UNIVERSITI PUTRA MALAYSIA

BAYESIAN APPROACH TO META-ANALYSIS WITH JOINT MODELLING OF LONGITUDINAL AND TIME-TO-EVENT OUTCOMES IN DEMENTIA AND SUBTYPES

CHRIS BAMBEY GUURE

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By

CHRIS BAMBEY GUURE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

August 2018

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DEDICATION

To all members of my family

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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August 2018

Chairman : **Professor Noor Akma Ibrahim, PhD**
Faculty : **Faculty of Science**

Meta-analysis is a statistical approach that combines results from published literature in order to obtain an overall grand mean effect estimate. The main problem that affects meta-analysis is publication bias; the first part of this thesis thus seeks to address this problem. This work goes further to address heterogeneity which affects the mean effect being evaluated due to the combination of different studies. Meta-analyses of cognitive decline, Alzheimers disease, vascular dementia and all causes of dementia are undertaken to evaluate the effect of physical activity on these diseases. Dementia is an organic disorder, related to the physical deterioration of the human brain tissue that is detected after a number of medical examinations. The relationship between exercise and the risk of developing cognitive decline is further evaluated using data from the Osteoporotic Fracture Study in the United States. Meta-analytic data is obtained and used as a prior information to the secondary data. The final part of this thesis looks at a study in dementia where measurements are collected on death of participants in addition to other covariates over a period of time. These types of repeated measurements collected from each individual over time violate a number of statistical models assumptions, especially when the

interest is to determine the risk factors that affect the study outcome. The aim of this approach is to examine and use these measurements to predict dementia patients probability of survival in the future.

Copas selection model which was developed to assess and account for publication bias is implemented in this research. One major disadvantage of this model is that, it relies on a number of sensitivity analysis which results in many effect size estimates with even a single meta-analytic data. In order to overcome the problems of the Copas selection model, a new Bayesian prior known as triangular prior has been developed and used to fit the parameters of the Copas model via a probability distribution. The developed prior is assessed through sensitivity analysis with comparison to other priors. It is also applied to antidepressant meta-analytic dataset. The newly developed prior is further applied to a meta-analyses of dementia and its subtypes. In order to control for the heterogeneity (between-study variation), a proposed Bayesian non-parametric modelling is implemented via a Dirichlet Process. A power prior is also proposed and applied to the meta-analytic (historical) data that is used as a prior to determine whether exercise has any effect on cognitive decline. The power prior is transformed into probabilistic values out of which posterior estimates are obtained. To analyse the repeated measurements and the time to event data in order to assess their effect on dementia, we propose to use a joint modelling approach. The proposed modelling framework involves the standard and extended relative risk models as well as linear mixed effects sub-models on the repeated measures of the longitudinal covariate.

The results from the simulations indicate that the triangular prior should be used. The estimated number of studies was similar to that of the frequentist trim and fill method. Our analysis reveal a protective effect of 21% for high physical activity on all cause dementia with an odds ratio of 0.79, 95% Credible Interval (CI) (0.69,0.88), a higher and better protective effect of 38% for Alzheimer's disease with an odds ratio of 0.62, 95% CI (0.49,0.75), a 33% for cognitive decline with odds ratio of 0.67, 95% CI (0.55, 0.78) and a non-protective effect for vascular dementia of 0.92, 95% CI (0.62, 1.30). Statistically significant results were obtained when the informative prior formulated from the meta-analytic data was used at face value for higher against lowest with odds of 0.69 95% CI (0.58, 0.80) and moderate against lowest 0.63 95% CI (0.50, 0.79) physical activity. The joint modelling approach found a strong relationship between the 3MS scores and the risk of mortality, where every unit decrease in 3MS scores results in a 1.135 (13%) increased risk of death via cognitive impairment with a 95% CI of (1.056, 1.215).

