Prevention of neural tube defects (NTDs) in ethnic communities in the UK: NTD epidemiology and pre-pregnancy knowledge, attitudes and health behaviour

Jordana Natalie Peake

A thesis presented for the degree
of Doctor of Philosophy

Institute of Women's Health and Institute of Child Health, UCL
Funded by a UCL Grand Challenges studentship
2016

Declaration

I, Jordana Peake, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I would firstly like to say a huge thank you to all of my supervisors Andrew Copp, Jill Shawe and Rachel Knowles, for their wisdom, guidance and support throughout my PhD. Particular thanks must go to Rachel for coming onto the supervisory board in the second year of my PhD and her sustained support with the epidemiological research and for always giving extremely helpful comments. Special thanks must also go to Mario Cortina Borja for providing statistical support and his very interesting insights about seasonality of birth.

There are also several other people without whom this PhD would not have been possible. For the quantitative research, a big thank you must go to Anna Springett from BINOCAR who provided me with the data and was always so willing to answer my (many) questions; representatives from local congenital anomaly registers for their help and support and Mary Grinsted from the DH, for putting the termination data together for me, answering my queries and her enthusiasm about the research. For the qualitative research, special thanks must go to Dr Dominic Thompson and Lindy May at GOSH as without their support, recruitment for the study would have been very difficult. I am immensely grateful to Lindy in particular for letting me sit in on so many spina bifida clinics and for all her help with the study. I would also like to thank Gill Yaz at SHINE for all her support for the research. Heartfelt thanks go to all the wonderful women who took part in the qualitative study, for letting me come into their homes and drink their tea and for speaking so openly about their experiences.

The final paragraph must be dedicated to my life's great loves. George, the font of all statistical knowledge and also my better half, I cannot thank you enough for all your love and support over the past months/years; to my mum who said she was proud of me even though she wasn't exactly sure what I was doing; to Dinah, my very sweet little cat who sat with me through the long, hard hours, both of us very busy (me writing and her sleeping) and to Debussy, Puccini, Hans Zimmer etc. for composing such exquisite music that helped to calm me, even in the most frantic moments.

Abstract

Neural tube defects (NTD) are severe congenital abnormalities, caused by failed closure of the embryonic neural tube, that affect approximately 1 in 1,000 pregnancies worldwide. There is a paucity of epidemiological and qualitative research on NTDs within different ethnic communities in the UK.

This thesis reports the findings of a mixed methods study conducted to explore NTD prevalence, pregnancy outcomes and attitudes towards prevention in different ethnic communities. For the quantitative study, congenital anomaly data supplemented with Department of Health termination data were used to explore the NTD prevalence and pregnancy decisions by maternal ethnicity. Semi-structured interviews, combined with grounded theory methodology, explored women's pre-pregnancy knowledge, attitudes and health behaviours with regard to folic acid supplementation, and subsequent pregnancy decisions.

After adjustment for maternal deprivation and age, NTD prevalence was found to be nearly twice as high in Indian mothers and almost three times as high in Bangladeshi mothers, as in mothers of White ethnicity. The excess was particularly marked in Indian mothers for non-isolated NTDs. Through qualitative interviews, women detailed how more information on why folic acid should be taken needs to be given and that health professionals (HPs), such as GPs, are the preferred information source. It was also indicated that HPs who rarely see children with spina bifida are less likely to give a balanced view of the condition, in relation to a decision on possible pregnancy termination.

An ethnic discrepancy in prevalence being more marked for non-isolated NTDs is indicative of the involvement of genetic factors. Increasing folic acid use among all population groups is essential and targeting a culturally sensitive education campaign at HPs is a crucial first stage in increasing supplementation among South Asian mothers. It is also of critical importance that those counselling mothers when spina bifida is detected, are fully informed of the condition themselves.

