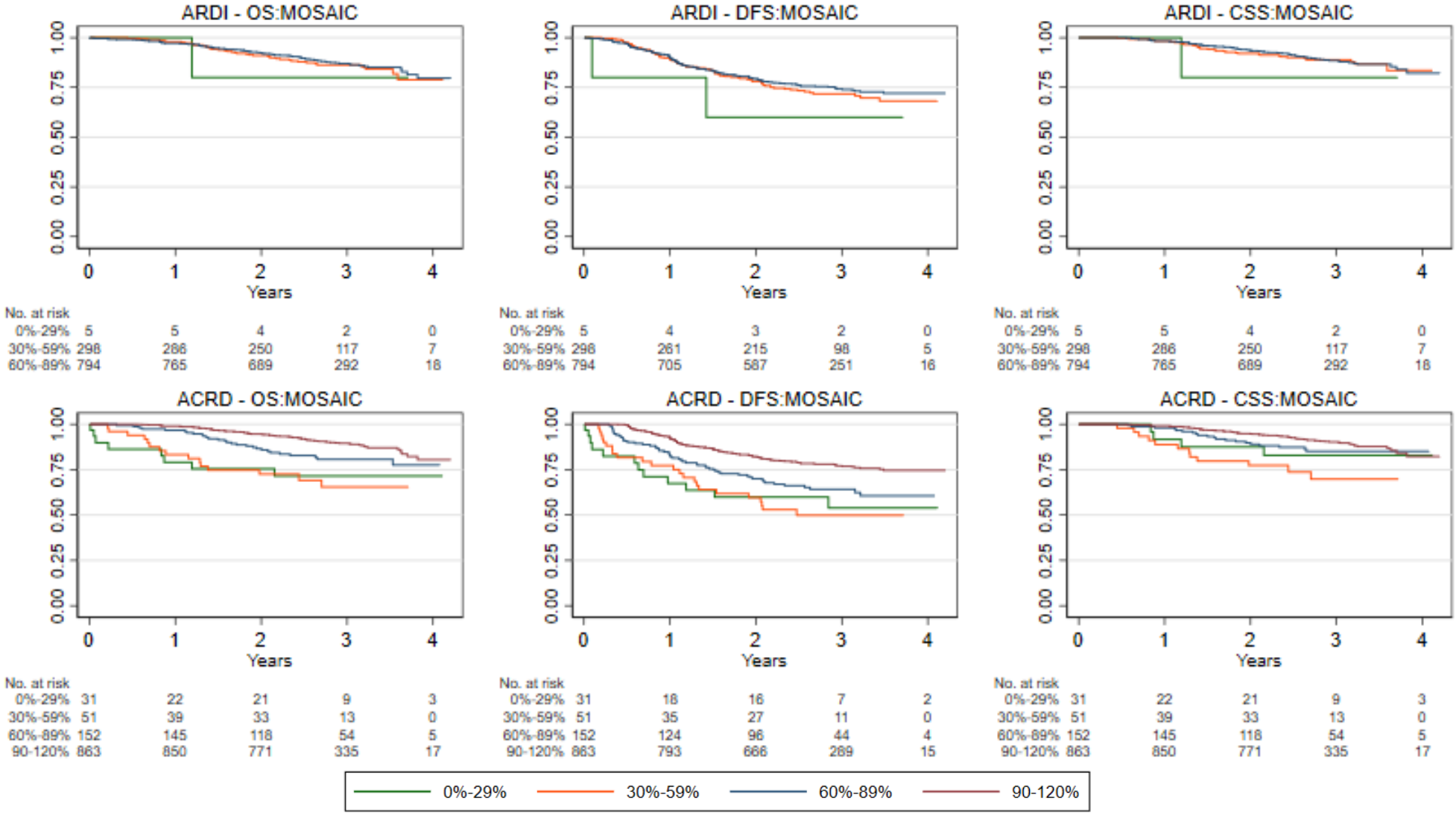


Figure A5.5 | Kaplan Meier curves for ARDI and ACRD (SCOT_3M)
Kaplan Meier survival curves for the effects of ARDI and ACRD (categorised) on overall, disease-free, and cancer-specific survival.

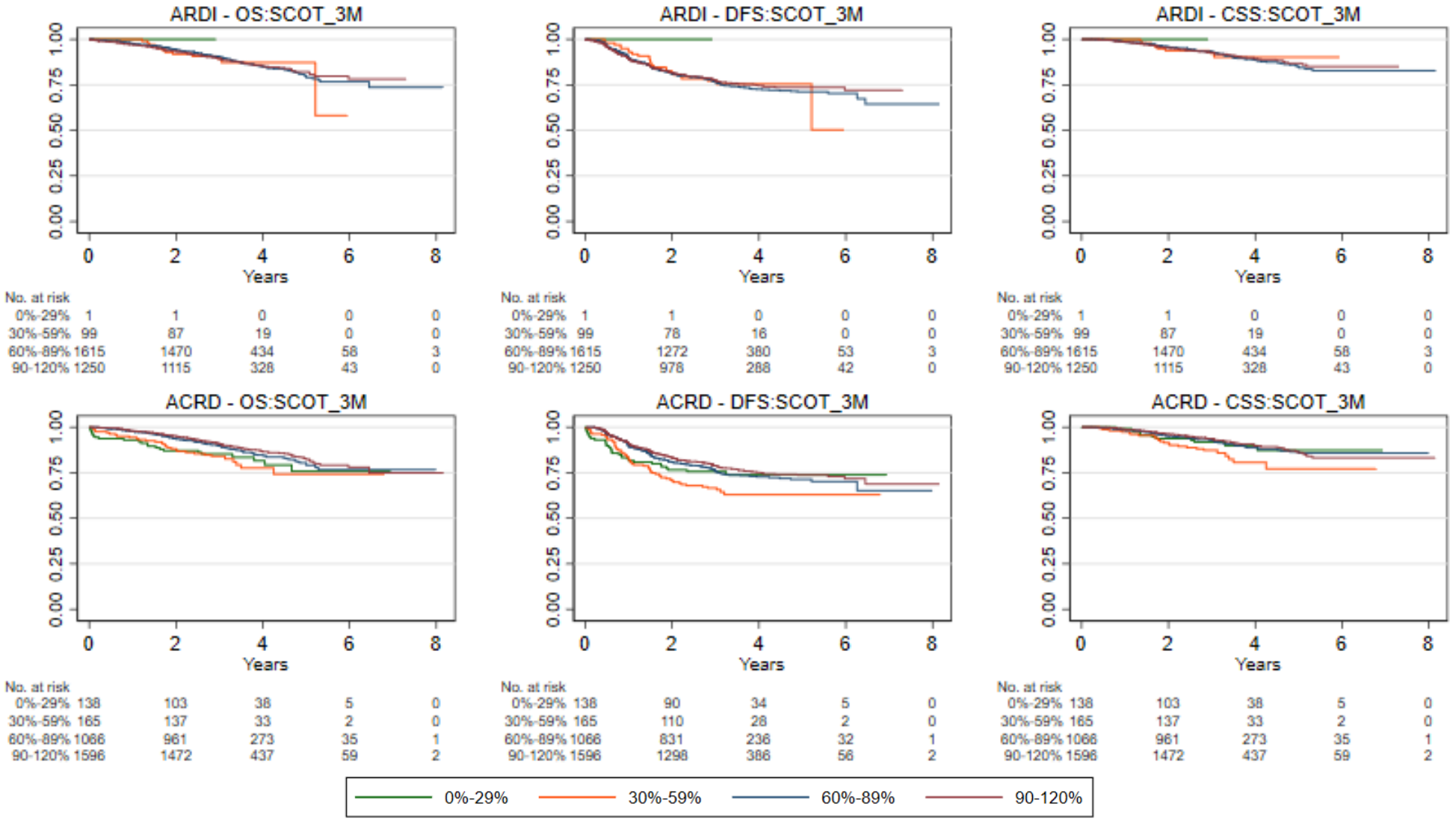


Figure A5.6 | Kaplan Meier curves for ARDI and ACRD (SCOT_6M)
Kaplan Meier survival curves for the effects of ARDI and ACRD (categorised) on overall, disease-free, and cancer-specific survival.

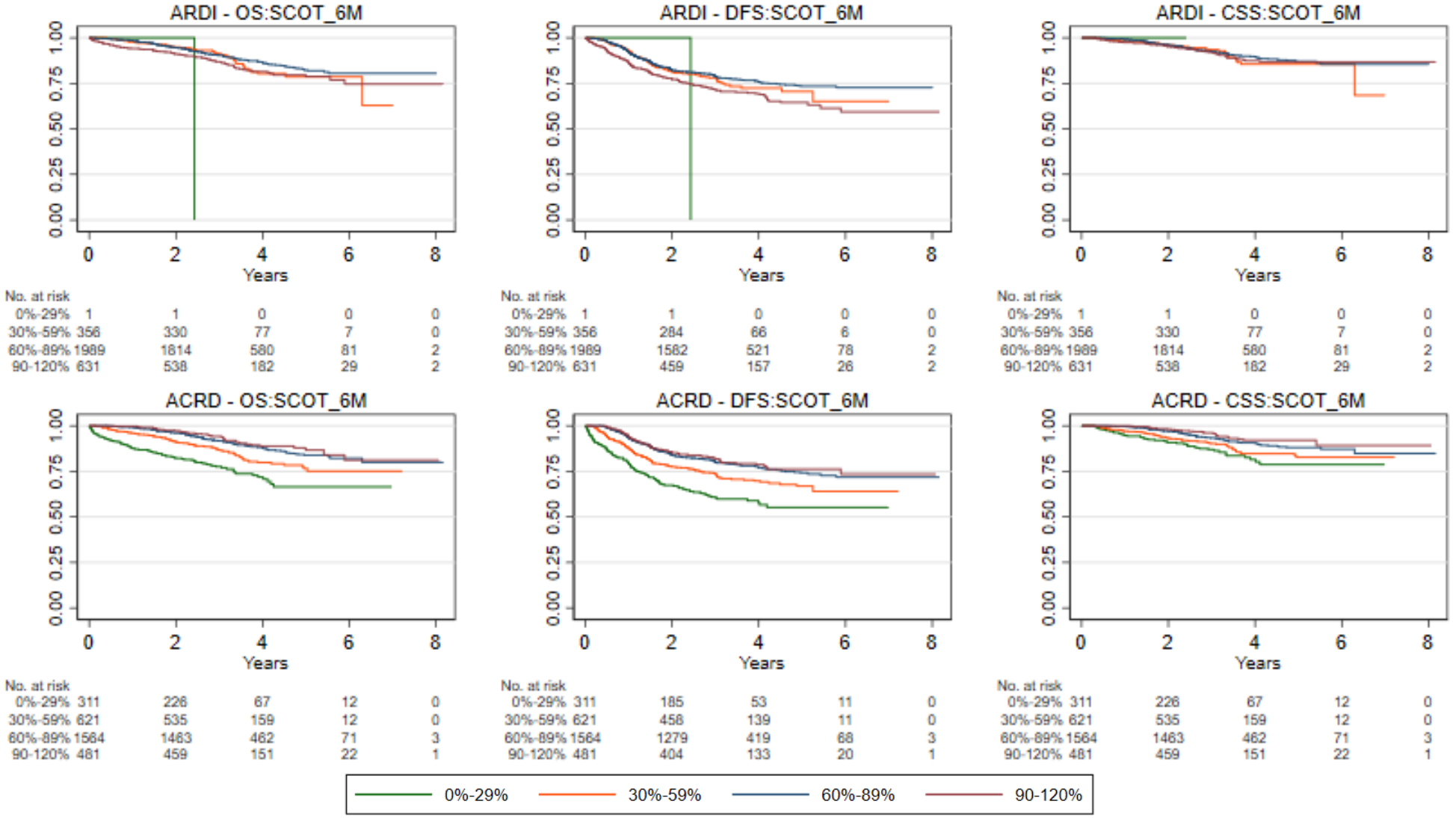


Figure A5.7 | Kaplan Meier curves for ARDI and ACRD (CHRONICLE)
Kaplan Meier survival curves for the effects of ARDI and ACRD (categorised) on overall, disease-free, and cancer-specific survival.

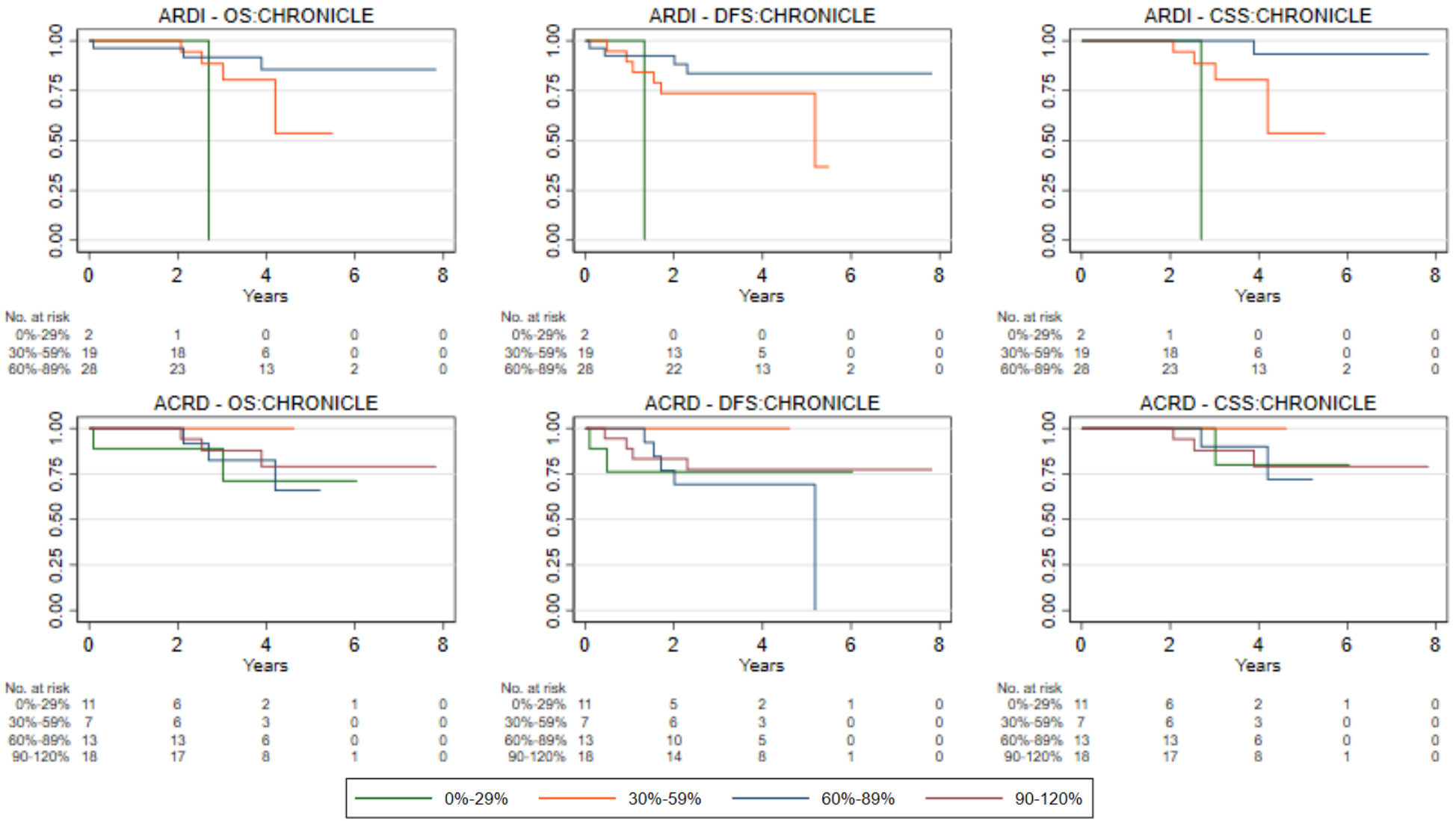


Figure A5.8 | Kaplan Meier curves for ARDI and ACRD (PS)
Kaplan Meier survival curves for the effects of ARDI and ACRD (categorised) on overall, disease-free, and cancer-specific survival.

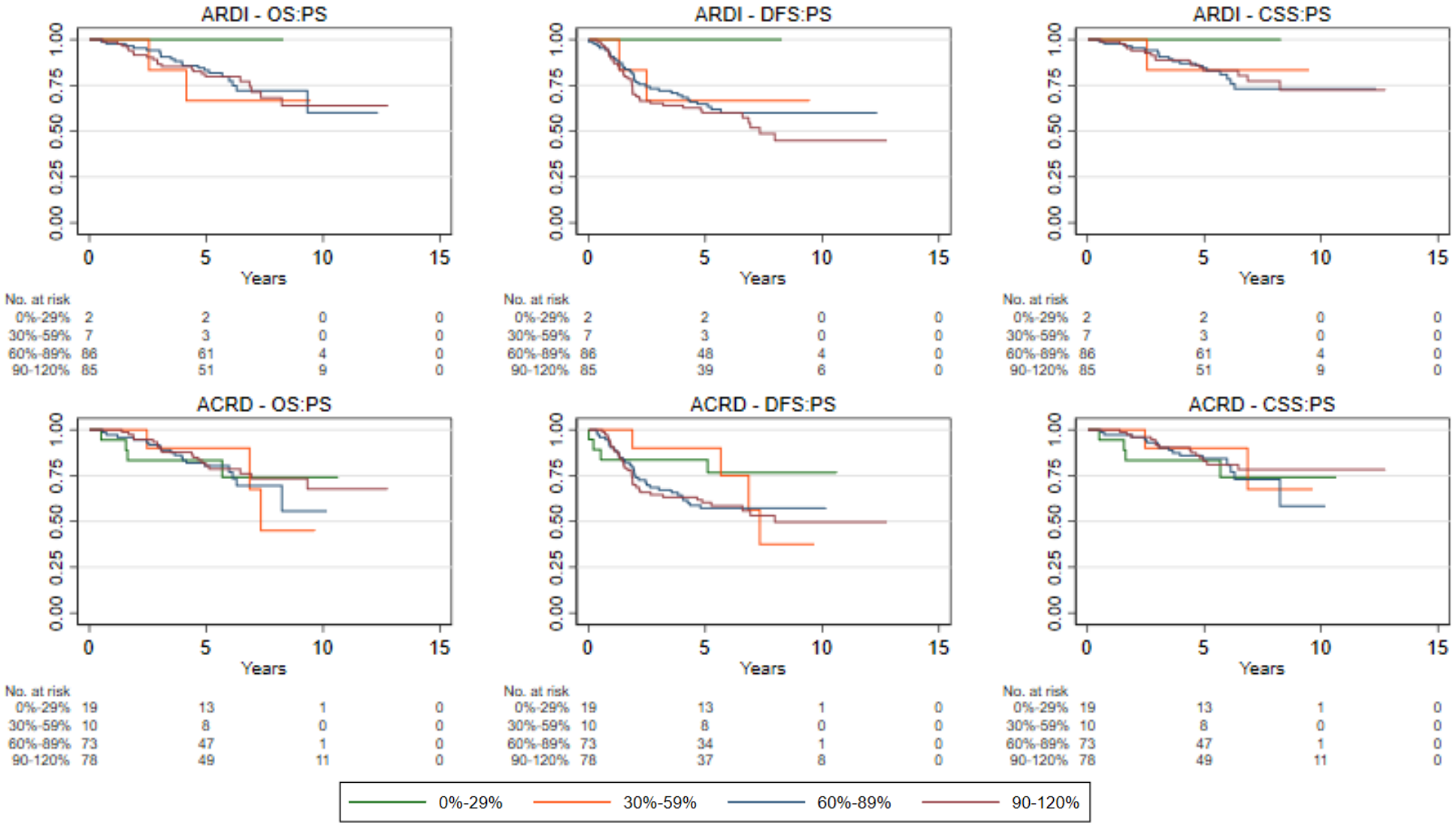


Figure A5.9 | Path *b* (ARDI) - Scaled Schoenfeld Residuals plots

Graphs demonstrating scaled Schoenfeld residuals from Cox models for path b (ARDI) total effects plotted against analysis time (years).