The triangular prior is a better alternative prior to use. The prior gives an

overall or grand mean effect that is far better than conducting several sensitivity analysis. The implementation of the Dirichlet process in the meta-analyses overcomes the problem of heterogeneity. In evaluating the effect of exercise on cognitive decline with the power prior, it becomes clear that elderly women who engage in moderate exercise will have a reduced risk of developing cognitive decline. In the joint modelling of the longitudinal measurements, the results show that a decrease in 3MS scores has a significant increase risk of mortality due to cognitive impairment when implemented via the joint model but insignificant under the standard relative risk model.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENDEKATAN BAYES BAGI ANALISIS-META DENGAN PEMODELAN TERCANTUM BAGI KESUDAHAN LONGITUD DAN PERISTIWA MASA DIMENSIA DAN SUBJENISNYA

Oleh

CHRIS BAMBEY GUURE

Ogos 2018

Pengerusi : **Professor Noor Akma Ibrahim, PhD**
Fakulti : **Fakulti Sains**

Analisis-meta adalah pendekatan berstatistik yang menggabungkan hasil daripada literatur yang diterbitkan untuk memperoleh anggaran kesan min keseluruhan. Masalah utama yang mempengaruhi analisis-meta ialah kepincangan penerbitan; bahagian pertama tesis ini bertujuan untuk mengatasi masalah ini. Kajian ini dilanjutkan untuk menangani keheterogenan yang menjejaskan kesan min dinilai kerana gabungan pengajian berbeza. Analisis-Meta bagi kemorosotan kognitif, penyakit Alzheimer, demensia vaskular dan semua penyebab demensia dijalankan untuk menilai kesan aktiviti fizikal terhadap penyakit ini. Demensia adalah gangguan berorganik, yang berkaitan dengan kemerosotan fizikal tisu otak manusia yang dikesan selepas beberapa ujian perubatan. Hubungan antara senaman dan risiko menyebab kemorosotan kognitif akan dinilai selanjutnya menggunakan data dari Kajian Retakan Osteoporotik di Amerika Syarikat. Data Analitik-Meta diperoleh dan digunakan sebagai maklumat prior untuk data sekunder. Bahagian akhir tesis ini melihat kajian demensia di mana pengukuran diambil terhadap kematian peserta selain daripada kovariat lain dalam tempoh masa tertentu. Jenis pengukuran berulang yang dikumpulkan dari setiap individu dari masa ke

masa melanggar beberapa andaian model berstatistik terutamanya apabila kepentingannya adalah untuk menentukan faktor risiko yang mempengaruhi hasil kajian. Tujuan dari pendekatan ini adalah untuk mengkaji dan menggunakan ukuran ini untuk meramal kebarangkalian kemandirian pesakit demensia di masa hadapan.

Model pemilihan Copas yang telah dibangunkan untuk menilai dan mengambil kira kepincangan penerbitan dilaksanakan dalam kajian ini. Satu kelemahan utama model ini adalah ia bergantung kepada beberapa analisis kepekaan yang menyebabkan terdapat banyak anggaran kepada ukuran kesan walaupun untuk satu data analitik-meta. Untuk mengatasi masalah model pemilihan Copas, prior Bayesian yang baharu yang dikenali sebagai prior segi tiga telah dibangunkan dan digunakan untuk menyesuaikan parameter model Copas melalui taburan kebarangkalian. Prior yang dibangunkan dinilai melalui analisis kepekaan berbanding dengan prior yang lain. Ia juga digunakan untuk set data meta-analitik antidepresan. Prior yang baharu dibangunkan ini selanjutnya digunakan untuk analisis meta bagi demensia dan subjenisnya. Untuk mengawal keheterogenan (variasi antara kajian), model tak berparameter Bayesian telah dilaksanakan melalui Proses Dirichlet. Suatu prior kuasa dicadangkan dan diaplikasikan ke atas data analitik-meta (bersejarah) dan digunakan sebagai prior untuk menentukan sama ada senaman menpunyai kesan keatas kemorosotan kognitif. Prior kuasa dijelmakan kepada nilai kebarangkalian yang mana penganggar posterior diperolehi. Untuk menganalisis pengukuran berulang dan data peristiwa masa untuk menilai kesannya terhadap demensia, kami mencadangkan untuk menggunakan pendekatan pemodelan tercantum. Rangka kerja pemodelan yang dicadangkan melibatkan model risiko relatif piawai dan model risiko lanjutan serta sub-model kesan campuran linear pada ukuran berulang kovariat berlongitud.

