MEATBOLIC RISK FACTORS OF SUICIDAL BEHAVIOUR

EXPLORING METABOLIC FACTORS AND HEATLH-RELATED BEHAVIOURS IN RELATION TO SUICIDAL BEHAVIOUR

By

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ABSTRACT

Background: Suicidal behaviour devastates families, communities, and societies, as well as the millions of individuals who survive suicide attempts. This thesis addresses an urgent need to develop new treatment and intervention strategies for millions of at-risk people by exploring potential metabolic risk factors of suicidal behaviour including, BMI, waist-circumference, serum total cholesterol, physical activity, tobacco use, and diet.

Methods: A systematic review and meta-analysis was performed to assess the association between BMI and suicidal behaviour. The review was conducted in accordance with an *a priori* published protocol. We explored the association between attempted suicide and various metabolic factors and health behaviours using data from the Determinants of Suicide Conventional and Emergent Risk (DISCOVER) study. DISCOVER is an age and sex matched case-control study comparing adult psychiatric inpatients who had made a recent suicide attempt (n=84) to psychiatric inpatients (n=104) and community members (n=93) who have never attempted suicide. The following potential risk factors were assessed using logistic regression analyses: BMI, waist-circumference, serum total cholesterol, physical activity, tobacco use, and dietary food groups.

Results: The systematic review included 38 studies. A meta-analysis established an inverse association between BMI and completed suicide, whereby being underweight is associated with the greatest risk of suicide and being obese or overweight is associated with a deceased risk of suicide relative to normal weight. Evidence for an association between BMI and attempted suicide remains equivocal. The review suggests no association between BMI and suicidal ideation. Analysis of DISCOVER data

demonstrated that even a small amount of regular physical activity is significantly associated with decreased risk of attempted suicide. Tobacco use was associated with an increased risk of attempted suicide. Contrary to prior research, obesity, serum-total cholesterol, and diet were not found to be significant risk factors.

Conclusion: BMI is inversely related to completed suicide. Obese individuals may be more likely to choose less lethal methods of suicide or may be less susceptible to fatal overdose or self-poisonings. Clinicians should monitor underweight patients for increased risk of suicide. Contrary to prior research, serum total cholesterol, BMI, and waist-circumference were not significantly associated with risk of attempted suicide. Increased physical activity was associated with a decreased risk of attempted suicide, and tobacco use was associated with an increased risk of attempted suicide. While people at risk of attempting suicide tend to use more tobacco products and exercise less than non-suicidal community members, so do non-suicidal psychiatric patients. For this reason, it remains unclear whether smoking habits represent a useful clinical predictor of suicide risk.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DISCOVER	Determinants of Suicidal Behaviour: Conventional and Emergent Risk
EMBASE	Excerpta Medica DataBase
HR	Hazard Ratio
MINI	Mini Neuropsychological Interview
MOOSE	Meta-Analysis of Observational Studies in Epidemiology
NOS	New Castle Ottawa Scale
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary author of each study included in this sandwich thesis. I assumed the primary role in each study by developing the research questions, drafting the study protocols, planning and conducting the statistical analyses, and drafting each manuscript. Detailed explanations of each authors' contributions are presented at the end of each study.

CHAPTER 1

1.1 THESIS OBJECTIVES

Globally, every 40 seconds a life is lost to suicide, resulting in over 800,000 deaths by suicide each year.[1] In 2012, suicide was the second leading cause of death among 15-29 year olds worldwide.[1] In addition to personal suffering, suicide adversely affects families, friends, and communities. Non-fatal suicidal behaviours include ideas, thoughts, plans, and actions with underlying intent to end one's life.[2] Attempted suicide is common; approximately 10-25 suicide attempts occur for every completed suicide.[2,3] Those who survive a suicide attempt are at increased risk of long-term suffering from psychiatric and medical comorbidity, repeated suicide attempt, hospitalization, poor socioeconomic standing, and societal stigma.[4] Individuals who attempt suicide are at an especially increased risk of completing suicide within a year of the initial attempt.[5] In 2014, the World Health Organization published a report calling for an increase in suicide prevention efforts from a public health and research standpoint.[1] Considering the personal and public health burden that suicide has on a global and local scale, it is imperative to research emergent and conventional risk factors of suicidal behaviour and to integrate them into comprehensive preventative strategies.

Suicide risk assessment is based on a holistic evaluation of individual risk factors, warning signs, and protective factors that may mitigate the risk.[6] A theoretical framework

that encompasses psychological, biological, social, and environmental stressors is needed to understand suicidality. Psychological risk factors of suicidal behaviour include psychiatric and substance use disorders, especially major depressive disorder and alcohol dependence due to acute intoxication during an attempt and the adverse social repercussions associated with alcoholism.[7,8] Schizophrenia is also associated with greater rates of suicide compared with the general population.[9] Females are more likely to attempt suicide and males are up to four times as likely to complete suicide.[3] A family history of suicidality is thought to increase risk of suicide, suggesting a genetic predisposition.[10] Other suicide risk factors include major life stressors (e.g. grief, unemployment), personality traits (e.g. impulsivity and aggressiveness), and adolescent and elderly age.[10,11]

Several conventional risk factors of suicidal behaviour are not modifiable nor predictive in clinical settings, and novel risk factors need to be studied in order to aid the identification of suicide risk. This thesis combines two studies exploring the association between metabolic or health-related factors and suicidal behaviours. The papers included are published or currently submitted for publication. The first two papers explore the association between body mass index (BMI) and suicidal behaviour. The third paper is a case-control study exploring potential associations between metabolic factors or health-related behaviours with attempted suicide, including, BMI, waist circumference, serum total cholesterol, tobacco use, physical activity, and dietary food groups.

The first study is comprised of two parts. Study 1 Part I (Chapter 2) is a systematic review protocol that documents *a priori* established methodology for Study 1 Part II (Chapter 3),

a systematic review and meta-analysis of the association between BMI and suicidal behaviour. Chapter 2 (the review protocol) is currently published in Systematic Reviews.[12] A growing body of literature suggests that BMI may play a role in quantifying the risk of suicidal behaviour,[13-15] albeit controversially. Therefore, a review and meta-analysis was conducted to systematically summarize and evaluate the literature to establish an association between BMI and risk of suicidality. Body weight is a modifiable factor and may have clinical use in identifying and mitigating suicide risk. A secondary objective of the review was to identify potential effect modifiers that may modify the association between BMI and suicidal behaviour (e.g. sex differences, differential selection of suicide method). The second paper in this thesis (Chapter 4) is a case-control study exploring the association between several metabolic factors or health-related behaviours in relation to attempted suicide, including BMI, waist-circumference, serum total cholesterol, physical activity, diet, and tobacco use. The study compares individuals who have made a recent suicide attempt with psychiatric inpatients and community members with no history of attempted suicide. We aim to explore associations with modifiable health behaviours that can aid prediction and rehabilitation in treatment settings.

FIGURES AND TABLES 1.2

Figure 1.2.1 Thesis Theoretical Framework

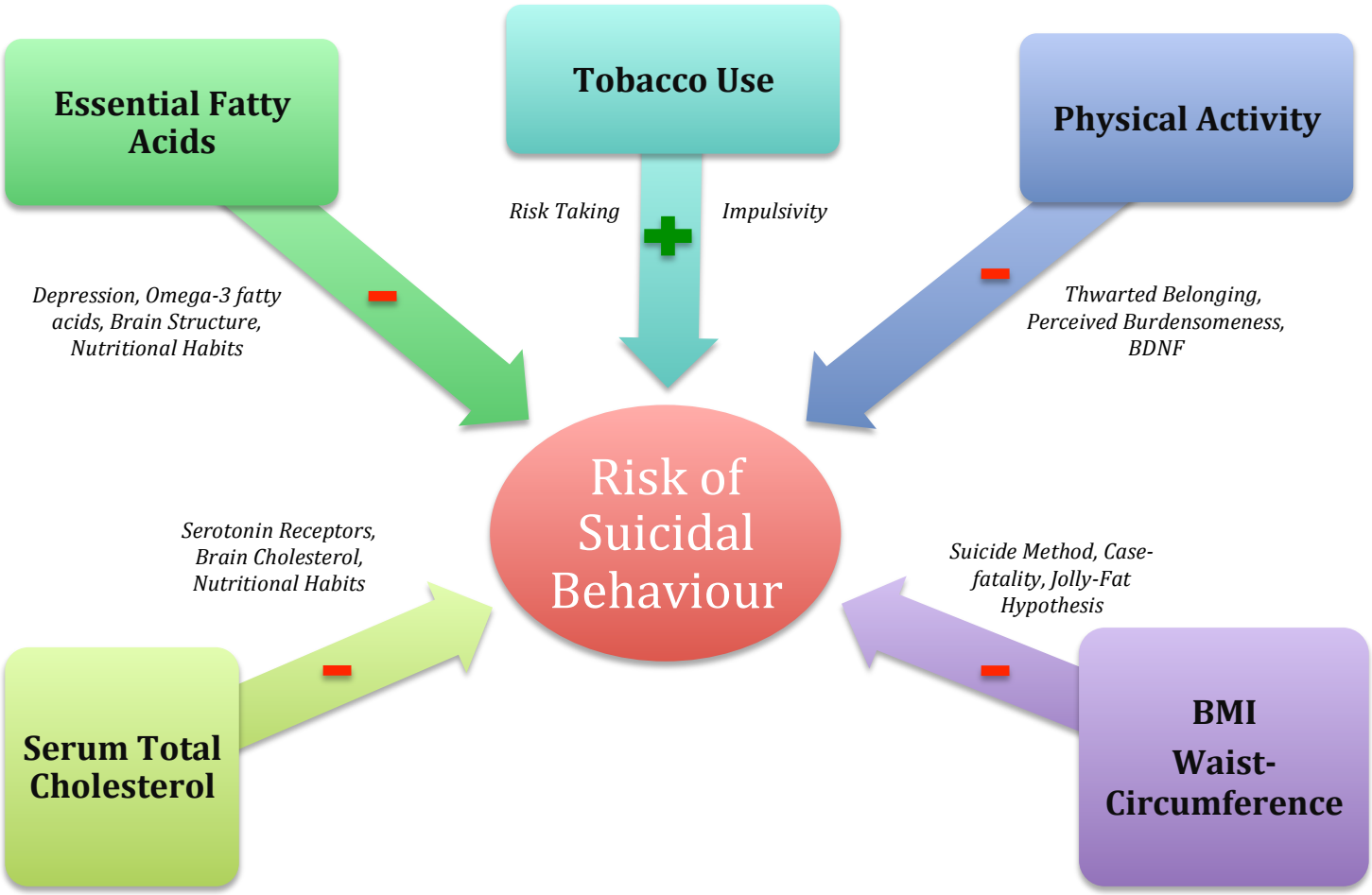

Figure 1.2.1- Thesis theoretical framework. The plus or minus signs indicate the hypothesized direction of association between each bolded metabolic factor and risk of suicidal behaviour. The words listed in italics are potential factors that may explain or mediate the association between each metabolic factor and risk of suicidal behaviour. Arrows are meant to represent a potential association and not necessarily a linear association.

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CHAPTER 2

Study 1 Part 1

Association between body mass index and suicidal behaviours: a systematic review protocol

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Publications

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This publication is located in appendix item i.

2.1 ABSTRACT

Background: Suicide is among the leading causes of death worldwide. Suicide attempts and suicidal ideation are more common than completed suicide and are associated with psychological distress. These behaviors are considered risk factors of completed suicide. Considering the psychosocial stigma and medical comorbidities associated with obesity, an accumulating body of studies have investigated body mass index (BMI) as a potential risk factor of suicide. However, several cohort studies have demonstrated an inverse relationship between BMI and completed suicide, suggesting a protective effect of increasing BMI against completed suicide. The association between BMI and attempted suicide is more equivocal, with several studies reporting both positive and negative relationships between BMI and attempted suicide. The primary objective of this study is to systematically review the literature to determine the association between BMI and suicidal behavior (including completed suicide, attempted suicide, suicidal ideation) in an adult population (18 years and older). The secondary objective is to explore whether sex, age, and the method used in suicide modify the relationship between BMI and suicidal behavior.

Methods/design: An electronic search will be conducted using PubMed/MEDLINE, PsycINFO, CINAHL, and EMBASE using a predefined search strategy; databases will be searched from their inception. Two authors (SP and RE) will independently screen articles using predefined inclusion and exclusion criteria and will extract pertinent data using a pilot tested extraction form. At all levels of screening, discrepancies between the two authors will be resolved by consensus, and in the case of disagreement, by consulting

a third author (ZS). The primary outcomes include the association between BMI and completed suicide, attempted suicide, and suicidal ideation. If appropriate, a meta-analysis will be conducted. Risk of bias and quality of evidence will be assessed.

Discussion: The results of this systematic review will inform health care professionals and researchers about whether BMI has a significant role in suicidal behavior and psychological well-being.

Systematic review registration: PROSPERO CRD42014014739.

2.2 INTRODUCTION

Suicide is a significant problem throughout the world, impacting society from a public health, community, individual, and often a family perspective. Globally, over 800,000 lives are claimed by suicide each year.[1] Suicide is a complex phenomenon and requires evidence-based guidelines designed to recognize and mitigate modifiable risk factors. A previous suicide attempt is considered a significant predictor of completed suicide in the general population.[2,3] Attempted suicide occurs 10 to 20 times more frequently than completed suicide.[4] Suicidal behaviors entail a complex set of ideas, thoughts, plans, and actions, which imply intention to end one's life.[5] There are several well-established risk factors that collectively affect an individual's vulnerability to suicidal behavior, including, psychiatric and substance use disorders, lack of social support, family environment (for example, disrupted marital status), the occurrence of a major life stressor (for example, unemployment, grief), and various demographic factors, including young and elderly age, as well as greater risk of attempted suicide among females and a greater risk of suicide completion among males.[4-7] Novel potential risk factors including biological markers, such as serum cholesterol,[8] and physical measurements, such as body weight, have yet to be fully elucidated in their potential impact on suicide. The present systematic review will focus on the association between body mass index (BMI) and suicidal behavior, including completed suicide, attempted suicide, and suicidal ideation. The number of obese and overweight people worldwide has dramatically increased over the past three decades, with the number of overweight and obese adults and children rising from approximately 857 million individuals in 1980 to

2.1 billion in 2013.[9] Excess body mass is a known risk factor of chronic illness, including cardiovascular disease, type 2 diabetes, osteoarthritis, and hypertension.[10,11] Furthermore, being overweight or obese is associated with social stigma among certain cultures, and negative attitudes towards obese individuals are evidently present in North American society.[12-14] As the prevalence of obesity rises globally,[9] it is important to investigate the psychosocial burden that adiposity may have on affected individuals. Thus, an emerging body of research has attempted to investigate the relationship between BMI and suicidal behavior. Collectively, these investigations have recruited samples across all weight groups, from underweight to morbidly obese individuals. The majority of such studies have used BMI as a measure of relative body weight and as a marker of adiposity.[15-21] Considering the psychosocial stigma[14] and health related complications[10] of obesity, several systematic reviews and meta-analyses have suggested a positive association between obesity and depression.[22-24] Furthermore, about 60% of suicides occur among individuals with mood disorders,[4] and 10% to 20% of patients hospitalized for depression complete suicide.[25] If obesity is indeed positively associated with depression, one might expect that a greater number of completed suicides are occurring among overweight and obese individuals. Surprisingly, however, several retrospective cohort studies have reported an inverse association between completed suicide and BMI, often in a dose-response type pattern, with the risk of suicide diminishing per unit increase in BMI.[15-18,21,26] The inverse association between suicide and BMI has been replicated in different countries using adult samples, albeit using predominantly male and Caucasian cohorts, including Swedish male conscripts,[15] United States' (US) male healthcare professionals,[21]

Norwegian men and women from a community cohort,[18] a cohort of Danish men using conscription data,[19] and a US general population cohort.[17] An American ecological study reported that statewide obesity rates were inversely correlated with rates of completed suicide,[27] and another ecological study conducted in the United Kingdom[28] similarly reported this inverse relationship in elderly females but found no such association among elderly males. Newer studies have since replicated an inverse relationship between BMI and completed suicide using longitudinal cohort designs,[29,30] as well as with a case-control post-mortem investigation.[31] However, some studies have reported either no association,[32-34] a J-shaped association,[35] or a positive association between BMI and competed suicide.[20,36] A recent case-control post-mortem investigation[33] conducted in Australia found no association between BMI and completed suicide, failing to replicate the results of the aforementioned post-mortem design[31] out of Germany.

Two recent longitudinal studies using Taiwanese[35] and German[36] cohorts reported a J-shaped and a positive relationship (respectively) between BMI and suicide. In summary, while many of the aforementioned studies point towards an inverse relationship between BMI and risk of completed suicide, the relationship remains equivocal and may depend on demographics such as sex or ethnicity. Moreover, the potential explanations for this apparent paradoxical inverse relationship remains unclear, with authors suggesting several potential mediating or correlative factors including impulsivity and case-fatality in relation to the chosen method of suicide,[26,37] serum levels of cholesterol and its relation to central serotonin,[8] leptin and leptin resistance,[38,39] an insulin resistance based model,[40] and dietary factors such as essential fatty acid intake.[41]

The relationship between BMI and attempted suicide is also inconsistently reported with fewer studies compared to completed suicide.[19,29,34,42-51] Cohort studies have demonstrated a decrease in risk for attempted suicide associated with increasing BMI,[19,29,34,45] while other studies have found a positive association between overweight and obese and suicide attempt.[42,43,47,48,51] Many of the studies examining BMI and attempted suicide are cross-sectional in design,[42,44,46-49] thus precluding the ability to infer temporal or causal pathways. Furthermore, sex may complicate the relationship between suicide attempts and BMI, as sex was an apparent effect modifier in some reports.[42] Additionally, suicidal ideation may have a different association with body weight. Only a few studies have examined the relationship between relative body weight and suicidal ideation,[42,47,48,50,52] limiting our ability to draw any conclusions. Two previous reviews have been published regarding the relationship between body weight and suicidal behavior.[53,54] One review provided a systematic review of the literature;[53] the other provided a narrative summary.[54] Both reviews cited that the collective studies were too few in number and heterogeneous to conduct a meta-analysis. Each review conducted a literature search up to 2011, and Klinitzke[53] did not include any studies published prior to January 2000. These reviews limited their searches to papers published in English, and Zhang[54] limited their search to PubMed only, precluding the inclusion of relevant articles from other databases. Zhang[54] did not present reasons for exclusion at each level of screening. Zhang reported on both adolescent and adult populations, and they classified some studies as using adult populations despite such studies including individuals as

young as 15.[55,56] The inclusion of both adolescents and adults is viewed critically due to differences in psychosocial development and differences in risk factors for suicide.

Since the conduct of these reviews, several observational studies have been published that have investigated body weight in relation to suicidal behavior,[29-31, 33-36,48-52] and an updated systematic review is required to contextually interpret the evidence. In addition, few studies included women in their samples when investigating BMI and suicidal behavior, and therefore, a more inclusive review will also help in understanding the association between BMI and suicidal behavior and the potential variation by sex.

2.2.1 Objectives

The present systematic review aims to elucidate the association between body mass index and suicidal behavior. More specifically, the review aims to answer the following research question: Is there a significant association between body mass index (BMI) and suicidal behavior (including completed suicide, attempted suicide, suicidal ideation) in an adult population (18 years and older)? A secondary objective will be to summarize evidence for specific factors including sex, age, and the method used in suicide to assess whether such variables modify the relationship between BMI and suicidal behavior.

2.3 METHODS/DESIGN

2.3.1 Inclusion and exclusion criteria

The present systematic review will include published observational studies that have reported results relating BMI to suicidal behaviors, including completed suicide, attempted suicide, and suicidal ideation, among an adult population defined as those who are 18 years or older. This adult population may include participants from population, clinical, and community-based samples. Considering that 90% of suicides occur in the context of a psychiatric disorder,[4] adults from clinical samples who have a psychiatric disorder will be included as well. Other than age, no demographic limitations will be applied. Studies investigating the risk of suicide following medical treatments of obesity such as bariatric surgery or pharmacotherapy for weight loss will be excluded as the effects of medically induced weight change may affect the risk of suicidal behavior independently of BMI. The primary outcome for this review is suicidal behavior, which includes suicidal ideation, attempted suicide, and completed suicide. These outcomes are further defined in Table 2.3.1, which highlights how they were described and measured in the literature.

2.3.2 Search strategy

All relevant studies will be sought and identified without any restrictions on language or time of publication. The following databases will be searched from inception: PubMed/MEDLINE, PsycINFO, EMBASE, and CINAHL. Pertinent keywords and search terms including the associated medical subject headings (MeSH) will be used in a

predefined search strategy outlined in Table 2.3.2. The search will be limited to human studies. A broad search will be conducted including titles, abstracts, and keyword fields to capture studies whose title may not directly reflect the topic being investigated. Additionally, the reference lists from retrieved full-text articles and past reviews will be manually scanned for a more comprehensive search, and Cochrane review bibliographies will be hand searched. Reviews, commentaries, abstracts, and gray literature will be excluded.

2.3.3 Data screening

Two independent raters (SP and RE) will screen all citations and abstracts retrieved using the search strategy outlined in Table 2.3.1, and they will subsequently identify all eligible articles according to pre-established criteria for full-text review. Discrepancies throughout the review process will be resolved by discussion and reevaluation. In cases where a consensus is not reached, a third author (ZS) will determine eligibility. Ineligible studies will be excluded from full-text review, and the reasons for exclusion will be documented. Inter-rater agreement will be calculated using the Kappa statistic[57] for each phase of screening. Authors of the included studies will be contacted if further data clarification is required.

2.3.4 Data extraction

The two raters (SP and RE) will independently extract data from the studies using a premade data extraction form that will be pilot tested before screening (see Additional file

1). The information collected will include the first author and year of publication, the name of the journal, the study title, the study design, the city and country of publication, the type of the study (for example, survey, cohort), and a brief description of study participants including the number of men and women, the number of completed suicides and attempted suicides when appropriate, mean age, and ethnicity. A summary of each study's results will be reported including the primary and secondary outcome measures, statistical analysis, and major conclusions. Authors will be contacted in the event of missing or incomplete data for clarification. If the extracted data are deemed to be suitable for a meta-analysis, individual study results will be combined to produce a summary estimate using a random-effects model as a certain degree of heterogeneity in included studies is expected.

2.3.5 Risk of bias assessment

The two independent raters (SP and RE) will independently assess the risk of bias of studies included in the full-text review using the Newcastle-Ottawa scale (NOS).[58] An adapted version of a modified NOS developed by Bawor et al.[59] will be used to assess risk of bias of observational studies included in this review. Bawor et al.'s modified NOS includes seven questions among four domains of risk assessment: methods for selecting study participants (selection bias), methods to control for confounding (performance bias), statistical methods (detection bias), and methods of exposure and outcome assessment (information bias). Risk of bias will be measured using a scale ranging from 0 (high risk of bias) to 3 (low risk of bias), and question specific descriptions including examples of varying degrees of bias are included. Furthermore, categories pertaining to

statistical methods, confounding effects, and reporting of missing data are included in this modified NOS to evaluate risk of biased methodology. Items from the original NOS pertaining to adequacy of follow-up, selection of participants (representativeness of sample), and ascertainment of outcomes, will be retained in the present adapted modified NOS, as these criteria are important to potential studies that may be included in our review.