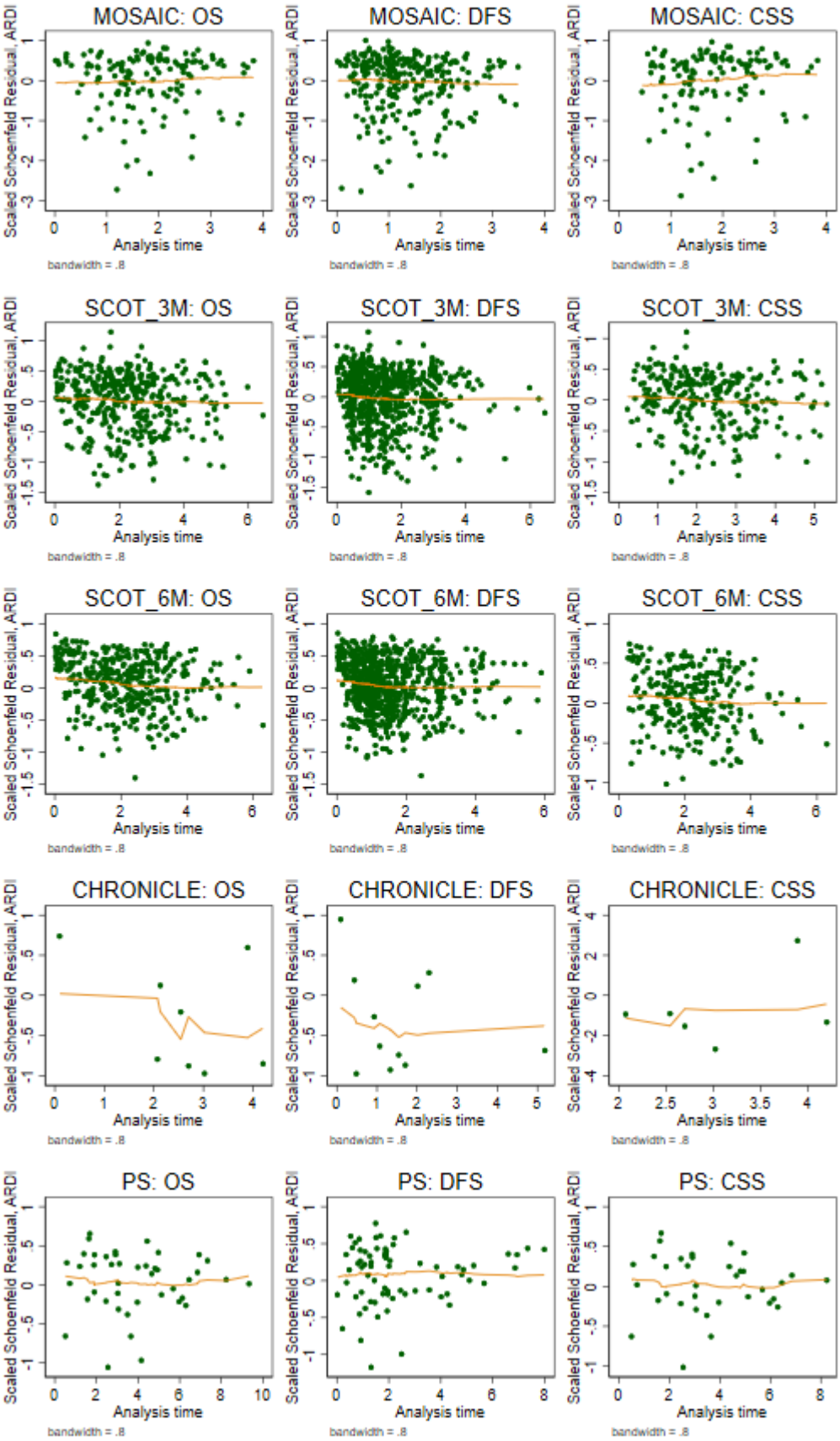


Figure A5.10 | Path *b* (ACRD) - Scaled Schoenfeld Residuals plots

Graphs demonstrating scaled Schoenfeld residuals from Cox models for path b (ARDI) total effects plotted against analysis time (years).

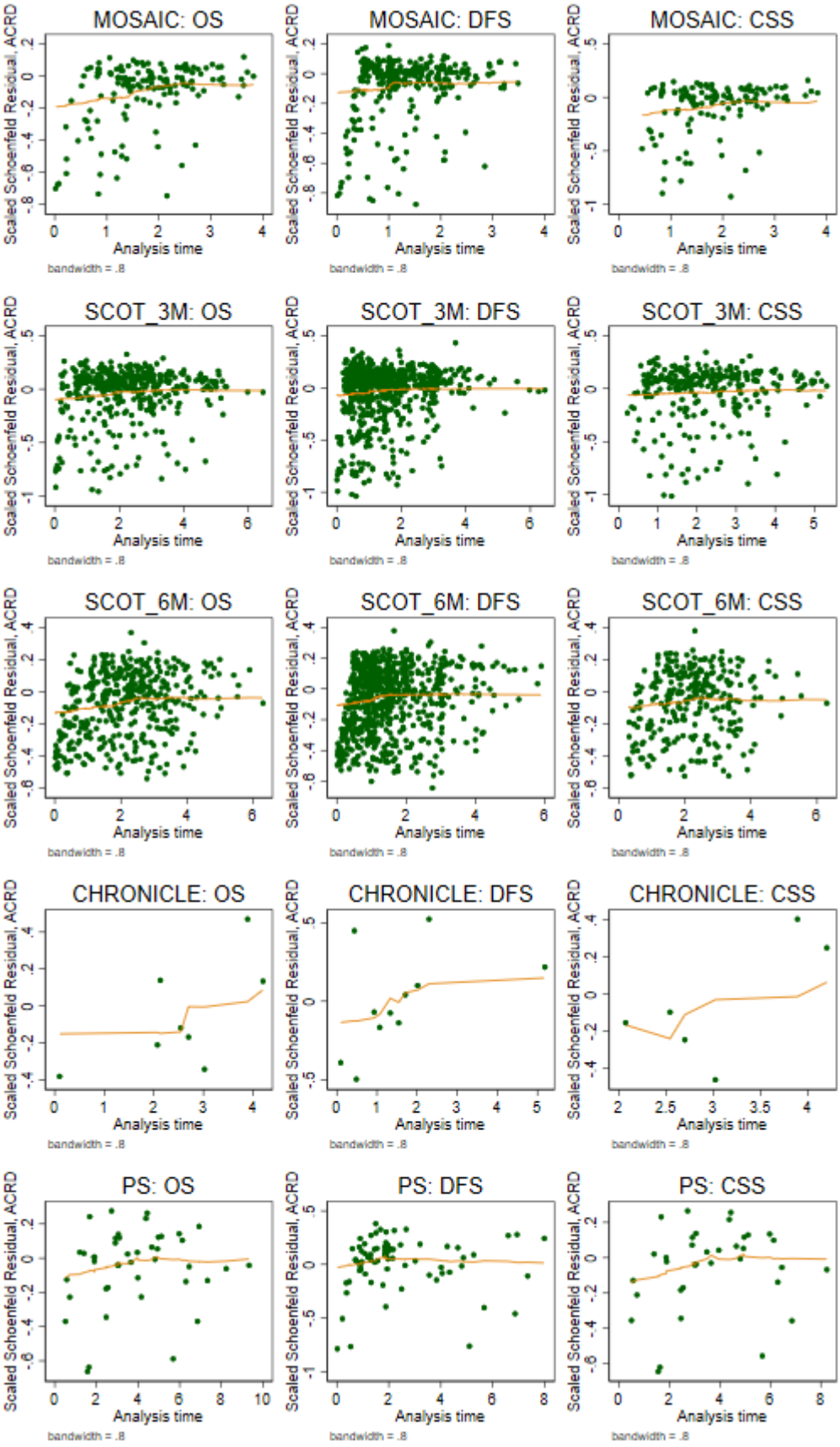


Figure A5.11a | Path *b* – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *b* total effects from Cox proportional hazards models for both ARDI and ACRD and for all three populations.

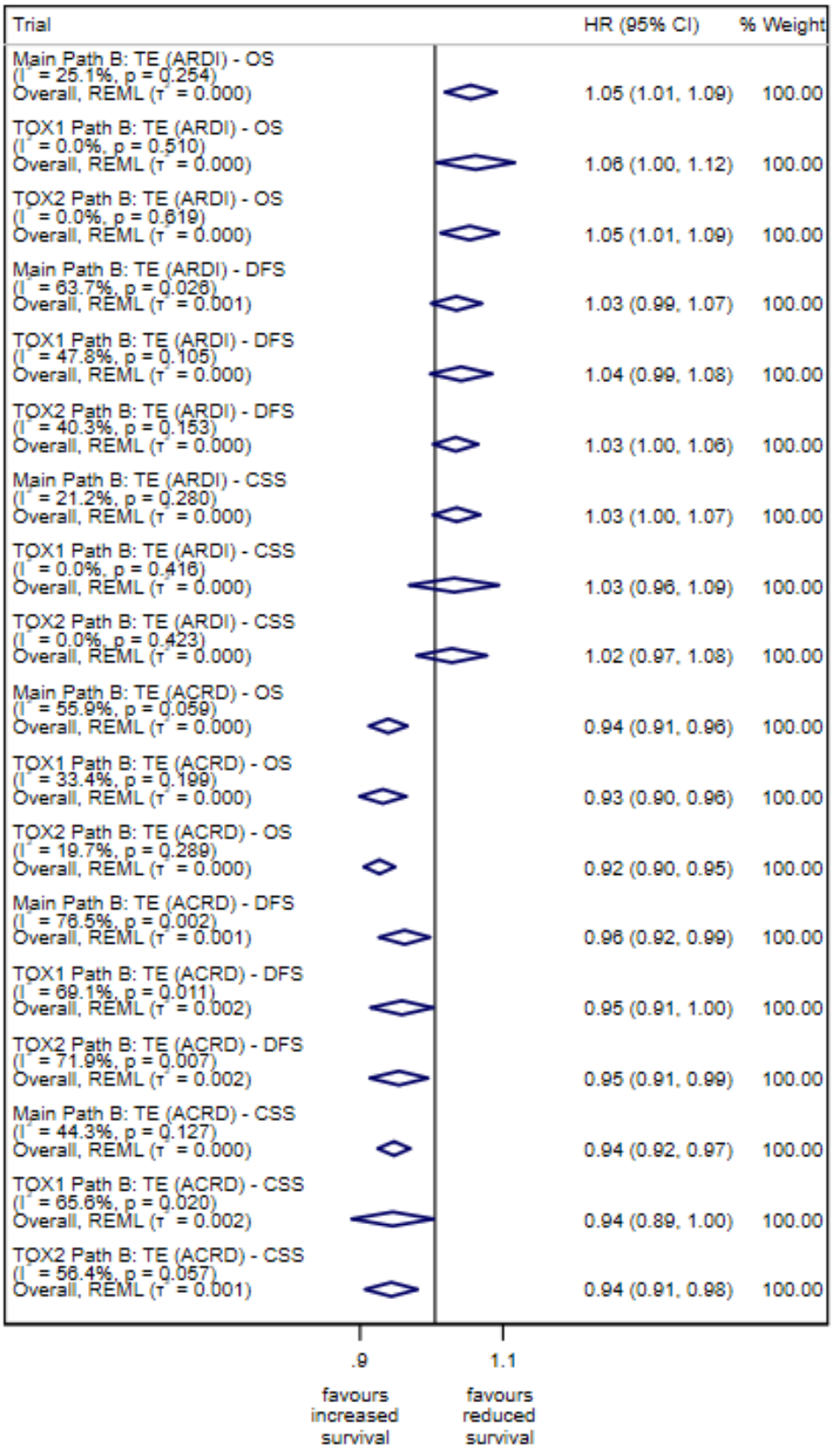


Figure A5.11b | Path *b* – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *b* biased total effects (models excluding toxicity) from Cox proportional hazards models for both ARDI and ACRD and for all three populations.

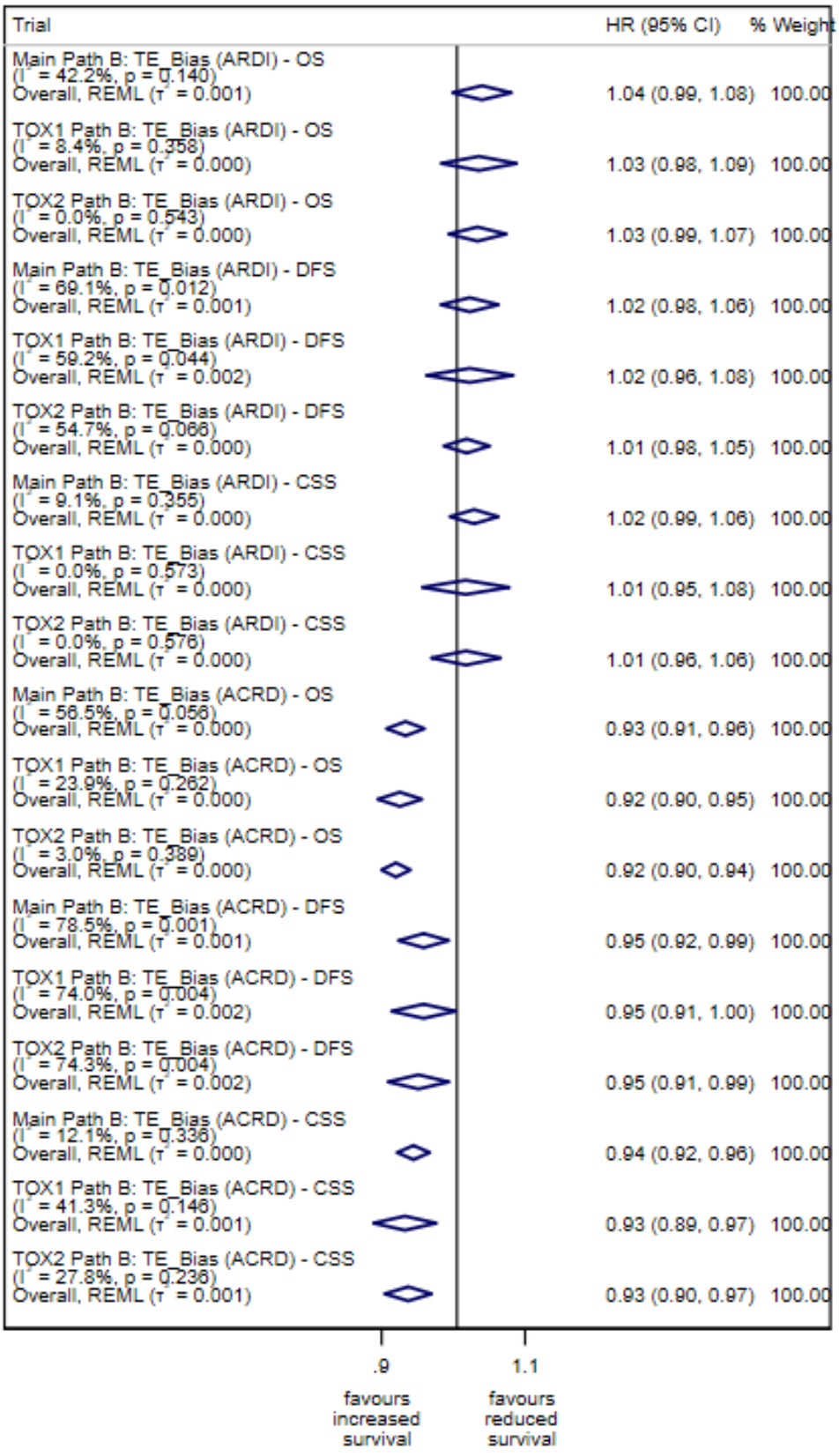


Figure A5.12 | Path b (ARDI-OS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ARDI increments on overall survival

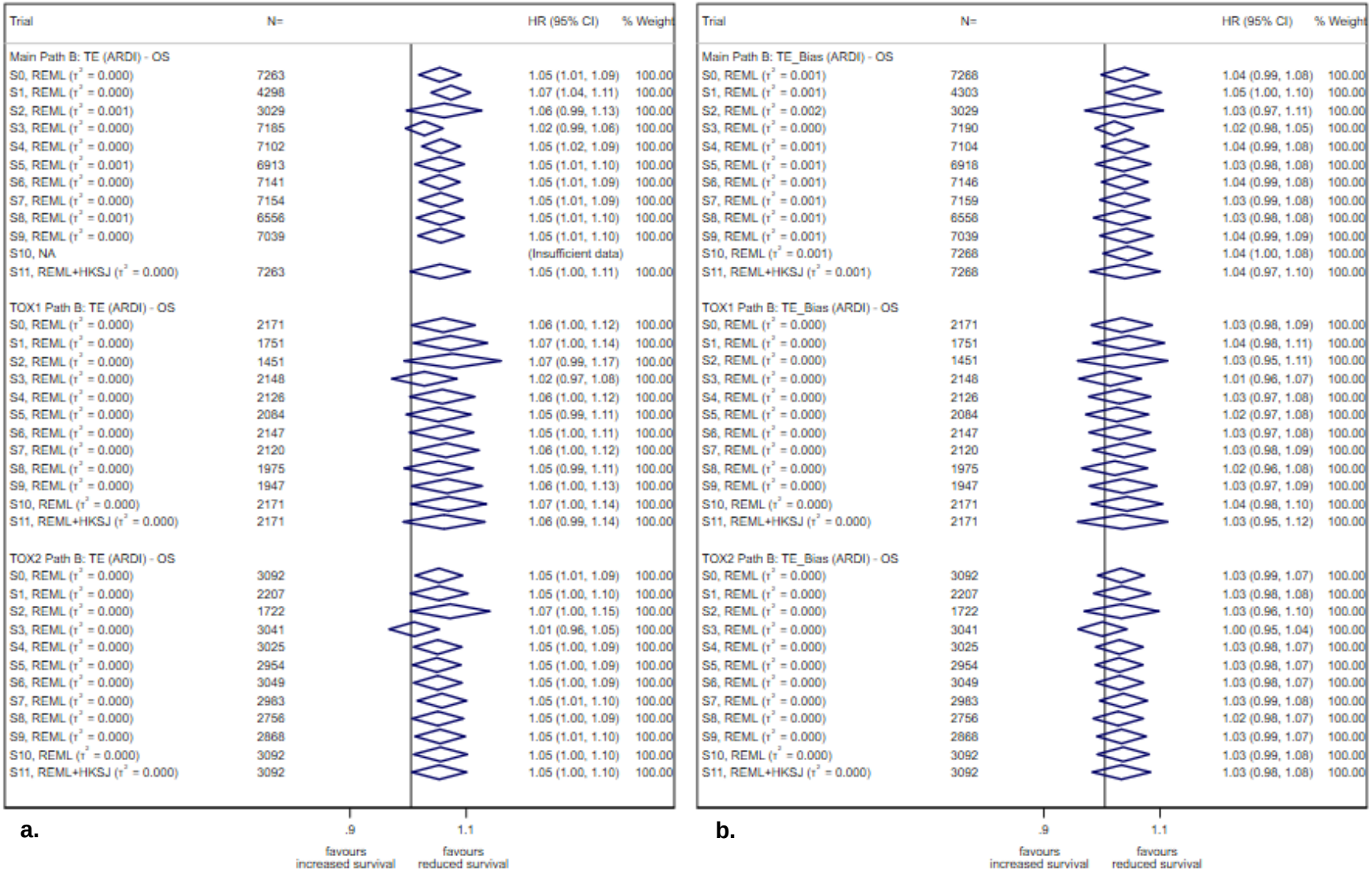


Figure A5.13 | Path b (ARDI-DFS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ARDI increments on disease-free survival.

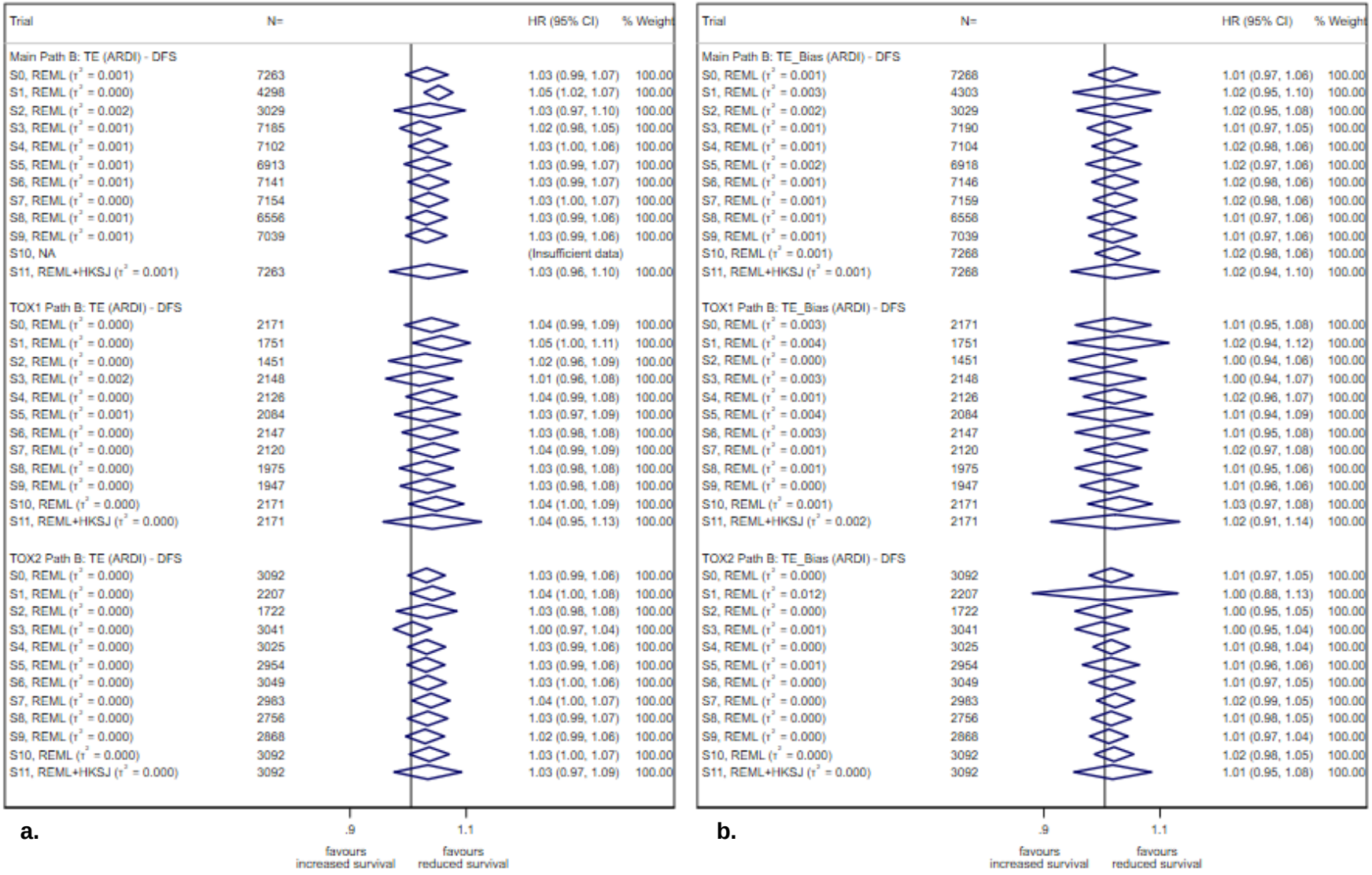


Figure A5.14 | Path *b* (ARDI-CSS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ARDI increments on cancer-specific survival.