Contents

1 INTRODUCTION TO NEURAL TUBE DEFECTS (NTDS) 17

1.1 CONGENITAL ANOMALIES OVERVIEW 17

1.2 CLINICAL PRESENTATION OF NTDS 18

1.3 NTD EPIDEMIOLOGY 19

1.4 PRIMARY PREVENTION OF NTDS: THE FOLIC ACID STORY 20

1.5 PRIMARY PREVENTION OF NTDS: OTHER FACTORS 24

1.6 SECONDARY PREVENTION OF NTDS: PRENATAL DETECTION AND TOPFA 26

2 NEURAL TUBE DEFECTS (NTDS) IN DIFFERENT ETHNIC COMMUNITIES 28

2.1 A GLOBAL PERSPECTIVE 28

2.1.1 Indian ethnicity 29

2.1.2 Black ethnicity 31

2.2 UK FOCUS: WHAT IS KNOWN ABOUT NTDS, SPECIFICALLY HOW THEY CAN BE PREVENTED, IN ETHNIC COMMUNITIES IN THE UK? 32

2.2.1 NTD Prevalence and Perinatal Mortality 32

2.2.2 Prenatal Screening and Termination of Pregnancy for Fetal Anomaly (TOPFA) 35

2.2.3 Knowledge and peri-conceptional use of folic acid: A systematic review and meta-analysis36

2.2.4 Knowledge and peri-conceptional use of folic acid: Research since the systematic review was published 46

2.2.5 Discussion 46

3 STUDY DESIGN AND METHODOLOGY 51

3.1 PHD RATIONALE 51

3.2 OVERALL PHD AIM 52

3.3 PHD OBJECTIVES 52

3.4 MIXED METHODOLOGY 53

3.4.1 Background 53

3.4.2 Justification for using mixed methods 53

3.4.3 Study design 54

3.5 INFORMATION GOVERNANCE 59

4 INTRODUCTION TO THE BRITISH ISLES NETWORK OF CONGENITAL ANOMALY REGISTERS (BINOCAR) DATASET AND PRELIMINARY EPIDEMIOLOGICAL EXPLORATIONS 60

4.1 BINOCAR DATA BY REGISTER 60

4.2 TWINS/MULTIPLE BIRTHS 67
4.2.1 Twins/multiple births in the BINOCAR dataset 67
4.2.2 Differences between singletons and twins / multiple births 68
4.3 SIBLINGS WITH ANOMALIES IN NTD DATASET 70
4.4 NTD SUBTYPE AND "BIRTH" PREVALENCE 71
4.4.1 BINOCAR birth prevalence equation 71
4.4.2 Merging numerator and denominator datasets to calculate prevalence 74
4.4.3 Using binomial regression to estimate NTD prevalence for aggregate binary data 74
4.4.4 NTD Prevalence for individual data years 75
4.4.5 NTD prevalence estimates by region 76
4.4.6 Quantifying the difference between including and excluding terminations in NTD birth prevalence denominator 78
4.4.7 Preliminary epidemiological explorations around NTD prevalence 79
4.5 CHAPTER SUMMARY AND IMPORTANT POINTS TO TAKE FORWARD 99

5 ETHNICITY: NTD BIRTH PREVALENCE AND THE NATURAL HISTORY OF NTD AFFECTED PREGNANCIES 101

5.1 INTRODUCTION 101
5.2 CALCULATING NTD PREVALENCE ESTIMATES FOR DIFFERENT ETHNIC GROUPS 104
5.2.1 Explorations around missing ethnicity data for different registers 109
5.2.2 Conclusions 116
5.3 NTD PREVALENCE IN ETHNIC COMMUNITIES IN EMSYCAR AND SWCAR 118
5.3.1 Isolated and Non-Isolated NTDs 118
5.3.2 Univariable explorations for ethnicity in the NTD dataset (EMSYCAR and SWCAR) 121
5.3.3 Multivariable model exploring the association between ethnicity and NTD prevalence 124
5.3.4 Conclusions 133
5.4 NATURAL HISTORY OF NTD AFFECTED PREGNANCIES IN EMSYCAR AND SWCAR FOR MOTHERS FROM DIFFERENT ETHNIC COMMUNITIES 134
5.4.1 Introduction 134
5.4.2 Preliminary analyses 135
5.4.3 Univariable analyses for an exploration of the association between maternal ethnicity and whether an NTD affected pregnancy is terminated or not 138
5.4.4 Multivariable analyses exploring the association between ethnicity and whether an NTD affected pregnancy is terminated or not using a logistic regression model 142
5.4.5 Conclusions 149
5.5 CHAPTER SUMMARY AND IMPORTANT POINTS TO TAKE FORWARD 151

6 EXPLORING THE PRE-PREGNANCY AND PREGNANCY KNOWLEDGE, ATTITUDES AND HEALTH BEHAVIOUR OF SOUTH ASIAN MOTHERS WITH A PREVIOUS NEURAL TUBE DEFECT (NTD) AFFECTED PREGNANCY 153

6.1 INTRODUCTION 153
6.2 METHODOLOGY 156
6.2.1 Background 156
6.2.2 Aligning research with theory 157
6.2.3 Statement about researcher involvement 159
6.2.4 Participant recruitment 159
6.2.5 Interview procedure 163
6.2.6 Data collection and analysis 163
6.2.7 Presentation of findings 165
6.3 FINDINGS 166
6.3.1 Pre-pregnancy knowledge and health behaviours, particularly with regards to folic acid: Giving meaning through detail and emphasis vs. gaining meaning through experience 166
6.3.2 Deciding to continue a spina bifida affected pregnancy: Seeing the whole picture (with human eyes) 188
6.4 CHAPTER SUMMARY AND IMPORTANT POINTS TO TAKE FURTHER 201