2.3.6 Statistical analysis and heterogeneity

The findings of this systematic review will be presented as a qualitative summary of the literature, and as a quantitative summary estimate, if possible. In order to determine the quality and validity of existing evidence on BMI and suicidal behavior, the results of each study will be individually and collectively assessed in terms of their study design, statistical methods, and conclusions. The I^2 test statistic will be used to assess heterogeneity. An I^2 value greater than 40% will be used to define substantial heterogeneity; however, regardless of the amount of heterogeneity across studies, a random-effects model will be employed when pooling the data in a meta-analysis. The random-effects model accounts for both within-study and between-study variability and it generally represents a more conservative estimate than a fixed-effects model.[60] Three separate meta-analyses will be conducted to investigate the association between BMI and completed suicide, BMI and attempted suicide, and BMI and suicidal ideation. To qualitatively assess heterogeneity, we will assess differences and similarities with respect to study samples, methods, and results. The definition of outcome may act as an additional source of heterogeneity, especially that of attempted and completed suicide (for

example, deaths classified as overdoses). As previously mentioned, women have a higher rate of attempted suicide in the general population, while men have a higher rate of completed suicide.[4] Therefore, the role of sex will be explored by stratifying results for males and females. Furthermore, it has been suggested that one's BMI may indirectly influence one's inclination towards a particular method of suicide, thus affecting the case-fatality of a suicidal act. For example, in a retrospective cohort study of over one million Swedish male conscripts,[45] Batty et al. reported a stepwise inverse association of decreasing attempted suicide with increasing BMI. However, they noted that the strongest associations were with those methods generally requiring greater physical exertion and agility, such as hanging and jumping. These methods may be less likely to be used by those with greater BMI. Moreover, case-fatality of self-poisonings may be lowered among those with greater BMI due to greater body size and distribution of body fat.[37,45] Therefore, the role of the method used in attempted and completed suicides will be qualitatively commented on as a potential effect modifier of the relationship between BMI and attempted and completed suicide. Lastly, age will be qualitatively examined as a potential effect modifier. Medical comorbidity such as cancer that is associated with older age, weight loss, depression, or suicidal ideation, may produce a different relationship between BMI and suicidal behavior among the young and elderly.[37] Furthermore, changes in muscle mass associated with aging may result in a less accurate assessment of obesity using BMI among the elderly.[21]

Review Manager 5.3 (The Cochrane Collaboration, London, UK) will be used for all statistical and pooled analyses. The results of the pooled analysis will be summarized by calculating odds ratios [ORs] or hazard ratios [HRs] and 95% confidence intervals.

2.3.7 Presenting and reporting of results

Our systematic review will be conducted and written in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[61] A summary flow chart will be used to outline the selection of articles and to display reasons for excluding articles (Figure 2.3.6). Summary tables will be used to present the relevant outcomes and details of each included study. Egger's plot will be used to assess potential publication bias among the selected studies. If the studies included in our systematic review are deemed suitable for pooling in a meta-analysis, the results of each analysis will be presented in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[62] Forrest plots will be used to present individual and pooled study estimates, and tables will be used to summarize individual study characteristics.

2.4 DISCUSSION

Body mass index may represent an important risk factor for suicidal behavior. The proposed systematic review will help to elucidate the association between BMI and suicidal behavior, allowing for better understanding of the controversial association between BMI and suicidal behavior. The paradox of an apparent inverse relationship between completed suicide and BMI remains to be solved. Several potential mediators, modifiers, or confounders that explain the latter association may be identified when viewing the literature systematically. BMI appears to be differentially related to completed suicide and attempted suicide, and clarifying this association may help to better understand separate etiologies that distinguish completed from attempted suicide.

2.5 ACKNOWLEDGEMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS

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2.6 FIGURES AND TABLES

Figure 2.3.6. : PRISMA Flow Diagram of Study Screening

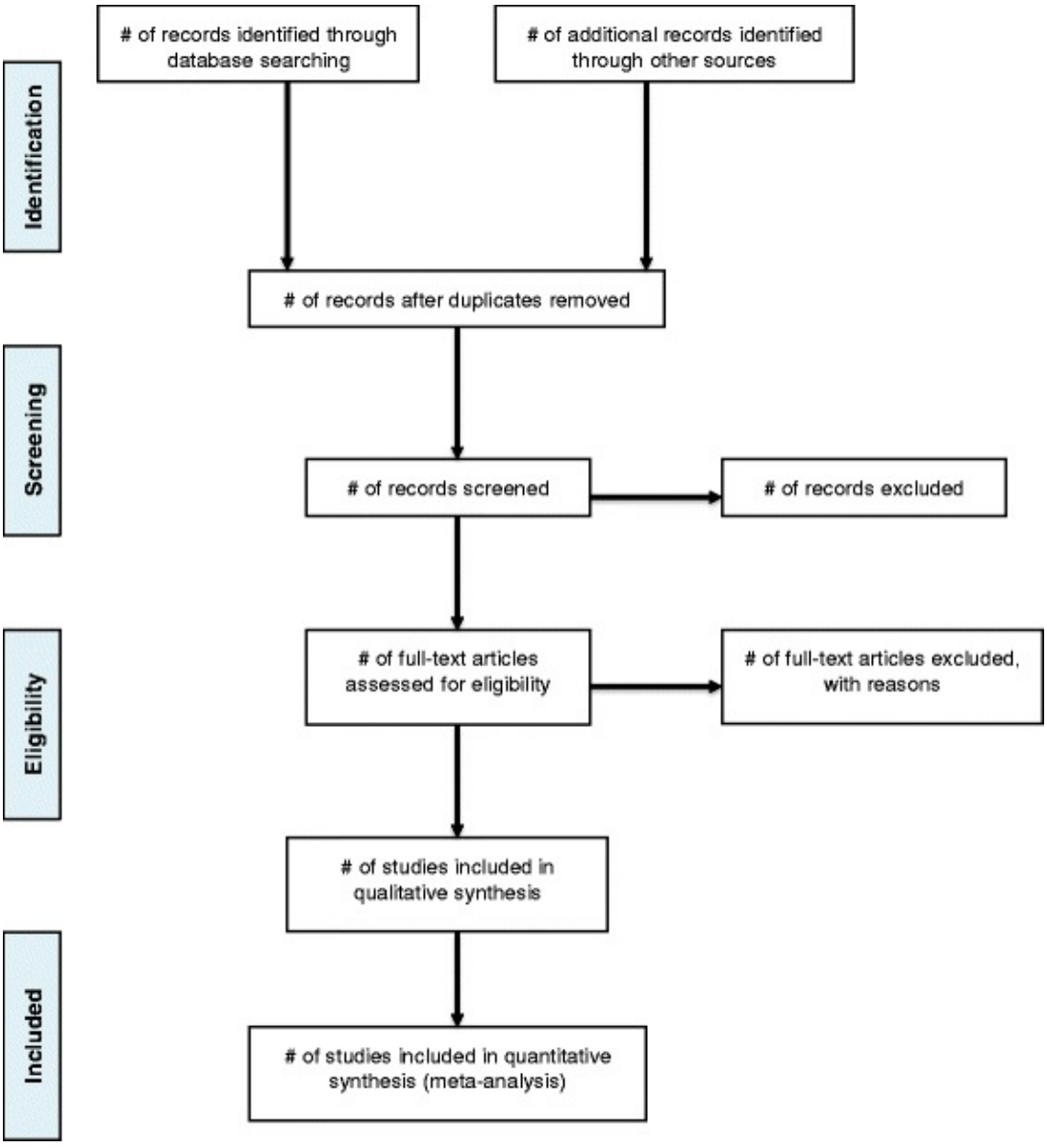

Table 2.3.1: Definitions and Statistical Measures of Suicidal Behaviours Outcomes

Outcome	Definition	Measurement of Variable	Statistics	Studies
Completed Suicide	Death caused by self-inflicted injurious behavior intended to end one's own life.	International Classification of Diseases (8^{th}. 9^{th}, or 10^{th} revisions) using diagnostic codes (E950-E950: ICD8, ICD9) or (X60-X84: ICD10). In some studies, associations were also estimated with undetermined deaths (deaths where it was uncertain whether the cause was suicide; (E980-E989: ICD 8, ICD 10) or codes (Y10-Y34, ICD 10). Verified using mortality registries (e.g. National Death Registry, National Death Index), by next of kin, and/or using pathology and medical records.	Cox proportional hazard model Linear regression Logistic regression Pearson Correlation (Ecological Analysis) Spearman's Rank Correlation (Ecological Analysis) Chi-square Wilcoxon-Mann-Whitney Test Incidence Rate Ratio	[15-21, 26-28, 32] *2012-present:* [29-31, 33-36]
Attempted Suicide	Potentially self-injurious behavior with a non-fatal outcome for which there is either explicit or implicit evidence that the person intended to kill him or herself.	Hospital Discharge Registries or Medical Records using aforementioned diagnostic codes for intentional injuries: (E950-E950: ICD8, ICD9) or (X60-X84: ICD10). Self-reported using questionnaire (E.g. Suicide Behaviours Questionnaire-Revised, AUDADIS, M-CIDI) Self-Reported using single-question (e.g. "How often have you already tried to take your own life)	Cox Proportional Hazard Model Logistic Regression Incidence Rate Ratio	*2012-present:*
Suicidal Ideation	Having thoughts, plans, and/or impulses for suicidal behavior, including contemplation of attempting or completing suicide.	Self-reported using questionnaire (E.g. Depressive Symptom Index-Suicidality Subscale, Suicide Behaviors Questionnaire-Revised).	Logistic Regression Linear Regression	

Table 2.3.2: Electronic Search Strategy

Data Base	Search Strategy
MEDLINE (n=837)	1. exp Suicide/ or suicid*.mp. 2. exp Self-injurious behavior/ or self-harm.mp. 3. exp Body Mass Index/ or body mass index.mp. 4. BMI.mp. 5. exp Body Weight/ body weight.mp. 6. exp Obesity/ or obes*.mp. 7. exp Overweight/ or overweight.mp. 8. 1 or 2 9. 3 or 4 or 5 or 6 or 7 10. 8 and 9 11. limit 10 to humans
PsycINFO (n=666)	1. exp Suicide/ 2. exp Attempted Suicide/ or attempted suicide.mp. 3. exp Suicidal Ideation/ or suicidal ideation.mp. 4. suicid*.mp. 5. exp Self Injurious Behavior/ or self-harm.mp. 6. exp Body Mass Index/ or body mass index.mp. 7. exp Body Weight/ or body weight.mp. 8. exp Obesity/ or obes*.mp. 9. BMI.mp. 10. exp Overweight/ or overweight.mp. 11. 1 or 2 or 3 or 4 or 5 12. 6 or 7 or 8 or 9 or 10 13. 11 and 12 14. limit 13 to human
EMBASE (n=3688)	1. exp suicidal behavior/ or suicid*.mp. 2. exp automutilation/ or self-harm*.mp. 3. exp body mass/ body mass index.mp.

	4. BMI.mp. 5. exp body weight/ body weight.mp. 6. exp obesity/ or obes*.mp. 7. overweight.mp. 8. 1 or 2 9. 3 or 4 or 5 or 6 or 7 10. 8 and 9 11. limit 10 to human
CINAHL (n=144)	1. (MH "Suicide+") OR "suicid*" 2. (MH "Self-Injurious Behavior") OR "self-harm" 3. (MH Body Mass Index) OR "body mass index" 4. (MH "Body Weight+") OR "body weight" 5. (MH "Obesity+") OR "obes*" 6. "BMI" 7. "overweight" 8. 1 or 2 9. 3 or 4 or 5 or 6 or 7 10. 8 and 9 (limiters human)

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CHAPTER 3

Study 1 Part II

The Association Between Body Mass Index and Suicidal Behavior Depends on Type of Suicidal Behavior: A Systematic Review and Meta-Analysis

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3.1 ABSTRACT

Public health concerns for the independent management of obesity and suicidal behavior are rising. Emerging evidence suggests body weight may play an important role in quantifying the risk of suicide. In light of these findings we aimed to clarify the association between body mass index (BMI) and suicidal behavior by systematically reviewing and evaluating the literature. Studies were identified by searching MEDLINE, EMBASE, PsycINFO, and CINAHL from inception to January 2015, supplemented by hand and grey literature searches. Study screening, data extraction, and risk of bias assessment were conducted in duplicate. We included 38 observational studies. Meta-analyses supported an inverse association between BMI and completed suicide. A qualitative summary of the literature demonstrated conflicting evidence regarding the association between BMI and attempted suicide, and revealed no association between BMI and suicidal ideation. BMI may be used to aid the identification of suicidal behaviour, especially that of completed suicide. However, unmeasured confounders and systematic biases of individual studies limit the quality of evidence.

Prospero Registration Number: CRD42015017887

Keywords: body mass index, BMI, obesity, suicidal behavior, suicide

3.2 INTRODUCTION

Suicide is a leading cause of death worldwide[1] that claims 800,000 lives each year.[2] Non-fatal suicidal behaviours are also a significant public health concern with rates for suicide attempt being 10-fold that of completion.[3] In 2014 the World Health Organization (WHO) identified the prevention of suicidal behaviors as a global health priority.[2] Several conventional risk factors of suicidal behaviour are not modifiable including age, sex, a personal or family history of attempted suicide, and unanticipated adverse life events.[3,4] It remains necessary to identify novel predictors of suicidal behaviour that can be recognized and mitigated in clinical settings.

Body weight is a modifiable factor that may aid suicide risk assessment. Research has consistently demonstrated an inverse relationship between BMI and completed suicide suggesting that being obese or overweight is associated with a decreased risk of suicide relative to normal weight.[5-7] These findings are counterintuitive considering the medical[8] and psychiatric[9,10] comorbidities associated with obesity, as well as the pervasiveness of social stigma towards obese persons in Western societies.[11,12] Some research has similarly demonstrated an inverse relationship between BMI and attempted suicide; [13,14] however, several positive[15-17] and non-significant[18] associations have also been reported. The impact of body weight on suicidal ideation remains unclear.[19]

Given rising public health concerns for the independent management of obesity[20] and suicidal behavior,[2] a holistic view of the literature is needed to clarify the association and direction of effect between body weight and risk of suicidality. A previous systematic review has investigated the relationship between obesity and suicidal behaviour.[21]

However, a new review is warranted given that several studies have been published since the last review concluded its search in 2011 (e.g.[5,13,14,22,23]). Klinitzke[21] included 15 studies whereas the present review includes 38 studies and especially adds to research investigating BMI in relation to attempted suicide and suicidal ideation. Furthermore, Klinitzke[21] focused on obesity and did not comment on the impact of overweight and underweight body types on risk of suicidal behaviour. A pooled estimate of effect to quantify the association between BMI and suicidal behaviour has yet to be computed in a meta-analysis.

Suicidal behaviors have heterogeneous mechanisms, risk factors, and prevalence depending on the severity and underlying intent;[3] therefore, it is important to understand whether BMI differentially impacts various manifestations of suicidality. The primary objective of this review was to elucidate the relationship between BMI and suicidal behavior among adults (≥ 18 years of age), including suicidal ideation, attempted suicide, and completed suicide. A secondary objective was to summarize evidence for potential effect modifiers of the association between BMI and suicidal behavior, such as sex and the method of suicide.

3.3 METHODS

The methods of this systematic review were published in an *a priori* designed protocol[19] that was registered with PROSPERO. We provide a summary of the methods below. This study was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[24] and the Meta-Analysis for Observational Studies in Epidemiology (MOOSE) guidelines.[25]

3.3.1 Search strategy and selection criteria

The following databases were searched from their inception until January 2015 by combining pertinent keywords and associated medical subject headings: MEDLINE®, EMBASE®, PsycINFO, and CINAHL. No language restrictions were applied. A medical librarian (NB) assisted with the development of the search strategy (see Table 1 of the published protocol).[19] We also hand searched the reference lists of included articles and past reviews. "Grey literature" was searched using ProQuest Dissertations and Theses Database. Two authors (SP and RE) independently screened titles and abstracts to assess their eligibility. The full-texts of abstracts meeting all inclusion criteria were reviewed. Full-texts that satisfied all inclusion criteria were included in the review for data extraction, risk of bias assessment, and qualitative and/or quantitative analysis. Throughout each level of screening, disagreements were resolved by consensus, and a third author (ZS) resolved disagreements if necessary.

We included observational studies (i.e. cohort, case-control, cross-sectional designs) examining associations between BMI and suicidal behavior. Suicidal behavior was

defined as ideas, thoughts, plans, and actions which imply intention to end one's life,[3] including suicidal ideation, attempted suicide, and completed suicide. BMI was defined as body weight in kilograms divided by height in meters squared. Studies were included only if they reported on this association in adult populations (≥18 years of age). No other demographic limitations were applied. Studies that investigated the risk of suicide following medical treatments of obesity such as bariatric surgery or pharmacotherapy for weight loss were excluded as the effects of medically induced weight change may affect the risk of suicidal behavior independent of BMI.[26]

3.3.2 Data extraction and risk of bias

Data were extracted in duplicate (SP and RE) using a pilot-tested form. The following information was extracted: study identifiers, study design, sample characteristics, number of individuals with suicidal behavior, number of suicidal events per body weight class, method of defining and assessing suicidal behavior and BMI, statistical methods, and crude and adjusted effect estimates. A modified version of the Newcastle Ottawa Scale[27] was used to assess risk of bias of individual studies.

3.3.3 Statistical analysis

The Cohen's Kappa (unweighted) statistic for inter-rater agreement was computed for each stage of study screening.[28] We computed pooled summary estimates if possible by pooling data from studies of the same design and with similar populations, comparator groups, and outcomes. The majority of studies (15 of 21) assessing BMI in relation to completed suicide were retrospective cohort studies allowing for feasible meta-analyses. We pooled data from studies that analyzed BMI as a continuous variable allowing for the

greatest statistical efficiency. Additional meta-analyses were conducted for studies that analyzed BMI categorically by comparing the risk of suicide among individuals with obese, overweight, and underweight body types relative to normal weight persons. Studies that investigated BMI in relation to attempted suicide or suicidal ideation were highly variable in study design and sample characteristics and thus were not meta-analyzed to avoid misleading estimates of effect. All meta-analyses were conducted using a random-effects model as a certain amount of heterogeneity was anticipated due to the observational study designs. The I^2 test statistic was used to assess heterogeneity as it quantifies the proportion of the variability in effect estimates that are caused by systematic differences between studies opposed to chance.[31] Hazard Ratios (HR's) were used in meta-analyses that pooled data from retrospective cohort studies. Forest plots were used to present individual and pooled study estimates and 95% confidence intervals.

3.4 RESULTS

3.4.1 Summary of results

We screened 4517 citations and 56 full-text articles, of which 38 studies were included in the review (Fig. 3.4.1). Cohen's unweighted kappa for title-screening, abstract-screening, and full-text screening were as follows: 0.793 (95% confidence interval [CI] 0.731-0.856), 0.740 (95% CI 0.623-0.856), and 0.633 (95% CI 0.427-0.839) indicating excellent agreement (≥0.75) for title screening and good agreement (0.60-0.74) for abstract and full-text screening as defined in the Cochrane Handbook For Systematic Reviews.[30] Studies focused on the association between BMI and varying suicidal behaviours, including 18 studies on completed suicide,[5-7,31-45] 5 studies on attempted suicide,[16,46-49] 5 studies on suicidal ideation,[23,50-54] 3 studies examining both completed and attempted suicide,[13,14,55] and 7 studies examining both attempted suicide and suicidal ideation.[15,17,18,22,56,57] Three tables (Tables 3.4.1a-3.4.1c) summarize study characteristics for each type of suicidal behavior.

3.4.2 BMI and completed suicide meta-analyses results

This review included 21 studies that examined the association between BMI and completed suicide, of which, 15 were retrospective cohort studies that were eligible to be pooled in meta-analyses.[5-7,13,14,31-34, 38, 40-42,45,55] The 15 retrospective cohort studies collectively included 10,130,420 participants, of which 19,061 had completed suicide. Six studies were excluded entirely from meta-analyses because the heterogeneous study designs precluded statistical combination (3 ecological analyses and 3 postmortem case-control studies).[35-37,39,43,44] Ma et al. (2011) was excluded from all meta-analyses because

their sample overlaps with Kaplan et al. (2007) whose study focused on BMI and completed suicide. Four meta-analyses were conducted to quantify the association between BMI and completed suicide. Subgroup analyses by sex were not feasible given that the majority of authors did not report separate estimates by sex or had samples consisting of entirely men.

A meta-analysis of 5 retrospective cohort studies reporting the risk of completed suicide per standard deviation (SD) increase in BMI was conducted using a random effects model (Fig. 3.4.2a). The pooled estimate demonstrated a HR of 0.90 (95% CI 0.86 to 0.95), indicating a 10% decreased risk of completed suicide per SD increase in BMI ($p = 0.0002$). Ten studies were excluded from the meta-analysis because they did not analyze BMI as a continuous variable,[5,7,13,38,41,42,45] or because they used unstandardized units.[6,31,32]

Three separate meta-analyses were conducted for studies analyzing BMI as a categorical variable, each comparing obese, overweight, and underweight individuals to normal weight individuals. These weight categories were defined according to the WHO guidelines in 11 of 15 cohort studies: underweight (BMI of <18.5 kg/m^2), normal/healthy weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Two studies had a different normal weight reference category of 18.5-22.9 kg/m^2 [18,39] and Kaplan et al. (2007) defined normal weight as a BMI of 20.0-24.9 kg/m^2 and underweight as a BMI <19.9 kg/m^2. Giltay et al. (2010) assessed BMI in their sample by comparing the upper three quartiles to the lowest quartile in BMI. Four studies distinguished between class I (30-34.9 kg/m^2), class II (35.0-39.9 kg/m^2), and class III (≥

40 kg/m^2) obesity as defined by WHO.[18,38,39,48] Jee et al. (2011) categorized BMI according to the WHO Asian-Pacific guidelines (BMI $\geq$ 25 is obese). Studies were pooled in meta-analyses only if they used similar reference categories for BMI.

A pooled estimate of 6 retrospective cohort studies indicated that obese individuals have a 29% decreased risk of completed suicide relative to normal weight individuals (HR = 0.71, 95% CI 0.56 to 0.89, p=0.01) (Figure 3.4.2b). This estimate was accompanied by substantial heterogeneity (I^2 = 62%, p =0.01). Each of these studies compared the risk of completed suicides among obese (BMI $\geq$ 30 kg/m^2) individuals relative to normal weight (18.5-24.9 kg/m^2) individuals; however, Kaplan et al. (2007) defined normal weight as 20-24.9 kg/m^2.

Among 7 retrospective cohort studies, pooled estimates indicated that overweight individuals have a 22% decreased risk of completed suicide (HR = 0.78, 95% CI 0.75 to 0.82, p < 0.00001) (Figure 3.4.2c). Each of these studies compared the risk of completed suicides among overweight (BMI 25-29.9 kg/m^2) individuals relative to normal weight (18.5-24.9 kg/m^2) individuals; however, Kaplan et al. (2007) defined normal weight as 20-24.9 kg/m^2.

A pooled estimate of 9 retrospective cohort studies indicated that underweight individuals have a 21% increased risk of completed suicide relative to normal weight persons (HR = 1.21, 95% CI 1.07 to 1.36, p=0.002) (Figure 3.3.2d). Each of these studies compared the risk of completed suicide among underweight (BMI <18.5 kg/m^2) individuals relative to normal weight (18.5-24.9 kg/m^2) individuals; however, Kaplan et al. (2007) defined normal weight as 20-24.9 kg/m^2 and underweight as BMI <19.9 kg/m^2. Additionally,

Chang et al. (2012) and Mukamal et al. (2010) defined normal weight as a BMI of 18.5-22.9 kg/m^2.