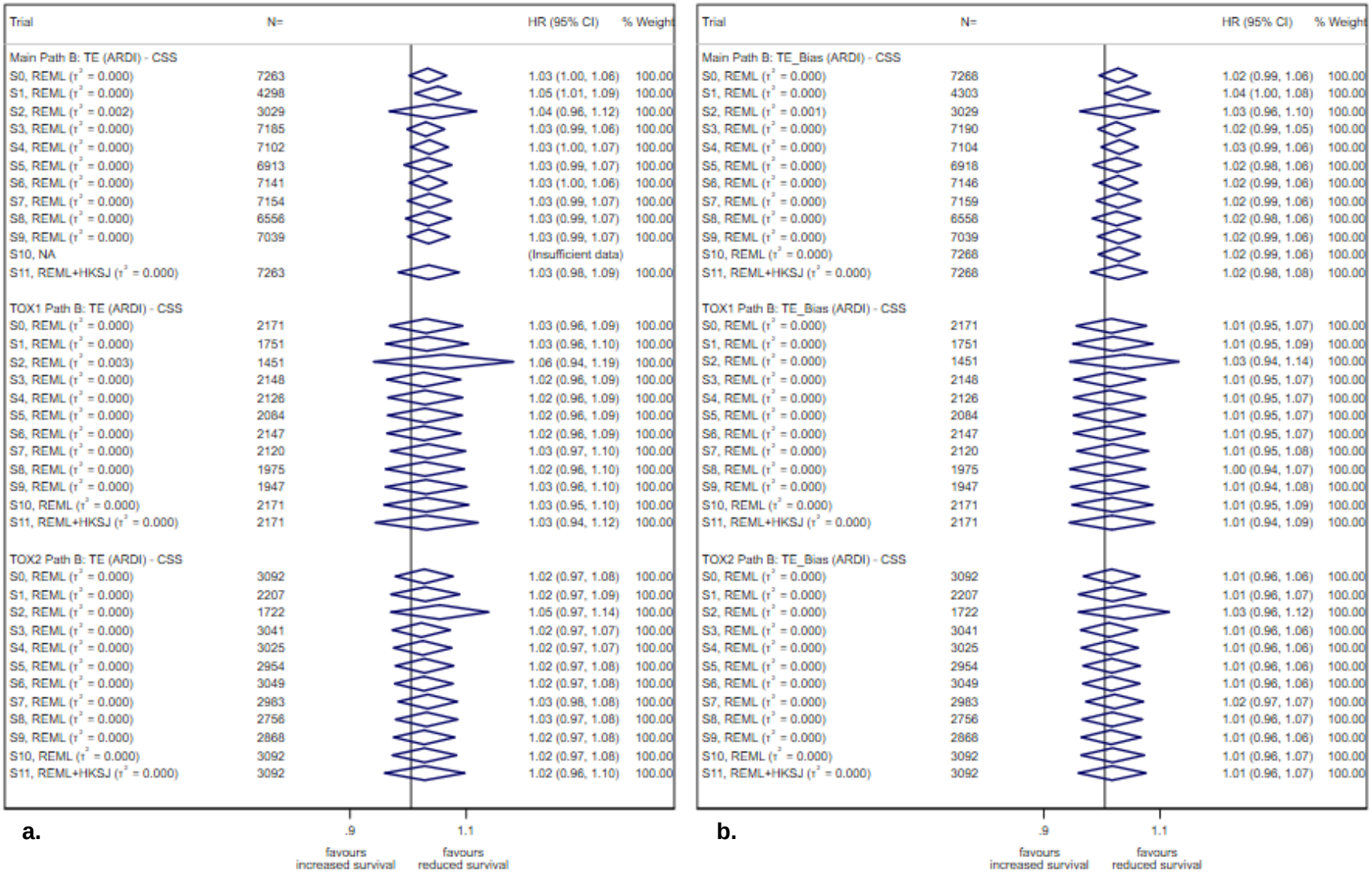
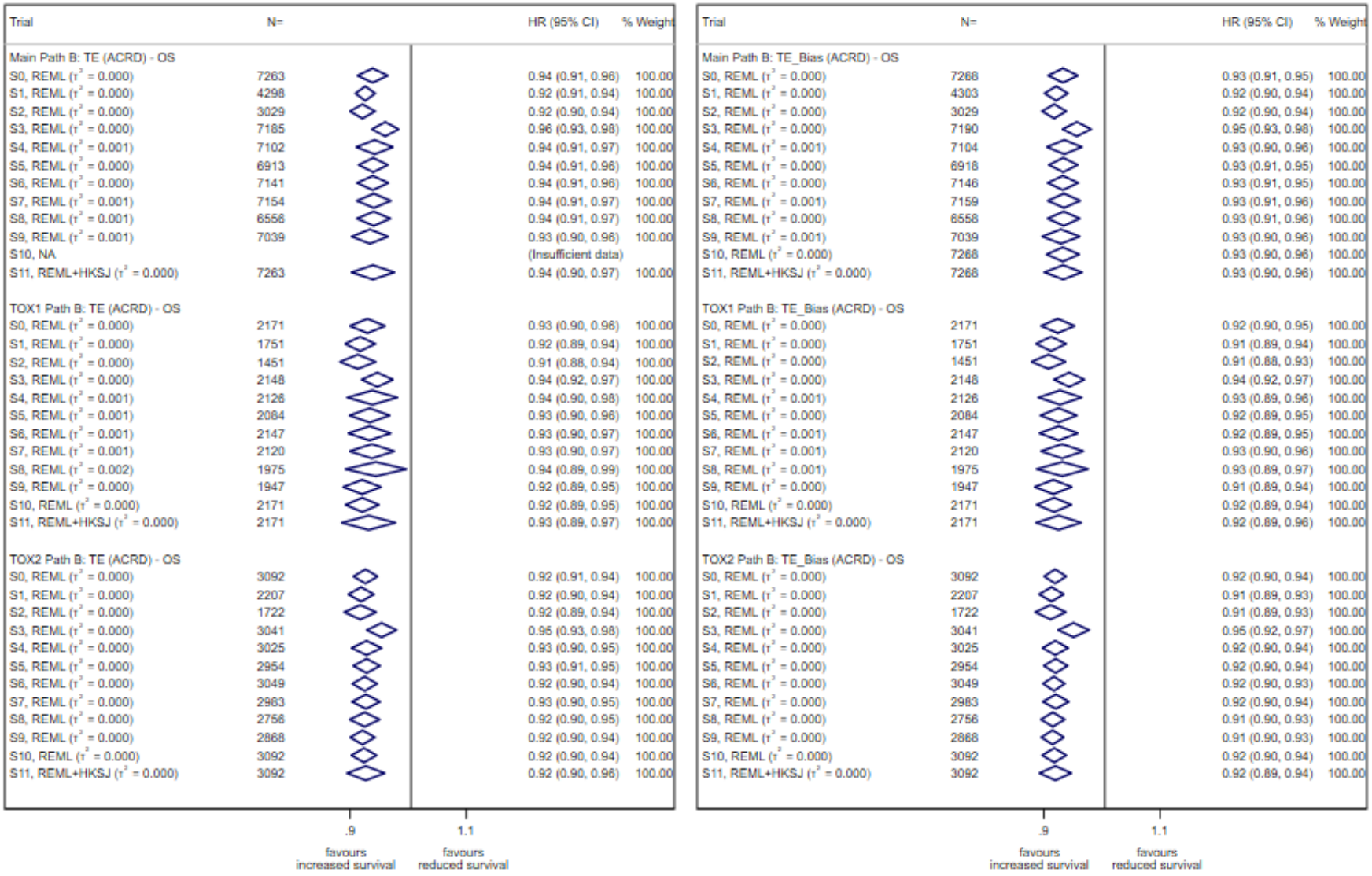


Figure A5.15 | Path b (ACRD - OS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ACRD increments on overall survival.



a. **b.**

Figure A5.16 | Path b (ACRD - DFS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ACRD increments on disease-free survival.

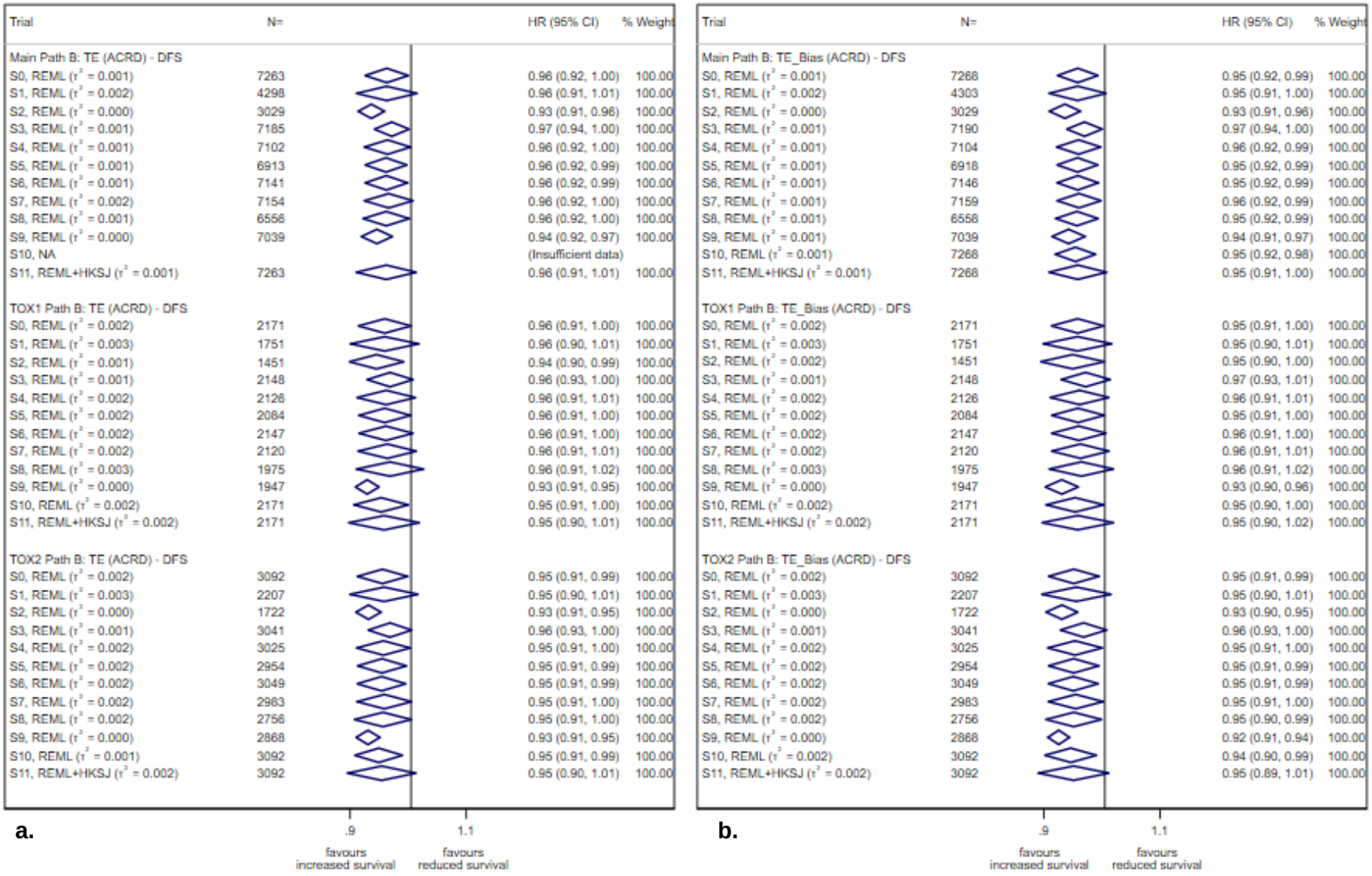


Figure A5.17 | Path b (ACRD - CSS) sensitivity analysis

Forest plot demonstrating the sensitivity analyses summary effect estimates of **a.** the total effect and **b.** the biased total effect (not adjusting for toxicity) of 5% ACRD increments on cancer-specific survival.

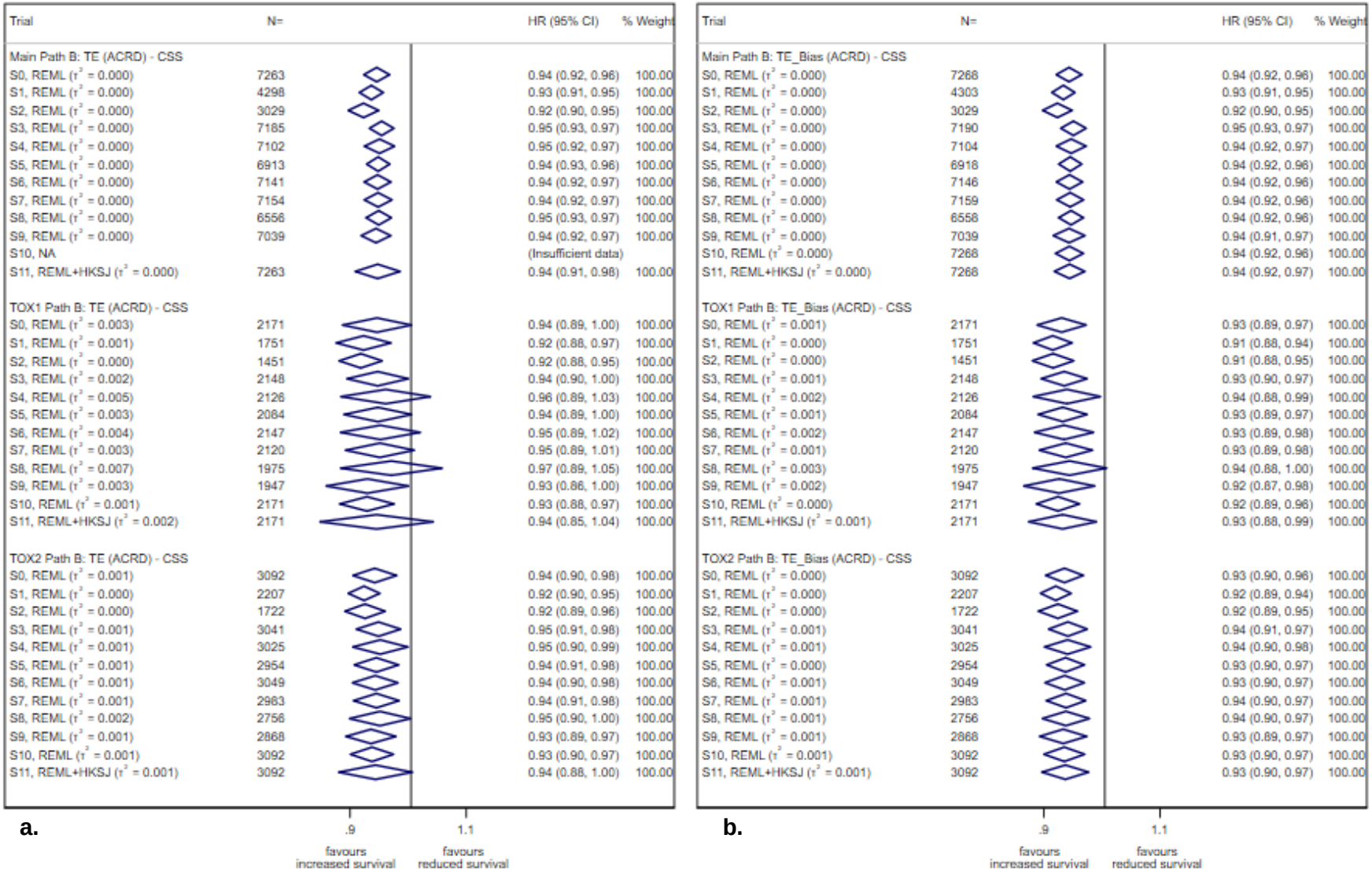


Figure A5.18 | Path e sensitivity analysis
Forest plot demonstrating the sensitivity analyses summary effect estimates of the total effect of toxicity on **a.** ARDI and **b.** ACRD.

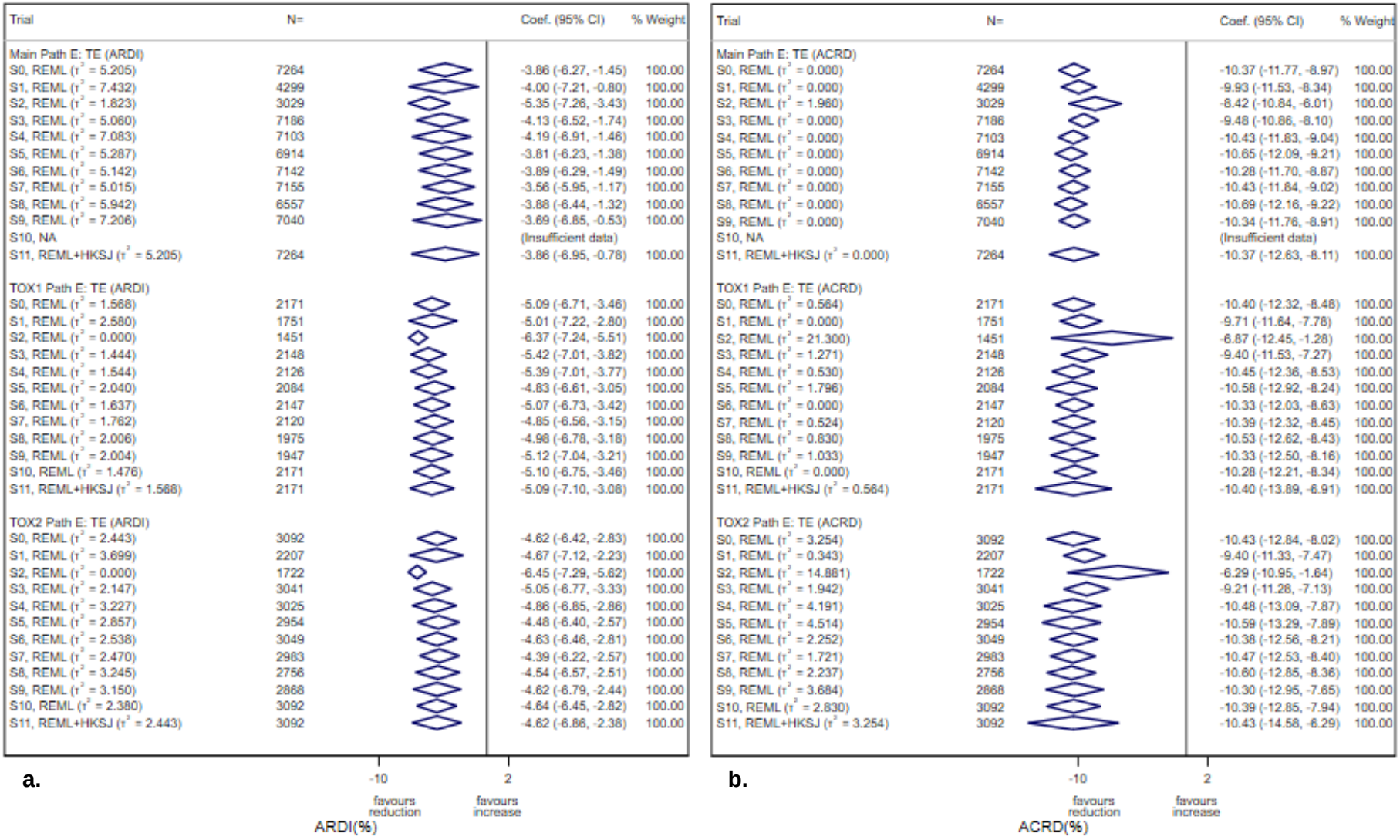
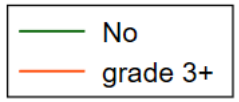


Figure A5.19a | Kaplan Meier curves according to grade 3 + toxicity

Kaplan Meier survival curves for the effects of grade 3+ toxicity on overall, disease-free, and cancer-specific survival. For toxicity populations only.