Keputusan daripada simulasi menunjukkan bahawa, prior segi tiga patut digunakan. Anggaran bilangan kajian adalah sama dengan pangkas kaedah dan isi. Analisis kami menunjukkan kesan perlindungan sebanyak 21% untuk aktiviti fizikal yang tinggi pada semua penyebab demensia dengan nisbah kemungkinan sebanyak 0.79, Selang Kredibiliti (SK) 95% (0.69,0.88), kesan perlindungan yang lebih tinggi dan lebih baik sebanyak 38% untuk penyakit Alzheimer dengan nisbah kemungkinan 0.62, SK 95% (0.49,0.75), 33% untuk penurunan kognitif dengan nisbah kemungkinan 0.67, SK 95% (0.55, 0.78) dan kesan bukan perlindungan untuk demensia vaskular 0.92, SK 95% (0.62, 1.30). Keputusan statistik yang signifikan telun diperolehi apabila prior informatif yang dirumus daripada data analitik-meta pada nilai muka dengan nisbah kemungkinan 0.69, SK 95% (0.58, 0.80) terhadap aktiviti fizikal yang tinggi dan paling rendah; 0.63 dengan SK 95% (0.50, 0.79) terhadap yang sederhana dan paling rendah. Pendekatan pemodelan

tercantum mendapati hubungan kuat antara skor 3MS dan risiko kematian yang mana keputusan menunjukkan setiap penurunan unit dalam skor 3MS terdapat peningkatan 1.135 (13%) risiko kematian melalui kemorosotan kognitif dengan SK 95% (1.056, 1.215).

Prior segi tiga adalah alternatif yang lebih baik untuk digunakan. Prior ini memberi kesan keseluruhan atau min keseluruhan yang jauh lebih baik daripada melakukan beberapa analisis kepekaan. Pelaksanaan proses Dirichlet dalam analisis-meta dapat mengatasi masalah keheterogenan. Dalam menilai kesan senaman terhadap kemerosotan kognitif dengan prior kuasa, didapati secara jelas wanita tua yang terlibat dalam senaman sederhana akan mempunyai risiko yang lebih rendah untuk mengalami penurunan kognitif. Dalam pemodelan tercantum pengukuran longitud, keputusan menunjukkan penurunan dalam skor 3MS mempunyai risiko peningkatan mortaliti yang signifikan disebabkan oleh penurunan kognitif apabila dilaksanakan melalui model tercantum tetapi ianya tidak signifikan dibawah model risiko relatif piawai.

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I certify that a Thesis Examination Committee has met on 27 August 2018 to conduct the final examination of Chris Bambey Guure on his thesis entitled "Bayesian Approach to Meta-Analysis with Joint Modelling of Longitudinal and Time-to-Event Outcomes in Dementia and Subtypes" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This is to confirm that:

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LIST OF ABBREVIATIONS

ETS	Environmental Tobacco Smoke
K-L	Kullback-Leibler
DIC	Deviance Information Criterion
RCT	Randomised Clinical Trials
LOCF	Last Observation Carried Forward
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
CD4	Cluster of Differentiation 4
MMSE	Mini Mental State Examination
PSA	Prostate Specific Antigen
IgG	Immunoglobulin G
IgM	Immunoglobulin M
3MS	Modified Mini Mental State Examination
USA	United States of America
FDA	Food and Drugs Administration
IG	Inverse Gamma
MSE	Mean Squared Error
MCMC	Markov Chain Monte Carlo
TS	Total Studies
CI	Credible Interval
CP	Coverage Probability
PA	Physical Activity
DSM	Diagnostic and Statistical Manual of Mental Disorder
APOE-e4	Apolipoprotein E gene
JBI-MAStARI	Meta-Analysis of State Assessment and Review Instrument
NINDS-AIREN	National Institute and Communicative Disorders and Association Internationale Pour la Reserche et I'Enseigment en Neuroscience Criteria
PICOS	Population/Patient/Problem, Intervention, Comparisons, Outcomes and Study Designs
PsycINFO	Psychological Information Database
MESH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OR	Odds Ratio
PP	Posterior Probability
ENS	Estimated Number of Studies
f-Up	Follow-Up
PS	Published Studies