3.4.3 BMI and completed suicide qualitative results

Suicide was assessed using official mortality records in all studies. The majority of participants were men and 6 of 15 studies included only men.[14,31,32,38,41,55] Studies adjusted for several sociodemographic, psychological, and medical confounders (Table 3.4.1a). Six studies demonstrated an inverse relationship between BMI and completed suicide.[5-7,31,32,34] One study demonstrated a significant inverse association between BMI and suicide among men, but no effect in women.[40] Three studies demonstrated no significant association in adjusted analyses.[13,14,55] Two studies focusing on several risk factors of suicide, including BMI, failed to demonstrate an association between BMI and suicide.[41,42] Conversely, two studies demonstrated that obesity at baseline was associated with an increased risk of completed suicide,[38,45] and another demonstrated a J-shaped association in which underweight and very obese individuals (BMI $\geq$ 35 kg/m^2) were at increased risk of completed suicide.[33]

This review included 3 case-control postmortem studies[35,36,39] including 718 individuals who died of suicide and 1184 controls who died of other causes. Two studies demonstrated no association between BMI and completed suicide.[35,39] However, one relied only on a univariate analysis.[35] The third study reported that the BMI of adults who completed suicide was significantly lower than controls.[36]

Three ecological analyses were included.[37,43,44] A study in the United States reported that statewide prevalence of obesity was strongly and inversely correlated with age adjusted

suicide rate.[44] Shah et al. (2010) reported an inverse association between global rates of suicide and obesity among elderly females. Contrarily, Lester et al. (1999) reported that 1980 national BMI scores were not significantly correlated with suicide rates from 27 different nations.

Ten studies reported on sex differences. Three retrospective cohort studies statistically analyzed sex as a potential effect modifier by adding an interaction term to the regression models.[7,13,40] Sex was not found to be a significant effect modifier of the association between BMI and completed suicide. Three retrospective cohort studies computed separate estimates of association for men and women.[7,13,40] Kaplan et al. (2007) reported a consistent inverse association between BMI and completed suicide among both men and women. Gao et al. (2013) did not find a significant association between BMI and completed suicide although they noted that incidence rates of completed suicide tended to decrease as BMI increased among both sexes. Jee et al. (2011) reported that the risk of suicide significantly decreased per standard deviation in BMI among men but not among women. Three post-mortem case control studies reported on sex differences.[35,36,39] Flaig et al. (2013) reported an inverse association between BMI and completed suicide among males and females. Stack and Lester (2007) and Austin et al. (2014) did not find a significant relationship between BMI and completed suicide among men and women. An ecological analysis among elderly (≥ 65 years) individuals demonstrated that national prevalence rates of obesity in 40 countries were significantly inversely associated with national suicide rates in elderly females independent of socioeconomic status, income

inequality, life expectancy, educational attainment, and marital status.[37] This association was not significant among elderly males.

We qualitatively evaluated whether the method of completed suicide modified the association between BMI and completed suicide. Austin et al. (2014) reported that BMI was significantly lower among individuals who hanged themselves compared to controls and cases using other methods. Flaig et al.[42] similarly reported that hangings were less common with increasing BMI, and that obese men predominantly completed suicide using firearms, while overweight and obese women killed themselves predominantly by self-poisoning. McCarthy et al. (2014) demonstrated that BMI was not a significant predictor of higher versus lower lethality methods. However, the authors noted that poisoning was most prevalent among patients who were obese, the use of firearms was most prevalent among those who were underweight, and that suffocation was most prevalent among normal weight persons. Mukamal et al. (2009) demonstrated an inverse relationship between state-wide obesity and suicide rates and reported a stronger correlation among non-firearm related suicides than firearm related suicides.

3.4.4 BMI and attempted suicide results

Fourteen studies reported on the association between BMI and attempted suicide including 6 retrospective cohort studies,[13,14,22,46,49,55] and 8 cross-sectional studies.[15-18,47,48,56,57] Overall, the association between BMI and attempted suicide was inconsistent across studies. The 6 cohort studies collectively included 2,188,596 participants and a total of 22,923 attempted suicides. Two cohort studies reported that the adjusted risk of attempted suicide significantly decreased per standard deviation increase in BMI,[14,46] and

another study demonstrated an inverse relationship that was borderline significant (p=0.05).[55] Contrastingly, one cohort study demonstrated a positive association between obesity and attempted suicide; however, adjusting for physical health conditions attenuated this relationship.[22] One retrospective cohort studies found no significant association.[49] Three of these cohorts are based on data from Swedish military conscription records and potentially reported on overlapping samples.[14,46,49]

Eight cross-sectional studies assessing the relationship between BMI and attempted suicide collectively included 64,946 participants, of which 827 had made a suicide attempt. Five cross-sectional studies demonstrated that obesity was associated with increased risk of attempted suicide,[15-17,47,48] including two studies of German community members,[15,17] and other studies of family data and obese probands,[16] bipolar outpatients,[48] and female prison inmates.[47] In a US military based study, no significant association between BMI and attempted suicide was found.[18]

Four studies reported on sex differences in relation to an association between BMI and attempted suicide.[13,17,18,56] A cohort study in the United Kingdom reported that the relationship between BMI and attempted suicide was modified by sex and depression.[13] The authors reported an overall inverse association between BMI and attempted suicide among men. However, among women with depression, there was an increased risk of attempted suicide in underweight individuals. In women without depression, they reported a U-shaped association between BMI and attempted suicide. Carpenter et al. (2000) reported a significant sex by BMI interaction. They demonstrated that obese men were at decreased odds of attempting suicide relative to normal weight individuals, and

that underweight men were significantly more likely to attempt suicide than normal weight individuals. However, BMI was not significantly associated with attempted suicide among women. Wagner et al. (2013) reported a positive association between BMI and attempted suicide; however, no sex differences were found. Smith et al. (2014) reported no significant association between BMI and attempted suicide consistent among men and women.

3.4.5 BMI and suicidal ideation results

Twelve studies examined the association between BMI and suicidal ideation, including 2 retrospective cohort studies [22,53] and 10 cross-sectional studies.[15,17,18,23,50-52,56-58] Overall there is little evidence supporting an association between BMI and suicidal ideation after taking important confounders and mediators into consideration. One retrospective cohort study reported no significant association between baseline BMI and incident suicidal ideation after controlling for covariates among American men and women.[22] An Australian cohort study suggested that only very obese persons (BMI > 33.02) were significantly more likely to experience suicidal ideation.[53] The most recent cross-sectional study reported a significant quadratic relationship between BMI and suicidal ideation among undergraduate students and individuals attending a community-based weight management clinic.[23] Dutton et al. (2013) reported that perceived burdensomeness (feelings of being a burden to others) mediated the relationship between BMI and suicidal ideation. A community-based study of young Korean women demonstrated that the relationship between BMI and suicidal ideation was attenuated after controlling for self-reported body weight perception.[50] A study conducted using a nationally representative

US sample found that the association between obesity and suicide was confounded by having chronic medical conditions and/or current depression.[51] A study examining severely obese individuals seeking surgical treatment did not find a significant association between BMI and suicidal ideation;[52] however, another study found that 23% of obese outpatients seeking bariatric surgery had some level of suicidal ideation.[63] Several other cross-sectional studies failed to find a significant relationship between BMI and suicidal ideation.[15,18]

Carpenter et al. (2000) reported sex to be a significant effect modifier. Increasing BMI was associated with increased odds of past year suicidal ideation among women and decreased odds of past year suicidal ideation among men. Furthermore, underweight men were at increased risk of suicidal ideation relative to average weight men. Palmer et al. (2003) found ethnicity to be a significant effect modifier of the relationship between BMI and suicidal thoughts among depressed women.[57] Obese White American females were at increased risk of suicidal thoughts relative to overweight and normal weight women, whereas no association was found between body weight and suicidal thoughts among African American women.

3.5 DISCUSSION

Findings from this review establish the association between BMI and completed suicide among adults. Body weight was associated with suicide, whereby risk of completed suicide increased among underweight individuals and decreased among overweight and obese individuals relative to normal weight persons. These findings were not consistent for attempted suicide. The majority of cross-sectional evidence suggests that obesity is a risk factor for attempted suicide. Retrospective cohort studies were less consistent demonstrating both inverse and no significant associations between BMI and attempted suicide. Research investigating body weight and risk of suicidal ideation suggests no association between BMI and suicidal ideation; however, further investigation is needed.

3.5.1 BMI and completed suicide

The evidence collectively supported an increased risk of completed suicide among underweight individuals and a decreased risk of suicide among overweight and obese individuals relative to normal weight persons. This suggests a dose-response type inverse relationship between BMI and suicide. The inverse relationship remained even after adjusting for sociodemographic factors (e.g. age, sex, socioeconomic and marital status), health behaviors (e.g. smoking history, alcohol consumption, self-reported exercise), and psychiatric and medical comorbidity.

When considering the counterintuitive evidence that suggests increasing BMI is associated with a decreased risk of suicide, one must consider the rigor of assessing potential confounders and systematic biases.[59] For example, 14 of 15 cohort studies implemented a single measure of BMI that was taken at baseline. Body weight is subject

to change over time, perhaps to a greater degree in the context of psychiatric and medical illness or major life stressors. Evidence suggests that BMI tends to be stable overtime in adulthood; however, when change does occur, BMI category is more likely to increase than decrease.[60] Repeated measures of BMI would strengthen the evidence of a longitudinal association between body weight and completed suicide and clarify how this association may change with age. The inverse relationship between BMI and completed suicide has been speculated to be confounded by changes in weight and appetite that are related to depression.[31] However, several of the cohort studies treated incident or baseline depression as a covariate. Additionally, some studies conducted sensitivity analyses to exclude suicides occurring within the first few years to rule out the possibility that psychiatric or medical illness at baseline was affecting BMI. The results were unaffected by such sensitivity analyses. Nonetheless, assessment of psychiatric diagnoses closer in proximity to the suicides is a significant challenge in verifying this paradoxical relationship.[59] Future studies should attempt to adjust for psychotropic medications that are associated with weight gain.[61] The large majority of studies on completed suicide used data that was collected before the year 2000. Considering that the prevalence of obesity has more than doubled since 1980,[20] future research is required to determine whether an inverse relationship would exist if BMI were assessed in recent samples.

The meta-analysis (Figure 3.4.1d) suggested that being underweight was associated with an increased risk of completed suicide. Underweight has been shown to be associated with significantly increased mortality from non-cancer and non-cardiovascular disease related mortality.[62] Hypotheses have linked personality factors such as neuroticism and

low conscientiousness to being underweight,[64] which may independently increase the risk of suicidal behaviour. However, the mechanisms conferring an increased risk of completed suicide among underweight individuals remains unclear, and future research should investigate personality factors (e.g. impulsivity, neuroticism, risk taking behaviours) and potential biological factors that may explain this association. Clinicians should monitor the risk of suicidal behaviour among underweight patients.

Sex was not found to be a significant effect modifier of the relationship between BMI and completed suicide. However, given that several studies included only males, cohorts including more women are needed to increase the generalizability of the findings to women and to have enough statistical power to investigate sex as a potential effect modifier. We sought to examine whether the method of suicide modifies the relationship between BMI and suicidal behaviors. A plausible theory suggests that BMI may influence the case-fatality ratio of attempted suicide by affecting one's likelihood of choosing a less lethal method of suicide or by reducing the case fatality of a specific method of suicide.[59] For example, the use of more lethal methods requiring greater physical exertion, such as hanging or jumping, may be less common among overweight and obese persons.[35,36,46] Some evidence suggests that self-poisoning is more common among obese persons in Western societies,[5,46] and perhaps greater BMI is associated with a lower risk of completed suicide due to body size and distribution of body mass, resulting in fewer fatal incidents from intentional overdoses.[46] Future research should aim to study body weight and suicidal behavior in relation to the means of attempting suicide.

3.5.2 BMI and attempted suicide

The evidence supporting a relationship between BMI and attempted suicide varied depending on the study design. Cross-sectional evidence suggests that obesity is associated with an increased risk of attempted suicide. These studies were primarily conducted in community-based settings most often among middle-aged adults. Only two studies were conducted in a psychiatric patient samples,[48,57] which is surprising considering that the majority of suicidal behaviors occur among individuals with a psychiatric illness.[65] Future research conducted among psychiatric samples is needed to understand the impact of BMI on the risk of suicidal behaviors among its most vulnerable population. Cross-sectional data is limited in that it cannot establish a causal association between BMI and attempted suicide. Nonetheless, given the relative rarity of suicidal behaviours in the general population, cross-sectional studies remain an economically feasible and important tool in suicide research given that systematic biases are minimized. For example, several cross-sectional studies assessed attempted suicide using a single self-reported 'yes or no' question. Studies should aim to use more rigorous assessments of attempted suicide such as validated assessment tools that clearly define the intent to take one's life, the lethality of the method chosen, the date of the attempt(s), and the severity of the attempt from a psychological and physical standpoint. Cross-sectional studies should aim to assess BMI in close proximity to a suicide attempt to avoid time-related biases.

Results from retrospective cohort studies examining the relationship between BMI and attempted suicide were more consistent with the inverse association between BMI and

completed suicide; however, some studies reported no significant association in adjusted analyses. It is unclear whether the discrepancies between results from cross-sectional and cohort studies are due to differences between temporal and cross-sectional relationships between BMI and attempted suicide, or factors specific to each study (e.g. the cohort studies primarily assessed young adults at baseline and used military data).

It is well established that women are more likely to attempt suicide and engage in non-fatal suicidal behaviors, and that men are more likely to complete suicide.[3] However, only a few studies analyzed sex as a potential modifier. One reported a significant interaction by sex and depression.[8] The authors reported an overall inverse linear association between BMI and attempted suicide among men. However, the relationship differed between depressed and non-depressed women, with an increased risk of attempted suicide among underweight women in both groups and increased risk amongst obese individuals in the non-depressed group. Among cross-sectional studies, one study reported that obesity increased the odds of reporting a past year suicide attempt among women, whereas obesity conferred a protective effect against attempted suicide among men similar to the aforementioned cohort study.[62]

3.5.3 BMI and suicidal ideation

The relationship between BMI and suicidal thoughts remains elusive. Cohort studies have failed to demonstrate a longitudinal association between baseline obesity and incident suicidal ideation. Cross-sectional studies suggest that the relationship between BMI and suicidal ideation is confounded by factors such as body weight perception,[56] depression,[57] and medical comorbidity.[57] The relationship between BMI and suicidal thoughts may be

mediated by cognitive factors such as perceived burdensomeness and self-esteem.[9] Future samples should include more men and greater ethnic diversity. Study results were biased from the use of self-reported height and weight to compute BMI. It is known that individuals tend to overestimate their height and underestimate their weight,[66] and therefore all studies examining an association between BMI and suicidal behavior should aim to use objective anthropometric measures.

3.5.4 Conclusions

Overall this systematic review demonstrated an inverse association between BMI and completed suicide, inconsistent evidence of an association between BMI and attempted suicide, and no independent association between BMI and suicidal ideation when taking confounders into consideration. Underweight individuals are at the greatest risk of completed suicide. Our results support the finding of a previously systematic review by Klinitzke et al. (2013) that similarly reported an inverse association between BMI and completed suicide. Prospective cohort studies that establish a temporal relationship between BMI and attempted suicide or suicidal ideation are needed to create a more definitive understanding of this association. Studies implementing repeated measures of BMI can strengthen evidence of an inverse association between BMI and completed suicide. Novel research can help to uncover potential mechanisms and variables underlying the relationship between BMI and suicidal behavior and should start by examining the method of suicide, sex, and ethnicity as potential effect modifiers.

3.5.5 Strengths and limitations

The present systematic review is the first to conduct a meta-analysis to quantify the relationship between BMI and completed suicide. Furthermore, a large number (k=38) of studies were included to provide an in-depth assessment of the impacts of body weight on suicidal behavior, providing some insight on weaknesses and unanswered questions that can be addressed by future research. However, interpretation must consider the methodological limitations of the included studies including the non-randomized observational study designs, unmeasured confounders, and systematic biases in individual studies. Future studies should comprehensively examine potential confounding factors including physical activity, psychiatric diagnoses, and psychiatric medications. Although BMI is easily assessed in a clinical setting, it does not distinguish between individuals with higher weights due to increased fat mass as opposed to increased muscle mass.[37] Nonetheless, BMI has a relatively strong correlation with other measures of body mass, such as waist circumference.

3.6 ACKNOWLEDGEMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS

S.P., R.E., B.D., M.B. (4), M.B. (5), N.B., and Z.S. helped in the conception and study design. S.P. and R.E. carried out the systematic search and screening of articles as well as the data extraction and risk of bias assessment. Z.S. was consulted as third reviewer if needed during article screening. S.P., R.E., M.B. (4), and B.D. wrote the main manuscript and all authors helped with critical revision. S.P., R.E., and M.B.(5) prepared and revised all tables. S.P. prepared all figures which were revised by R.D., L.H., and Z.S. All authors reviewed and approved the final manuscript.

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3.7 FIGURES AND TABLES

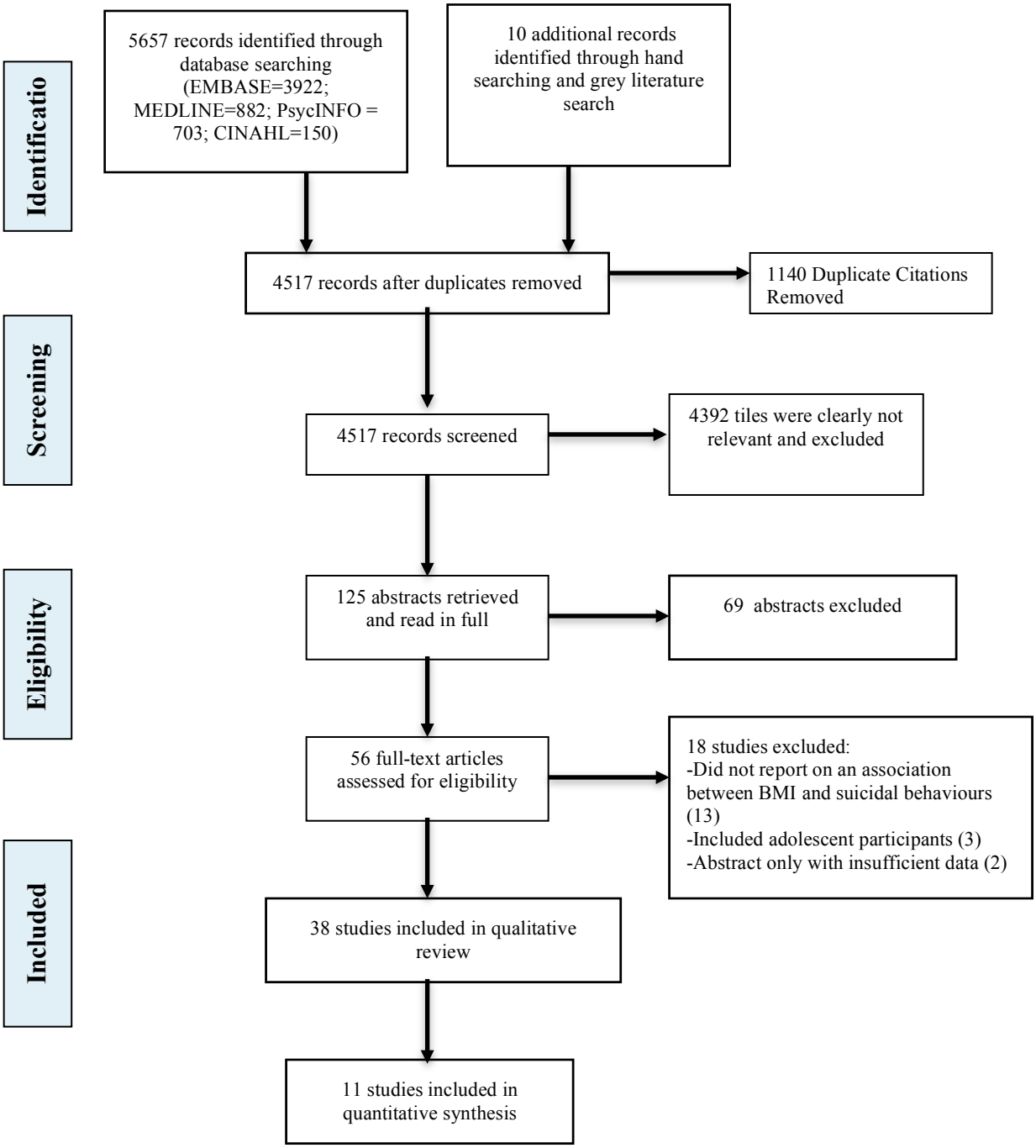

Figure 3.4.1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

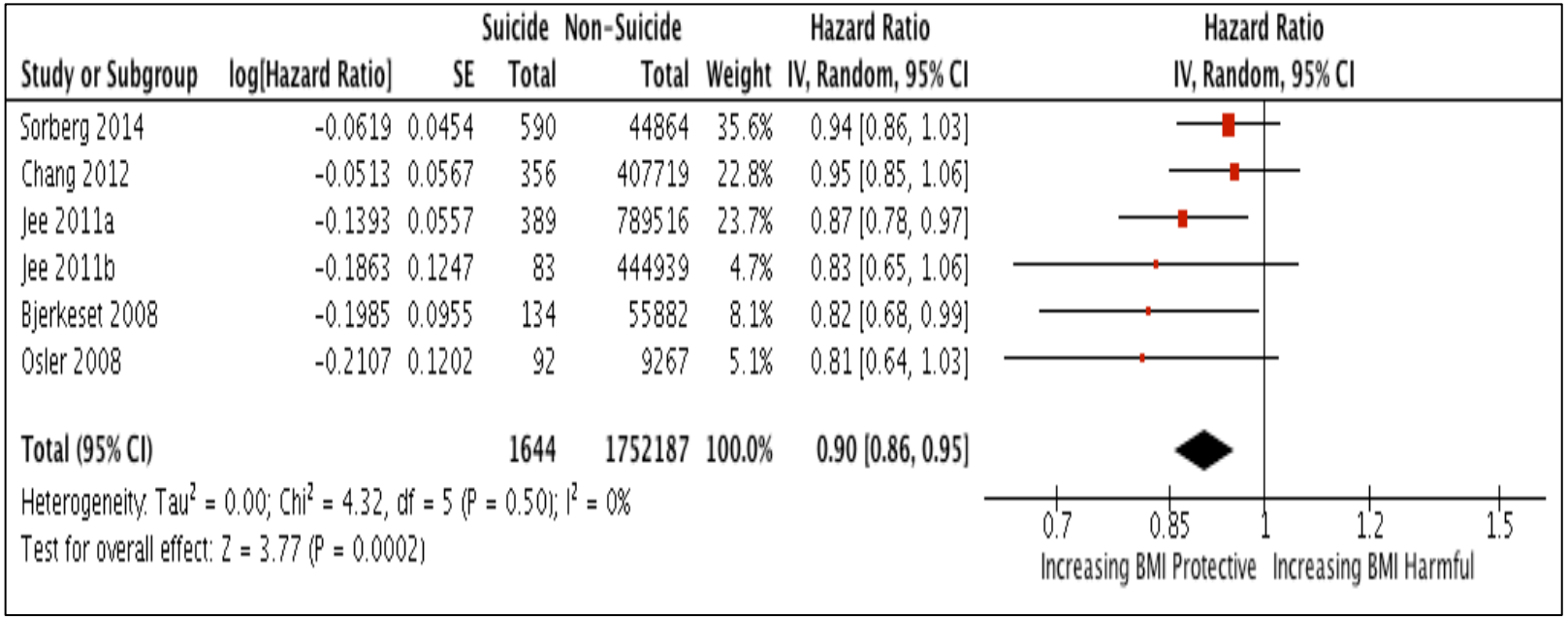

Figure 3.4.2a : Forest plot presenting the risk of suicide per standard deviation increase in BMI computed by pooling 5 retrospective cohort studies.