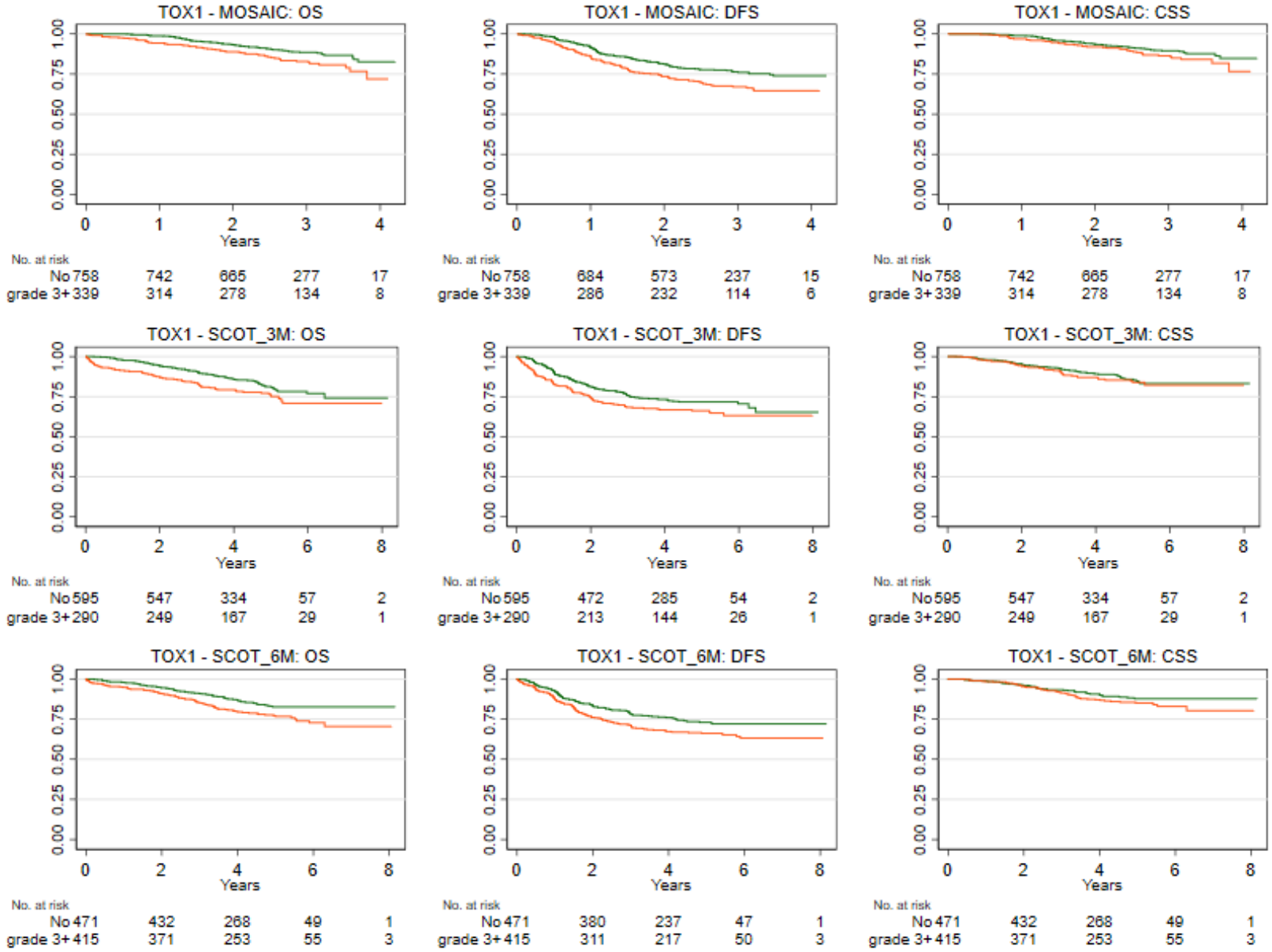
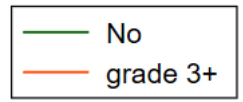


Figure A5.19b | Kaplan Meier curves according to grade 3 + toxicity

Kaplan Meier survival curves for the effects of grade 3+ toxicity on overall, disease-free, and cancer-specific survival. For toxicity populations only



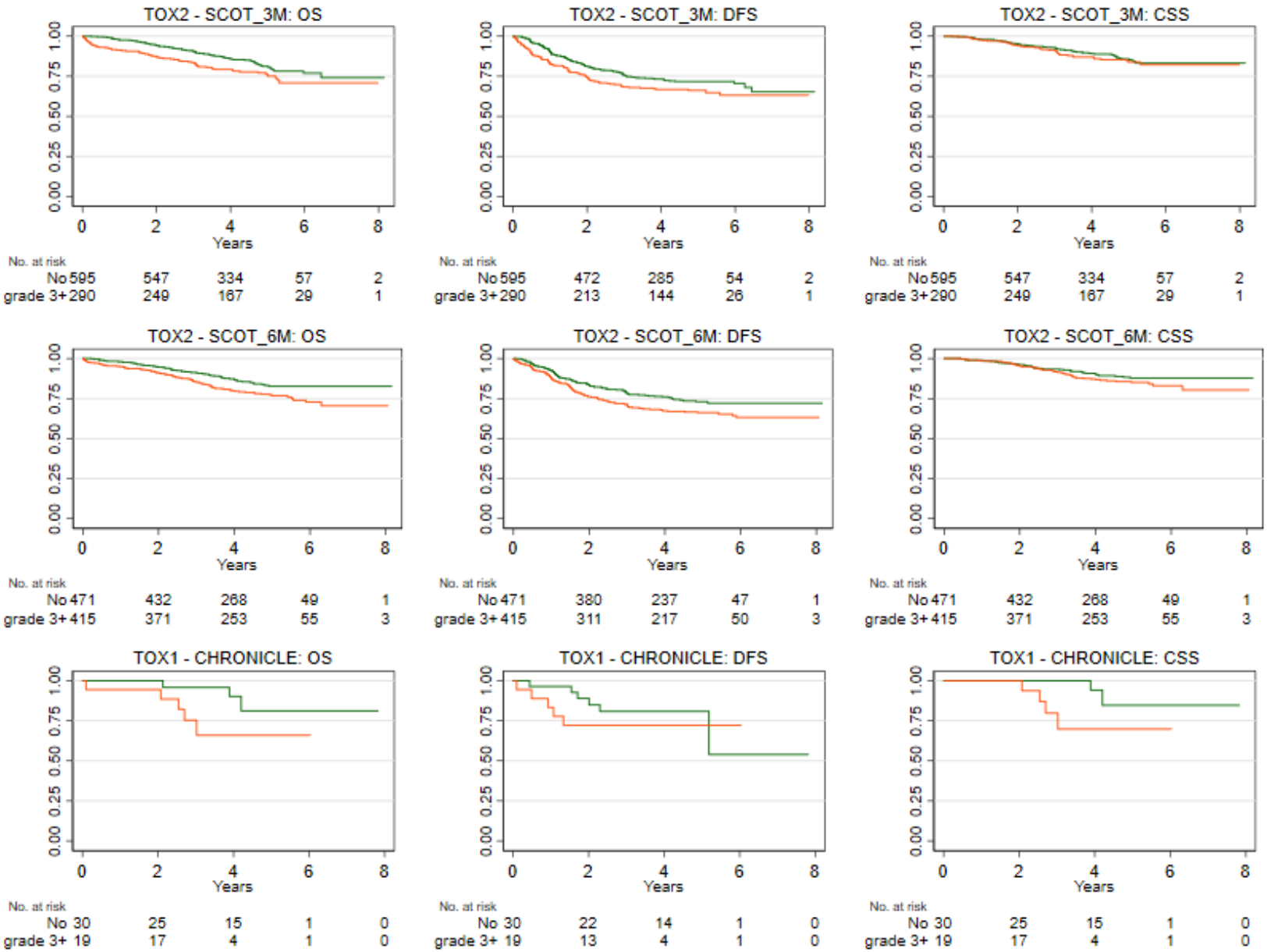
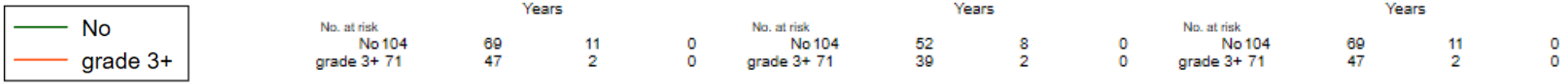
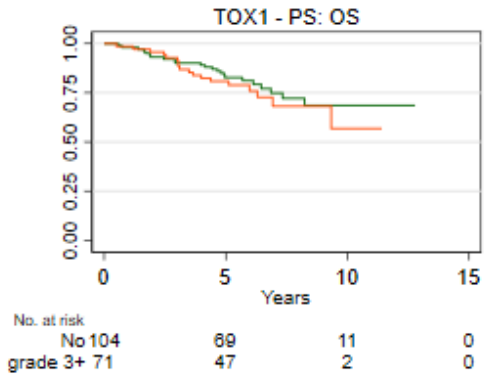
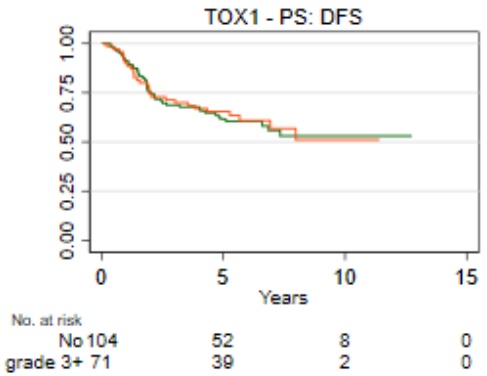


Figure A5.19c | Kaplan Meier curves according to grade 3 + toxicity

Kaplan Meier survival curves for the effects of grade 3+ toxicity on overall, disease-free, and cancer-specific survival. For toxicity populations only







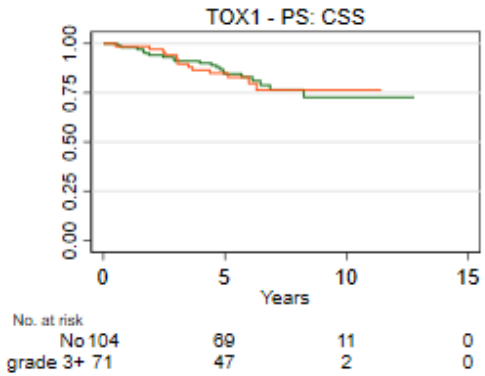


Figure A5.20a | Path *f* - Scaled Schoenfeld Residuals plots

Graphs demonstrating scaled Schoenfeld residuals from Cox models for path *f* total effects plotted against analysis time (years).

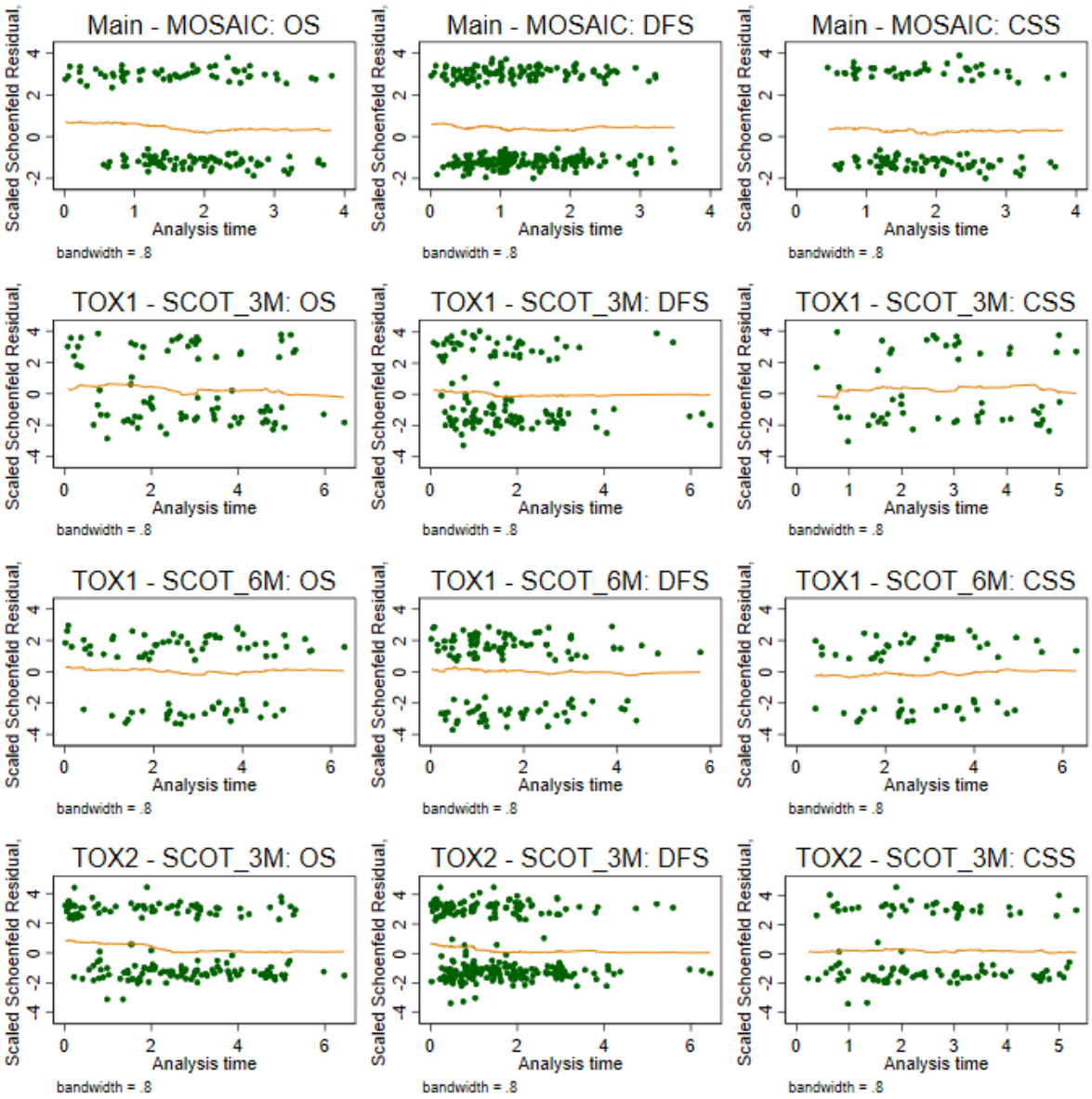


Figure A5.20b | Path *f* - Scaled Schoenfeld Residuals plots

Graphs demonstrating scaled Schoenfeld residuals from Cox models for path *f* total effects plotted against analysis time (years).

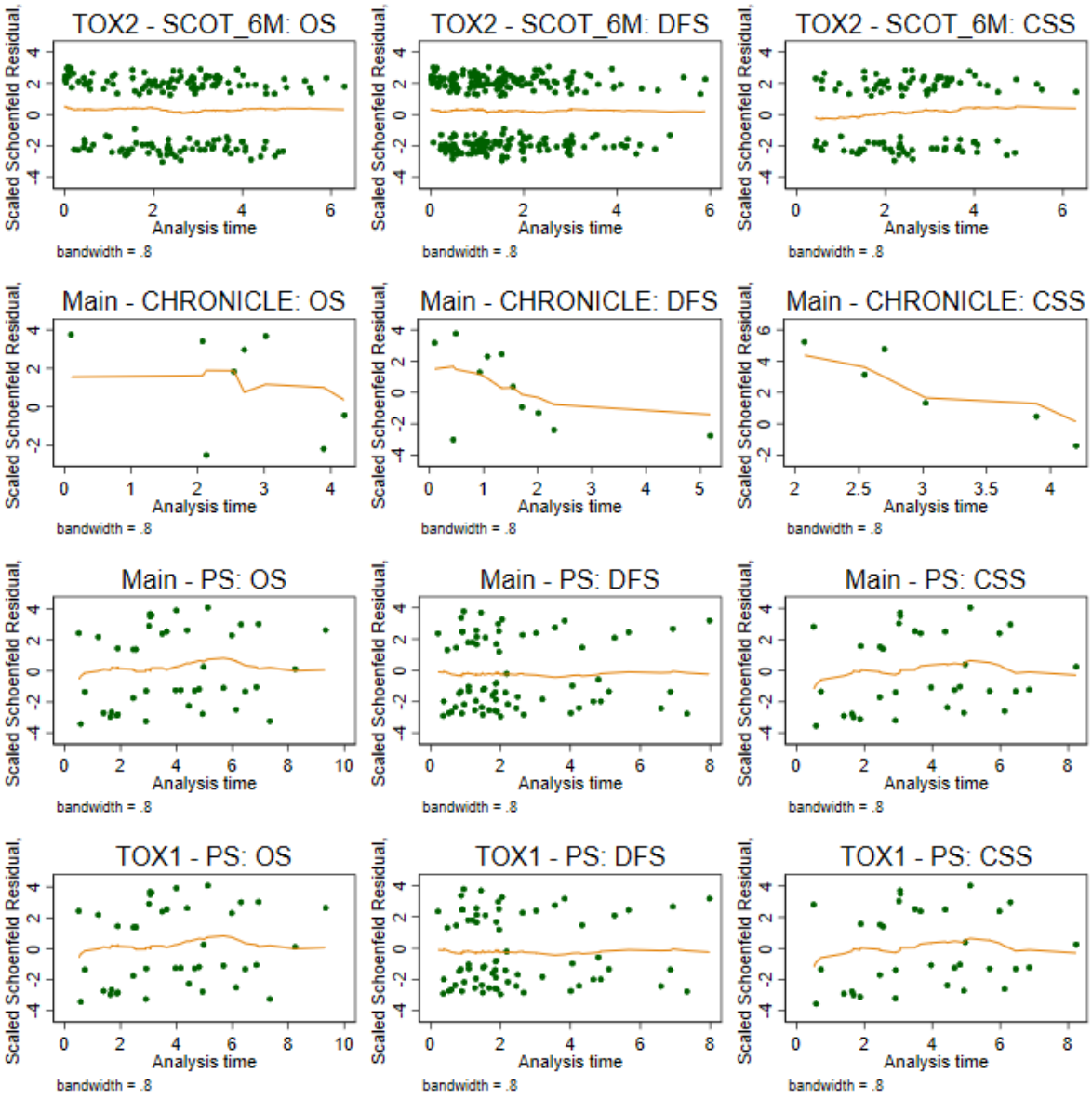


Figure A5.21a | Path *f* (total effects) – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *f* total from Cox proportional hazards models for all three populations.

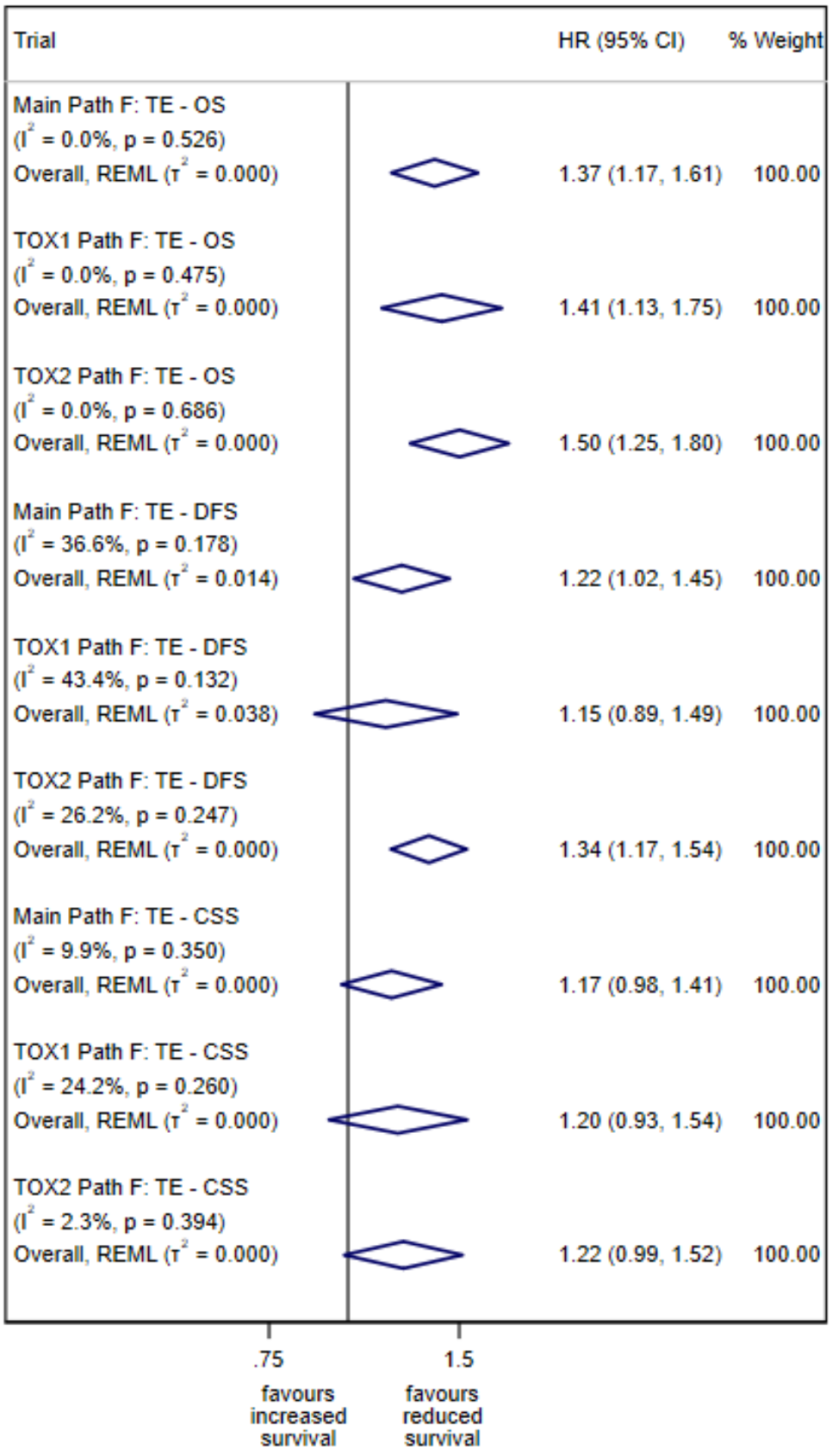


Figure A5.21b | Path *f* (direct effects) – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *f* total effects and **b.** direct effects (adjusted for ARDI or ACRD) from Cox proportional hazards models for all three populations.