HPA	High Physical Activity
MPA	Moderate Physical Activity
P_{low}	Probability of Low
P_{large}	Probability of Large
SOF	Study of Osteoporotic Fractures
GDS	Geriatric Depression Scale
CAPE	Clifton Assessment Procedures for the Elderly
BMI	Body Mass Index
BEST	Bayesian Estimation Supersedes the $t-$ Test
SD	Standard Deviation
HDI	Highest Posterior Interval
SS	Smoke Status
CHD	Coronary Heart Disease
MoCA	Montreal Cognitive Assessment
ICD-9-CM	International Classification of Disease, 9th Revision Clinical Modification
LME	Linear Mixed Effects
COF	Coffee
COMP	Health Comparison
CVD	Cardiovascular Disease
HYP	Hypertension

CHAPTER 1

BACKGROUND

1.1 Bayesian Statistics

Bayesian statistics dates back to the eighteenth century by a British Clergyman and mathematician named Thomas Bayes. In Bayes and Price (1763) landmark paper titled, "An essay towards solving a problem in the doctrine of chance", the foundations were laid. It was not until Laplace rediscovered the Bayesian principle in a much greater clarity and generality and then proceeded to apply it solve to problems in population statistics and meteorology that it gained wider attention (Jaynes, 1986).

Bayesian statistics is based on theory of conditional probabilities. In Bayesian methods, the data can be represented by y and the model parameters θ and these parameters are observed to be random quantities. The data can either be continuous or discrete with the likelihood, distribution or density function represented by $p(y|\theta)$, which is then taken to be the plausibility of the data given the parameters of the model. In the Bayesian context, θ is the unknown random variable and y represents the sample of n independent and identically distributed observations. Bayesian statistics deals with joint distributions which is expressed as the likelihood of the data y given the parameter θ, and denoted as $L(y|\theta)$.

The model parameters, described as unknown quantities and assigned prior distributions, are specified for the parameters of the model. These prior distributions can be obtained on the bases of external evidence available to the analyst and related to the current study of interest, by either soliciting experts opinion (Sutton et al., 2000) or previous studies (Bradlow et al., 1999; Smith et al., 1995; Cohen et al., 2013). These types of priors are referred to as *informative* or *subjective* priors (refer to Subsection 2.3.2 for details). The second type of prior are known as the *non-informative*, and these are based on *Jeffreys* prior which is invariant under parametrization. These priors are used in situations where scientific objectivity are of much interest to the analyst (Berger, 2006).

1.2 Meta-Analysis

The science of meta-analysis, which is the combination of results from independent multiple studies in a defined area of interest has witnessed an explosive growth in the scientific literature especially of recent times. However, it was not until the 20th

century that Simpson and Pearson (1904), applied the idea of combining results from clinical trials. A high number of research reports by the middle of the 20th century compelled researchers to focus on delivering and applying methods to synthesize results (Pratt et al., 1940; Light and Smith, 1971; Smith and Glass, 1977). The term meta-analysis according to Glass (1976), is defined as "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating findings".

The works of Simpson and Pearson (1904) and Pratt et al. (1940), led to the recognition of meta-analysis by many authors (Rosenthal, 1978; Hedges and Olkin, 2014; Elwood, 2006). Berlin et al. (1989) described meta-analysis as the quantitative formalization of the literature review process. Elwood (2006) applied the idea of meta-analysis to determine the effectiveness of aspirin on the recurrence of heart attack. The idea behind meta-analysis is to quantitatively synthesise evidences from different studies on a specific area to provide a numerical summary of a pooled or overall estimate for an outcome of interest to possibly resolve conflicting issues or reports.