7 DISCUSSION 203

7.1 WHY IS AN ETHNIC DISCREPANCY IN NEURAL TUBE DEFECT (NTD) PREVALENCE OBSERVED? 203
7.1.1 Quantitative Study Limitations 206
7.1.2 Conclusions 209
7.2 WHAT ARE THE BEST PREVENTION STRATEGIES FOR NTDS IN ETHNIC COMMUNITIES? 210
7.2.1 Qualitative study limitations 212
7.2.2 Conclusions 213
7.3 WHY DO WOMEN DECIDE TO CONTINUE A SPINA BIFIDA AFFECTED PREGNANCY AND HOW CAN WE ENSURE IT IS A FULLY INFORMED DECISION 214
7.3.1 Conclusions 215
7.4 APPROPRIATENESS OF USING MIXED METHODOLOGY 216
7.5 IMPLICATIONS FOR PRACTICE AND PREVENTION 217
7.6 FURTHER RESEARCH 219
7.7 SUMMARY 220

8 APPENDIX A 237

9 APPENDIX B 245

10 APPENDIX C 252

11 APPENDIX D 253

12 APPENDIX E 257

List of Figures

Figure 1: Schematic representation for the four main severe neural tube defects (NTDs) 19
Figure 2: Change in NTD prevalence between 1964 and 2004 23
Figure 3: Flow diagram detailing process of selection of studies for inclusion in systematic review and meta-analysis 40
Figure 4: Meta-analysis of pre-conceptional folic acid use in Caucasians/Whites compared to non-Caucasians/non-Whites. 45
Figure 5: Phases of research in relation to quantitative and qualitative study sequence 58
Figure 6: Natural History of NTD affected pregnancies with a focus on "birth" outcomes included in the BINOCAR birth prevalence calculation 73
Figure 7: Process of merging pregnancy level and aggregated data to calculated prevalence estimates 74
Figure 8: Birth prevalence by year for all NTD affected pregnancies and by NTD type 75
Figure 9: NTD birth prevalence estimates using all NTD cases and only live and still birth cases 76
Figure 10: NTD prevalence per 10,000 conceptions by month of conception for all NTDs combined and by NTD subtype 97
Figure 11: Ethnic breakdown for NTDs in EMSYCAR 110
Figure 12: Ethnic breakdown for EMSYCAR births 110
Figure 13: Ethnic breakdown for NTDs in SWCAR 110
Figure 14: Ethnic breakdown for SWCAR births 110
Figure 15: Ethnic breakdown for NTDs in NorCAS 110
Figure 16: Ethnic breakdown for NorCAS births 110
Figure 17: Ethnic breakdown for NTDs in CAROBB 110
Figure 18: Ethnic breakdown for CAROBB births 110
Figure 19: Ethnic breakdown for NTDs in CARIS 111
Figure 20: Ethnic breakdown for CARIS births 111
Figure 21: Proportion of missing ethnicity data by NTD type and register 113
Figure 22: Proportion of missing ethnicity data by whether the NTD is isolated or not and register 114

Figure 23: NTD pregnancy outcomes by maternal ethnicity 136
Figure 24: Proportion of NTD affected pregnancies resulting in TOPFA or not for different ethnic groups in EMSYCAR and SWCAR..... 139
Figure 25: Possible pathways for "knowing" and "not knowing" about folic acid benefits and pregnancy outcomes 166

List of Tables

Table 1: Key information for individual studies included in systematic review 41
Table 2: Breakdown by ethnicity of the number and proportion of participants in each study 42
Table 3: BINOCAR register description 62
Table 4: Missing data for key variables by register 65
Table 5: Breakdown of number of NTD affected babies that are singletons or part of a multiple set (twins or triplets), by register 67
Table 6: Breakdown of the number malformed in multiple set by register 67
Table 7: Breakdown of siblings with anomalies variable (number and proportion) by register 71
Table 8: Prevalence by year and 95% confidence intervals for all NTD affected pregnancies 76
Table 9: Prevalence by register and 95% confidence intervals for all NTD affected pregnancies 78
Table 10: Number of NTD affected pregnancies and Birth Prevalence for all NTDs and different subtypes 78
Table 11: Number and proportion of NTD affected pregnancies falling into the different multiple malformation groupings 81
Table 12: NTD prevalence by type and whether the NTD is isolated or not 82
Table 13: Sex (number and proportion) breakdown for NTD affected pregnancies from different registers 83
Table 14: Female to male prevalence rate ratios by NTD subtype for affected pregnancies of any gestation length and those with gestation lengths of 18 weeks or longer 84
Table 15: Female to male prevalence rate ratios by NTD type for isolated and non-isolated affected pregnancies of 18 weeks gestation length or longer 84
Table 16: Prevalence for isolated NTD cases by register and NTD type 84
Table 17: Prevalence for non-isolated NTD cases by register and NTD type 85
Table 18: Maternal age group (number and proportion) breakdown for NTD affected pregnancies from different registers 86
Table 19: NTD prevalence by maternal age group and NTD type 87
Table 20: NTD prevalence rate ratios by maternal age group and NTD type 87