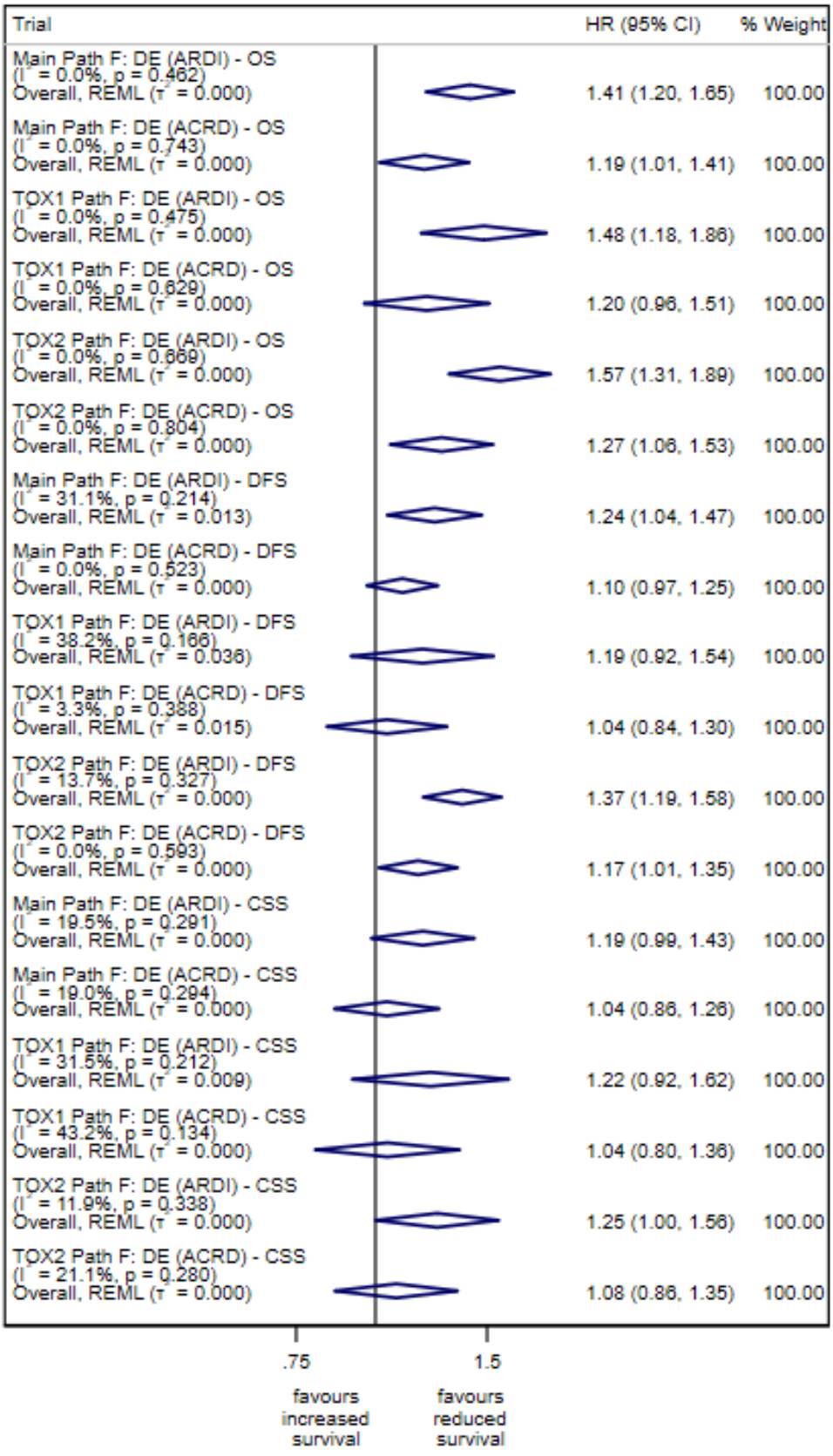


Figure A5.22a | Path *f* (OS) sensitivity analysis - Main
Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on overall survival for the main population.

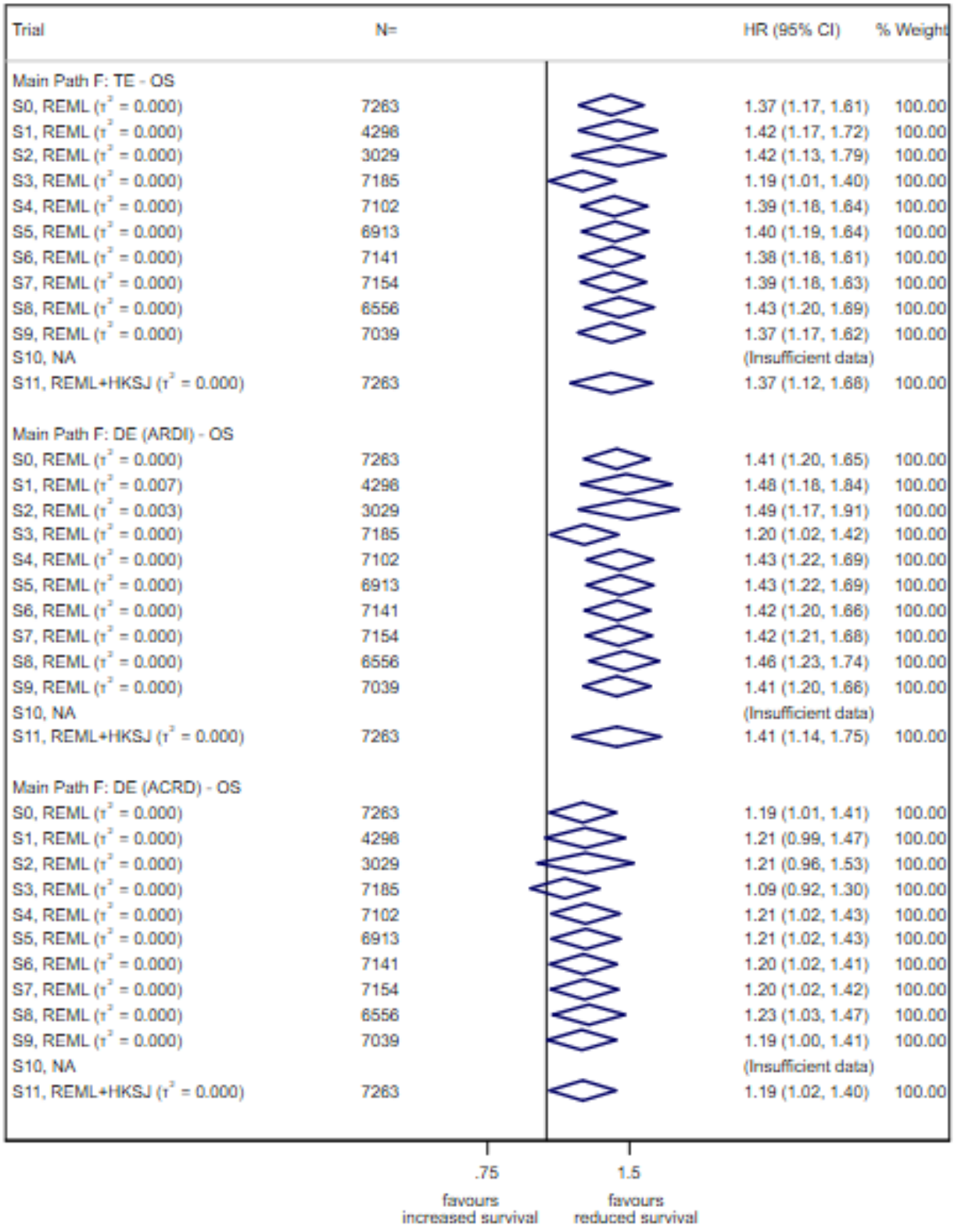


Figure A5.22b | Path *f* (OS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on overall survival for the **a.** TOX1 and **b.** TOX2 populations.

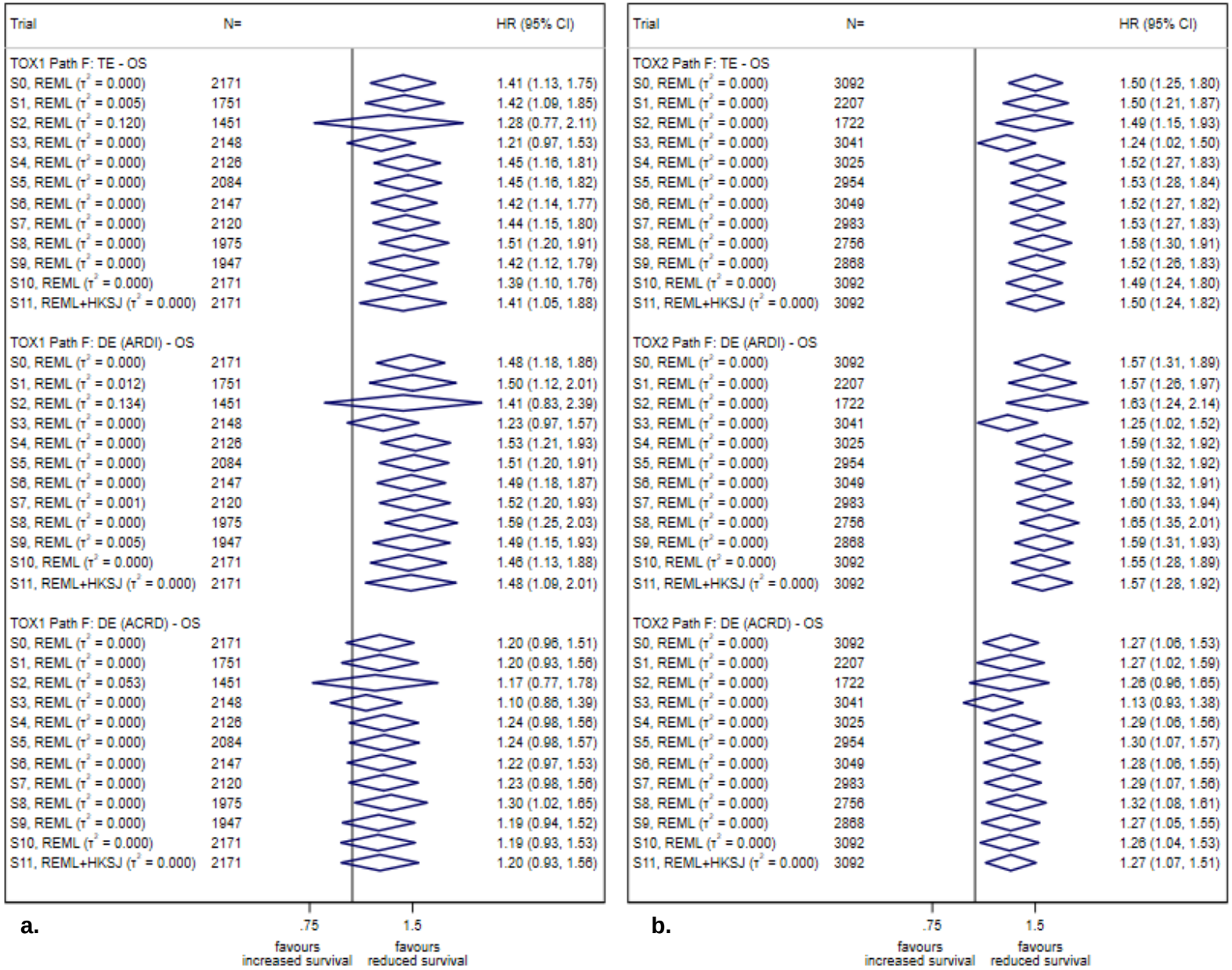


Figure A5.23a | Path f (DFS) sensitivity analysis - Main
Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on disease-free survival for the main population.

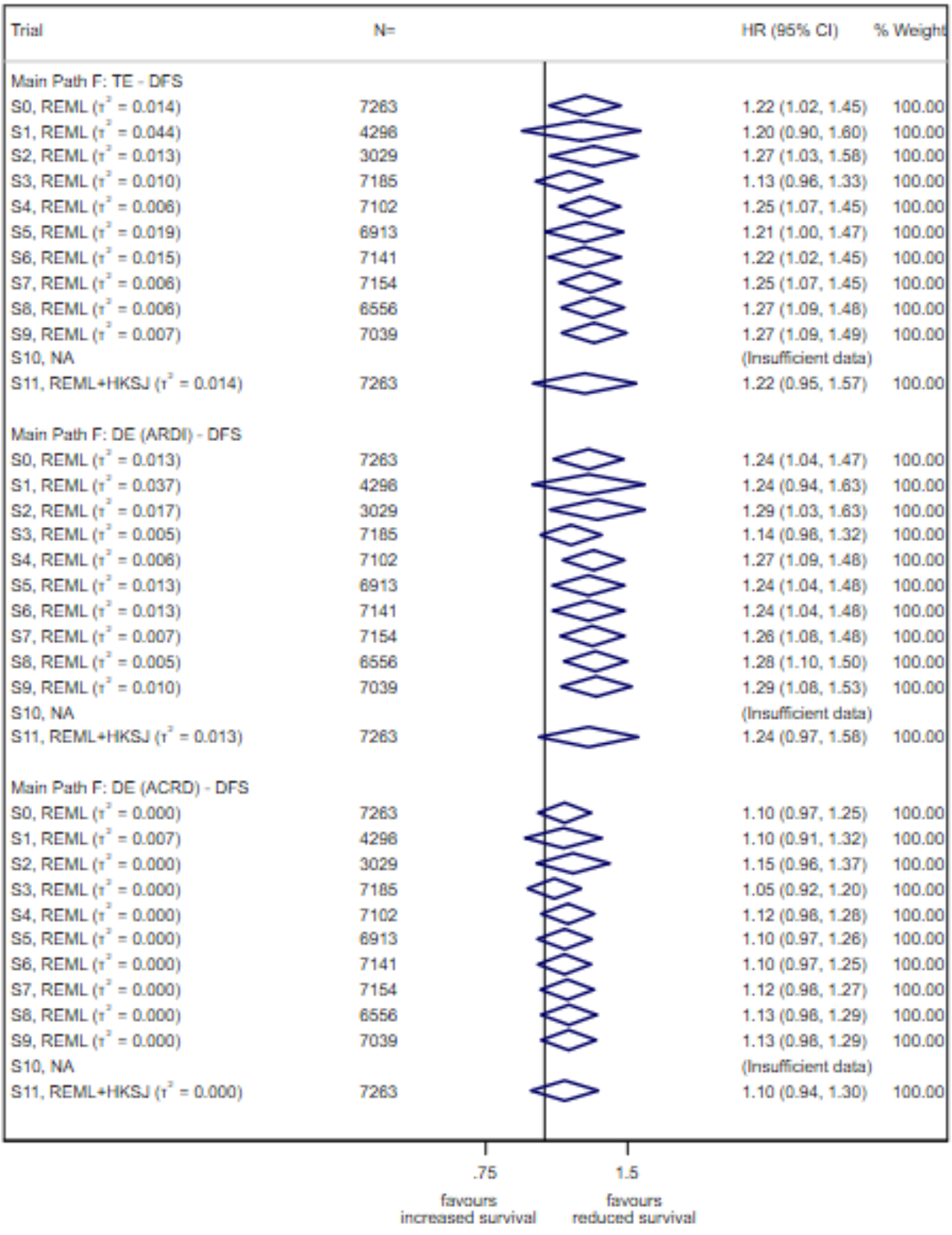


Figure A5.23b | Path f (DFS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on disease-free survival for the **a.** TOX1 and **b.** TOX2 populations.

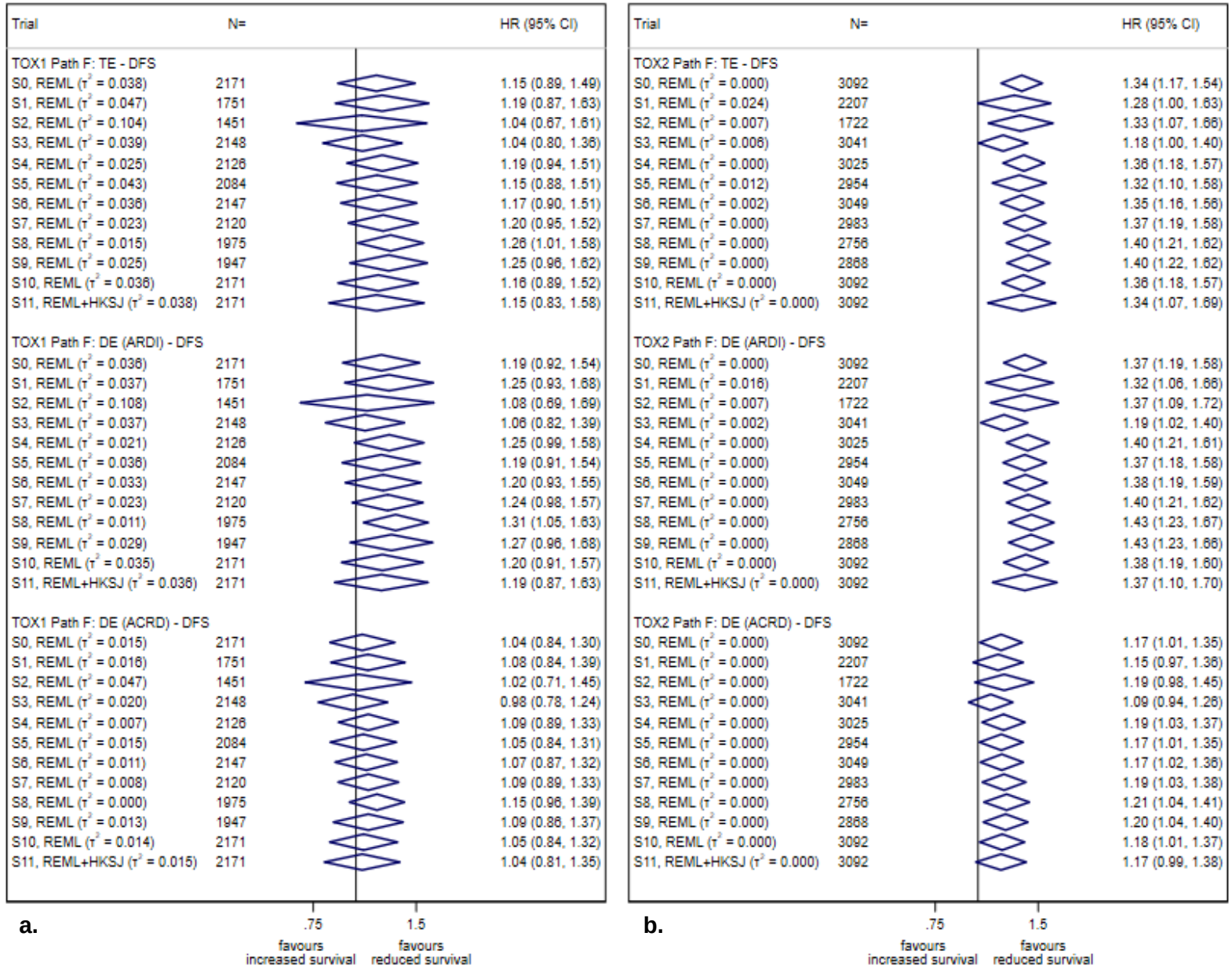


Figure A5.24a | Path f (CSS) sensitivity analysis - Main

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on cancer-specific survival for the main population.