Note: Jee et al. (2011) reported estimates for men (a) and women (b) separately. Sorberg et al. (2014) and Osler et al. (2008) included only male participants.

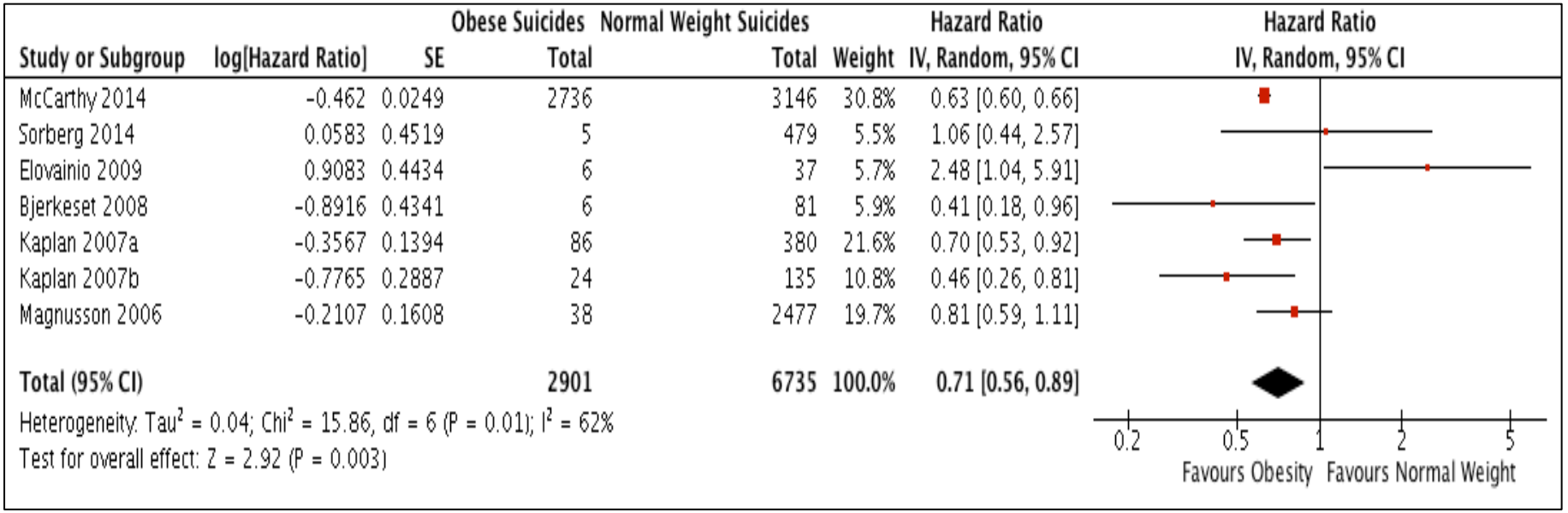

Figure 3.4.2b: Pooled estimate of the risk of completed suicide if obese relative to normal weight.

Forest plot presenting the risk of completed suicide of obese individuals relative to normal weight individuals (HR= 1.00) by pooling 6 retrospective cohort studies.

Note: Kaplan et al. (2011) presented separate estimates for men (a) and women (b). Sorberg et al. (2014), Elovainio et al. (2009), and Magnusson et al. (2006) included only male participants.

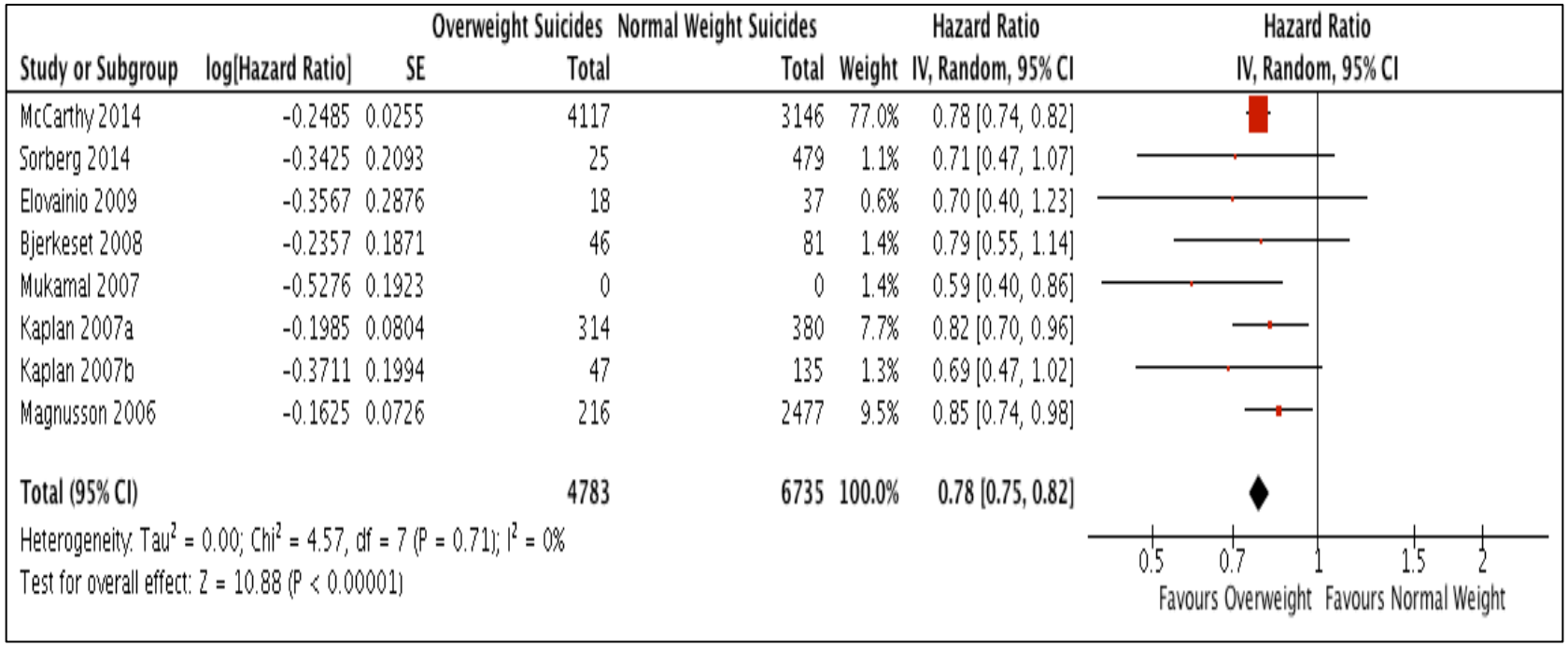

Figure 3.4.2c: Pooled estimate of the risk of completed suicide if overweight relative to normal weight.

Forest plot presenting the risk of completed suicide of overweight individuals relative to normal weight individuals (HR=1.00) by pooling 7 retrospective studies.

Note: Kaplan et al. (2011) presented separate estimates for men (a) and women (b). Mukamal et al. (2007) did not report the number of suicides per body weight class. Sorberg et al. (2014), Elovainio et al. (2009), Mukamal et al. (2007), and Magnusson et al. (2006) included only male participants.

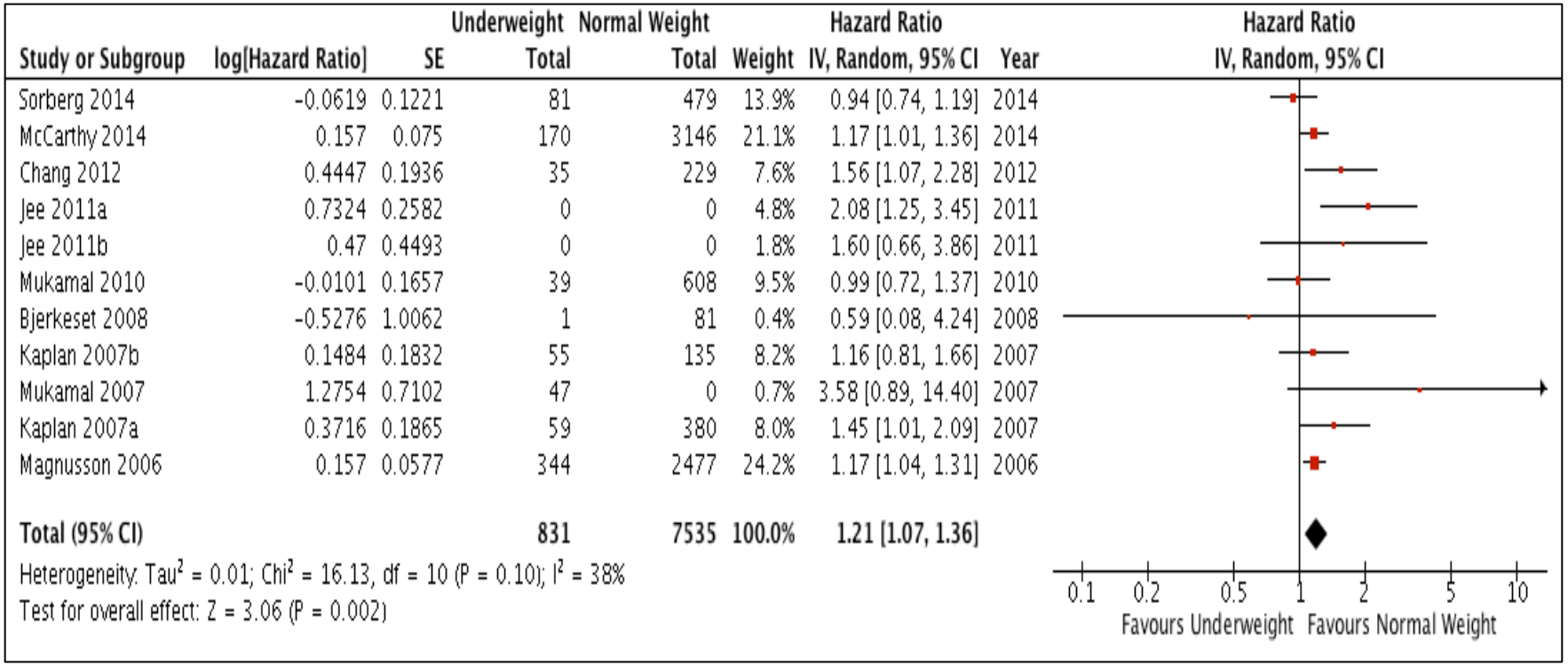

Figure 3.4.2d: Pooled estimate of the risk completed suicide if underweight relative to normal weight.

Forest plot presenting the risk of completed suicide of underweight individuals relative to normal weight individuals (HR=1.00) by pooling 7 retrospective cohort studies.

Note: Kaplan et al. (2007) and Jee et al. (2011) presented separate estimates for men (a) and women (b). Sorberg et al. (2014), Mukamal et al. (2010), and Magnusson et al. (2006) included only male participants.

Table 3.4.1a- Body Mass Index and Completed Suicide

Author (Year)	Study Design/Sample (Country)	Length of Follow-Up	Number of Participants (% Female)	Baseline Mean Age (SD or Range)	How was BMI assessed?	Total Number of Suicides and Proportion of Suicides in Each Weight Class	Statistical Analysis and Covariates Adjusted For in Multivariable Analysis	Primary Results/Adjusted Estimates
Austin et al. (2014)	Postmortem Case-Control: Forensic Science SA (Australia)	N/A	200 (50% F)	N/R	Autopsy examination	Total: 100 Mean BMI (range) Per Group: Cases: 26.6 kg/m^2 (17.3-53.6) Controls: 26.8 kg/m^2 (14.9-46.0)	Univariate analyses (age and sex matched)	Mean BMI in case and control groups were not significantly different (p=0.72) No significant differences in BMI categories between cases and controls (p=0.16)
Bjerkeset et al. (2008)	Retrospective Cohort: Nord-Trøndelag Health Study: HUNT (Norway)	1984-2002, 18 years	Total: 74,332 (50.9% F) Full Covariate Data: 53,016	M: 48.8 (17.2) F: 49.8 (17.7)	Clinical Examination	Total: 183 With Confounder Information: 134 Underweight: 1 (1)* Normal Weight: 108 (81)* Overweight: 61 (46)* Obese: 13 (6)* *(with all covariate data)	Cox proportional hazards regression: Age, sex, education, marital status, smoking, frequency of alcohol use, physical activity, nervousness, calmness, cheerfulness, and frequency of tranquilizer use.	Subset w/ Confounding Info (n=53016): *Underweight:* HR 0.59 (0.08-4.24) *Overweight:* HR 0.79 (0.50-1.14) *Obese:* HR 0.41 (0.18-0.96) *Per 1 SD increase in BMI:* HR 0.82 (0.68-0.98)
Chang et al. (2012)	Retrospective Cohort: Health Check-Up Program: MJ Health Management Intuition (Taiwan)	1994-2008, 14 years	542,088 (n=408,075 with full confounder information) (50.1% F)	Men: 40.5 (13.5) Women: 40.1 (13.6)	Clinical Examination	Total: 573 (n=356 with confounding information) BMI <18.5: 35/35,301 BMI 18.5-22.9: 139/182,378 BMI 23.0-24.9: 86/82,068 BMI 25.0-26.9:	Cox proportional hazards regression: Age, sex, educational level, marital status, smoking, frequency of alcohol use, physical activity level, diabetes history, and cancer history.	*Per 1 SD increase in BMI:* HR = 0.95 (0.85-1.06) BMI <18.5: HR 1.56 (1.07-2.28) BMI 23.0-24.9: HR 1.18 (0.89-1.55) BMI 25.0-26.9: HR 0.91 (0.65-1.28) BMI 27.0-29.9: HR

						48/55,604 BMI 27.0-29.9: 31/37,317 BMI 30.0-34.9: 11/13,379 BMI ≥35: 6/2,028		0.87 (0.58-1.29) BMI 30.0-34.9: HR 0.91 (0.49-1.70) BMI ≥35:HR 3.62 (1.59-8.22)
Elovainio et al. (2009)	Retrospective Cohort: The Whitehall Study (non-industrial London based government employees) (United Kingdom)	1967-2005, 38 years	18,784 (0% F)	52.0 (6.7)	Clinical Examination	Total: 61 Underweight: 0/237 Normal Weight: 37/10,073 Overweight: 18/7673 Obese: 6/801	Cox proportional hazards regression: Age, unexplained weight loss (self-reported based upon past year)	*Overweight:* HR 0.70 (0.39-1.23) *Obese:* HR 2.48 (1.04-5.92)
Flaig 2013	Postmortem Case-Control: Institute of Forensic Medicine of the Goethe-University (Germany)	N/A	245 suicides 566 controls (34.0% F)	Male Cases: 49.0 (18.5) Male Controls: 48.1 (17.7) Female Cases: 49.3 (15.7) Female Controls: 59.3 (21.5)	Autopsy examination	Total: 245	Univariate analyses	Female (p=0.002) and male (p=0.018) suicide victims had significantly lower BMIs than control group
Gao et al. (2013)	Retrospective Cohort: The Health Improvement	2000-2007, 7 years	849,434 (56.0% F)	Range: 18-89	Clinical Examination	Total: 75 Underweight: 3/17,302 Normal Weight:	Cox proportional hazards regression: Age, smoking status, Type 2 diabetes,	*Underweight:* IRR 2.13 (0.65-7.01) *Overweight:* IRR 0.77 (0.45-1.30)

	Network (United Kingdom)					29/307,878 Overweight: 28/310,421 Obese: 15/213,833	hypertension, and dyslipidemia.	*Obese:* IRR 0.59 (0.31-1.11)
Giltay et al. (2010)	Retrospective Cohort: Seven Countries Study For Coronary Risk Factors in Middle-Aged Men (Finland, Greece, Italy Serbia)	40 years	5321 (0% F)	Finland: 49.4 (5.5) Serbia: 48.4 (5.9) Greece: 49.0 (5.5) Italy: 49.0 (5.1)		Total: 64	Cox proportional hazards regression: Age, socioeconomic status, marital status, smoking, forced vital capacity, serum total cholesterol, systolic blood pressure, body height	Quartile 1 HR 1.00 (reference) Quartile 2 HR 1.00 (0.51-1.97) Quartile 3 HR 0.92 (0.45-1.85) Quartile 4 HR 0.72 (0.34-1.56)
Jee et al. (2011)	Retrospective Cohort: The Korean Cancer Prevention Study (South Korea)	14 years	1,234,927 (36.0% F)	46.56 (11.60)	Clinical Examination	Total: 472 (389 M, 83 F) Men: Underweight: 17/18,467 Normal weight:176/361,561 Overweight: 120/223,687 Obese: 76/186,190 Women: Underweight: 6/21,653 Normal weight: 37/202,983 Overweight: 20/102,699 Obese: 20/117,687	Cox proportional hazards regression: Age, smoking status, alcohol intake, exercise, height, blood pressure, blood cholesterol, blood glucose.	Males: Underweight (15-18.4 kg/m^2): HR 2.08 (1.26-3.45) Overweight (23-24.9 kg/m^2): HR 1.08 (0.86-1.37) Obese (25+ kg/m^2): HR 0.85 (0.65-1.12) Per 1 SD increase in BMI: HR = 0.87 (0.78-0.97) Females: Underweight: HR 1.60 (0.67-3.86) Overweight: HR 0.90 (0.52-1.56) Obese: HR 0.70 (0.40-1.24)

								Per 1 SD increase in BMI: HR = 0.83 (0.65-1.05)
Kaplan et al. (2007)	Retrospective Cohort: National Health Interview Survey (USA)	1986-2002, 16 years	719,060 (53.7% F)	N/R	Unclear/Not Explicitly Stated	Total: 1099 (M 838; F 261)	Cox proportional hazards regression: Age, marital status, living arrangement, race/ethnicity, education, employment status, place of residence, region of residence, number of chronic and psychiatric conditions, activity limitation, self-rated health.	Males: *Underweight (< 19.9):* HR 1.45 (1.01-2.09) *Overweight 25.0-29.9):* HR 0.82 (0.71-0.96) *Obese (≥30):* HR 0.70 (0.54-0.92) *Per 5kg/m^2 increase in BMI*: HR 0.82 (0.73-0.91) Females: *Underweight:* HR 1.16 (0.81-1.66) *Overweight:* HR 0.69 (0.47-1.02) *Obese:* HR 0.46 (0.26-0.81) *Per 5kg/m^2 increase in BMI:* HR 0.76 (0.66-0.87)
Ma et. al. (2011)	Retrospective Cohort: National Health Interview Survey (USA)	1987-1995, 8 years	112,328 (56.6% F)	Range: 18-39 years	Self-reported or reported by an adult family member	Underweight: 6 Normal Weight: 137 Overweight: 48 Obese: 11 Extremely Obese: 6	Cox proportional hazards regression: Age, sex, race/ethnicity, education, smoking status	Underweight: HR 0.68 (0.31-1.48) Overweight: HR 0.55 (0.39-0.79) Obese: HR 0.57 (0.30-1.08) Extremely Obese: HR 0.73 (0.30-1.75)
Magnusson et al.	Retrospective Cohort:	1968-1999,	1,299,177 (0% F)	Range: 18-19	Unclear/Not Explicitly	Total: 3075 Underweight:	Cox proportional hazards regression:	*Underweight:* HR 1.17 (1.04-1.31)

(2006)	Swedish Military Service Conscription Register (Sweden)	31 Years			Stated	344/106,839 Normal Weight: 2477/1,047,329 Overweight: 216/120,415 Obese: 38/24,594	Year of birth, conscription test center, psychiatric diagnosis at conscription examination, and parental socioeconomic index and education.	*Overweight:* HR 0.85 (0.74-0.98) *Obese:* HR 0.81 (0.59-1.11) *Per 5kg/m^2 increase in BMI:* HR = 0.85 (0.79-0.91)
McCarthy et al. (2014)	Retrospective Cohort: Veterans Health Administration National Patient Care Database (USA)	2002-2009, 7 years	4,005,640 (5.30% F)	62.0 (14.4)	Unclear/Not Explicitly Stated	Total: 10,169 (261 F, 9908 M) Underweight: 170/53,858 Normal Weight: 3146/ 971,552 Overweight: 4117/ 1,625,348 Obese: 2736/1,354,882	Cox proportional hazards regression: Age, sex, psychiatric/medical diagnoses, nicotine dependence, eating disorders, mental health services receipt, VA regional network	*Underweight:* HR 1.17 (1.01-1.36) *Overweight:* HR 0.78 (0.74-0.82) *Obese:* HR 0.63 (0.60-0.66)
Mukamal et al. (2010)	Retrospective Cohort: Cancer Prevention Study II (USA)	1982-2004, 22 years	1,154,963	Range: 18-39	Self-report	Total: 2231 (1740 M; 491 F) BMI <18.5: 39/363,320 BMI 18.5-22.9: 608/6,326,344 BMI 23.0-24.9: 504/4,721,784 BMI 25.0-27.4: 608/5,356,772 BMI 27.5-29.9: 275/2,259,138 BMI 30.0-34.9: 173/1,848,908 BMI ≥35: 24/ 486,244	Cox proportional hazards regression: Age, race, smoking, comorbidity, geographical region, physical activity, marital status, religion, education. alcohol consumption, psychoactive medication use, recent stressful life event	*Per 5kg/m^2 increase in BMI:* HR = 0.85 (0.80-0.90) <18.5: HR 0.99 (0.72-1.37) 23.0-24.9: HR 0.78 (0.69–0.88) 25.0-27.4: HR 0.73 (0.65–0.82) 27.5-29.9: HR 0.72 (0.62–0.83) 30.0-34.9 HR 0.77 (0.65–0.92) ≥35 HR 0.55 (0.36–0.83)

Mukamal et al. (2009)	Statewide ecological study: (USA)	N/A	All 50 states included	N/A	Self-report from the 2004 Behavioural Risk Factor Surveillance System	N/R (ecological study comparing statewide rates of obesity and suicide)	Population-weighted Pearson correlations of state specific rates of obesity and age-adjusted suicide	Statewide prevalence of obesity was inversely correlated with age-adjusted suicide rate (multivariable-adjusted $r = -0.66$; $P < 0.001$) Obesity rates inversely correlated with rates of suicidal acts using firearms ($r = -0.53$; $P < 0.02$) and suffocation ($r = -0.76$; $P < 0.001$) but not other methods.
Mukamal et al. (2007)	Retrospective Cohort: Health Professionals Follow-Up Study (USA)	1986-2002, 16 years	46,755 (0% F)	Range: 40-75	Self-report	Total: 131	Cox proportional hazards regression: Age, smoking, alcohol consumption, geographic region, average daily exertion, marital status. In sensitivity analysis: Further adjusted for individual intake of energy, caffeine, and omega-3-fatty acids.	*Underweight:* HR 3.58 (0.89-14.39) *Overweight:* HR 0.59 (0.40-0.86) *Obese:* HR 0.29 (0.10-0.79) Obese (Class II and III): HR 1.05 (0.41-2.70) Per 1-U increase in BMI: Updated BMI: 0.89 (0.84-0.95) Baseline BMI: 0.90 (0.85-0.96)
Osler et al. (2008)	Retrospective Cohort: Danish Metropolit cohort linked with Danish military	1972-2003, 31 years	9359 (0% F)	18 (N/R)	Clinical Examination	Total: 92	Cox proportional hazards regression: Father's occupational social class at birth, born	*Per 1 SD increase in BMI:* HR = 0.81 (0.64-1.02)

	conscription data (Denmark)						outside of marriage, birth weight, cognitive function, height, school education and mental disorders at 18 years of age.	
Schneider et al. (2014)	Retrospective Cohort: MONICA/KORA Augsburg Surveys (Germany)	1984-1995, mean:12 years	12,888 (49.9% F)	M: 48.4 (13.7) F: 47.7 (13.4)	Clinical Examination	Total: 38 (8 F, 30 M) Non-Obese: 25/10,261 Obese: 12/2461	Cox proportional hazards regression: Age, sex, survey, depressed mood.	*Obese Vs. Non-Obese:* HR: 2.73 (1.35–5.54)
Sorberg et al. (2014)	Retrospective Cohort: Swedish Military Conscription Data (Sweden)	1971-2008, 37 years	45,454 (total) 44,440 (with adulthood covariate information) (0% F)	Range: 18-20	Clinical Examination	Total:590 Underweight: 81/6222 Normal Weight: 479/36,239 Overweight: 25/2632 Obese: 5/361 408 (with adulthood covariate information) Underweight: 61/6072 Normal Weight: 323/35,398 Overweight: 20/2578 Obese: 4/352	Cox proportional hazards regression: Childhood SEP, crowded housing, height, emotional control, risky use of alcohol, smoking, depressed mood, psychiatric diagnosis at conscription, adulthood marital status, adulthood SES, and psychiatric diagnosis in adulthood	Childhood/Adolescent covariates: *Underweight:* HR 0.94 (0.74-1.19) *Overweight:* HR 0.71 (0.48–1.07) *Obese:* HR 1.06 (0.44–2.57) *Per 1 SD increase in BMI:* HR = 0.94 (0.86-1.02) Further adjusting for adulthood covariates (SES, marital status, incident psychiatric illness): *Underweight:* HR 1.01 (0.77-1.33) *Overweight:* HR 0.83 (0.53-1.31) *Obese:* HR 1.16 (0.43-

								3.11) *Per 1 SD increase in BMI:* HR = 0.96 (0.87-1.06)
Shah et al. (2010)	Cross-national ecological study: Data from the World Health Organization and United Nations	N/A	National prevalence rate of obesity and suicides for 35 countries (M) and 40 countries (F)	Elderly: 65 +	Unclear/ Not Explicitly Stated	N/R (National suicide rates presented in study)	Multiple regression analysis (obesity and elderly suicide rates): Gross national domestic product, income inequality, life expectancy, educational attainment, marriage and divorce rates	Females (64-74): r = -0.42; P < 0.008 Females (75+): r = -0.36; P < 0.022 r= correlation between prevalence of obesity and suicide rates Females (65-74): B=-0.81, p=0.001 Females (75+): B=-1.18, p=0.003 B= beta from multiple regression examining independent association between obesity and suicide rates No significant findings among elderly males.
Stack and Lester 2007	Case-Control (Postmortem): National Mortality Follow-Back Survey	N/A	373 suicides 518 controls (22.5% F)	N/R	Unclear/Not Explicitly Stated	373 suicides (84 F; 289 M)	Logistic regression: Marital status, living status, alcohol abuse, race, age, region of country	Females: (B = 0.3966, SE = 0.3437, Wald $\chi^2 = 1.11$, p > .05). Males: (B = 0.177, SE = 0.212, Wald $\chi^2 = 0.71$, p > .05).