1.3 Joint Modelling of Longitudinal and Survival outcomes

Longitudinal data emanate from observational and clinical trials studies that are measured repeatedly on subjects over a specified time period. These type of repeated measurements are encountered in health sciences that aids the health practitioners to comprehend and appreciate the level and development of a particular type of disease under investigation. Most of these longitudinal data are collected alongside time-to-event outcomes that may be of interest to the practitioner (Rizopoulos, 2012b). Longitudinal studies are also used to characterize human growth and ageing. It is also used to determine factors associated with some human health as well as evaluate the treatment effects. Some of the advantages of longitudinal studies are their ability to measure the change in outcome or exposure on an individual. With longitudinal study, one is able to measure the occurrence or timing of the disease onset which may be correlated with changes in patient exposure (Rizopoulos, 2012b).

Two main disadvantages of analysing longitudinal data are; there is risk of bias due to incomplete follow-up or drop-out of participants during the study period. This becomes more of a problem if follow-up subjects to the end of the study differ from subjects who discontinued. Also, analyses of longitudinal data requires statistical methods that can properly account for the intra-subject correlation of the response measurements while determining the risk of an outcome of interest. These types of scenarios occur for instance in HIV clinical trials where CD4 cell counts are considered as biomarkers measured repeatedly over a period of time alongside time to the occurrence of Acquired Immune Deficiency Syndrome (AIDS) or death (Rizopoulos, 2012a). There are two main types of methods used in jointly modelling longitudinal and time-to-event outcomes, these are; linear mixed effects and survival models. These models are elaborated in details in Sections 2.4 and 2.5.

1.4 Dementia

Dementia constitute a number or set of behaviours or symptoms that result in difficulties with individuals cognitive functions. One is said to have dementia when that person is observed not to be able to undertake everyday task pertaining to his/her daily activities, is unable to live independently without being cared for. Dementia is an organic disorder, related to the physical deterioration of the human brain tissue that is detected through a brain scan of autopsy after death. Dementia patients symptoms get worse over time which is not just due to normal ageing (Alzheimer-Disease-Association, 2017). Due to the progressive nature of the disease, it is possible that by the time one is diagnosed of it, it would have reached an advanced stage making it difficult for a realistic cure to be carried out. Some of the primary symptoms include confusion, personality changes, memory loss, unable to plan and unable to do task orderly (Alzheimer-Disease-Association, 2017).

1.5 Problem Statement

Most of the methods used by researchers for data analysis focus on single survey types. In most of the cases, a study is conducted by either a researcher or group of researchers and the data collected by these researchers are analysed in a way that other previous studies are not incorporated into the statistical model. In analysing these types of data, the general assumptions are that the previous studies are either prone to bias or were conducted elsewhere which may not be relevant or appropriate to be combined with the current study.

The inappropriate nature of this approach stems from the fact that in this scientific world a single problem affect almost everybody irrespective of one's geographical location. There are significant number of scientist or researchers who have previously investigated similar studies that there is the need for the present researchers to understand and incorporate these previous findings into their "current" research so as to make more informed decisions.

The statistical approach that combines all relevant findings from previous studies to enable researchers obtain a pooled estimate about an outcome of interest that might not have been observed from individual studies is known as meta-analysis (Sutton et al., 2000). The term meta-analysis according to Glass (1976) is defined as "statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating findings".

The commonly used methods for meta-analysis are the fixed effects (Yusuf et al., 1985) and random effects (DerSimonian and Laird, 1986). Since the purpose of combining results is to ensure an efficient overall pooled estimate of all findings, it is

important that, any statistical model specified for these analyses take into consideration all relevant information order than just synthesizing and obtaining statistical summaries. Though the frequentist random effects model has a similar hierarchical form as that of the Bayesian random effects model, it does not incorporate external sources of information that will enable a better estimate of the overall pooled effect size. Studies that are combined to obtain a pooled effect size estimate are mostly heterogeneous and with different sample sizes ranging from small to very large. It is therefore important, that external information or different statistical approaches are sought and incorporated or applied to the model in order to reduce the effect of heterogeneity for a more accurate summary estimates.