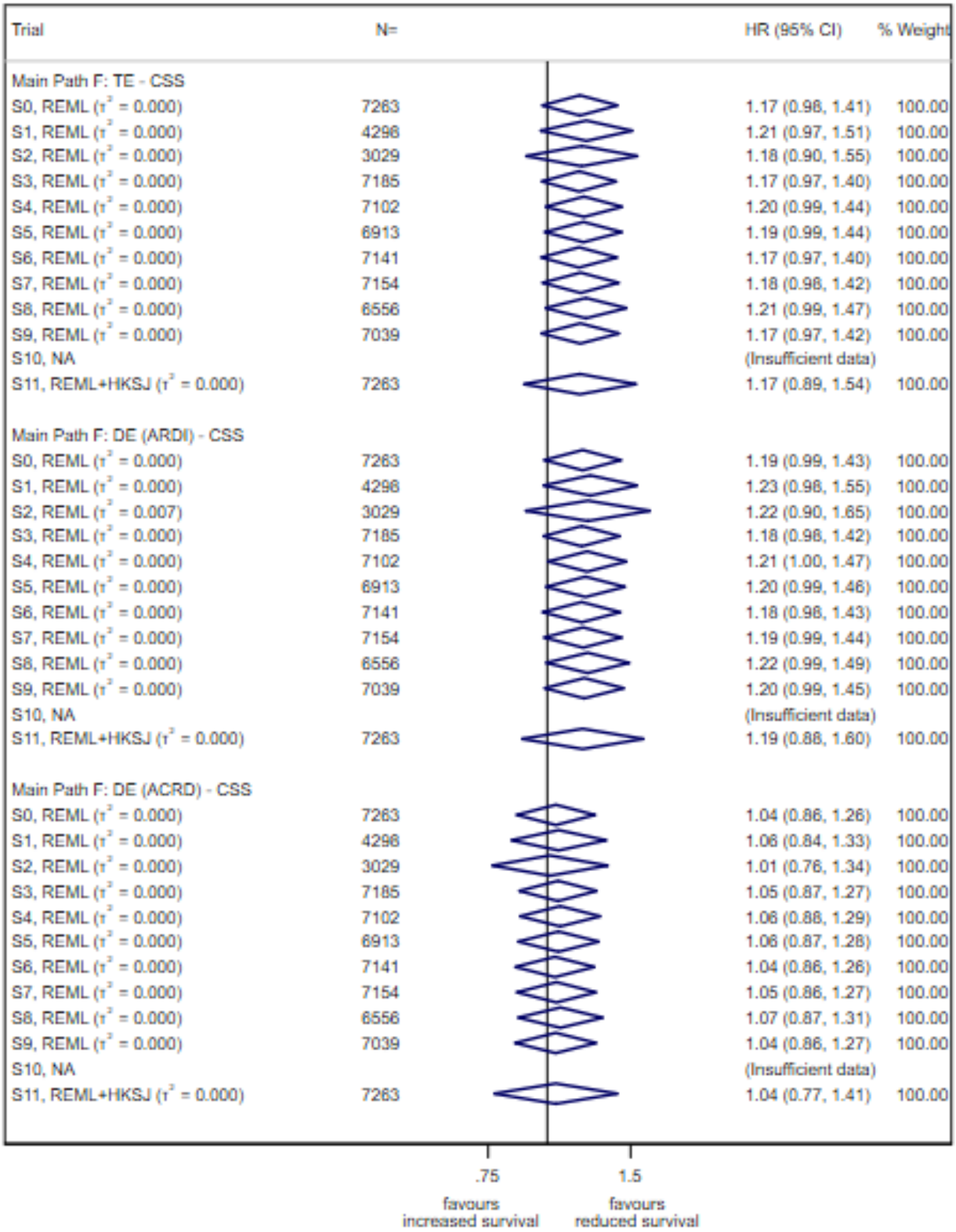


Figure A5.24b | Path *f* (CSS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of toxicity on cancer-specific survival for the **a.** TOX1 and **b.** TOX2 populations.

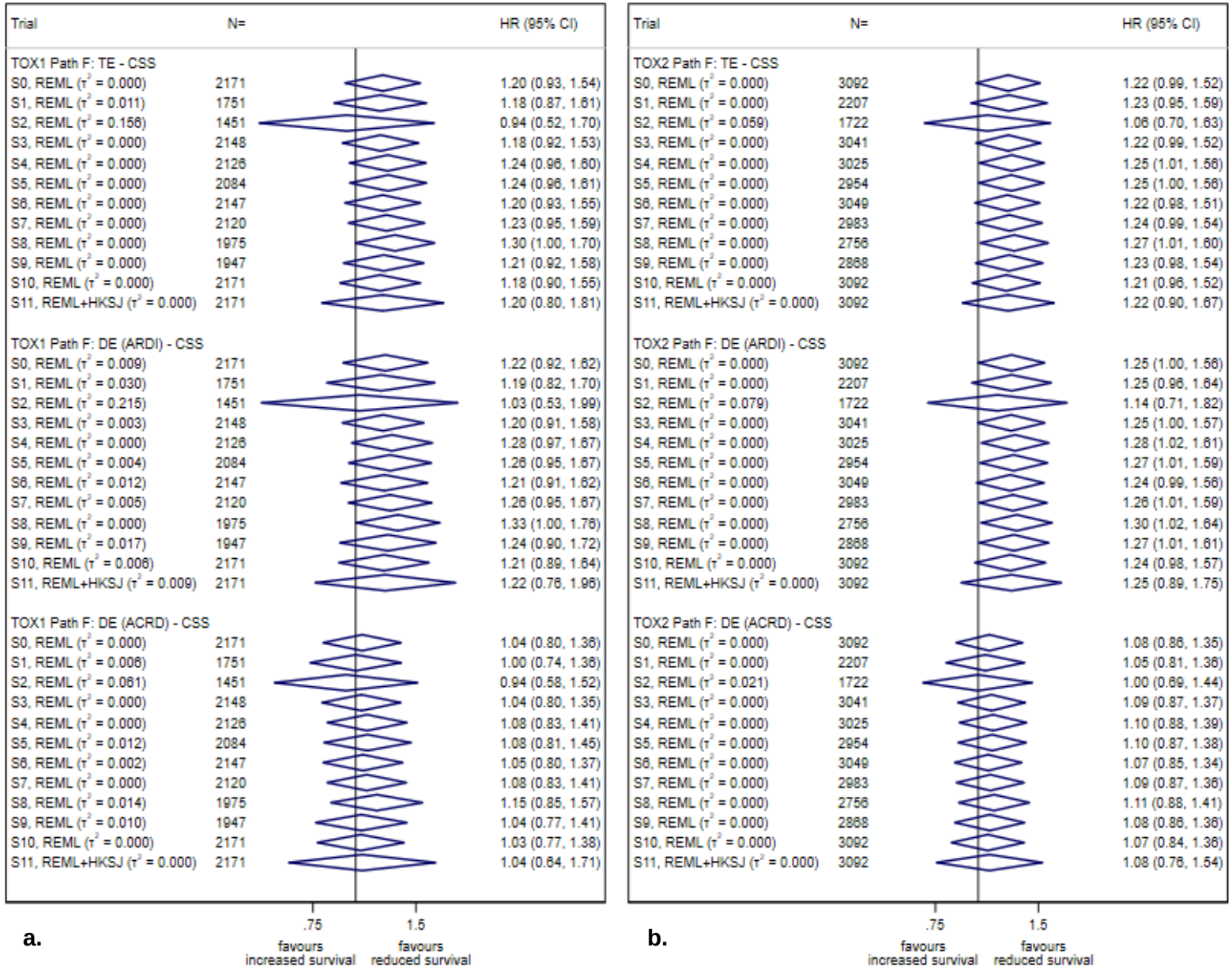
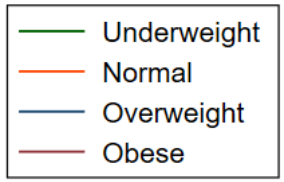


Figure A5.25a | Kaplan Meier curves according to BMI categories

Kaplan Meier survival curves for the effects of BMI categories on overall, disease-free, and cancer-specific survival.



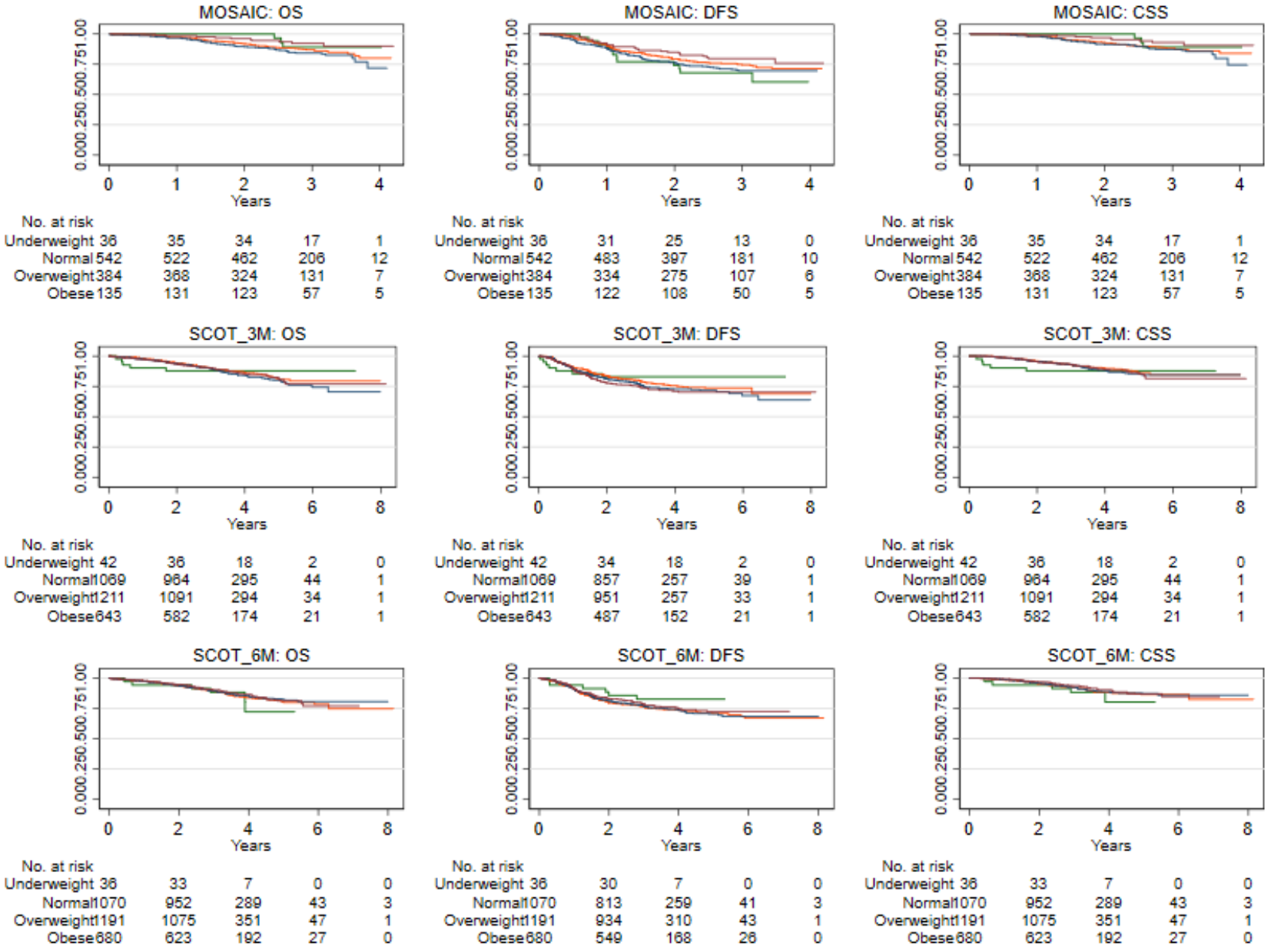
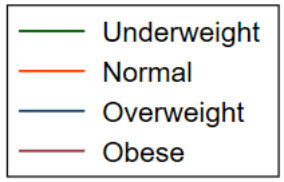


Figure A5.25b | Kaplan Meier curves for path *c* according to BMI categories

Kaplan Meier survival curves for the effects of BMI categories on overall, disease-free, and cancer-specific survival.



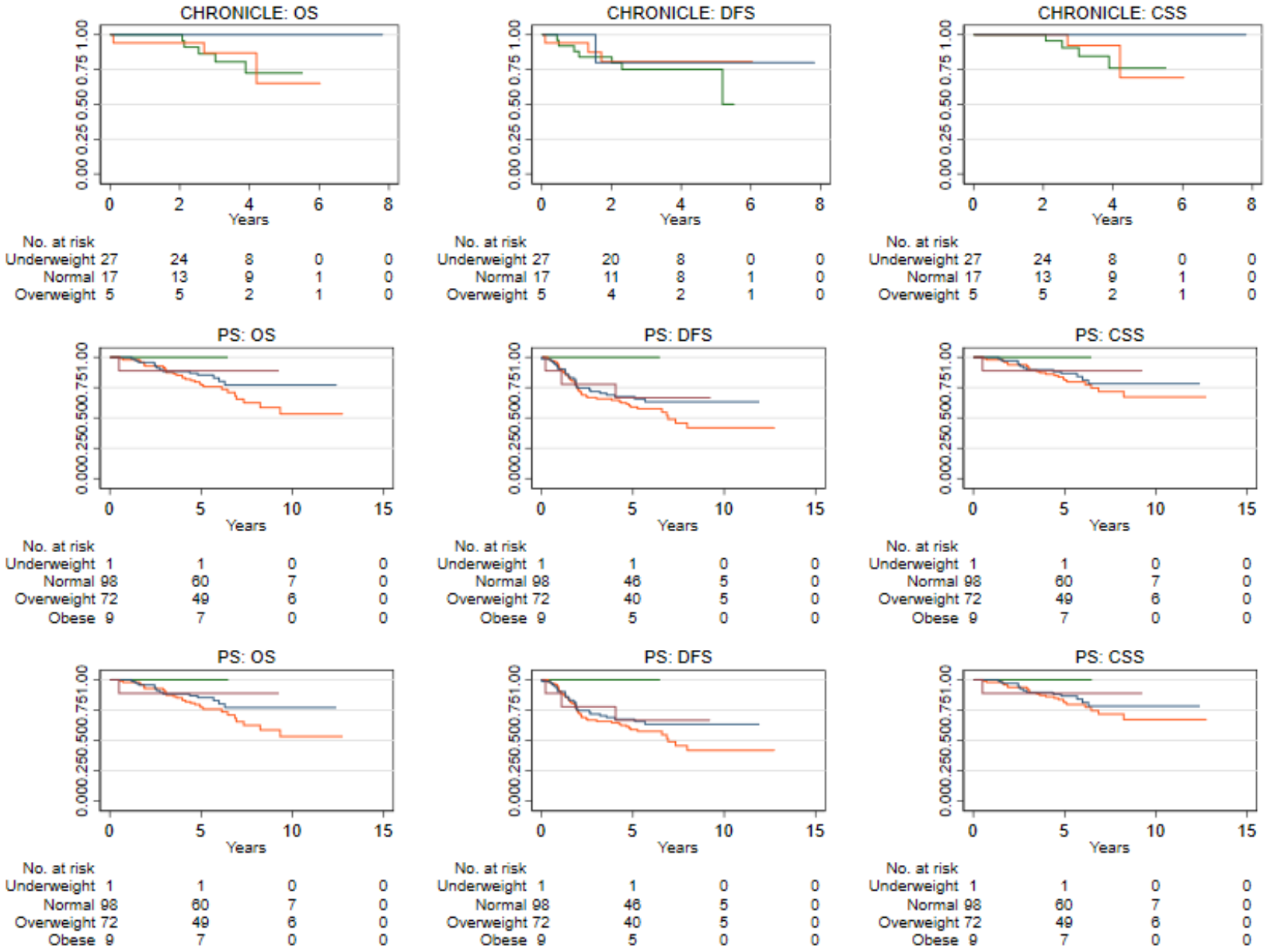


Figure A5.26 | Path c - Scaled Schoenfeld Residuals plots

Graphs demonstrating scaled Schoenfeld residuals from Cox models for path *c* total effects (main population) plotted against analysis time (years).

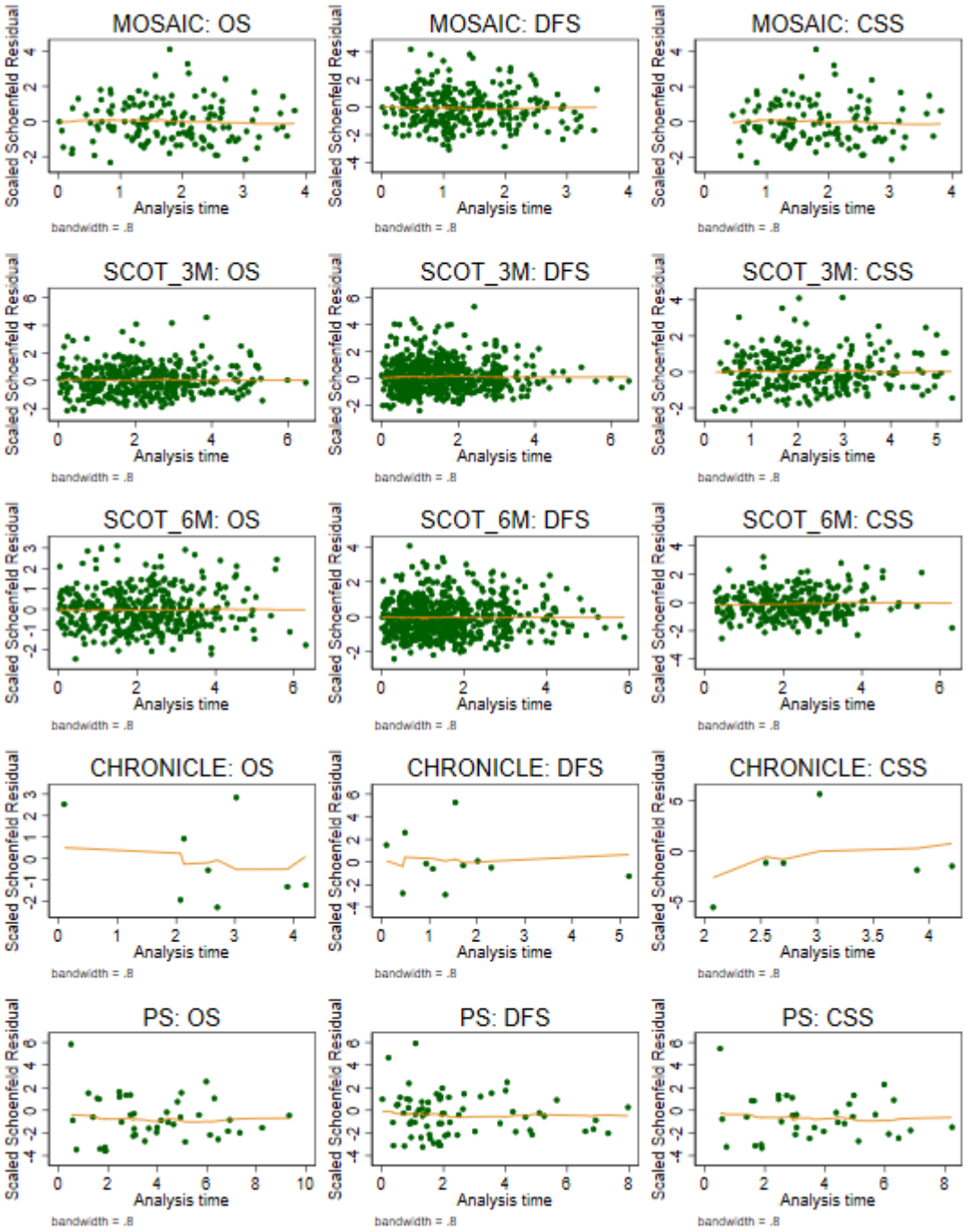


Figure A5.27a | Path c (total effects) – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *c* total effects from Cox proportional hazards models for all three populations**.**

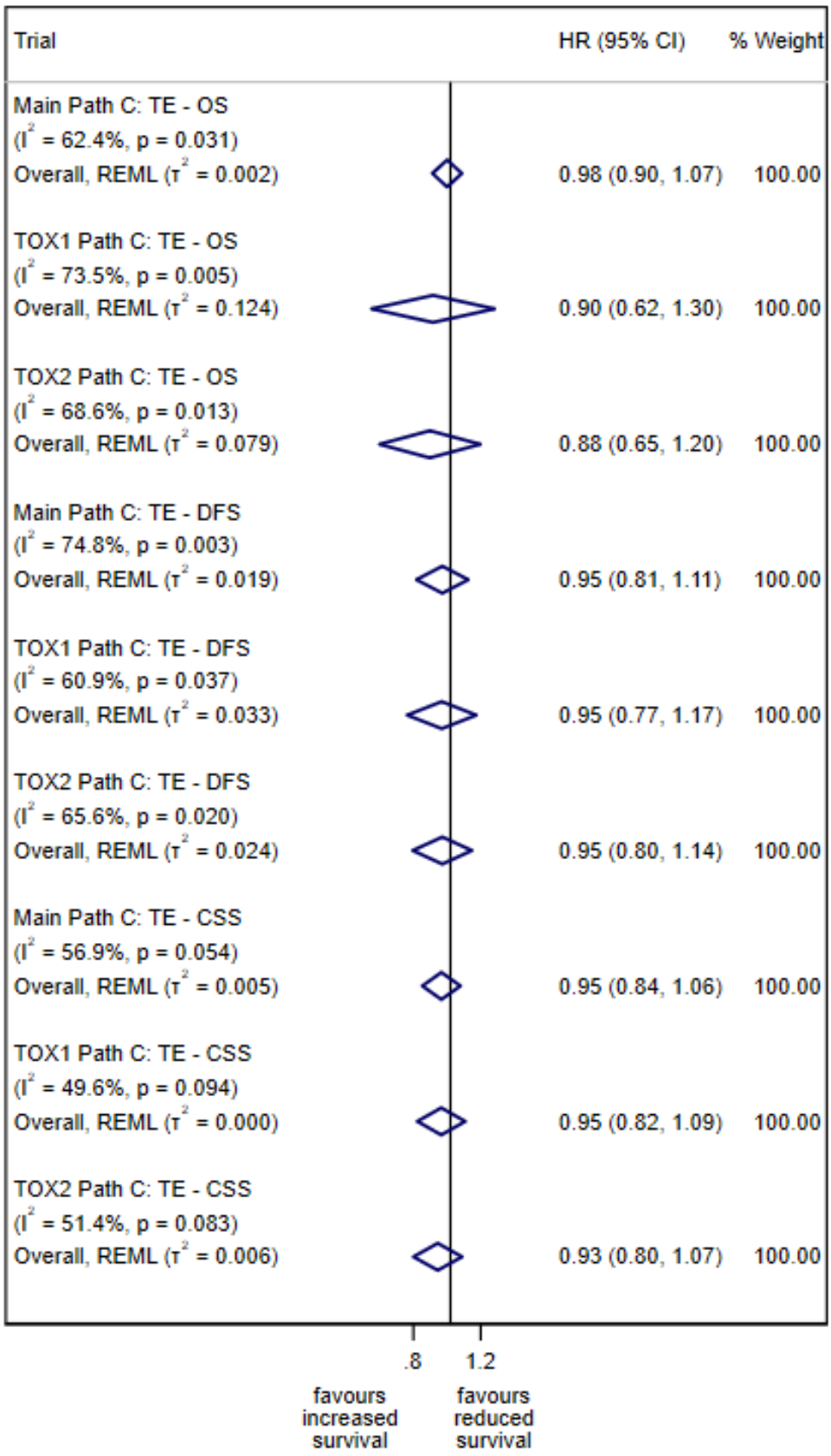


Figure A5.27b | Path c (direct effects) – Summary estimates for Cox models.
Forest plot demonstrating summary estimates for path *c* direct effects (adjusted for ARDI or ACRD) from Cox proportional hazards models for all three populations**.**