Table 21: NTD prevalence rate ratios by maternal age group and whether the NTD is isolated or not 88
Table 22: Maternal deprivation quintile (number and proportion) breakdown for NTD affected pregnancies for English registers 89
Table 23: Maternal deprivation quintile (number and proportion) breakdown for NTD affected pregnancies for Welsh register 90
Table 24: NTD prevalence rate ratios by deprivation quintile and NTD type for English registers only 90
Table 25: NTD prevalence rate ratios by deprivation quintile and NTD type for NTD isolated cases for English registers only 91
Table 26: NTD prevalence rate ratios by deprivation quintile and NTD type for non-isolated NTD cases for English registers only 91
Table 27: NTD prevalence risk ratios by deprivation quintile for all NTD cases and broken down by whether the NTD is isolated or not for the Welsh register (CARIS) 91
Table 28: Proportion of mothers in the NTD NorCAS dataset falling into the different BMI categories, including missing cases 93
Table 29: Folic acid use breakdown for CARIS 94
Table 30: Folic acid use breakdown for SWCAR 94
Table 31: NTD prevalence per 10,000 conceptions for month-pairs for all NTD affected pregnancies and by NTD subtype 96
Table 32: NTD prevalence per 10,000 conceptions for month-pairs for all isolated NTD affected pregnancies and by subtype 97
Table 33: NTD prevalence per 10,000 conceptions for month-pairs for all non-isolated NTD affected pregnancies and by subtype 98
Table 34: NTD prevalence per 10,000 conceptions for month-pairs for all NTD affected pregnancies in NorCAS and CARIS vs. EMSYCAR, CAROBB and SWCAR 99
Table 35: Breakdown of number and proportion of NTD cases in the BINOCAR dataset with mothers falling into the different ethnic groups collected by registers 102
Table 36: NTD birth prevalence estimates by ethnicity for all registers 105
Table 37: NTD birth prevalence rate ratios by ethnicity for all registers 105

Table 38: NTD birth prevalence rate ratio estimates by ethnicity for isolated NTD affected pregnancies for all registers 106
Table 39: NTD birth prevalence rate ratio estimates by ethnicity for non-isolated NTD affected pregnancies for all registers 106
Table 40: NTD birth prevalence estimates by ethnicity for EMSYCAR and SWCAR only 108
Table 41: NTD birth prevalence rate ratio estimates by ethnicity for EMSYCAR and SWCAR 108
Table 42: NTD birth prevalence rate ratio estimates by ethnicity for isolated NTD affected pregnancies for EMSYCAR and SWCAR 108
Table 43: NTD birth prevalence rate ratio estimates by ethnicity for non-isolated NTD affected pregnancies for EMSYCAR and SWCAR 108
Table 44: Comparing aetiological vs. EUROCAT algorithm classification for isolated and non-isolated NTD cases in EMSYCAR 118
Table 45: Comparing aetiological and EUROCAT algorithm classification systems for mothers of White, Indian and Bangladeshi ethnicity in EMSYCAR 119
Table 46: Breakdown of sex of baby by maternal ethnicity for NTD affected pregnancies in EMSYCAR and SWCAR, where sex is known and the gestation length is 18 weeks or longer 124
Table 47: Binomial regression model to explore the association between ethnicity and NTD prevalence, unadjusted and adjusted for IMD quintile and maternal age for EMSYCAR and SWCAR 126
Table 48: Binomial regression model to explore the association between ethnicity and NTD prevalence, stratified by deprivation quintile and adjusted for maternal age for EMSYCAR and SWCAR 127
Table 49: Binomial regression model to explore the association between ethnicity and NTD prevalence, stratified by whether the NTD is anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR and SWCAR 129
Table 50: Binomial regression model to explore the association between ethnicity and NTD prevalence for isolated NTDs, stratified by whether the NTD is anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR 131
Table 51: Binomial regression model to explore the association between ethnicity and NTD prevalence for non-isolated NTDs, stratified by whether the NTD is

anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR 132
Table 52: Missing data for additional variables by register 135
Table 53: Breakdown for different pregnancy outcomes in the NTD dataset for EMSYCAR and SWCAR 136
Table 54: Number and proportion of prenatally detected NTD affected pregnancies that are terminated or not for different NTD subtypes in EMSYCAR and SWCAR 137
Table 55: Logistic regression model exploring the association between maternal ethnicity and whether the NTD affected pregnancy is terminated or not, unadjusted and adjusted for NTD type; maternal age; age, in weeks, at which the NTD is discovered; and deprivation of maternal residence for EMSYCAR and SWCAR ... 145
Table 56: Logistic regression model exploring the association between ethnicity and whether the NTD affected pregnancy is terminated or not, stratified by whether the NTD is anencephaly or spina bifida and adjusted for maternal age; age, in weeks, at which the NTD is discovered and deprivation of maternal residence for EMSYCAR and SWCAR 147
Table 57: Logistic regression model exploring the association between ethnicity and whether the isolated, spina bifida affected pregnancy is terminated or not, and adjusted for maternal age; age, in weeks, at which the NTD is discovered and deprivation of maternal residence for EMSYCAR 149
Table 58: Key self-reported participant characteristics 162