Table 3.4.1b- Body Mass Index and Attempted Suicide

Author (Year)	Study Design and Name (Country)	Length of Follow-Up if Applicable	Number of Participants (% Female)	Mean Age (SD or Range)	How was BMI assessed?	How was attempted suicide assessed?	Number of Attempted Suicides	Primary Statistical Test and Covariates Adjusted For	Primary Estimates/Adjusted Estimates
Batty et al. (2010)	Retrospective Cohort: Swedish Military Service Conscription Data (Sweden)	1969-2006, 37 years	1,133,019 (0% F)	18.3 (0.6)	Clinical Examination	Swedish Hospital Discharge Register using International Classification of Disease codes for attempted suicide	Total: 18,277 Underweight: 2018/97,754 Normal Weight: 14,493/904,972 Overweight: 1461/94,141 Obese: 305/17,875	Cox proportional hazard regression: Age, conscription center, year of birth, childhood SES, adult SES, education	*Underweight:* HR 1.12 (1.07-1.18) *Overweight:* HR 0.88 (0.83-0.93) *Obese:* HR 0.88 (0.78–0.98) *Per 1 SD increase in BMI:* HR = 0.93 (0.91-0.94)
Brewer-Smyth et al. (2014)	Cross-sectional: Female prison inmates (USA)	N/A	81 (100% F)	N/R	Unclear/Not Explicitly Stated	Self-report, verified by related evidence of physical and emotional trauma if records available	Total: 29	Multivariable Logistic Regression: Age, current smoking, BDI-II depression scores, currently using SSRI	*Obese Vs. Non-Obese:* OR 14.25 (3.14-64.65)
Brunner et al. (2006)	Cross-sectional: German National Health Interview and Examination Survey and its Mental Health Supplement:	N/A	4181	42.0 (18-65)	Unclear/Not Explicitly Stated	Series of CIDI suicidality questions that are a part of the depression section.	Total: 16	Logistic regression: Age, sex	*Per 1 SD increase in BMI:* OR 1.66 (1.12-2.47) *High vs. Low:* OR 5.50 (1.38-21.96) *High vs. Normal:* OR 3.75 (1.06-13.27) *Low Vs. Normal:* OR 0.68 (0.19-2.43)

	(Germany)								
Carpenter et al. (2000)	Cross-sectional: 1992 National Longitudinal Alcohol Epidemiologic Survey (USA)	N/A	40,086 (58.2% F)	M: 38.6 (0.20) 43.03 (0.21) 44.9 (0.36) F: 40.4 (0.36) 45.9 (0.23) 47.3 (0.35)	Self-Report	Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS): Major Depression Section	Total: 244 (past-year)	Logistic regression: Age, race, education, past-year income, self-reported disease history, race-by-weight interaction term.	Males: *Obese Vs. Average Weight:* OR 0.63 (0.48-0.83) *Underweight Vs. Average Weight:* OR 1.77 (1.34-2.33) *Continuous weight (BMI):* OR 0.45 (0.40-0.51) Females: *Obese Vs. Average Weight:* OR 1.23 (0.74-2.03) *Underweight Vs. Average Weight:* OR 0.88 (0.55-1.41) *Continuous weight (BMI):* OR 1.22 (0.91-1.63)
Dong et al. (2006)	Cross-sectional: Sample of 608 nuclear families obtained nationwide through obese probands	N/A	2547 (68.2% F)	N/R	Self-Report	Self-report questionnaire	Total: 95	Logistic regression: Familial depression history, chronic physical disorders, sociodemographic factors	*30- <40kg/m^2:* OR 2.25 (1.04-4.90) *40- <50kg/m^2:* OR 3.37 (1.59-7.13) *≤50kg/m^2:* OR 3.85 (1.71-8.66)

	(USA)								
Gao et al. (2013)	Retrospective Cohort: The Health Improvement Network (United Kingdom)	2000-2007, 7 years	849,434 (56.0% F)	Range: 18-89	Clinical Examination	Identified using the Read codes for suicide and then by confirming the patient was alive for at least 3 months following the event.	Total: 3111	Age, smoking status, Type 2 diabetes, hypertension, and dyslipidemia	*Patients With Depression History:* *Females* *Underweight:* IRR 1.61 (1.14-2.29) *Overweight:* IRR 0.90 (0.76-1.08) *Obese Class I:* IRR 0.97 (0.78-1.20) *Class II:* IRR 1.10 (0.83-1.45) *Class III:* IRR 0.83 (0.56-1.23) *Males* *Underweight:* IRR 0.83 (0.39-1.79) *Overweight:* IRR 0.79 (0.62-1.01) *Obese:* IRR 0.65 (0.47-0.91) Class II: IRR 0.63 (0.36-1.09) Class III: IRR 0.49 (0.18-1.33)

									Patients Without Depression History: *Females* *Underweight:* IRR 1.58 (1.2-2.08) *Overweight:* IRR 0.78 (0.67-0.90) *Obese:* IRR 0.79 (0.65-0.95) Class II: IRR 0.90 (0.69-1.16) Class III: IRR 1.30 (0.98-1.74) *Males* *Underweight:* IRR 2.25 (1.61-3.13) *Overweight:* IRR 0.64 (0.55-0.74) *Obese:* IRR 0.60 (0.49-0.74) Class II: IRR 0.81 (0.59-1.10) Class III: IRR 0.79 (0.48-1.30)
Gomes et al., (2010)	Cross-Sectional: Outpatients with bipolar	N/A	255 (72.5% F)	41.51 (11.78)	Unclear/Not Explicitly Stated	"Best-available records: Interviews	Total:133 (lifetime history of suicide	Logistic regression: Age, sex, bipolar disorder subtype,	*Obese Vs. Non-Obese:* OR 1.97 (1.06-3.69)

	disorder (type I or II) (Brazil)					with patients, relatives, and reviews of medical records"	attempt)	rapid cycling, anxiety and substance abuse disorders, and HAM-D score	
Heinriksen et al. (2014)	Retrospective Cohort: Waves 3 and 4 of the Baltimore Epidemiologic Catchment Area Study (USA)	1993-2004, 11 years	1024 (62.1% F)	47.6 (12.8)	Wave 3: Self-report Wave 4: Measured by personnel	Self-Report "Have you ever attempted suicide?" Follow-up queries regarding onset and recency.	Total: 16 Normal Weight: 6 (1.6%) Overweight: 1 (0.3%) Obese: 9 (3.2%)	Logistic Regression: Age, sex, education, race, marital status, lifetime diagnosis of the psychiatric diagnosis at wave 3, other incident psychiatric disorders at wave 4.	*Obese:* OR 10.46 (1.86-58.87) *Obese:* OR 5.56 (0.91-34.02) (additionally adjusting for baseline physical health conditions).
Jiang et al. (1999)	Retrospective cohort: Swedish Military Service Conscription Registry	1991-1994, 2 years	150,395 (0% F)	Range: 18-19	Clinical Examination	National-wide hospital in-patient registry using ICD codes for attempted suicide	Total 155	Cox proportional hazards regression: Height, psychological performance scores	BMI 16-17: RR 0.47 (0.06-3.37) BMI 18-19: RR 1.04 (0.26-4.28) BMI 22-23: RR 0.81 (0.25-2.60) BMI 24-25 RR 0.82 (0.35-1.90) BMI 26-27: RR 0.62 (0.33-1.19) BMI 28-29: RR 0.79 (0.51-1.22) BMI 30-31: RR 0.91 (0.58- 1.42) BMI >=32: RR 1.18 (0.54-2.60)
Osler et al.	Retrospective	1972-	9359	18 at	Clinical	Suicide	Total: 228	Father's	*Per 1 SD increase in*

(2008)	cohort: Danish Metropolit cohort linked with Danish conscript data (Denmark)	2003, 31 years	(0% F)	baseline	Examination	attempt was defined as a registered cause of psychiatric or somatic hospital admission and/or discharge diagnosis based on ICD		occupational social class at birth, born outside of marriage, birth weight, cognitive function, height, school education and mental disorders at 18 years of age	*BMI:* HR = 0.87 (0.75-1.00)
Palmer et al. (2003)	Cross-sectional: Clinically depressed female inpatients (USA)	N/A	165 (100% F)	Range: 17-60	Unclear/Not Explicitly Stated	Suicide Risk Scale: "A 15-item questionnaire that measures how similar a test-taker resembles the prototype suicide attempter or suicide completer."	Total: 108 (history of suicide attempt) African American Healthy Weight: 15 (60%) Overweight: 18 (72%) Obese: 16 (64%) White American Health Weight: 21 (70%) Overweight: 17 (57%) Obese: 21 (70%)	Age, BMI, self-esteem, and suicide risk were included in correlation analyses	*African American Females Suicide Risk Score (M and SD, Max Score = 15):* *Health Weight: 9.7 (3.05)* *Overweight: 9.8 (3.09)* *Obese: 9.9 (3.02)* *White American Females Suicide Risk Score (M and SD):* *Health Weight: 9.7 (2.83)* *Overweight: 9.8 (2.92)* *Obese: 11.5 (2.29)* *p=0.01*

Sorberg et al. (2014)	Retrospective Cohort: Swedish Military Conscription Data (Sweden)	1973-2008, 35 years	45,365 (total) 44,440 (with adult covariate information) (0% F)	Range: 18-20	Clinical Examination	Swedish Hospital Discharge Records (International Classification of Diseases)	Total: 1136 Underweight: 196/6210 Normal Weight: 878/36,166 Overweight: 56/2630 Obese: 6/359 With confounder info: 821 Underweight: 141/6222 Normal Weight: 634/36,239 Overweight: 41/2632 Obese: 5/361	Cox Proportional Hazard Regression: Childhood SEP, crowded housing, height, emotional control, risky use of alcohol, smoking, depressed mood, and psychiatric diagnosis at conscription	*Underweight:* HR 1.20 (1.03-1.40) *Overweight:* HR 0.84 (0.64-1.11) *Obese:* HR 0.66 (0.29–1.46) *Per 1 SD increase in BMI:* HR = 0.89 (0.84-0.95) Additionally adjusting for adult covariates (SES, marital status, incident psychiatric illness): *Underweight:* HR 1.14 (0.95-1.37) *Overweight:* HR 0.82 (0.60-1.13) *Obese:* HR 0.64 (0.27-1.56) *Per 1 SD increase in BMI:* HR = 0.93 (0.86-1.00)

Smith et al. (2014)	Cross-sectional: 2005 Department of Defense Survey of Health Related Behaviors (USA)	N/A	15,195 (25% F)	17-20: 1187 21-30: 6180 31-39: 4610 40+: 3218	Self-report	Respondents self-reported suicide attempts in the previous year.	Total: 112	Logistic Regression: Age, education, race, marital status, cigarette smoking, alcohol intake, physical activity, self-reported stress, weight perception based on BMI	*Gender BMI Interaction Term:* Females: *Underweight:* OR 0.001 (0.163-5.68) *Overweight:* OR 1.7 (0.68-4.48) *Obese:* OR 1.3 (0.35-4.88) Males: *Underweight:* OR 0.3 (0.05-1.91) *Overweight:* OR 0.8 (0.41-1.61) *Obese:* OR 1.4 (0.42-4.72)
Wagner et al. (2013)	Cross-sectional: Survey Questionnaire (Germany)	N/A	2436 (52.5% F)	M: 50.41 (17.49) F: 50.70 (17.46)	Self-report	Suicidal Behaviors Questionnaire-Revised (SBQ-R). "How often have you already tried to take your own life?"	Total: 90 (47F, 43M) Underweight: 2 Normal Weight: 37 Overweight: 28 Obese I: 14 Obese II: 3 Obese III: 6	Logistic Regression: Age, sex, socioeconomic status	*Underweight:* OR 1.23 (0.27-5.55) *Overweight:* OR 0.93 (0.56-1.59) *Obese (class I):* OR 3.49 (1.76-6.90) Obese (class II): OR 3.00 (0.66-13.54) Obese (class III): OR 12.43 (3.87-39.86)

Table 3.4.1c- BMI And Suicidal Ideation

Author (Year)	Study Design and Name (Country)	Number of Participants (% Female)	How was attempted suicide assessed?	Mean Age (SD or Range)	How was BMI assessed?	Number of Participants Experiencing Ideation	Primary Statistical Test and Covariates Adjusted For	Primary Results/ Adjusted Estimate
Brunner et al. (2006)	Cross-Sectional: German National Health Examination Survey (Germany)	4181	Series of 6 CIDI suicidality questions	42 (range: 18-65)	Unclear/Not Explicitly Stated	0.4% of total sample	Logistic regression: Age, sex	Thinking a lot about death (past 12 months): per SD increase in BMI: OR 1.21 (0.99-1.46)
Carpenter et al. (2000)	Cross-sectional 1992 National Longitudinal Alcohol Epidemiologic Survey	40086 (58.2% Women)	Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) major depression section	N/R	Self-report	1454	Logistic regression: Age, sex, rage, education, past-year household income, disease status.	Males: *Obese Vs. Average Weight:* OR 1.02 (0.98-1.06) *Underweight Vs. Average Weight:* OR 1.81 (1.71-1.89) *Continuous weight per 10 kg/m^2 increase in BMI: OR 0.74 (.64-0.86)*

								Females: *Obese Vs. Average Weight:* OR 1.20 (0.96-1.50) *Underweight Vs. Average Weight:* OR 1.10 (0.88-1.34) *Continuous weight per 10 kg/m^2 increase in BMI:* OR 1.22 (1.13-1.32)*
Chen et al. (2012)	Cross-sectional: Severely obese bariatric surgery seeking individuals: pre-surgery (USA)	344 (76.0% F)	Current: Beck Depression Inventory Question asking about suicidal thoughts in the last 2 weeks on a 4-point Likert scale. Lifetime: Suicidal Behaviours Questionnaire: "Have you thought about or attempted to kill yourself in your lifetime?" on a 7-point Likert scale	43.8 (11.4)	Self-reported height and weight were validated by clinician assessment (latter used if discrepant)	21 suicidal, 313 non suicidal	Linear regression (Univariate: "We conducted separate linear regressions for each potential independent variable of interest")	Relationship between BMI with suicide ideation as the dependent variable R^2 = 0.006, B =.003, p = 0.165

Dutton et al. (2013)	Cross-sectional: Undergraduate students and obese persons seeking weight management (USA)	271 (n=151 undergraduates; n=120 obesity treatment participants) (% F N/R)	Depressive Symptom Index-Suicidality Subscale (DSI-SS)	32 (17.0)	Self-report	Total: N/R	Linear Regression: Age, sex.	No significant linear relationship: b=.009, t=1.59, p>.11, partial r=.10) Significant quadratic relationship: b=.001, t=2.21, p=.03, partial r=.14
Heinriksen et al. (2014)	Cohort: Baltimore Epidemiologic Catchment Area (USA)	1024 (62.1% F)	Self-Report "Have you ever felt so low you thought about committing suicide?" Follow-up queries regarding onset and recency.	47.6 (12.8)	Wave 3: Self-report Wave 4: Measured by personnel	Total: 51 Normal Weight: 25 (6.8%) Overweight: 11 (3.3%) Obese: 15 (5.2%)	Logistic Regression: Age, sex, education, race, marital status, lifetime diagnosis of the psychiatric diagnosis at wave 3, other incident psychiatric disorders at wave 4.	*Overweight:* OR 0.68 (0.23-1.97) *Additionally adjusted for physical health conditions at wave 3:* *Overweight* OR 0.76 (0.26-2.22) *Obese:* OR 1.07 (0.38-2.95) *Additionally adjusted for physical health conditions at wave 3:*

								Obese: OR 1.25 (0.49-3.18)
Kelly et al. (2011)	Retrospective Cohort: South Australian Monitoring and Surveillance System between 2002-2009 (Australia)	42,807	Four questions on suicidal ideation from the General Health Questionnaire dichotomized into positive or negative responses. Suicidal ideation was defined as a positive response to any of the questions.	N/R	Self-report	N/R	Logistic Regression: Age socioeconomic status, smoking, alcohol consumption, physical activity.	BMI <20.90: 1.08 (p=0.771) BMI 20.91-22.45: 1.28 (p=.265) BMI 22.46-23.71: 1.06 (p=0.797) BMI 23.72-24.90 (ref): BMI 24.81-25.89: 0.97 (p=0.905) BMI 25.90-27.03: 0.95 (p=0.822) BMI 27.04-28.39: 0.95 (p=0.799) BMI 28.40-30.12: 0.96 (p=.866) BMI 30.13-33.01: 1.35 (p=0.136) BMI 33.02: 1.71 (p=0.007)
Kim et al.,	Cross-Sectional:	953	Self-report: "Have	Range:	Clinical	19.9% (2001)	Logistic	2001 KHANES

(2011)	Korean National Health and Nutrition Examination Surveys (2001 and 2005)	(100% F)	you ever thought of killing yourself during the past 12 months"	20-29	Examination	females 16.6% (2005) females reported thinking about suicide in the past 12 months	regression: Age, marital status, education, employment status, smoking, alcohol intake, regular exercise, and body weight perception.	(n=568) Overweight: OR 1.73 (1.07-2.79) Overweight (Adjusted for BWP): OR 1.29 (0.71-2.34) 2005 KHANES (n=385) Overweight: OR 2.54 (1.35-4.81) Overweight (Adjusted for BWP): OR 1.69 (0.79-3.62)
Lester et al. (2011)	Cross-Sectional: Obese outpatients seeking surgery to treat their obesity referred for a psychiatric evaluation prior to surgery	70 (80% F)	MMPI-2: 6-items that assess suicidal ideation and attempts	42.7 (12.8)	Medical Examination	23% of this sample of obese patients had some suicidal risk (MMPI-2 scores in the range of 1-4)	N/A	N/A
Palmer et al. (2003)	Cross-sectional: Clinically depressed female inpatients (USA)	N/A	165 (100% F)	N/R	Unclear	Suicide Risk Scale	Total: 108 (history of suicide attempt) African American Healthy Weight:	Age, BMI, self-esteem, and suicide risk were included in correlation

							15 (60%) Overweight: 18 (72%) Obese: 16 (64%) White American Health Weight: 21 (70%) Overweight: 17 (57%) Obese: 21 (70%)	analyses
Smith et al. (2014)	Cohort: 2005 Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel (USA)	15,195 (25% F)	Screen for suicidal ideation (past year) from the Patient Health Questionnaire	17-20: 1187 21-30: 6180 31-39: 4610 40+: 3218	Self-report	659 reported past year suicidal ideation	Logistic Regression: Age, education, race, marital status, cigarette smoking, alcohol intake, physical activity, self-reported stress, weight perception based on BMI	Males: *Underweight:* OR 1.1 (0.28-4.38) *Overweight:* OR 1.0 (0.69-1.42) *Obese:* OR 1.2 (0.75-1.94) Females: *Underweight:* OR 1.2 (0.28-5.00) *Overweight:* OR 0.9 (0.60-1.50) *Obese:* OR 1.2 (0.65-2.08)
Wagner et al. (2013)	Cross-sectional: Survey	2436 (52.5% F)	Suicidal Behaviors	M:	Self-report	Total: 94 reported	Logistic	*Underweight:*

	Questionnaire (Germany)		Questionnaire-Revised (SBQ-R)	50.41 (17.49) F: 50.70 (17.46)		suicidal behaviour using the SBQ-R (57F, 37M)	Regression: Age, sex, socioeconomic status	OR 0.59 (0.07-4.60) *Overweight:* OR 1.41 (0.85-2.32) *Obese (class I):* OR 3.02 (1.50-6.08) Obese (class II): OR 1.35 (.17-10.41) Obese (class III): OR 21.22 (6.51-69.20)
Zhao et al. (2012)	Cross-sectional: 2005-2008 National Health and Nutrition Examination Survey	3732 (100% F)	Item 9 of the Patient Health Questionnaire-9 (past 2-weeks)	20-39: 1,195 40-59: 1,283 ≥60: 1,254	Trained health technicians	Age-adjusted prevalence of suicidal ideation: 3.0% (95% CI 2.4-3.8)	Logistic Regression: Age, race, education, marital status, poverty-income ratio, smoking, alcohol intake, physical activity, number of chronic conditions, current depression.	*Q1: Reference* *Q2:* OR 1.45 (0.63-3.34) *Q3:* OR 1.66 (1.00-2.75) *Q4:* OR 1.73 (0.81–3.72)

3.7 References

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CHAPTER 4

Study 2

The Association Between Metabolic Factors and Suicide Attempts: A Case-Control Study

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4.1 ABSTRACT

Background: Suicide attempts are more frequent than completed suicide. Suicide attempts are associated with substantial morbidity and utilize healthcare resources including hospitalizations often when assessed at emergency departments. There are several risk factors identified to be associated with suicidal behavior; however, few of these factors are modifiable. It is imperative to identify modifiable risk factors that can be used to mitigate the risk of suicide. The potential associations between metabolic factors, health-related behaviours, and attempted suicide may lead to novel strategies to aid suicide risk identification and prevention.