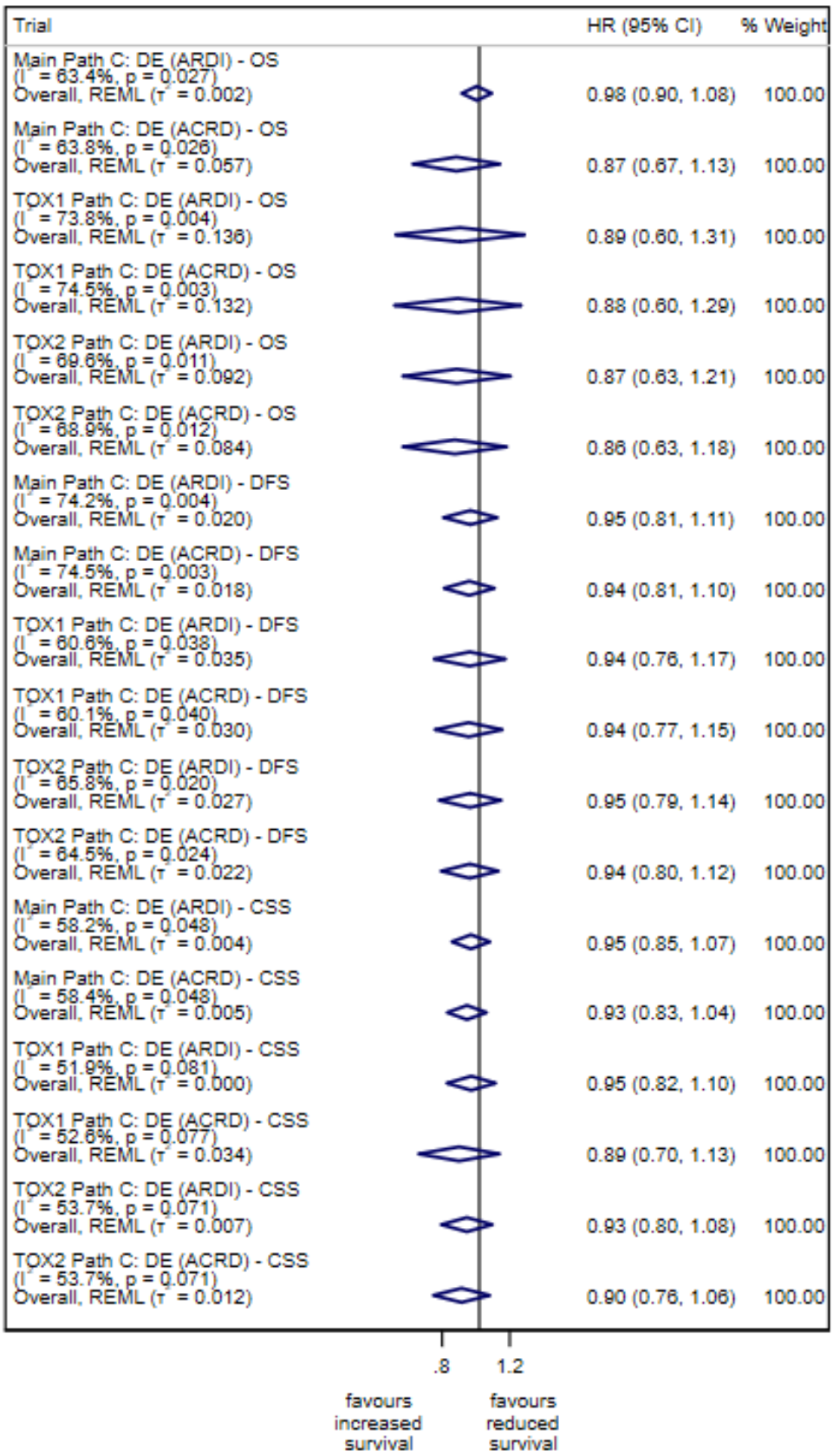


Figure A5.28a | Path c (OS) sensitivity analysis - Main
Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on overall survival for the main population.

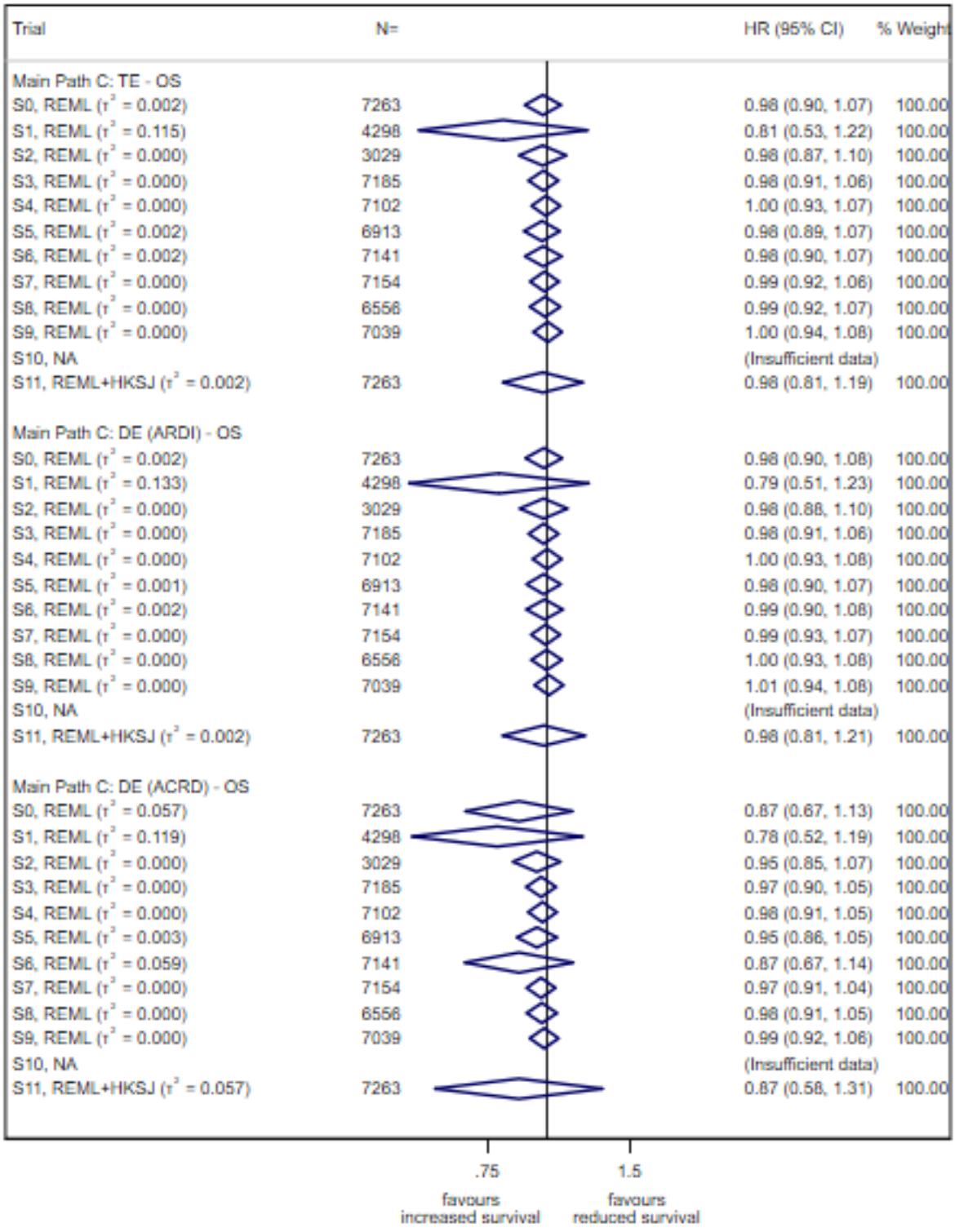


Figure A5.28b | Path *c* (OS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on overall survival for the **a.** TOX1 and **b.** TOX2 populations.

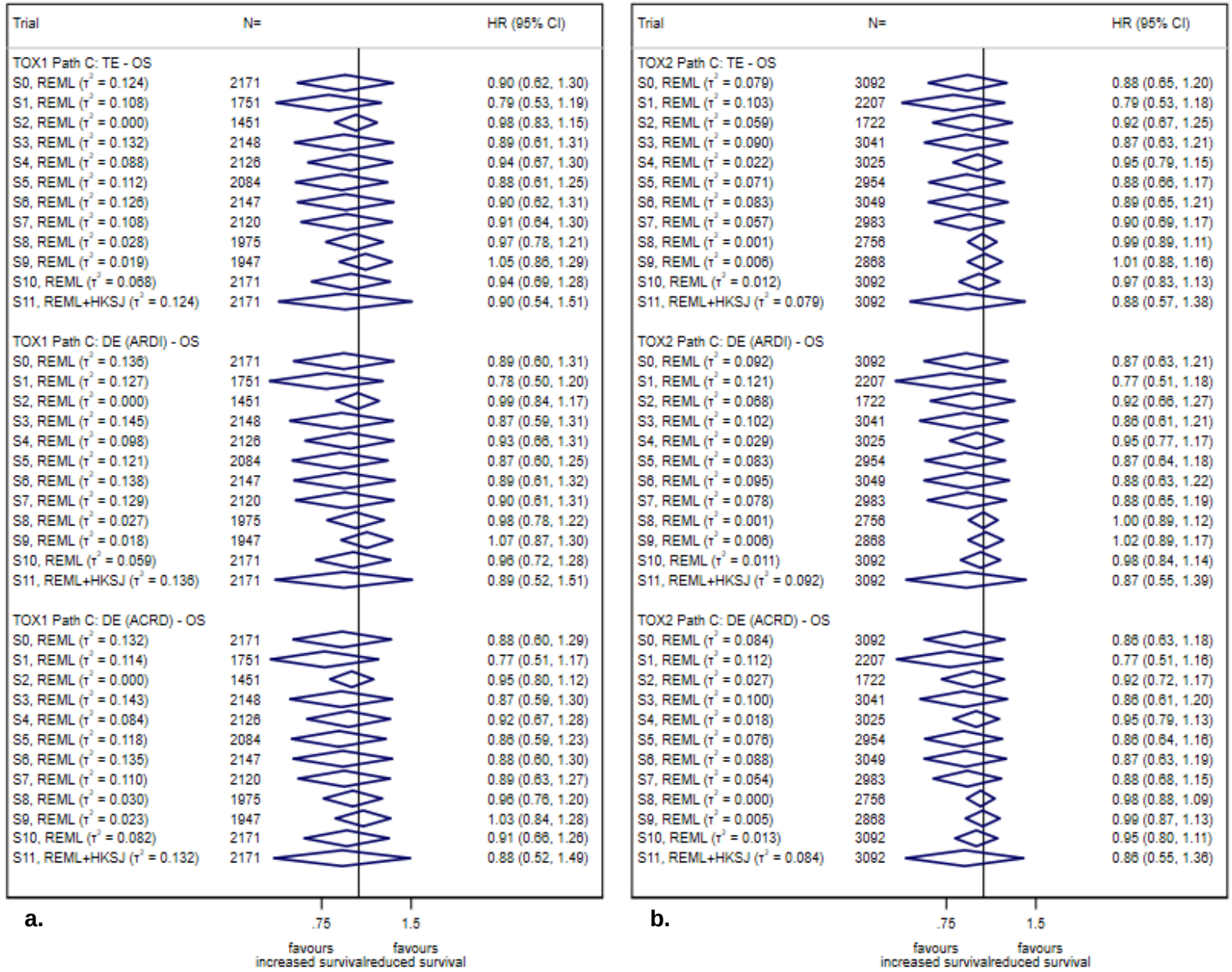


Figure A5.29a | Path *c* (DFS) sensitivity analysis - Main

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on disease-free survival for the main population.

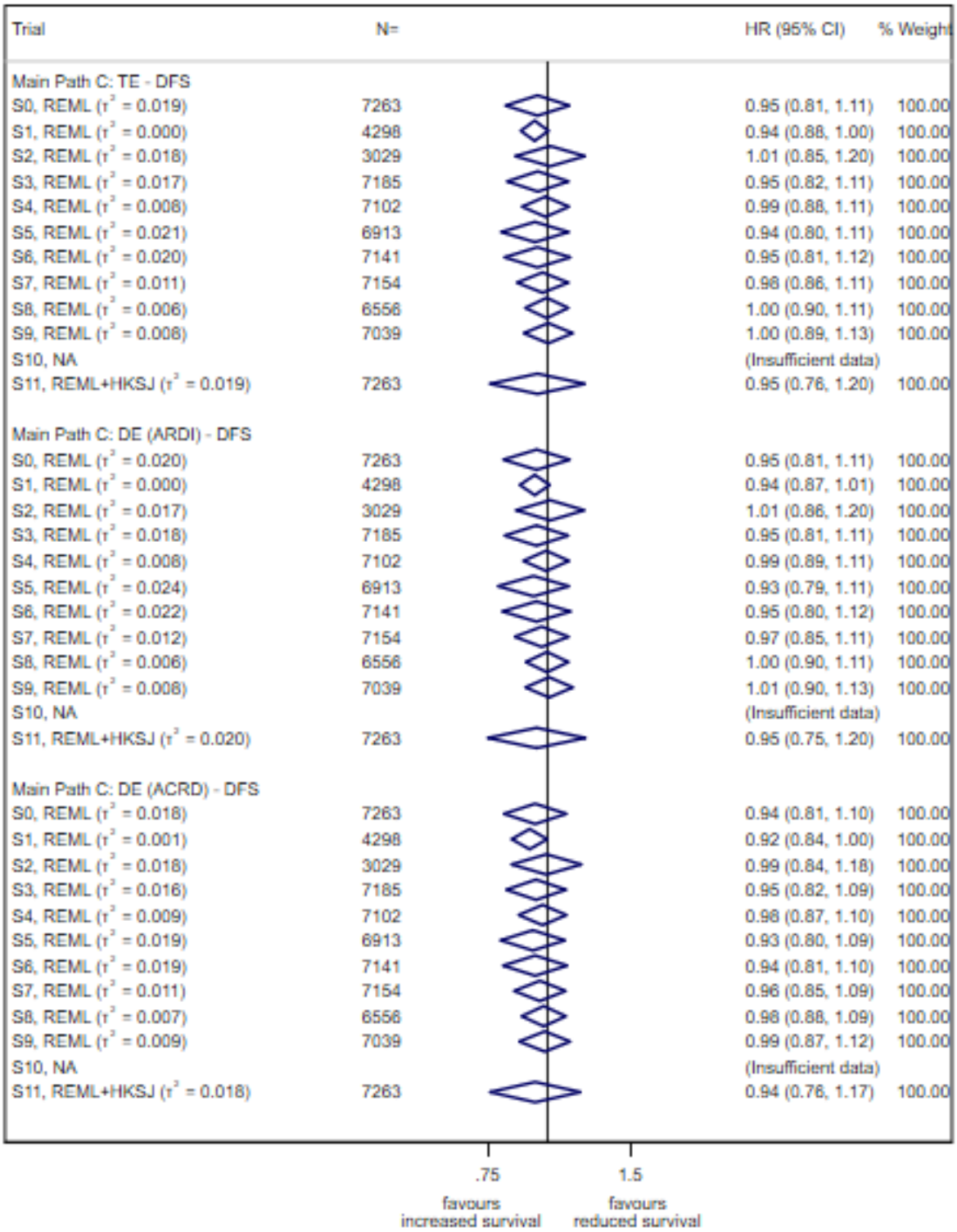


Figure A5.29b | Path *c* (DFS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on disease-free survival for the **a.** TOX1 and **b.** TOX2 populations.

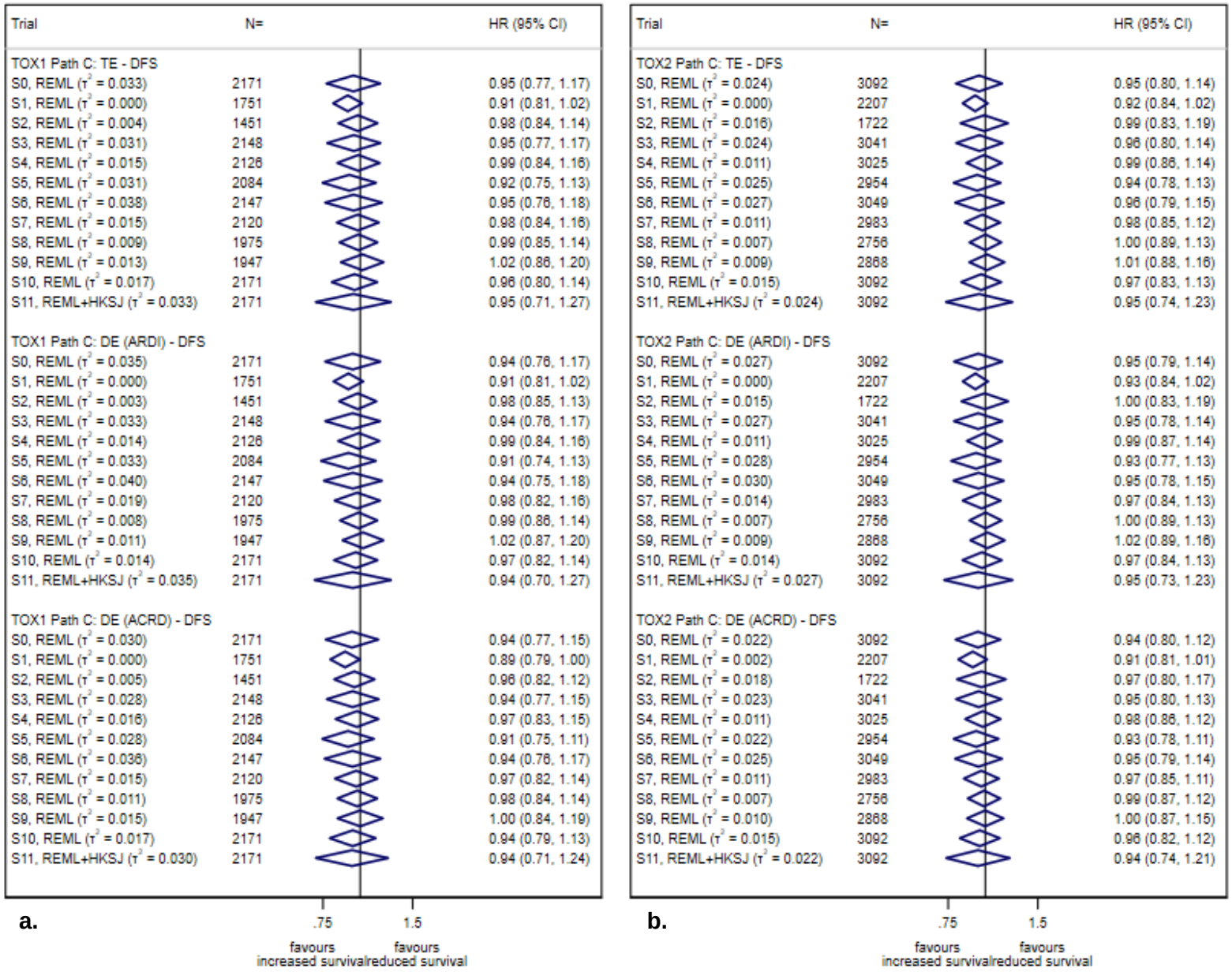


Figure A5.30a | Path *c* (CSS) sensitivity analysis - Main

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on cancer-specific survival for the main populations.