List of abbreviations

ART	Assisted Reproductive Technology
BINOCAR	British Isles Network of Congenital Anomaly Registers
BME	Black and minority ethnic
BMI	Body mass index
CARIS	Congenital Anomaly Register and Information Service for Wales
CAROBB	Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire
CMACE	Centre for Maternal and Child Enquiries
CMO	Chief Medical Officer
CNS	Central Nervous System
DH	Department of Health
EMSYCAR	East Midlands and South Yorkshire Congenital Anomalies Register
EUROCAT	European Surveillance of Congenital Anomalies
FSA	Food Standards Agency
GOSH	Great Ormond Street Hospital
GP	General Practitioner
HEA	Health Education Authority
ICD-10	International Classification of Diseases – version 10
IMD	Indices of multiple deprivation
LSOA	Lower super output area
MRC	Medical Research Council

MTHFR	Methylene tetrahydrofolate reductase
NCARDRS	National Congenital Anomaly and Rare Disease Registration Service
NCAS	National Congenital Anomaly System
NHS	National Health Service
NorCAS	Northern Congenital Abnormality Survey
NTD	Neural tube defect
ONS	Office for National Statistics
OR	Odds ratio
PCT	Primary Care Trust
PRR	Prevalence rate ratio
REC	Research Ethics Committee
SACN	Scientific Advisory Committee on Nutrition
SHINE	Spina Bifida, Hydrocephalus, Information, Networking, Equality Association
SWCAR	South West Congenital Anomaly Register
TOPFA	Termination of pregnancy for fetal anomaly
WHO	World Health Organisation

1 Introduction to Neural Tube Defects (NTDs)

In this Chapter, a general overview of congenital anomalies is given before the content is focused specifically on neural tube defects (NTDs). The clinical presentation of NTDs, their epidemiology and details of primary and secondary NTD prevention from the literature are given.

1.1 Congenital anomalies overview

Congenital anomalies (birth defects) are a diverse group of developmental disorders of the embryo and fetus (1). They have complex aetiology, involving both genetic and environmental factors, and in most cases the anomaly cannot be attributed to a single factor (2). Due to early miscarriages before the pregnancy is confirmed and later miscarriages where the anomaly has not been diagnosed, it is difficult to calculate a true incidence for congenital anomalies and birth prevalence is typically given (1). It is still termed birth prevalence when termination of pregnancy for fetal anomaly (TOPFA) cases are included as it would be expected that the majority of these would survive to birth if the pregnancy had not been terminated (2). Based on case ascertainment that includes live births, still births, fetal deaths from 20 weeks gestation and termination of pregnancy for fetal anomaly (TOPFA), approximately 1 in 40 pregnancies in Europe (2;3) are affected by birth defects: 80% result in live births and 18% in TOPFA in this setting (2). Congenital anomalies are the second most prevalent cause of infant deaths in the UK (1).

Congenital heart defects are the most common group of birth defects followed by neural tube defects (NTDs), severe congenital abnormalities caused by failed closure of the embryonic neural tube. Closure is normally complete by day 28 of pregnancy, before many women know they are pregnant. NTDs affect between 0.5 and 2 in every 1000 pregnancies worldwide (4).

1.2 Clinical presentation of NTDs

The clinical severity varies between different types of NTD. Open spina bifida (myelomeningocele) is the most common type of NTD and results from a failure of the closure of the neural tube along the body axis during fetal development (3). The open spina cord is either covered by a meningeal sac or exposed. This phenotype is usually compatible with postnatal survival, however there is neurological impairment below the level of the lesion and some children will be unable to walk and commonly experience bowel and bladder problems (5). Hydrocephalus, a build-up of fluid in the brain, is often associated with open spina bifida. The open spinal lesion is typically closed surgically soon after the child is born or may be closed in utero in specific centres in recent years (3).

Anencephaly, slightly less common than open spina bifida, results from failed closure of the cranial neural tube and there is a lack of brain and cranial vault. This severe NTD type is not compatible with life after birth. Craniorachischisis is much rarer and is characterised by the entire neural tube remaining open and, like anencephaly, affected pregnancies will result in either fetal loss or stillbirth.

Encephalocele is more common than craniorachischisis but still relatively rare, and is characterised by the meningeal sac, which usually contains brain tissue, protruding from the skull. This phenotype can be lethal, depending on the extent of brain damage (5) (a schematic representation for all four NTDs described above is given in Figure 1).