The two most important issues that affect meta-analysis results as indicated in Subsection 2.2 are publication bias and heterogeneity among studies (Sutton and Abrams, 2001). There is a limited literature on publication bias from the Bayesian perspective. The first Bayesian methodological approach to estimate and adjust for publication bias was by Givens et al. (1997). Givens et al. (1997) proposed a data augmentation approach via a hierarchical model. The number of outcomes of the studies assumed missing or unobserved were simulated and added to the observed effect size estimates for analysis.

The second approach was an implementation of the Copas selection model via a Bayesian paradigm by Mavridis et al. (2013). These authors examined and applied it in network meta-analysis. The Copas model assumes that very large studies (with small standard errors) have high probabilities of being published than small studies (with large standard errors) and the probability that a study will be published and selected depends on its effect size. They obtained informative prior for the model parameters by soliciting external data and eliciting experts opinions. The Copas selection model involves both the probability of publication and effect size. The Copas model assumes that in the presence of publication bias, the propensity of publication will be correlated with the effect size. This Copas model relies on sensitivity analysis such that the probability a study is published is determined under different possibilities or scenarios Copas and Shi (2001).

The difficulty in using this Copas model proposed by Copas and Li (1997) via the Bayesian methods is the use of more than four or five different prior distributions on the model parameters which yields about four or five different posterior estimates thereby resulting in conflicting interpretations with just one outcome of interest. The first part of this study addresses this problem by developing a prior distribution to estimate the Copas model parameters (without one necessarily conducting sensitivity analysis) and this is evaluated and applied to both randomised clinical trials and observational (dementia and its subtypes) studies. A Bayesian nonparametric approach is also proposed to control for the non-normality of the meta-analytic data.

Studies (such as dementia) collect information on deaths of participants in addition to other covariates of interest which are often measured intermittently at different time points (Rizopoulos, 2012a). These are measurements that are taking repeatedly for

each participant over a time period. For instance, the Mini Mental State Examination (MMSE). This instrument is not predictive in nature and hence should be considered as an instrument that is measured with some degree of errors. Measurements of this type violates a number of statistical models assumptions, especially when the interest is to determine the risk factors that affect the survival of dementia patients. It is therefore imperative that a more robust statistical approach is adopted to be able to handle the repeated measurements of the MMSE scores while determining the factors that affect the survival of these group of people. The prognostic values of this covariate is also usually of interest in this type of studies because they shed light on the natural history of the disease (Rizopoulos, 2012b).

For one to study the relationship between these covariates and the survival outcome of interest, it is possible to use the covariates as time-dependent or time-varying covariates in a relative risk model or better known as a Cox proportional hazards regression model (Cox and Hinkley, 1979). The Cox model stipulates the necessity of having a complete knowledge of the covariate history for all individuals in order to maximize the partial likelihood and thereby estimate the model parameters accurately. In other to again, implement this approach, we must understand that the covariate value need to be a time-continuous process measured without errors. Though the approach of using the covariate as a time-varying measured without errors have been adopted in literature to determining the risk of survival among dementia patients. The most important variables of interest (3MS) violates this assumption. This therefore causes the estimated parameters to be biased towards the null.

In this study we have proposed and implemented the Joint or Shared parameter modelling to;

1. the longitudinal measurements of the modified Mini-Mental State Examination over a 21-year follow-up dataset, considered to be measured with errors,
2. the 3MS variable directly to mortality of individuals via cognitive impairment,
3. jointly model the relationship between the repeated measures of the variable 3MS and the risk of mortality using standard and extended relative risk, and linear mixed effects models,
4. establish the possibility of predicting participants' survival probability based on their 3MS scores to enable physicians have a better understanding of their patients' risk of mortality via cognitive impairment,
5. propose a model that is capable of accurately predicting future 3MS scores based on their previous measurement(s) to enable practitioners keep track of their patients' health.