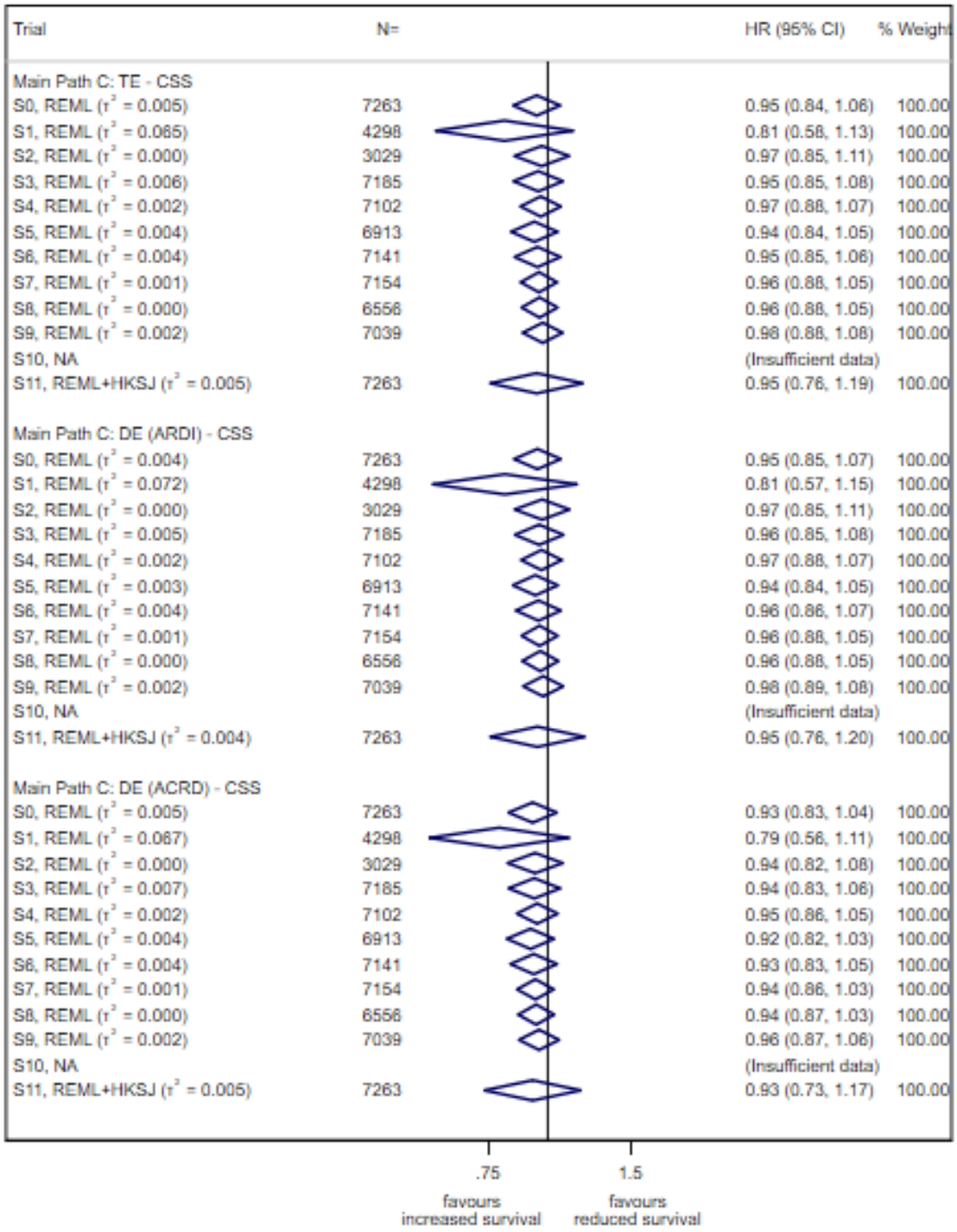
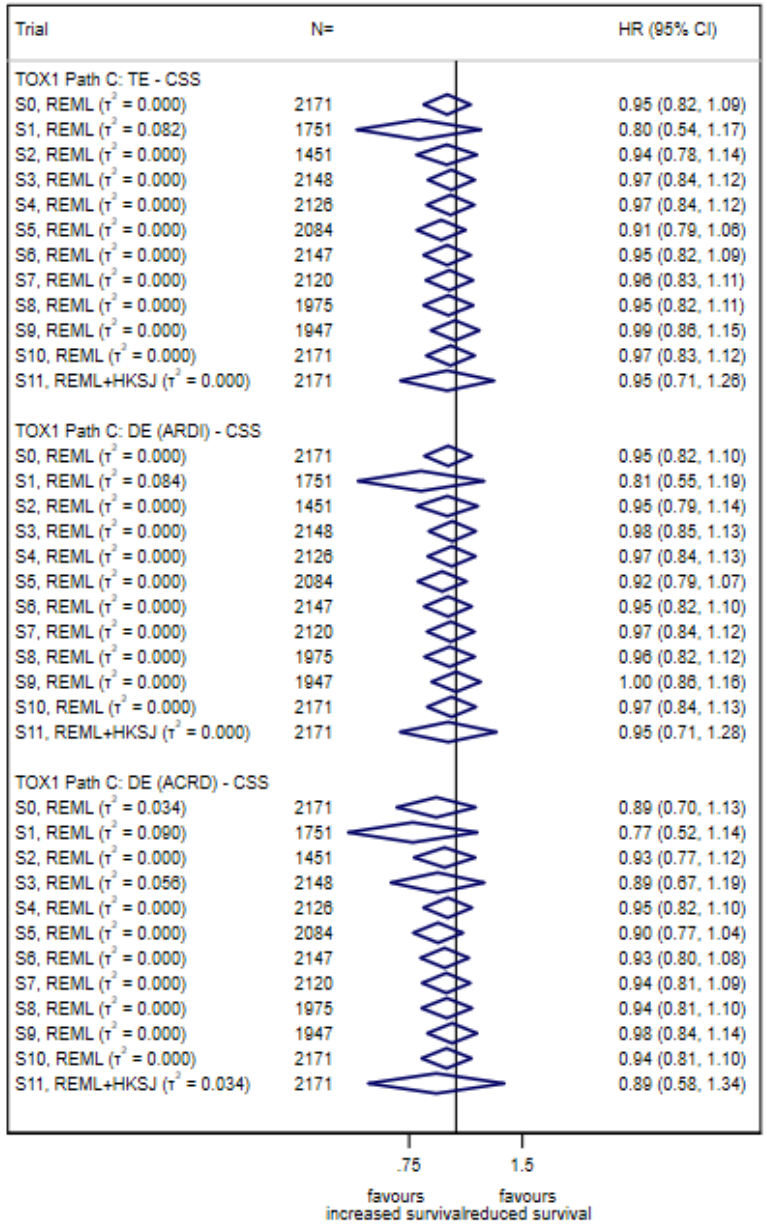
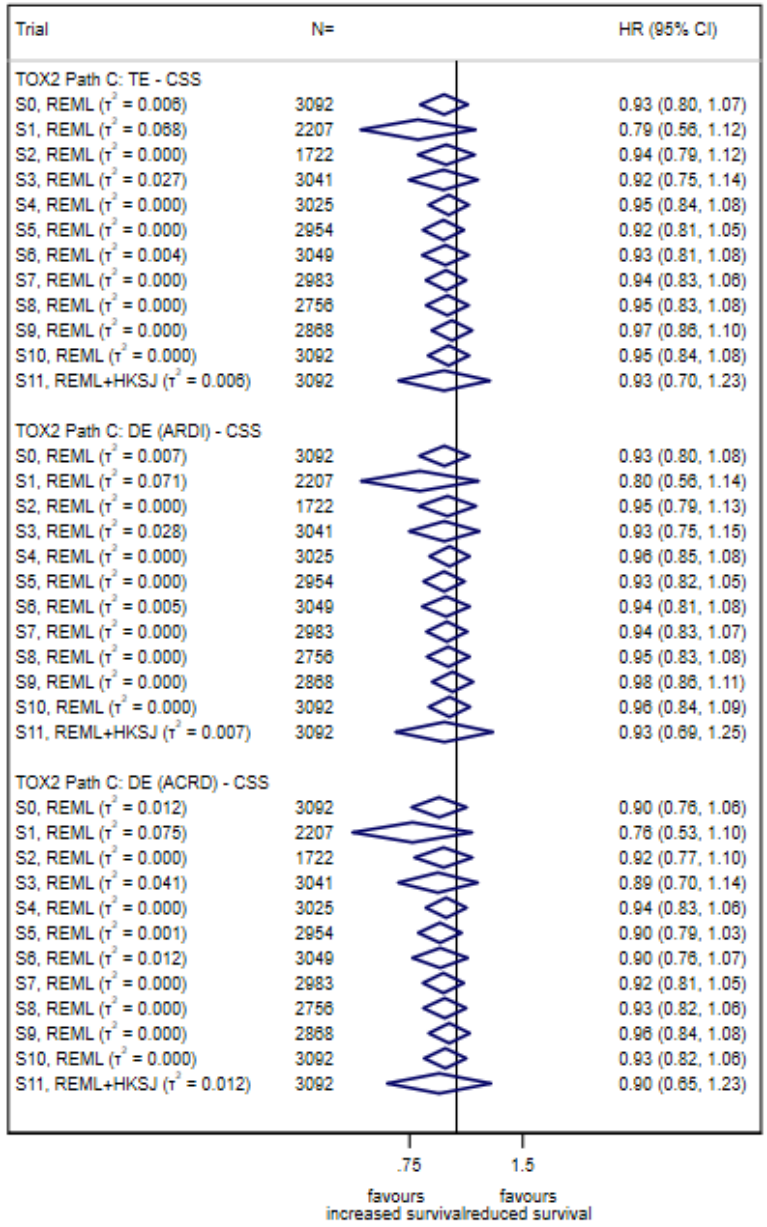


Figure A5.30b | Path *c* (CSS) sensitivity analysis - Tox

Forest plot demonstrating the sensitivity analyses summary effect estimates of the total and direct effects of BMI on cancer-specific survival for the **a.** TOX1 and **b.** TOX2 populations.



a.



b.

Table A6.1 | Path *c* 3-year overall survival (toxicity populations) - Paramed

Trial-level results of path *c* mediation analyses using the paramed command in Stata for TOX1 and TOX2 populations. Results are demonstrated for models including toxicity as a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the odds ratio scale (OR) and confidence intervals are calculated with bootstrapping methods.

			ARDI				ACRD			
			Path C		Path C Biased		Path C		Path C Biased	
Trial & Population		Effect	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SCOT_3M	TOX1	CDE	1.542	(0.978, 2.233)	1.427	(0.947, 2.082)	1.428	(0.943, 2.105)	1.380	(0.930, 2.032)
		NIE	0.955	(0.865, 1.006)	0.974	(0.894, 1.011)	1.021	(0.995, 1.102)	1.017	(0.992, 1.095)
		TE	1.473	(0.924, 2.195)	1.389	(0.901, 2.024)	1.458	(0.948, 2.129)	1.403	(0.941, 2.051)
	TOX2	CDE	1.164	(0.909, 1.417)	1.133	(0.891, 1.367)	1.119	(0.890, 1.372)	1.100	(0.883, 1.353)
		NIE	0.978	(0.948, 1.004)	0.985	(0.958, 1.005)	1.017	(1.000, 1.049)	1.015	(0.992, 1.048)
		TE	1.139	(0.887, 1.402)	1.116	(0.884, 1.357)	1.138	(0.904, 1.393)	1.117	(0.894, 1.371)
SCOT_6M	TOX1	CDE	0.902	(0.599, 1.380)	0.910	(0.605, 1.363)	0.902	(0.592, 1.377)	0.899	(0.600, 1.350)
		NIE	0.970	(0.883, 1.002)	0.969	(0.883, 1.001)	0.975	(0.873, 1.020)	0.980	(0.880, 1.025)
		TE	0.875	(0.563, 1.280)	0.882	(0.583, 1.275)	0.879	(0.545, 1.352)	0.882	(0.574, 1.331)
	TOX2	CDE	0.811	(0.616, 1.059)	0.821	(0.622, 1.070)	0.822	(0.616, 1.062)	0.828	(0.631, 1.075)
		NIE	0.989	(0.961, 1.006)	0.990	(0.962, 1.006)	0.975	(0.929, 1.010)	0.975	(0.924, 1.012)
		TE	0.802	(0.611, 1.055)	0.812	(0.622, 1.063)	0.801	(0.601, 1.035)	0.807	(0.608, 1.037)
PS	TOX1	CDE	0.530	(0.067, 2.641)	0.538	(0.083, 2.697)	0.442	(0.095, 2.671)	0.425	(0.113, 1.725)
		NIE	0.918	(0.009, 1.084)	0.895	(0.009, 1.090)	1.180	(0.993, 1.770)	1.163	(0.990, 1.834)
		TE	0.487	(0.052, 2.657)	0.481	(0.056, 2.234)	0.522	(0.131, 3.953)	0.495	(0.149, 3.379)

Abbreviations: ARDI, average relative dose intensity; **ACRD**, average cumulative relative dose; **NDE** Natural direct effect; **NIE**, Natural indirect effect; **OR,** Odds ratio; **TE,** Total Effect;

[a] Path C – including toxicity modelled as a standard confounder.

[b] Path C Biased – modelled excluding toxicity as a confounder

Table A6.2 | Path *c* 3-year overall survival (toxicity populations) - gformula

Trial-level results of path *c* mediation analyses using the gformula command in Stata for the TOX1 and TOX2 populations. Results are demonstrated for models including toxicity as a time-varying confounder (path *c* - TVC), a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the odds ratio scale (OR) and confidence intervals are calculated with bootstrapping methods.

			ARDI						ACRD					
			Path C - TVC		Path C		Path C Biased		Path C - TVC		Path C		Path C Biased	
Trial & Population		Effect	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
SCOT_3M	TOX1	CDE	1.014	(0.958, 1.074)	**1.066**	**(1.005, 1.131)**	1.054	(0.995, 1.116)	1.022	(0.967, 1.079)	1.056	(0.997, 1.119)	1.041	(0.984, 1.102)
		NIE	0.993	(0.950, 1.037)	0.983	(0.941, 1.028)	0.993	(0.951, 1.036)	1.002	(0.961, 1.045)	1.005	(0.962, 1.049)	1.014	(0.972, 1.059)
		TE	1.007	(0.951, 1.067)	1.049	(0.991, 1.109)	1.046	(0.991, 1.104)	1.024	(0.969, 1.082)	**1.061**	**(1.005, 1.121)**	**1.056**	**(1.001, 1.115)**
	TOX2	CDE	**1.045**	**(1.006, 1.085)**	1.021	(0.983, 1.059)	1.000	(0.963, 1.038)	1.032	(0.995, 1.070)	1.019	(0.983, 1.057)	1.016	(0.979, 1.054)
		NIE	1.005	(0.975, 1.035)	0.997	(0.968, 1.027)	1.009	(0.979, 1.040)	1.000	(0.971, 1.030)	0.993	(0.964, 1.024)	0.987	(0.956, 1.018)
		TE	**1.050**	**(1.012, 1.090)**	1.017	(0.981, 1.055)	1.009	(0.973, 1.046)	1.032	(0.996, 1.070)	1.013	(0.976, 1.050)	1.002	(0.967, 1.039)
SCOT_6M	TOX1	CDE	1.014	(0.964, 1.067)	0.991	(0.943, 1.041)	0.998	(0.950, 1.047)	0.993	(0.945, 1.043)	0.979	(0.933, 1.028)	0.977	(0.931, 1.025)
		NIE	0.988	(0.952, 1.027)	0.998	(0.961, 1.036)	0.998	(0.961, 1.035)	1.007	(0.970, 1.045)	0.991	(0.956, 1.027)	0.998	(0.962, 1.035)
		TE	1.002	(0.957, 1.050)	0.988	(0.942, 1.037)	0.995	(0.949, 1.044)	1.000	(0.954, 1.048)	0.970	(0.926, 1.016)	0.975	(0.931, 1.021)
	TOX2	CDE	1.008	(0.973, 1.044)	1.000	(0.966, 1.035)	1.008	(0.973, 1.044)	1.025	(0.991, 1.061)	1.002	(0.968, 1.038)	0.999	(0.964, 1.035)
		NIE	0.995	(0.969, 1.023)	1.001	(0.974, 1.029)	1.002	(0.976, 1.029)	0.978	(0.951, 1.005)	0.998	(0.971, 1.025)	1.001	(0.974, 1.029)
		TE	1.003	(0.969, 1.039)	1.001	(0.967, 1.036)	1.010	(0.976, 1.045)	1.002	(0.969, 1.037)	1.000	(0.966, 1.035)	1.000	(0.966, 1.035)
PS	TOX1	CDE	0.972	(0.895, 1.055)	0.983	(0.906, 1.067)	0.983	(0.907, 1.065)	0.983	(0.913, 1.058)	0.994	(0.925, 1.069)	0.994	(0.926, 1.067)
		NIE	0.989	(0.942, 1.038)	1.017	(0.971, 1.066)	1.029	(0.980, 1.081)	1.006	(0.962, 1.051)	1.006	(0.962, 1.052)	0.994	(0.951, 1.039)
		TE	0.961	(0.889, 1.038)	1.000	(0.923, 1.083)	1.011	(0.937, 1.092)	0.989	(0.915, 1.068)	1.000	(0.927, 1.078)	0.989	(0.918, 1.065)

Table A6.3 | Path *c* overall survival (toxicity populations) – Regmedint

Abbreviations: ARDI, average relative dose intensity; **ACRD**, average cumulative relative dose; **NDE** Natural direct effect; **NIE**, Natural indirect effect; **OR,** Odds ratio; **TE,** Total Effect; **TVC,**

Time-varying confounding

[a] Path C TVC – including toxicity modelled as a time-varying confounder.
[b] Path C – including toxicity modelled as a standard confounder.
c Path C biased – modelled excluding toxicity as a confounder.

Trial-level results of path *c* mediation analyses using the regmedint package in R for the TOX1 and TOX2 populations. Results are demonstrated for models including toxicity as a normal confounder (path *c*) and excluding toxicity (path *c* biased). Outcomes are on the mean survival time ratio (MSR) scale [<1 worse survival; >1 improved survival] and confidence intervals are calculated with bootstrapping methods.

			ARDI				ACRD			
			Path C[a]		Path C Biased[b]		Path C[a]		Path C Biased[b]	
Trial & Population		**Effect**	**MSR**	**95% CI**	**MSR**	**95% CI**	**MSR**	**95% CI**	**MSR**	**95% CI**
SCOT_3M	**TOX1**	**CDE**	**0.803**	**(0.624, 0.989)**	0.825	(0.656, 1.010)	0.816	(0.640, 1.003)	0.828	(0.661, 1.007)
		NIE	1.006	(0.977, 1.043)	1.001	(0.975, 1.027)	0.991	(0.959, 1.011)	0.993	(0.964, 1.009)
		TE	**0.808**	**(0.631, 0.998)**	0.826	(0.661, 1.012)	**0.808**	**(0.631, 0.995)**	0.823	(0.651, 1.003)
	TOX2	**CDE**	0.886	(0.757, 1.040)	0.908	(0.781, 1.064)	0.908	(0.781, 1.058)	0.920	(0.797, 1.067)
		NIE	1.007	(0.997, 1.025)	1.003	(0.994, 1.017)	0.989	(0.970, 1.002)	0.991	(0.971, 1.006)
		TE	0.892	(0.764, 1.044)	0.911	(0.787, 1.065)	0.898	(0.770, 1.048)	0.912	(0.784, 1.060)
SCOT_6M	**TOX1**	**CDE**	1.046	(0.872, 1.317)	1.043	(0.870, 1.316)	1.060	(0.884, 1.324)	1.060	(0.883, 1.329)
		NIE	1.017	(0.997, 1.058)	1.018	(0.996, 1.059)	1.013	(0.980, 1.055)	1.011	(0.975, 1.051)
		TE	1.064	(0.888, 1.351)	1.061	(0.884, 1.343)	1.074	(0.890, 1.353)	1.071	(0.891, 1.354)
	TOX2	**CDE**	1.078	(0.913, 1.299)	1.073	(0.912, 1.298)	1.075	(0.911, 1.278)	1.073	(0.911, 1.275)
		NIE	1.006	(0.997, 1.023)	1.005	(0.997, 1.022)	1.016	(0.991, 1.048)	1.016	(0.989, 1.048)
		TE	1.085	(0.921, 1.311)	1.079	(0.916, 1.302)	1.092	(0.926, 1.308)	1.089	(0.923, 1.306)
PS	**TOX1**	**CDE**	**1.795**	**(1.178, 2.751)**	**1.803**	**(1.193, 2.741)**	**1.801**	**(1.205, 2.775)**	**1.805**	**(1.223, 2.758)**
		NIE	1.018	(0.963, 1.130)	1.015	(0.964, 1.121)	0.960	(0.868, 1.030)	0.960	(0.868, 1.027)
		TE	**1.827**	**(1.184, 2.832)**	**1.830**	**(1.193, 2.800)**	**1.728**	**(1.147, 2.708)**	**1.732**	**(1.156, 2.674)**

[a] Path C – including toxicity modelled as a standard confounder.

[b] Path C Biased – modelled excluding toxicity as a confounder