Methods: An age and sex matched case-control study was conducted to compare body weight, serum total cholesterol, physical activity, tobacco use, and dietary food groups among adults who had made a suicide attempt (n=84) to psychiatric inpatients (n=104) and community controls (n=93) without history of suicide attempt. We used logistic regression to investigate the association between metabolic risk factors and attempted suicide.

Results: Current tobacco use was associated with an increased risk of attempted suicide (odds ratio [OR] 2·25, 95% confidence interval [CI] 1·07-4·73, p = 0·031). Physical activity (moderate/strenuous (OR 0·42, 95% CI 0·19-0·95, p = 0·036) and mild (OR 0·35, 95% CI 0·16-0·76, p = 0·008)) was associated with a decreased risk of attempted suicide. Obesity, serum total cholesterol, and diet were not significantly associated with risk of attempted suicide. Subgroup analyses demonstrated that differences in physical activity and tobacco use were only evident when cases were compared to community controls as opposed to psychiatric controls.

Interpretations: Increased physical activity and smoking cessation may decrease the risk of attempted suicide. Obesity and serum total cholesterol were not significantly related to risk of attempted suicide, contrary to prior research.

4.2 INTRODUCTION

Suicide is a leading cause of death that adversely impacts families, communities, and societies worldwide. Globally, over 800,000 lives are lost to suicide per year.[1] Non-fatal suicide attempts are more prevalent; the Centers for Disease Control and Prevention estimates that there are 25 suicide attempts for every death by suicide.[2] However, the prevalence and incidence of suicidal behaviour are likely underestimated due to societal stigma, lack of systematic clinical inquiry, misclassified causes of death, and the absence of national registries of suicidal events.[3] Individuals who survive a suicide attempt are at risk of long-term suffering from psychiatric and medical comorbidity, repeated suicide attempts, hospitalization, living in poverty, and death by suicide.[4,5] Several known risk factors for attempted suicide are not modifiable, such as being a female, young and elderly age group, unanticipated adverse life events, and a family or personal history of suicidal behaviour.[6,7] Research investigating modifiable risk factors such as metabolic factors and health behaviours are needed to identify potential opportunities for suicide prevention in clinical settings.

Emerging evidence suggests that body weight may be associated with suicidal behaviour, albeit controversially.[3] Despite the psychiatric comorbidity,[7] medical illnesses,[8] and social stigma[9] associated with obesity, evidence suggests an inverse association between body mass index (BMI) and completed suicide.[10,11] However, several studies have identified obesity as a risk factor of attempted suicide.[3,12,13] Given that obesity[14] and suicidal behaviour[1] remain significant public health concerns, it is necessary to clarify the association and direction of effect between body weight and attempted suicide.

Research has demonstrated a significant association between low serum total cholesterol and an increased risk of attempted suicide, albeit inconsistently.[16-18] [16] A few studies have investigated potential relationships between diet and suicidal behaviour[22,23] and have focused on polyunsaturated fatty acids (PUFA) given their potential association with major depressive disorder.[24] Research evaluating diets rich in PUFA (e.g. seafood, nuts) in association with suicide attempts remains sparse.[24]

The present study investigates the association of metabolic factors and health behaviours with attempted suicide. Factors investigated are body mass index (BMI), abdominal obesity as measured by waist-circumference, serum total cholesterol, tobacco use, diet, and physical activity. The primary objective was to assess these factors among adults (≥ 18 years) who had attempted suicide and were admitted to hospital in comparison to psychiatric inpatients and community controls without history of suicide attempts.

4.3 METHODS

4.3.1 Sample Characteristics and Eligibility Criteria

Data for this investigation are from the Study of Determinants of Suicide Conventional and Emergent Risk (DISCOVER),[25] a case-control study designed to investigate risk factors associated with suicide attempts. Recruitment and data collection were conducted between March 2011 and November 2014 in Hamilton, Ontario, Canada. Participants were recruited from the city hospitals, and the greater Hamilton community.

The study inclusion criteria were as follows: men and women ≥ 18 years of age, able to provide written informed consent, communicate in English, and willing to follow study procedures. The cases included individuals who had made a suicide attempt within 3 months of recruitment, defined as self-directed injury with specific intent to die that necessitated admission to a hospital. All cases were inpatient at the time of recruitment to the study. The controls consisted of two distinct comparator groups. The first group comprised psychiatric inpatients without a history of suicide attempts and who were admitted to the psychiatric hospital within the same time frame as the cases. The second group comprised individuals recruited from the community or from non-psychiatric hospital services without history of suicide attempts. Cases were age (± five years) and sex matched to controls.

This study was approved by the Hamilton Health Sciences (#10-661) and St. Joseph's Healthcare Research Ethics Boards (#11-3479). Our findings are reported in accordance with the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[26]

4.3.2 Procedure and Data Collection

Potentially eligible inpatients were consecutively approached by trained research personnel who provided detailed information about the study and obtained written consent upon agreement to participate. For community control recruitment, researchers distributed advertisements in general hospitals and community settings requesting volunteers to participate in the study. Data were collected from each participant by trained research personnel who conducted a face-to-face structured interview consisting of validated rating scales and questionnaires. Data collected included sociodemographic factors (age, sex, socioeconomic status). Validated questionnaires included the Pierce Suicide Intent Scale[27] to assess circumstances and intent regarding participants' suicide attempts, the Mini-International Neuropsychiatric Interview (M.I.N.I.)[28] to assess psychiatric disorders, and the Physical Activity Questionnaire[29] which was administered to assess physical activity specifically during leisure time given that the majority of cases were unemployed (73·49%). Dietary patterns were measured with a short food frequency questionnaire (SFFQ) that assessed the intake of the following food groups over the past year: fish and seafood, nuts, fruits, and vegetables. A typical serving size for each food item was provided and participants were asked to report the number of times that they consumed a serving of each particular food group per day, per week, or per month. These selections were then converted into the average daily intake in grams per day using reference values from the SHARE FFQ,[30] a FFQ designed to be generalizable to a Canadian population including different ethnic groups.

Research personnel measured participants' height, weight, and waist circumference using standardized procedures. Height was measured in centimeters (cm). A standardized scale was used to record weight in kilograms (kg) rounding to one decimal place. Waist-circumference was measured to the nearest 0·1 cm at the end of a normal expiration, using a non-stretchable standard tape measure attached to a spring balance exerting a force of 750 grams.

4.3.3 Laboratory Methods

Blood samples were collected and assayed for serum total cholesterol using the Beckman UniCelDxC600 Reagent (Synchron Systems Cholesterol Reagent). Serum samples were analyzed blinded to the case/control status. After 30 minutes of clotting time, tubes were spun at 1500 x g (3000 rpm) for 15 minutes until blood was well separated. Serum samples were then aliquoted and stored in cryrovials within 2 hours of collection, then frozen in liquid nitrogen (- 196°C) at the Clinical Research and Clinical Trials Laboratory, Hamilton.

4.3.4 Statistical Analyses

STATA version 13 was used to perform all analyses. Sample characteristics are summarized in Table 1 as mean and standard deviation (SD) for continuous variables and as frequency (percent) for categorical variables. We performed student's t-tests and Analysis of Variance (ANOVA) to compare continuous variables across different study groups and chi-square (χ^2) tests to compare proportions for categorical variables. Non-parametric equivalent tests were used for continuous variables that were not normally distributed and Fisher's Exact Test when one or more expected values in the contingency table were below 5.

Estimates of association for each variable were assessed using logistic regression analyses to compute odds ratios [ORs] and accompanying 95% confidence intervals (CIs), and p-values adjusted for age and sex. The level of significance was set alpha = 0·05. A multivariable logistic regression model was also created using all study variables to assess the association between each metabolic variable of interest while controlling for the effects of all other variables. We present the results pictorially for all regression analyses (Figures 4.4.1a-c).

We used unmatched analyses because perfect matching was not feasible and would result in exclusion of participants reducing sample size. In our primary logistic regression analyses, the psychiatric inpatients and community members were combined as a single comparator group. Subgroup analyses were conducted using logistic regression to compute separate odds ratios and 95% CIs when cases were compared to each control group separately. The Hosmer-Lemeshow test was used to assess the goodness-of-fit of each logistic regression model.

As a sensitivity analysis, multiple imputation using chained equations was performed to adjust for the missing data in the age/sex and multivariable models. Age, sex, obesity, waist circumference, serum total cholesterol, physical activity, tobacco use, and diet were used to aid in the multiple imputation prediction of missing values.

4.4 RESULTS

The final study sample comprised 281 individuals, including 84 cases and 197 controls (psychiatric n= 104, community n= 93). Figure 1 outlines the recruitment flow diagram. The mean age of cases and controls were 43·00 years (SD = 14·02) and 45·66 years (SD = 15·99) respectively. The case group included 52·38% (n=44) females and the control group included 49.75% females (n=98). The majority of the cases were European (Caucasian) (91·67%), while 72.82% of controls were European (Caucasian) and the next most common ethnicity among controls was African (black) (12.82%). Table 4.4a provides the study participants' characteristics. Table 4.4b summarizes the primary metabolic factors of interest by study group.

4.4.1 Overall Effect of Risk Factors

A. Age and sex adjusted model:

Figure 4.4.1a summarizes the overall odds ratios for individual risk factors adjusted for age and sex (a) and multivariable adjustment for all risk factors (b). Physical activity (mild (OR 0·31, 95% CI 0·16-0·62, p = 0·001) and moderate/strenuous (OR 0·32, 95% CI 0·16-0·64, p = 0·001)) during leisure time was associated with a decreased risk of suicide attempts compared to a sedentary lifestyle. Current (OR 3·15, 95% CI 1·66-5·95, p < 0·001) and former (OR 2·09 95% CI 1·04-4·19, p = 0·039) use of tobacco products was associated with an increased risk of suicide attempts. Obesity and overweight (BMI > 25), abdominal obesity (waist circumference > 102cm men, > 88 cm women), and serum total cholesterol were not significantly associated with suicide attempts (4.4.1a, p-values > 0·05).

Daily food consumption in grams per day was split into tertiles and individuals in the upper and middle tertile were compared to those in the lowest tertile for each food group. Cases reported less fish/seafood, nuts, and fruits and vegetables intake on average; however, only daily consumption of nuts was significantly associated with a decreased risk of suicide attempts among those in the middle tertile (but not the highest tertile) compared to those in the lowest tertile (OR 0·51, 95% CI 0·28-0·92, p = 0·026).

B. Multivariable adjusted model:

The multivariable logistic regression model including all variables (age, sex, obesity/overweight, abdominal obesity, exercise, serum total cholesterol, tobacco use, and dietary variables) demonstrated that current tobacco use (OR 2·25, 95% CI 1·07-4·73, p = 0·031) is significantly associated with an increased risk of suicide attempts. Mild (OR 0·35, 95% CI 0·16-0·76, p = 0·008) and moderate/strenuous (OR 0·42, 95% CI 0·19-0·95, p = 0·036) physical activity is also significantly associated with a decreased risk of suicide attempts (Figure 4.4.1a). Former tobacco use (OR 2·03, 95% CI 0·93-4·43, p=0·074) was no longer significant in the multivariable model. BMI, waist-circumference, serum total cholesterol, and each dietary food group are not associated with suicide attempts in this model.

4.4.2 Subgroup Analyses

Subgroup analyses (Figures 4.4.1b and 4.4.1c) revealed that the relationship between metabolic risk factors and attempted suicide differed depending on whether cases were compared to community or psychiatric controls. BMI, serum total cholesterol, and waist circumference remained unassociated with suicide attempts regardless of the comparator group. The magnitude of the association between current (OR 5.78, 95% CI 2.05-16.31,

p= 0·001) and former (OR 3.43, 95% CI 1.30-9.05, p= 0·013) tobacco use was increased when cases were compared to community controls (Figure 4.4.1b). Mild (OR 0.12, 95% CI 0.04-0.39, p< 0.001) and moderate/strenuous (OR 0.15, 95% CI 0.05-0.48, p= 0·001) physical activity was associated with a greater decreased risk of suicide attempts when cases were compared to community controls. When cases were compared to community controls, both the middle tertile (OR 0·35, 95% CI 0·17-0·70, p= 0·003) and upper tertile (OR 0·29, 95% CI 0·12-0·72, p= 0·008) of nut consumption were associated with a decreased risk of suicide attempts compared to those in the lowest tertile in age/sex adjusted models but not after multivariable adjustment. However, fish and fruit/vegetable consumption did not statistically differ between individuals who had attempted suicide and community controls. Tobacco use and moderate or strenuous exercise were no longer significantly associated with attempted suicide when psychiatric controls were used as the comparator group (Figure 4.4.1c).

4.4.3 Missing Data Management (Sensitivity Analysis)

The majority of participants, (n=270 (96·1%)), had their height and weight measured, 264 participants (94·0%) had their waist-circumference measured, and 263 (93·6%) participants had serum total cholesterol data. For questionnaires, 263 (93·6%) participants had completed the Physical Activity Questionnaire and Short FFQ and 273 individuals (97·2%) had self-reported their tobacco use. All participants had data on age and sex. However, in the multivariable logistic regression, 239 (85·1%) participants were included in the final model in a complete-case analysis. We performed multiple imputation as a sensitivity analysis to determine the impact of the missing data on our primary and subgroup analyses. The results were not changed in the imputed model as

current tobacco use remained significantly associated with an increased risk of attempted suicide (OR 2·41, 95% CI 1·21-4·79, p= 0·012) and physical activity remained associated with a decreased risk of attempted suicide (mild (OR 0·36, 95% CI 0·17-0·74, p= 0·006) moderate/strenuous (OR 0·39, 95% CI 0·18-0·85, p= 0·018)). Moreover, obesity, waist circumference, serum total cholesterol, and diet remained unassociated with attempted suicide (p-values >0.05). In the imputed multivariable subgroup models, tobacco use remained associated with an increased risk of attempted suicide and physical activity remained associated with a decreased risk attempted suicide when cases were compared to community controls (mild (OR 0·16, 95% CI 0·05-0·46, p= 0·006) moderate/strenuous (OR 0·20, 95% CI 0·07-0·57, p= 0·018)). Similarly, no metabolic factors or heath behaviours were significantly associated with attempted suicide in an imputed subgroup model comparing cases to psychiatric controls (p-values >0.05).

4.5 DISCUSSION

The present study sought to investigate metabolic factors and health behaviours in relation to suicide attempts, including obesity, physical activity, serum total cholesterol, tobacco use, and diet. While several of these variables have previously been investigated individually in relation to suicidal behaviour, our study is the first case-control study to comprehensively examine potential metabolic risk factors among individuals with suicide attempt compared to two types of controls.

Our results showed physical activity during leisure time was significantly associated with a decreased risk of suicide attempts relative to a sedentary lifestyle. These results are consistent with findings from a previous study that demonstrated an inverse association between physical activity and suicide risk in an inpatient sample of veterans.[31] Increased physical activity may have several advantages explaining the reported findings. Physical activity may improve quality of life of suicidal individuals by producing physical health benefits and by alleviating psychiatric and social disability.[32] In addition, perceived burdensomeness and thwarted belongingness are well supported cognitive constructs associated with suicidal behaviour.[33] Increased physical activity may decrease perceived burdensomeness by improving overall physical health, mood, and by producing a sense of accomplishment.[31] Exercise programs may help to reduce social isolation by offering opportunities for social connectivity.[32] Moreover, strenuous exercise may produce an increased release of endorphins which have been hypothesized to positively affect mood by binding with motivation and pleasure centres in the brain and altering neurotransmission.[34] It has been demonstrated that individuals with psychiatric disorders are less physically active than the general population,[32] and this was reflected by our

subgroup analyses which showed no significant differences in physical activity between cases and psychiatric controls, indicating that a decreased physical activity pattern is not unique to attempted suicide but is seen in all patients with psychiatric disorders.

Current and former use of tobacco products was significantly associated with an increased risk of suicide attempts. Our results confirm the findings of many previous studies that have identified an association between smoking and both completed and attempted suicide.[35] Several previous studies have compared smoking status and suicidal behaviour in community based samples; however, considering the high rates of smoking among psychiatric populations,[36] smoking may be difficult to identify as a risk factor for suicidal behavior among psychiatric patients.

Our data showed no significant association between excess body weight and risk of suicide attempts. This finding however is not consistent with several previous studies that reported a decreased risk of completed [3,10] and attempted[12,13] suicide in obese and overweight individuals. We believe one reason for this inconsistency is the lack of adjustment of confounding such as psychiatric disorders, self reported physical measurements, and the choice of comparator in the previous studies. The present study has addressed previous bias which may account for the previously reported spurious findings. For example, it is known that people tend to overestimate their height and underestimate their weight,[37] and self-reported assessments of BMI may have biased past results (e.g.[12,13]). Previous studies have assessed past-year[38] or lifetime suicide attempts[12,39,40] in relation to body weight or have assessed a longitudinal association between a single measure of BMI taken at baseline with suicide attempts that occurred years later.[41-43] Body weight is subject to change over time, perhaps to a greater degree in

the context of psychiatric and medical illness or major life stressors. Repeated measures of BMI in future prospective cohort studies are required for further support of an inverse association between BMI and suicidal behavior.

BMI does not distinguish between body weight that is carried as muscle or fat, and has been criticized as being an inappropriate measure of obesity for certain groups of individuals such as the elderly who may have atypical changes in muscle mass. Waist circumference is an alternative measure of obesity used to assess health risks associated with abdominal obesity and therefore if this measure of adiposity was used in previous literature addressing BMI and suicidal behavior, the results may have been different.

While previous evidence has suggested that low serum total cholesterol is a risk factor for suicidal behaviour,[16-18,44,45] our study demonstrated no association between total cholesterol and suicide attempts. Our findings are consistent with other reports that have failed to find a significant association between cholesterol and risk of suicidal behaviour.[19,20] It is important to adjust for psychiatric illness or to use psychiatric comparator groups to understand whether levels of cholesterol are related to suicidal behaviour and to rule out the possibility that low serum total cholesterol may be a marker of psychiatric illness (e.g. major depressive disorder) rather than suicidal behaviour itself.

Dietary consumption of foods rich in poly unsaturated fatty acids (PUFA) (e.g. nuts, fish/seafood) was lower among individuals with suicide attempts compared to community controls but not psychiatric controls, supporting the results of previous work.[23,24] However the FFQ used in the present study was limited to major food groups and therefore unable to provide detailed data on specific nutrients. Further studies should consider more detailed diet questionnaires or food records which may confirm whether

lower consumption of fish and nuts among those attempting suicide is related to lower intake of PUFA and suicide risk.

Many previous studies investigating BMI, cholesterol, and other factors potentially related to suicidal behaviour have compared cases to medically and psychiatrically healthy individuals. While conventional risk factors of suicidal behaviour may dramatically differ between individuals who are suicidal and healthy community members,[6] these differences may not be as strong when individuals who attempted suicide are compared to psychiatric individuals with no history of suicide attempts. This was reflected by our subgroup analyses which revealed that exercise and tobacco use were only significantly associated with attempted suicide when cases were compared to community controls but not when they were compared to psychiatric controls. It is imperative to identify risk factors that distinguish patients with psychiatric disorders who made a suicide attempt from psychiatric patients without history of suicide attempts as individuals with psychiatric disorders are the most vulnerable population for suicidal behaviour.[6]

4.5.1 Strengths and Limitations

Strengths of this study include the inclusion of multiple comparator groups from psychiatric and community populations, and the quality of assessing suicide attempts which were relatively recent (within 3 months of recruitment) and required hospitalization. BMI, waist-circumference, and serum total cholesterol were measured robustly. A sensitivity analysis was conducted to multiply impute missing data, and the results were consistent with our complete-case analyses suggesting minimal bias due to missing data.

There are several study limitations that should be considered. Firstly, our study is cross-sectional in design, precluding the inference of causal relationships between risk factors investigated and suicide attempts. It is possible that some variables were non-significantly associated with risk of attempted suicide due to the modest statistical power in our regression analyses.

4.5.2 Conclusions

This study found that smoking is associated with increased risk of suicide attempts while physical activity is protective against suicide attempts**.** Future intervention and treatment strategies should focus on integrating smoking cessation and exercise as means of alleviating factors contributing to increased suicide risk.