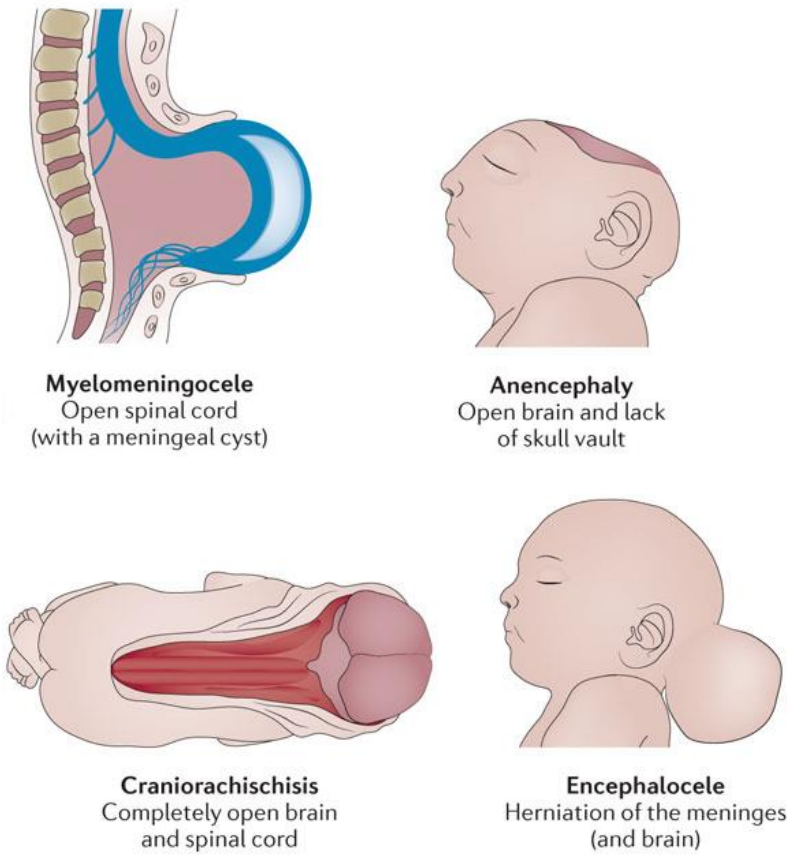

Figure 1: Schematic representation for the four main severe neural tube defects (NTDs)
Source: Copp et al, Natures Reviews Disease Primers (6)

1.3 NTD epidemiology

The report by Record and McKeown in 1949 was the first to highlight the complex epidemiology of NTDs, including the excess anencephaly prevalence in girls and the relative importance of parity when compared to maternal age (7). However, as early as 1844, the importance of the interaction of genetic and environment factors, specifically the importance of nutrition, in the aetiology of NTDs was identified (8). It is argued that an analysis in 1974 by Carter of the epidemiological data (9), led to the current view of a multifactorial cause of NTDs, with a genetic predisposition that is polygenic and involvement of several environmental factors (5). It has been argued that results from epidemiological studies have been used to dissect the role of genetic factors on NTDs (10). Studies showing NTD recurrence within families and an increase in NTD prevalence in same-sex twins, provide evidence for a genetic influence (11). However, our understanding of the genetic basis for NTDs in

humans remains limited and few of the genes identified in mouse models have been implicated in human NTDs (4).

A recent review of the epidemiological data by Au and colleagues describes how other factors shown to be associated with NTD risk include socio-economic status, ethnicity, maternal diabetes, maternal obesity, parental occupational exposures, hyperthermia during early pregnancy, caffeine use and medication use (10). Geographical variation in the prevalence of NTDs has been observed. In China, the NTD prevalence has been shown to be much higher in the North than the South since the early 1990's (12). In the British Isles there is also a North South Divide with a higher prevalence observed in the North West when compared to the South East of England (11). Seasonal variation in NTD prevalence has been reported by some studies (13). An association between previous spontaneous abortions and NTDs, has also been reported (11). Finally, it is important to note that maternal use of valproic acid, used to treat epilepsy, is associated with significantly increased risk of NTDs in offspring (14).

1.4 Primary prevention of NTDs: The folic acid story

The most significant finding to emerge from NTD epidemiological studies is the link between intake of folic acid before and during early pregnancy (peri-conceptionally) and NTD prevention. Evidence from observational and non-randomised controlled trials on the effectiveness of folic acid supplementation had been building up over several years (15), including a case control study conducted in Western Australia using data collected between 1982 and 1984 (16). However, it was the 1991 Medical Research Council (MRC) double blind multicentre randomised controlled trial that was the first to provide unambiguous evidence of an association between folic acid intake and reduction in NTDs. There was shown to be a 72% reduction in NTD recurrences in women taking folic acid supplements (17). It was argued that although the trial was concerned with NTD recurrences, there was no reason to expect that folic acid wouldn't have the same effect on first occurrence NTDs (17). Indeed, a randomised clinical trial in Hungary in 1992 confirmed that folic acid also has a protective effect for first occurrence NTDs (18).