1.6 Justification of the Study

1. The development of a robust Bayesian prior for the Copas model parameters to be used to assess and account for publication bias in meta-analysis based on which just one overall effect estimate can be obtained. This ameliorates the problem of conducting sensitivity analysis which results in a more number of effect size estimates with likely different posterior mean effects. This culminates into varied interpretations from just a single meta-analysis.
2. This study further develops a new approach that deals with the issues of heterogeneity and non-normality in meta-analytic data. Heterogeneity of studies has the potential to seriously bias the grand/overall mean effect which is of essence in evidence-based medicine (meta-analysis). It is a well established fact that in any data analysis, parametric (linear) models are preferred to non-parametric ones if and only if the variables of interest satisfy the assumptions of normality especially with relatively small samples. This study sort to advance this statistical fact by proposing and applying the idea of a Bayesian non-parametric methodological approach to meta-analysis of observational studies when normality is a problem.
3. In the Bayesian framework, there are two types of approaches; these are subjective and objective. One of the purposes of this study is to establish the point that meta-analytic data can be used to construct Bayesian prior that has the potential of satisfying these two approaches in a single analysis. This makes interpretation of the results more general and acceptable to all.
4. Finally, there are two types of variables, endogenous (measured with errors) and exogenous (measured without errors). Therefore, any statistical approach should clearly delineate between these two variables for a better, precise and accurate estimation of the specified model's parameters/coefficients. This will allow for a meaningful interpretation and conclusion to be drawn. The weakness of ignoring or assuming that all variables can be considered as exogenous or time-varying covariates which has the potential to give misleading results to both researchers and practitioners have been considered in this work.

1.7 Research Objectives

This study develops Bayesian prior distribution to assess and account for publication bias and heterogeneity and as well proposes a more robust Bayesian statistical approach to model data collected repeatedly and apply to dementia and its sub-types. This research seek:

1. To develop a Bayesian new prior for the Copas selection model parameters to assess and account for publication bias in meta-analysis.
2. To propose a Bayesian non-parametric approach to handle heterogeneity in meta-analysis.

3. To formulate an informative prior using meta-analytic data through a power transformation approach to determine the effect of exercise on the risk of cognitive decline among older women.
4. To explore, develop and implement a joint modelling approach to a longitudinal measurement of a marker which is measured with some degrees of errors.

1.8 Thesis Outline/Organisation

This thesis is organized into seven different chapters. The first two chapters give an overview (background) and literature review. The first introduces the concept of Bayesian analysis, meta-analysis, joint modelling as well as the problem statement and objectives of the study. It also introduces the concept of cognitive decline, dementia and its subtypes which constitute the basis for this research. The second chapter includes some literature reviews on meta-analysis, the relative risk survival model (Cox proportional hazards model) and linear mixed effects model. The next four chapters constitute the four main objectives of this thesis. The final part summarizes the results of all chapters presiding it and with some recommendations and suggested future work.

Chapter Three of this thesis, develops a Bayesian prior referred to as *triangular prior*. Its performance is assessed against other known choices of prior distributions for the Copas selection model through sensitivity analysis with simulated meta-analytic data. It is validated using meta-analytic data from the United States Food and Drugs Administration.

Chapter Four applied the proposed prior in a meta-analysis of physical activity on cognitive decline, Alzheimer's disease, vascular dementia and all cause-dementia. In the same Chapter, we proposed a Bayesian non-parametric approach to meta-analysis via the *Dirichlet Process*. The purpose of this approach is to overcome issues with non-normality of the meta-analytic data.

Chapter Five, details a completely different way of analysing data from the subjective and objective Bayesian perspective taking into consideration an informative prior formulated from previous studies obtained through meta-analysis. This is used to determine the effect of physical activity on cognitive decline.

In Chapter Six of this thesis, a proposal on Bayesian methodological approach to handle observations measured repeatedly overtime is presented. For instance, 3MS in cognitive impairment or dementia. This approach will be extended into predicting survival probabilities as well as the repeated measurements that will enable practitioners to have a better understanding of their patients health. Chapter Seven provides conclusions, recommendations and suggestions for future

work/research.

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