4.6 ACKNOWLEDGEMENTS, FUNDING, AND AUTHOR CONTRIBUTIONS

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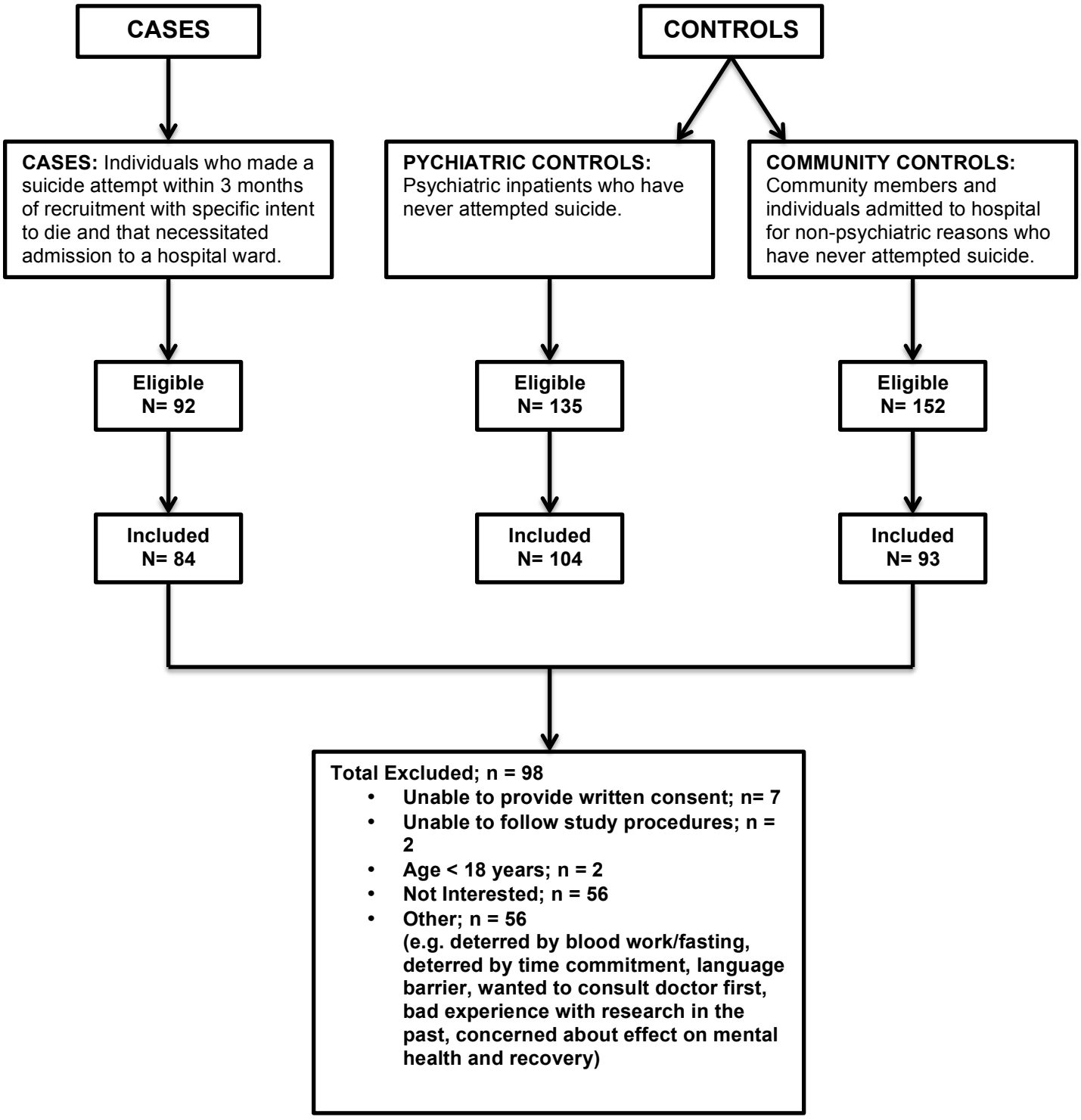
4.7 FIGURES AND TABLES



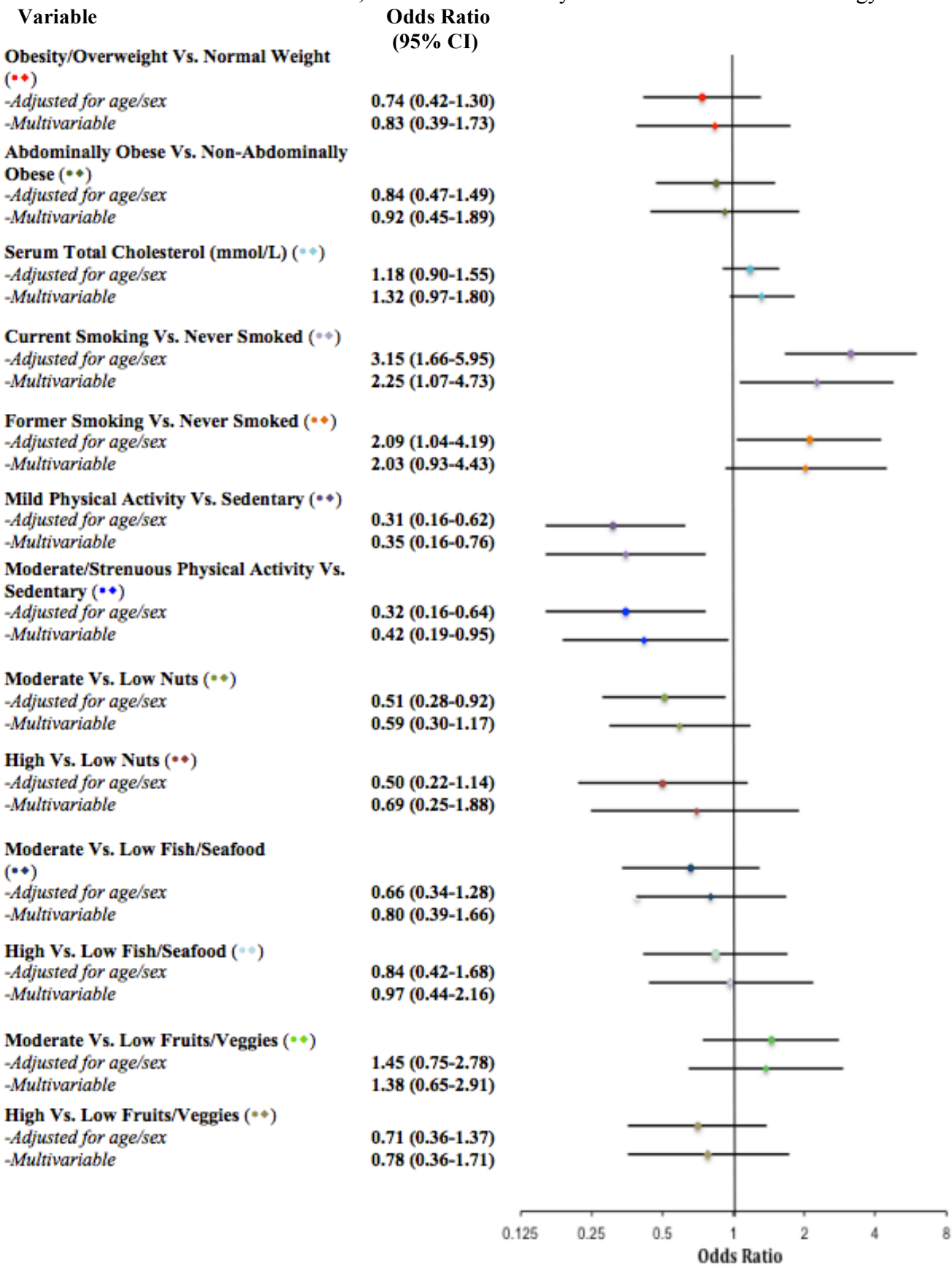


Figure 4.4.1a Primary Logistic Regression Analyses: Forest plot summarizing the odds ratios (OR) and confidence intervals (CI) from multivariable (•) and age/sex (⬥) adjusted logistic regression analyses when treating the psychiatric inpatients and community members as a combined control group. Multivariable analysis included age/sex and all variables listed in the forest plot.

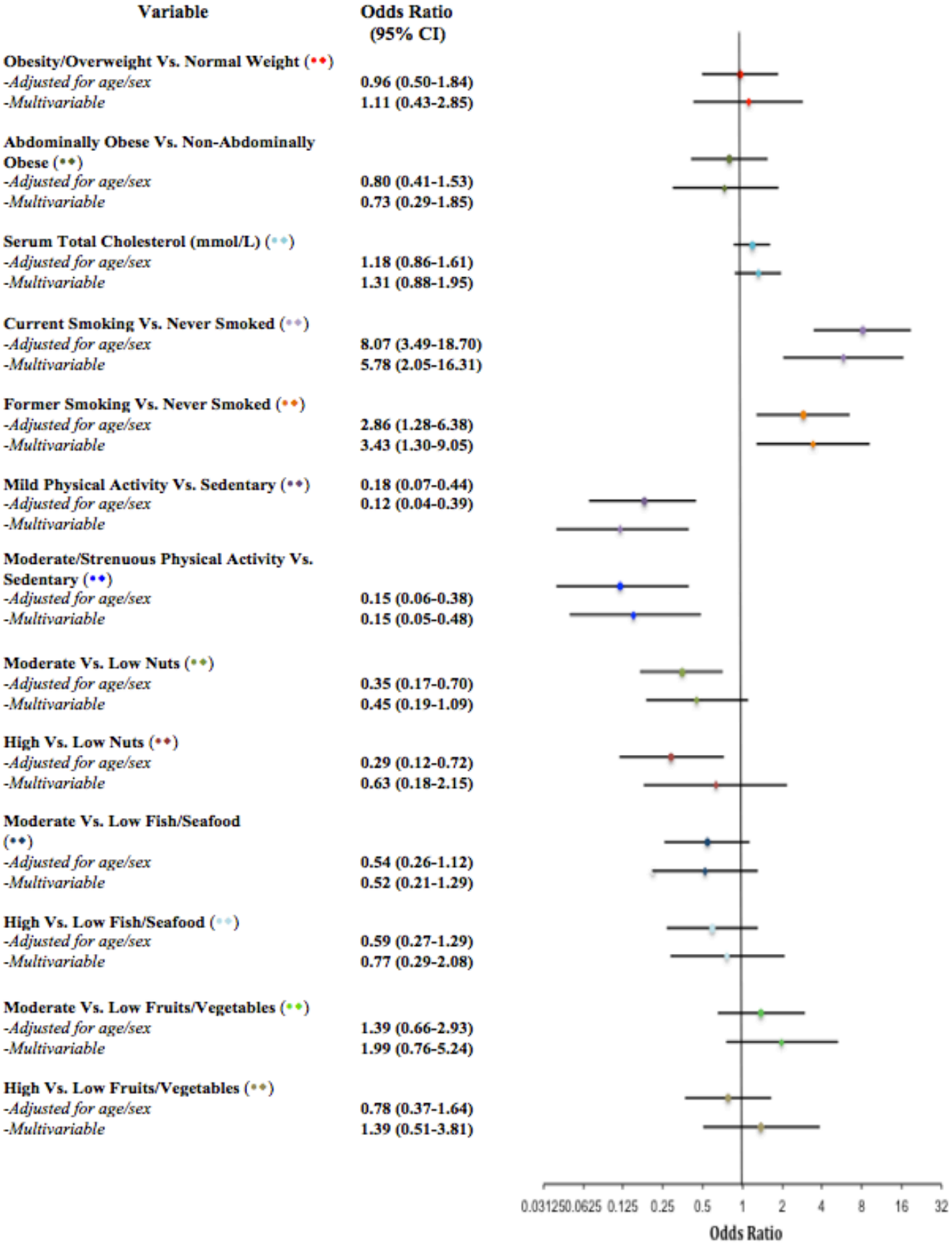


Figure 4.4.1b Subgroup Logistic Regression Analyses: Forest plot summarizing the odds ratios (OR) and confidence intervals (CI) from multivariable (•) and age/sex (⬥) adjusted logistic regression analyses using only community members as the control group. Multivariable analysis included age/sex and all variables listed in the forest plot.

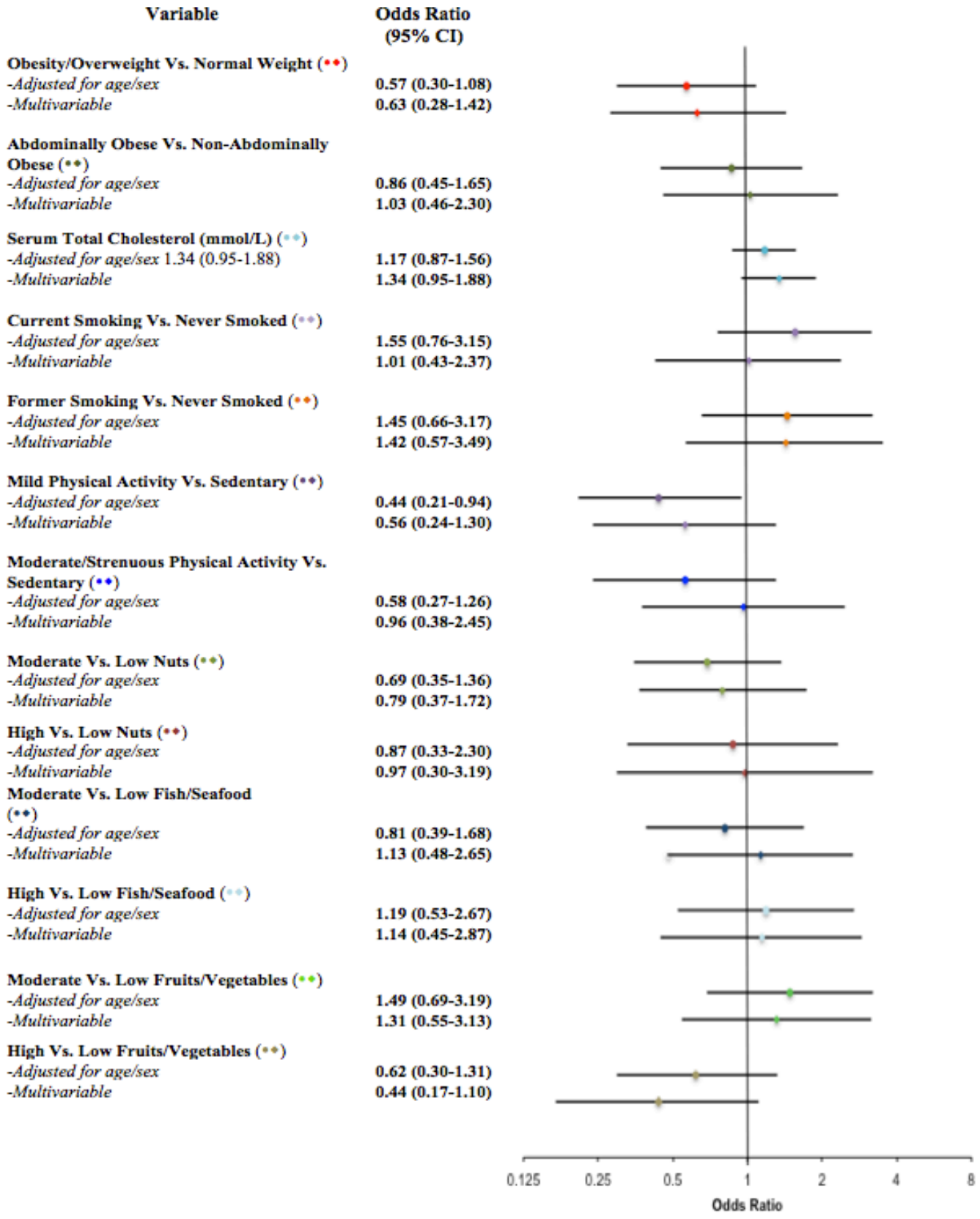


Figure 4.4.1c Subgroup Logistic Regression Analyses: Forest plot summarizing the odds ratios (OR) and confidence intervals (CI) from multivariable (•) and age/sex (⬥) adjusted logistic regression analyses when only using psychiatric inpatients as the control group. Multivariable analysis included age/sex and all variables listed in the forest plot.

Table 4.4a- Descriptive Characteristics of Cases and Controls						
	Cases (n= 84)	**Controls (n= 197)**	**Univariate Differences[1]**	**Psychiatric Controls (n=104)**	**Community Controls (n=93)**	**Univariate Differences[2]**
Demographic Information						
Age (years): mean (SD)	43.00 (14.02)	45.66 (15.99)	Z=1.25 p=0.212	45.04 (14.25)	46.35 (17.78)	F=1.05 df= 2, 278 p=0.353
Sex [n (% female)]	44 (52.38)	98 (49.75)	χ^2=0.164 df =1 p = 0.686	52 (50.00)	46 (49.46)	χ^2=0.169 df= 2 p = 0.919
Completed Post-Secondary Education or More, n (%)	35 (42.68)	121 (62.69)	χ^2=9.39 df =1 p = 0.002	50 (50.00)	71 (76.34)	χ^2=23.01 df= 2 p<0.001
Employed n (%)	22 (26.51)	88 (45.36)	χ^2=8.63 df =1 p=0.003	33 (32.67)	55 (59.14)	χ^2=22.80 df= 2 p<0.001

[1] Univariate differences[1] compares the cases to the psych/community controls combined. Univariate differences[2] 2 treats the psych/community controls as two separate groups.
[2] Analysis of variance tests (ANOVA) were used to compare means for continuous variables. Chi-square tests were used to compare proportions for categorical variables. Fisher's exact test was used for categorical variables when one or more values in the contingency table were below 5.

Table 4.4b- Metabolic Factors and Health Behaviours Across Groups						
	Cases (n= 84)	**Controls (n= 197)**	**Univariate Differences[1]**	**Psychiatric Controls (n=104)**	**Community Controls (n=93)**	**Univariate Differences[2]**
Demographic Information						
Body Mass Index (kg/m^2): Mean (SD)	27.85 (7.27)	28.40 (6.38)	z=1.07 p=0.284	29.05 (6.56)	27.72 (6.15)	F=1.13 df= 2, 267 p=0.323
Obese (BMI ≥ $30kg/m^2$): n (%)	23 (28.75)	64 (33.68)	χ^2=1.99 df=3 p=0.574	36 (37.11)	28 (30.11)	χ^2=4.26 df=6 p=0.641
Overweight (BMI 25-29.99 kg/m^2): n (%)	26 (32.50)	68 (35.79)	χ^2=1.99 df=3 p=0.574	36 (37.11)	32 (34.41)	χ^2=4.26 df=6 p=0.641
Normal Weight (BMI 18.5-24.99 kg/m^2): n (%)	28 (35.00)	54 (28.42)	χ^2=1.99 df=3 p=0.574	23 (23.71)	31 (33.33)	χ^2=4.26 df=6 p=0.641
Underweight (BMI <18.5 kg/m^2): n (%)	3 (3.75)	4 (2.11)	χ^2=1.99 df=3 p=0.574	2 (2.06)	2 (2.15)	χ^2=4.26 df=6 p=0.641
Waist-Circumference (cm): Mean (SD)	Males: 90.34 (17.76) Females: 87.5 (21.95)	Males: 95.34 (16.50) Females: 82.37 (18.24)	Z=0.44 p=0.681	Males: 92.49 (18.49) Females: 82.79 (18.35)	Males: 98.32 (13.70) Females: 81.93 (18.31)	F=0.51 df= 2, 261 p=0.600
Serum Total Cholesterol (mmol/L): Mean (SD)	4.78 (1.12)	4.64 (0.96)	Z=-0.46 p=0.649	4.63 (1.02)	4.65 (0.90)	F=0.54 df= 2, 260 p=0.581
Tobacco Use						
Current Tobacco Use: n (%)	35 (43.21)	46 (23.96)	χ^2=12.78 df=2 p=0.002	35 (35.35)	11 (11.83)	χ^2=28.57 df=4 p<0.001
Former Tobacco Use: n (%)	22 (27.16)	49 (25.52)	χ^2=12.78 df=2 p=0.002	26 (26.26)	23 (24.73)	χ^2=28.57 df=4 p<0.001
Never Tobacco Use: n (%)	24 (29.63)	97 (50.52)	χ^2=12.78 df=2 p=0.002	38 (38.38)	59 (63.44)	χ^2=28.57 df=4 p<0.001
Physical Activity						
Mainly Sedentary: n (%)	30 (49.47)	32 (17.11)	χ^2=15.04 df=2 p=0.001	23 (24.47)	9 (9.68)	χ^2=22.25 df=4 p<0.001
Mild Exercise: n (%)	22 (28.95)	77 (41.18)	χ^2=15.04 df=2	39 (41.49)	38 (40.86)	χ^2=22.25 df=4

			p=0.001			p<0.001
Moderate/Strenuous Exercise: n (%)	24 (31.58)	78 (41.71)	χ^2=15.04 df=2 p=0.001	32 (34.04)	46 (49.46)	χ^2=22.25 df=4 p<0.001
Play sports or exercise during leisure time: n (%)	20 (26.32)	70 (37.43)	χ^2=2.97 df=1 p=0.085	28 (29.79)	42 (45.16)	χ^2=7.88 df=2 p=0.019

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CHAPTER 5

5.1 THESIS CONCLUSION

5.1.1 Overview

While some suicide risk factors remain beyond anyone's control, others can be clinically managed, modified, and mitigated. This thesis provides novel evidence regarding the association between several potentially modifiable metabolic factors and suicidal behaviour. Body mass index (BMI) is a factor that can be measured and managed in clinical settings and has been suggested to controversially play a role in suicide risk assessment. This thesis provides a comprehensive systematic summary of the literature of the association between BMI and suicidal behaviour. A meta-analysis demonstrated that underweight is associated with an increased risk of suicide and that obesity and overweight are associated with a decreased risk of suicide relative to normal weight. Evidence for an association between BMI and attempted suicide remains equivocal. An association between BMI and suicidal ideation may be confounded by self-esteem, body weight perception, depression, and physical illness. The case-control study of this thesis identified several potentially controllable health behaviours that may mitigate suicide risk including increased physical activity and decreased tobacco use. This thesis calls into question the influence of other factors that were previously believed to be important predictors of attempted suicide including serum total cholesterol and obesity.

5.1.2 Body Mass Index and Suicidal Behaviour

The systematic review and meta-analysis conducted for this thesis demonstrated strong evidence of an inverse association between BMI and completed suicide, unclear evidence of an association between BMI and attempted suicide, and no association between BMI

and suicidal ideation. Results from the meta-analysis suggest that underweight patients with preexisting risk factors for suicidal behaviour (e.g. psychiatric illness, history of suicide attempts) should be monitored for increased risk of suicidality. It remains unclear why obesity and overweight is associated with a decreased risk of death by suicide relative to normal weight. A plausible mechanism is the likelihood to select particular methods of suicide and case-fatality associated with particular methods of suicide. Specifically, obese and overweight persons may be less likely to choose more fatal methods of suicide such as hanging and jumping, and may be less likely to die by intentional overdose or self-poisoning due to a slower rate of metabolism. Further prospective research involving repeated measured of BMI is needed to clarify the association between BMI and attempted suicide. Novel research is needed to study body-weight perception and body related self-esteem in association with risk of suicidal behaviour as these cognitive factors appeared to confound or mediate any association between BMI and suicidal ideation.

5.1.3 Metabolic Factors and Attempted Suicide

The primary study in this thesis is the first case-control study to comprehensively examine metabolic factors in relation to attempted suicide as compared to two comparator groups (psychiatric and community controls). Given that we found a strong association between increased physical activity and decreased risk of attempted suicide when those who had attempted suicide were compared to community controls, integrating exercise into future intervention and treatment strategies could make a significant difference for people at risk of taking their own lives. Furthermore, we found that current tobacco use was associated with a greater risk of attempted suicide, and smoking

cessation programs may be valuable in suicide prevention and rehabilitative efforts. Conversely, several metabolic factors previously thought to affect suicidal behaviour – BMI, abdominal obesity, and serum-total cholesterol – demonstrated no significant association, suggesting that suicide prevention efforts might better be focused elsewhere. Finally, while people at risk of attempting suicide tend to use more tobacco products and exercise less, so do non-suicidal psychiatric patients. For this reason, it remains unclear whether smoking and physical activity habits represent a useful clinical predictor of suicide risk. While future research will offer additional clarity as to which factors most affect those at risk, this current study already provides important direction for prevention and intervention strategies.

5.1.4 Future Directions

Future studies investigating the role of BMI in relation to suicidal behaviour should aim to explore potential mechanisms underlying the inverse association between BMI and completed suicide. Studies may explore effect modification by the method of suicide to determine whether body weight affects the choice of method used to attempt suicide and the case-fatality associated with a particular method of suicide. Prospective research with repeated measures of BMI are needed to strengthen the evidence of an association between BMI and suicidal behaviour. Research is needed to study body weight perception and self-esteem in relation to suicidal ideation and suicide attempts given that these related cognitive factors were demonstrated to confound the association between BMI and suicidal thoughts.

A larger study with more detailed and varied measures of physical activity (e.g. step-counter, Fitbit) is needed to replicate the relationship between increased physical activity

and decreased risk of attempted suicide. Future studies may also explore whether the benefits of increased physical activity also mitigate suicidal ideation. A randomized controlled trial may be conducted to explore the effects of an exercise program on subsequent suicidal behaviour among those with a history of attempted suicide or severe suicidal ideation.

Among the most important take away messages from this thesis is the importance of including a psychiatric comparator group when conducting a study on suicidal behaviour. Individuals living with a psychiatric or substance abuse disorder are the most vulnerable to have suicidal tendencies and it is vital to identify risk factors that distinguish individuals living with a psychiatric disorder who attempt suicide from those who do not. This was seen in our subgroup analyses which revealed that levels of physical activity and tobacco use only differed when those when those who attempted suicide were compared to community members opposed to psychiatric inpatients who had never attempted suicide.

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SYSTEMATIC REVIEWS

PROTOCOL Open Access

Association between body mass index and suicidal behaviors: a systematic review protocol

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Abstract

Background: Suicide is among the leading causes of death worldwide. Suicide attempts and suicidal ideation are more common than completed suicide and are associated with psychological distress. These behaviors are considered risk factors of completed suicide. Considering the psychosocial stigma and medical comorbidities associated with obesity, an accumulating body of studies have investigated body mass index (BMI) as a potential risk factor of suicide. However, several cohort studies have demonstrated an inverse relationship between BMI and completed suicide, suggesting a protective effect of increasing BMI against completed suicide. The association between BMI and attempted suicide is more equivocal, with several studies reporting both positive and negative relationships between BMI and attempted suicide. The primary objective of this study is to systematically review the literature to determine the association between BMI and suicidal behavior (including completed suicide, attempted suicide, suicidal ideation) in an adult population (18 years and older). The secondary objective is to explore whether sex, age, and the method used in suicide modify the relationship between BMI and suicidal behavior.