Establishing what the minimum effective dose for preventing NTDs is, has proved problematic (15) . Daly and colleagues described how a 22%, 41% and 47% reduction in risk of NTDs were associated with an intake of 100, 200 and 400 µg folic acid, respectively and that fortifying with folic acid doses above 400 µg, offers little further benefit (19). However, based on 14 studies that explored the effect of different doses of folic acid up to 1 mg per day on serum folate levels, Wald and colleagues described how there is a constant inverse dose-response relationship. They also found that a greater effect was observed when there was a lower baseline serum folate concentration. Although only doses of folic acid of up to 1 mg were included, it was argued based on a prediction model generated from the existing data, that NTD risk can be reduced by as much as 85% if 5 mg folic acid is taken daily (20). Described problems with such a model are that it doesn't take into account heterogeneity of NTDs and population differences (15). In the 1991 MRC vitamin study 4mg folic acid was used to assess impact on NTD recurrences and in the 1992 Hungarian study by Czeizel and Dudas, 0.8mg to assess impact on first occurrence NTDs. A larger study subsequently conducted in China found a protective effect for first occurrence NTDs using 400 µg folic (21) (15). It is based on these studies and trials that it is recommended that all women planning to get pregnant take 400 µg folic acid per day and that 4 or 5 mg folic acid per day is taken by those at high risk of NTDs (3). Due to natural food folates being approximately 50% less bioavailable than synthetic folic acid, it is of paramount importance that the latter is taken in addition to consuming any folate as part of a balanced diet (15).

As stated in the introduction to the systematic review conducted and published as part of this PhD (22), in 1992 the Centers for Disease Control and Prevention in the United States recommended that 400 µg folic acid be taken daily by women who could become pregnant and 4mg by those with a previous NTD affected pregnancy. However, this advice and the subsequent major public health campaign in the United States, were shown to result in limited behavior change. As a result of this, and due to 50% of pregnancies in the United States being unplanned, the fortification of staple foods with folic acid was mandated in January 1998. There was also mandatory fortification less than a year later in Canada (15). Including

prenatal diagnoses of NTDs, there was shown to be a 27% decline in NTDs postfortification in the United States (23) and 46% decline in Canada (24).

National recommendations for the peri-conceptional use of folic acid were also introduced in Australia in 1992 (25), with voluntary fortification of some foods with folic acid introduced in 1996 and mandatory fortification of bread in 2009 (25). Mandatory fortification was also considered in New Zealand but due to industry and consumer concerns, an enhanced voluntary bread fortification programme was adopted instead (25). It has been shown that post-fortification in Australia, there has been a population level increase in serum and red blood cell folate levels (26). There has been a marked decrease in the NTD prevalence in the Aboriginal population in Australia in the post-fortification period (27); this is of critical importance as health promotion campaigns for folic acid supplement use and voluntary fortification were shown to have little impact for this population group (28).

In 1992, as a result of the landmark MRC study, the Department of Health (DH) recommended that 400 μg of folic acid be taken before conception and for the first twelve weeks of pregnancy (29). This is increased to 5 mgs for women at increased risk of NTDs (those with a previous NTD affected pregnancy, at risk of folate deficiency and mothers with diabetes and epilepsy). A Health Education Authority (HEA) Campaign was launched in February 1996 (30) as a result of findings that compliance with the DH recommendations were poor (29). Only 3% of the women in the study sample had taken folic acid in the preconception period (29). An audit of the impact of the HEA campaign in 1996 to 1997 found that although knowledge of the beneficial effects of folic acid had increased, compliance was still low (31).

Wald and Morris published research in 2007 that described how the NTD prevalence has changed between 1964 and 2004. However, they also accounted for under-reporting of NTD terminations, which is critical in presenting "true" prevalence estimates across all study years (32). NTD Prevalence over this time period is shown in Figure 2. The figure shows that since the late 1980's the prevalence has remained fairly constant. A previous publication from the same authors, but more broadly accounting for under-reporting of central nervous

system (CNS) defect terminations, also described a similar pattern (33). The authors detailed how the British National Food Survey estimated that between the early 1980s and 1997 there was an increase in dietary folate by about 20% and that this would have at least partly influenced the decline in NTD prevalence. However, Wald and Morris also argued that folate intake might have been even greater than estimated, due to increased fortification of foods with folic acid in this period (33).