Methods/design: An electronic search will be conducted using PubMed/MEDLINE, PsycINFO, CINAHL, and EMBASE using a predefined search strategy; databases will be searched from their inception. Two authors (SP and RE) will independently screen articles using predefined inclusion and exclusion criteria and will extract pertinent data using a pilot tested extraction form. At all levels of screening, discrepancies between the two authors will be resolved by consensus, and in the case of disagreement, by consulting a third author (ZS). The primary outcomes include the association between BMI and completed suicide, attempted suicide, and suicidal ideation. If appropriate, a meta-analysis will be conducted. Risk of bias and quality of evidence will be assessed.

Discussion: The results of this systematic review will inform health care professionals and researchers about whether BMI has a significant role in suicidal behavior and psychological well-being.

Systematic review registration: PROSPERO CRD42014014739.

Keywords: Suicide, Attempted suicide, Suicidal ideation, Suicidal behavior, Body mass index, BMI, Obesity, Systematic review, Protocol

Background

Suicide is a significant problem throughout the world, impacting society from a public health, community, indi- vidual, and often a family perspective. Every year, over 800,000 lives are claimed by suicide [1]. Suicide is a com- plex phenomenon and requires evidence-based guidelines designed to recognize and mitigate modifiable suicide risk factors. A previous suicide attempt is considered a significant predictor of completed suicide in the general population [2,3]. Attempted suicide occurs 10 to 20 times more frequently than completed suicide [4]. Suicidal behaviors entail a complex set of ideas, thoughts, plans, and actions, which imply intention to end one's life [4]. There are several well-established risk factors that collectively affect an indi- vidual's vulnerability to suicidal behavior, including psychi- atric and substance use disorders, lack of social support, family environment (for example, disrupted marital status),

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the occurrence of a major life stressor (for example, unemployment, grief), and various demographic factors, such as higher risk of attempted suicide among females and a greater risk of suicide completion among males [4-7]. Novel potential risk factors including biological markers, such as serum cholesterol [8], and physical measurements, such as body weight, have yet to be fully elucidated in their poten- tial impact on suicide. The present systematic review will focus on the association between body mass index (BMI) and suicidal behavior, including completed suicide. The number of obese and overweight people worldwide has dra- matically increased over the past three decades, with the number of overweight and obese adults and children rising from approximately 857 million individuals in 1980 to 2.1 billion in 2013 [9]. Excess body mass is a known risk factor of chronic illness, including cardiovascular disease, type 2 diabetes, osteoarthritis, and hypertension [10,11]. Further- more, being overweight or obese is associated with social stigma among certain cultures, and negative attitudes to- wards obese individuals are evidently present in North American society [12-14]. As the prevalence of obesity rises globally [9], it is important to investigate the psychosocial burden that adiposity may have on affected individuals. Thus, an emerging body of research has attempted to in- vestigate the relationship between BMI and suicidal behav- ior. Collectively, these investigations have recruited samples across all weight groups, from underweight to morbidly obese individuals. The majority of such studies have used BMI as a measure of relative body weight and as a marker of adiposity [15-21].

Considering the psychosocial stigma [14] and health related complications [10] of obesity, several systematic reviews and meta-analyses have suggested a positive association between obesity and depression [22-24]. Furthermore, about 60% of suicides occur among indi- viduals with mood disorders [4], and 10% to 20% of pa- tients hospitalized for depression commit suicide [25]. If obesity is indeed positively associated with depression, one might expect that a greater number of completed suicides are occurring among overweight and obese individuals. Surprisingly, however, several retrospective cohort studies have reported an inverse association between completed suicide and BMI, often in a dose- response type pattern, with the risk of suicide diminish- ing per unit increase in BMI [15-18,21,26]. The inverse association between suicide and BMI has been replicated in different countries using adult samples, albeit using predominantly male and Caucasian cohorts, including Swedish male conscripts [15], United States' (US) male healthcare professionals [21], Norwegian men and women from a community cohort [18], a cohort of Danish men using conscription data [19], and a US general population cohort [17]. An American ecological study [27] reported that statewide obesity rates were inversely correlated with rates of completed suicide, and another ecological study conducted in the United Kingdom [28] similarly reported this inverse relationship in elderly females but found no such association among elderly males. Newer studies have since replicated an inverse relationship between BMI and completed suicide using longitudinal cohort designs [29,30], as well as with a case-control post-mortem investi- gation [31]. However, some studies have reported either no association [32-34], a J-shaped association [35], or a positive association between BMI and competed suicide [20,36]. A recent case-control post-mortem investigation [33] conducted in Australia found no association between BMI and completed suicide, failing to replicate the results of the aforementioned post-mortem design [31] out of Germany. Two recent longitudinal studies using Taiwanese [35] and German [36] cohorts reported a J-shaped and a positive relationship (respectively) between BMI and suicide. In summary, while many of the aforementioned studies point towards an inverse relationship between BMI and risk of completed suicide, the relationship remains equivocal and may depend on demographics such as sex or ethnicity. Moreover, the potential explanations for this apparent para- doxical inverse relationship remains unclear, with authors suggesting several potential mediating or correlative factors including impulsivity and case-fatality in relation to the chosen method of suicide [26,37], serum levels of cholesterol and its relation to central serotonin [8], leptin and leptin resistance [38,39], an insulin resist- ance based model [40], and dietary factors such as es- sential fatty acid intake [41].

The relationship between BMI and attempted suicide is also inconsistently reported with fewer studies com- pared to completed suicide, and the results are mixed [19,29,34,42-51]. Cohort studies have demonstrated a decrease in risk for attempted suicide associated with increasing BMI [19,29,34,45], while other studies have found a positive association between overweight and obese and suicide attempt [42,43,47,48,51]. Many of the studies examining BMI and attempted suicide are cross- sectional in design [42,44,46-49], thus precluding the ability to infer temporal or causal pathways. Further- more, sex may complicate the relationship between suicide attempts and BMI, as sex was an apparent effect modifier in some reports [42]. Additionally, suicidal ideation may have a different association with body weight. Only a few studies have examined the relation- ship between relative body weight and suicidal ideation [42,47,48,50,52], limiting our ability to draw any conclu- sions. Two previous reviews have been published regard- ing the relationship between body weight and suicidal behavior [53,54]. One review provided a systematic re- view of the literature [53]; the other provided a narrative summary [54]. Both reviews cited that the collective studies were too few in number and heterogeneous to

conduct a meta-analysis. Each review conducted a litera- ture search up to 2011, and Klinitzke [53] did not in- clude any studies published prior to January 2000. These reviews limited their searches to papers published in English, and Zhang [54] limited their search to PubMed only, precluding the inclusion of relevant articles from other databases. Zhang [54] did not present reasons for exclusion at each level of screening. Zhang reported on both adolescent and adult populations, and they classi- fied some studies as using adult populations despite such studies including individuals as young as 15 [55,56]. The inclusion of both adolescents and adults is viewed critic- ally due to differences in psychosocial development and differences in risk factors for suicide.

Since the conduct of these reviews, several observational studies have been published that have investigated body weight in relation to suicidal behavior [29-31, 33-36,48-52], and an updated systematic review is required to contextually interpret the evidence. In addition, few studies included women in their samples when investigat- ing BMI and suicidal behavior, and therefore, a more inclu- sive review will also help in understanding the association between BMI and suicidal behavior and the potential variation by sex.

Objectives

The present systematic review aims to elucidate the associ- ation between body mass index and suicidal behavior. More specifically, the review aims to answer the following re- search question: Is there a significant association between body mass index (BMI) and suicidal behavior (including completed suicide, attempted suicide, suicidal ideation) in an adult population (18 years and older)? A secondary objective will be to summarize evidence for specific factors in- cluding sex, age, and the method used in suicide to assess whether such variables modify the relationship between BMI and suicidal behavior.

Methods/design

Inclusion and exclusion criteria

The present systematic review will include published ob- servational studies that have reported results relating BMI to suicidal behaviors, including completed suicide, attempted suicide, and suicidal ideation, among an adult population defined as those who are 18 years or older. This adult population may include participants from popu- lation, clinical, and community-based samples. Considering that 90% of suicides occur in the context of a psychiatric disorder [4], adults from clinical samples who have a psychiatric disorder will be included as well. Other than age, no demographic limitations will be applied. Studies investi- gating the risk of suicide following medical treatments of obesity such as bariatric surgery or pharmacotherapy for weight loss will be excluded as the effects of medically induced weight change may affect the risk of suicidal be- havior independently of BMI. The primary outcome for this review is suicidal behavior, which includes suicidal ideation, attempted suicide, and completed suicide. These outcomes are further defined in Table 1, which highlights how they were described and measured in the literature.

Search strategy

All relevant studies will be sought and identified without any restrictions on language or time of publication. The following databases will be searched from inception: PubMed/MEDLINE, PsychINFO, EMBASE, and CINAHL.

Pertinent keywords and search terms including the associ- ated medical subject headings (MeSH) will be used in a predefined search strategy outlined in Table 2. The search will be limited to human studies. A broad search will be conducted including titles, abstracts, and keyword fields to capture studies whose title may not directly reflect the topic being investigated. Additionally, the reference lists from re- trieved full-text articles and past reviews will be manually scanned for a more comprehensive search, and Cochrane review bibliographies will be hand searched. Reviews, commentaries, abstracts, and gray literature will be excluded.

Data screening

Two independent raters (SP and RE) will screen all cita- tions and abstracts retrieved using the search strategy outlined in Table 2, and they will subsequently identify all eligible articles according to pre-established criteria for full-text review. Discrepancies throughout the review process will be resolved by discussion and reevaluation. In cases where a consensus is not reached, a third author (ZS) will determine eligibility. Ineligible studies will be excluded from full-text review, and the reasons for ex- clusion will be documented. Inter-rater agreement will be calculated using the Kappa statistic [57] for each phase of screening. Authors of the included studies will be contacted if further data clarification is required.

Data extraction

The two raters (SP and RE) will independently extract data from the studies using a premade data extraction form that will be pilot tested before screening (see Additional file 1). The information collected will include the first author and year of publication, the name of the journal, the study title, the study design, the city and country of publication, the type of the study (for example, survey, cohort), and a brief description of study participants including the number of men and women, the number of completed suicides and attempted suicides when appropriate, mean age, and ethni- city. A summary of each study's results will be reported in- cluding the primary and secondary outcome measures, statistical analysis, and major conclusions. Authors will be contacted in the event of missing or incomplete data for

Table 1 Definitions and statistical measures of suicidal behavior outcomes

Outcome	Definition	Measurement of variable	Statistics	Studies
Completed suicide	Death caused by self-inflicted injurious behavior intended to end one's own life	International classification of diseases (eighth, ninth, or tenth revisions) using diagnostic codes (E950-E950: ICD8, ICD9) or (X60-X84: ICD10)	Cox proportional hazard model	[15-21,26-28,32]
			Linear regression	
			Logistic regression	
		In some studies, associations were also estimated with undetermined deaths (deaths where it was uncertain whether the cause was suicide; (E980-E989: ICD 8, ICD 10) or codes (Y10-Y34, ICD 10))	Pearson correlation (ecological analysis)	
			Spearman's rank correlation (ecological analysis)	
			Chi-square	
			Wilcoxon-Mann-Whitney test	
		Verified using mortality registries (for example, National Death Registry, National Death Index), by next of kin and/or using pathology and medical records.	Incidence rate ratio	
Attempted suicide	Potentially self-injurious behavior with a non-fatal outcome for which there is either explicit or implicit evidence that the person intended to kill him or herself [63].	Hospital Discharge Registries or Medical Records using aforementioned diagnostic codes for intentional injuries: (E950-E950: ICD8, ICD9) or (X60-X84: ICD10).	Cox proportional hazard model	[42-47] 2012 to present: [29,34,48-51]
			Logistic regression	
		Self-reported using questionnaire (for example, Suicide Behaviours Questionnaire - Revised, AUDADIS, M-CIDI)	Incidence rate ratio	
		Self-reported using single-question (e.g. "How often have you already tried to take your own life")		
Suicidal ideation	Having thoughts, plans, and/or impulses for suicidal behavior, including contemplation of attempting or completing suicide.	Self-reported using questionnaire (for example, Depressive Symptom Index - Suicidality Subscale, Suicide Behaviors Questionnaire - Revised).	Logistic regression Linear regression	[42,47] 2012 to present: [48,50,52]

clarification. If the extracted data are deemed to be suitable for a meta-analysis, individual study results will be com- bined to produce a summary estimate using a random- effects model as a certain degree of heterogeneity in in- cluded studies is expected.

Risk of bias assessment

The two independent raters (SP and RE) will independ- ently assess the risk of bias of studies included in the full-text review using the Newcastle-Ottawa scale (NOS) [58]. An adapted version of a modified NOS developed by Bawor et al. [59] will be used to assess risk of bias of observational studies included in this review (see Additional file 2). Bawor et al.'s modified NOS includes seven questions among four domains of risk assessment: methods for selecting study participants (selection bias), methods to control for confounding (performance bias), statistical methods (detection bias), and methods of ex- posure and outcome assessment (information bias). Risk of bias will be measured using a scale ranging from 0 (high risk of bias) to 3 (low risk of bias), and question- specific descriptions including examples of varying de- grees of bias are included. Furthermore, categories per- taining to statistical methods, confounding effects, and reporting of missing data are included in this modified NOS to evaluate risk of biased methodology. Items from the original NOS pertaining to adequacy of follow-up, selection of participants (representativeness of sample), and ascertainment of outcomes, will be retained in the present adapted modified NOS, as these criteria are im- portant to potential studies that may be included in our review.

Statistical analysis and heterogeneity

The findings of this systematic review will be presented as a qualitative summary of the literature, and as a quan- titative summary estimate, if possible. In order to deter- mine the quality and validity of existing evidence on

Table 2 Search strategy (conducted on 5 January 2015)

Database	Search strategy
MEDLINE (*n* = 837)	1. exp Suicide/or suicid*.mp.
	2. exp Self-injurious behavior/or self-harm.mp.
	3. exp Body Mass Index/or body mass index.mp.
	4. BMI.mp.
	5. exp Body Weight/body weight.mp.
	6. exp Obesity/or obes*.mp.
	7. exp Overweight/or overweight.mp.
	8. 1 or 2
	9. 3 or 4 or 5 or 6 or 7
	10. 8 and 9
	11. limit 10 to humans
PsycINFO (*n* = 666)	1. exp Suicide/
	2. exp Attempted Suicide/or attempted suicide.mp.
	3. exp Suicidal Ideation/or suicidal ideation.mp.
	4. suicid*.mp.
	5. exp Self-Injurious Behavior/or self-harm.mp.
	6. exp Body Mass Index/or body mass index.mp.
	7. exp Body Weight/or body weight.mp.
	8. exp Obesity/or obes*.mp.
	9. BMI.mp.
	10. exp Overweight/or overweight.mp.
	11. 1 or 2 or 3 or 4 or 5
	12. 6 or 7 or 8 or 9 or 10
	13. 11 and 12
	14. limit 13 to human
EMBASE (*n* = 3688)	1. exp suicidal behavior/or suicid*.mp.
	2. exp automutilation/or self-harm*.mp.
	3. exp body mass/body mass index.mp.
	4. BMI.mp.
	5. exp body weight/body weight.mp.
	6. exp obesity/or obes*.mp.
	7. overweight.mp.
	8. 1 or 2
	9. 3 or 4 or 5 or 6 or 7
	10. 8 and 9
	11. limit 10 to human
CINAHL (*n* = 144)	1. (MH "Suicide+") OR "suicid*"
	2. (MH "Self-Injurious Behavior") OR "self-harm"
	3. (MH Body Mass Index) OR "body mass index"
	4. (MH "Body Weight+") OR "body weight"
	5. (MH "Obesity+") OR "obes*"
	6. "BMI"
	7. "overweight"
	8. 1 or 2
	9. 3 or 4 or 5 or 6 or 7
	10. 8 and 9 (limiters human)

BMI, body mass index.

BMI and suicidal behavior, the results of each study will be individually and collectively assessed in terms of their study design, statistical methods, and conclusions. The I^2 test statistic will be used to assess heterogeneity. An I^2 value greater than 40% will be used to define substantial heterogeneity; however, regardless of the amount of het- erogeneity across studies, a random-effects model will be employed when pooling the data in a meta-analysis. The random-effects model accounts for both within-study and between-study variability and it generally rep- resents a more conservative estimate than a fixed-effects model [60]. Three separate meta-analyses will be con- ducted to investigate the association between BMI and completed suicide, BMI and attempted suicide, and BMI and suicidal ideation. To qualitatively assess heterogen- eity, we will assess differences and similarities with respect to study samples, methods, and results. The defin- ition of outcome may act as an additional source of hetero-geneity, especially that of attempted and completed suicide (for example, deaths classified as overdoses).

As previously mentioned, women have a higher rate of attempted suicide in the general population, while men have a higher rate of completed suicide [4]. Therefore, the role of sex will be explored by stratifying results for males and females. Furthermore, it has been suggested that one's BMI may indirectly influence one's inclination towards a particular method of suicide, thus affecting the case-fatality of a suicidal act. For example, in a retro- spective cohort study of over one million Swedish male conscripts [45], Batty et al. reported a stepwise inverse association of decreasing attempted suicide with increasing BMI. However, they noted that the strongest associations were with those methods generally requiring greater phys- ical exertion and agility, such as hanging and jumping. These methods may be less likely to be used by those with greater BMI. Moreover, case-fatality of self-poisonings may be lowered among those with greater BMI due to greater body size and distribution of body fat [37,45]. Therefore, the role of the method used in attempted and completed suicides will be qualitatively commented on as a potential effect modifier of the relationship between BMI and attempted and completed suicide. Lastly, age will be quali- tatively examined as a potential effect modifier. Medical co- morbidity such as cancer that is associated with older age, weight loss, depression, or suicidal ideation, may produce a different relationship between BMI and suicidal behavior

among the young and elderly [37]. Furthermore, changes in muscle mass associated with aging may result in a less accurate assessment of obesity using BMI among the elderly [21].

Review Manager 5.3 (The Cochrane Collaboration, London, UK) will be used for all statistical and pooled analyses. The results of the pooled analysis will be summarized by calculating odds ratios [ORs] or hazard ratios [HRs] and 95% confidence intervals.

Presenting and reporting of results

Our systematic review will be conducted and written in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [61]. A summary flow chart will be used to outline the selection of articles and to display reasons for excluding articles (Figure 1). Summary tables will be used to present the relevant outcomes and details of each included study.

Egger's plot will be used to assess potential publication bias among the selected studies.

If the studies included in our systematic review are deemed suitable for pooling in a meta-analysis, the results of each analysis will be presented in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [62]. Forrest plots will be used to present individual and pooled study estimates, and tables will be used to summarize individual study characteristics.

Discussion

Body mass index may represent an important risk factor for suicidal behavior. The proposed systematic review will help to elucidate the association between BMI and suicidal behavior, allowing for better understanding of the controversial association between BMI and suicidal behavior. The paradox of an apparent inverse relationship between completed suicide and BMI remains to be

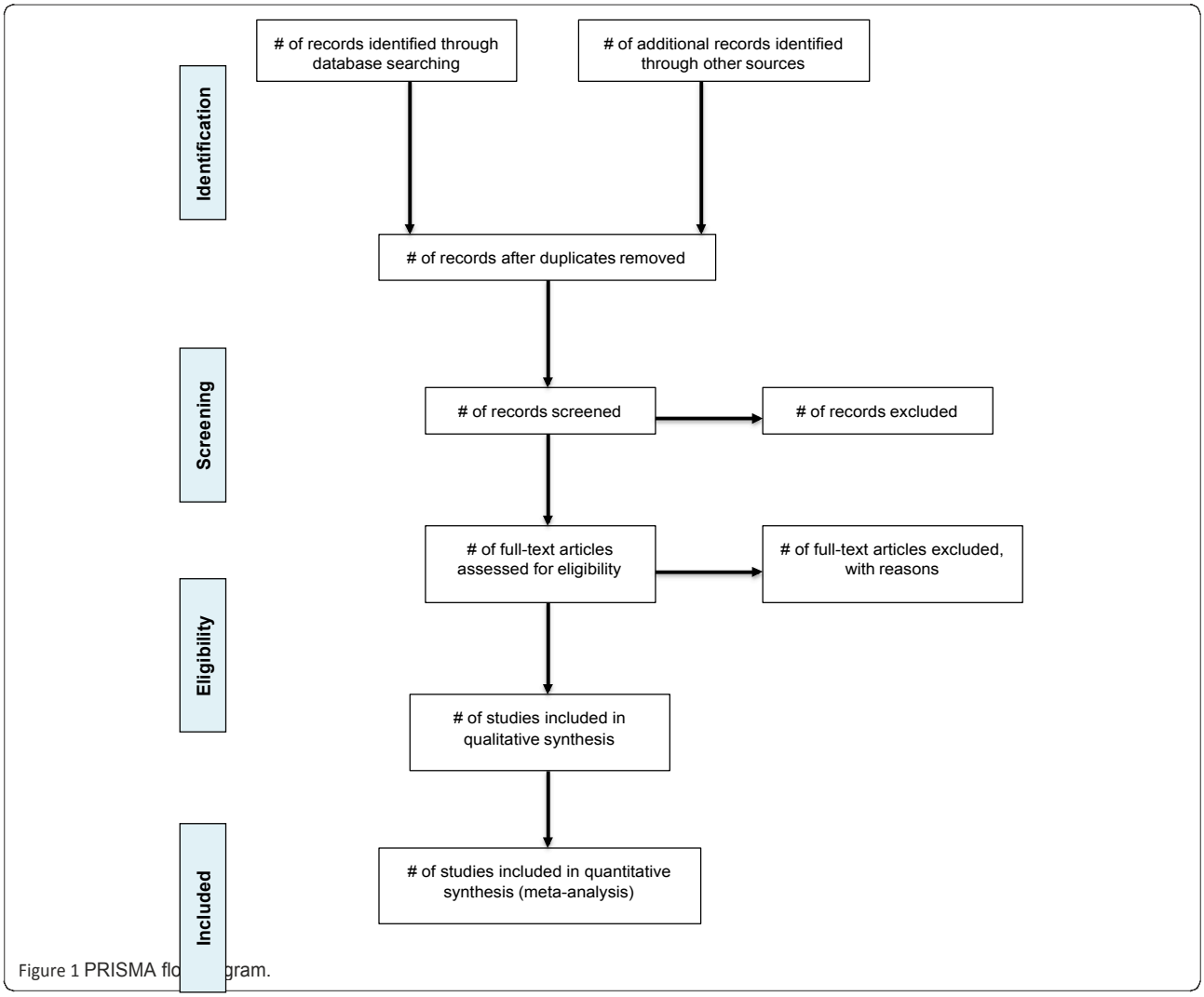

Figure 1 PRISMA flow diagram.

solved. Several potential mediators, modifiers, or confounders that explain the latter association may be identified when viewing the literature systematically. BMI appears to be differentially related to completed suicide and attempted suicide, and clarifying this association may help to better understand separate etiologies that distinguish completed from attempted suicide.

Additional files

Additional file 1: Data extraction form.

Additional file 2: Modified Newcastle-Ottawa scale.

Abbreviations

BMI: Body mass index; NOS: Newcastle-Ottawa scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SP helped in the conception and study design, manuscript writing, critical revision, development of data extraction form, revision of quality assessment tool, and final approval of the manuscript. RE helped to draft the manuscript, methodology and interpretation, critical revision, and final approval of the manuscript. MB helped in the critical revision, development of quality assessment tool, and final approval of the manuscript. BBD helped in the critical revision, development of quality assessment tool, and final approval of the manuscript. RD helped in the critical revision, methodology, and final approval of the manuscript. LT helped in the methodology, critical revision, and final approval of the manuscript. ZS helped in the conception and study design, methodology, critical revision, and final approval of the manuscript.

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