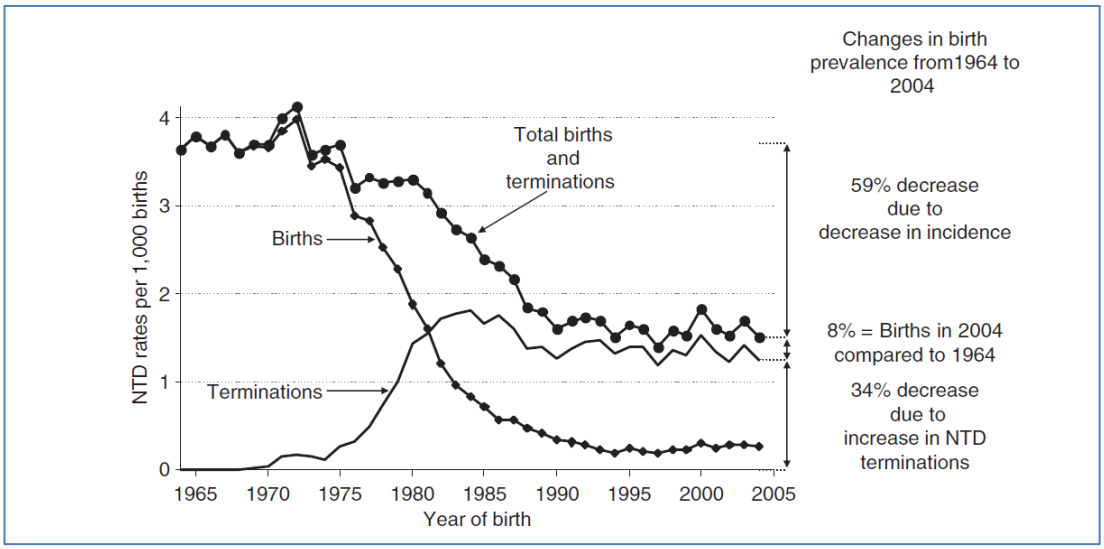

Figure 2: Change in NTD prevalence between 1964 and 2004
Source: Morris and Wald, Journal of Medical Screening (32)

Another study reported that, up to six years after the folic acid supplementation policy was introduced in 1992 in the U.K., the rate of decline in NTD prevalence did not differ from the rate of decline before the policy had been implemented (34). A study conducted including data from a slightly later time period found that there has been a 32% decline in NTDs in the period 2000-2002 when compared with 1989-1991 in the U.K. and Ireland. However, this continued a pre-existing rate of decline in NTD frequency (35). Although it also difficult to ascertain how much of the decline detailed for the United States and Canada post-fortification is due to a pre-existing reduction, a causal link is indicated by a drop in NTD rates co-occurring with an increase in red blood cell folate concentrations (36).

No mandatory fortification policy has as yet been introduced in the U.K., or in fact anywhere in Europe. Due to poor compliance with the health advice, The Food Standards Agency (FSA) recommended mandatory fortification in 2007 in the U.K.

after conducting substantial research which showed that mandatory fortification was the option most favoured by consumers. However, this was deferred due to the Chief Medical Officer (CMO) having concerns about the link between high levels of folic acid intake and colorectal cancer (Tedstone et al, 2007). A subsequent review, commissioned by the CMO, found that there was not substantial evidence of an association between folic acid and colorectal cancer to alter the original recommendation (SACN, 2009). Mandatory fortification is currently under review by UK health minsters.

In countries where there is no mandatory fortification policy, improvement in knowledge of the benefits of folic and its peri-conceptional use, is of particular importance. A recent survey conducted in 18 European countries exploring awareness and use of folic acid by women of reproductive age found that only 17% of women knew that folic acid can reduce NTD prevalence. 37% of women with a child reported taking folic acid (37).

Studies using human subjects to investigate genes involved in the causation of human NTDs, have mainly focused on genes involved in folate one-carbon metabolism. The most widely studied and important finding to emerge from these studies is the C677T and A1298C polymorphisms of methylene tetrahydrofolate reductase (MTHFR), a gene encoding a crucial enzyme involved in folate metabolism (3). However, increased NTD risk in those with the C677T polymorphism, specifically the TT genotype, has only been found in some populations (38).

1.5 Primary prevention of NTDs: Other factors

It is argued that based on the findings of the key clinical trials showing the effectiveness of folic acid supplementation in NTD reduction (17;18;21), it is estimated that folic acid can prevent between 50 and 70% of NTDs (15). Heseker and colleagues describe how, looking at studies exploring the effectiveness of folic acid supplementation, there is a greater decline in NTD prevalence in regions or populations with a higher baseline prevalence than those with a lower baseline

prevalence (39) (in line with what was observed by Wald and colleagues, detailed above(20)). It is argued there is a floor effect, a certain level below which folic acid does not seem to be effective, and countries with a prevalence of 7 to 8 per 10,000 pregnancies might already have reached this "floor" level (39).

It is of importance to note that the majority of NTD affected pregnancies in fact have folate levels which are within the normal range (40) and mouse models have shown that folate deficiency only causes NTDs in the presence of a genetic predisposition (3).

The effectiveness of inositol in preventing folate-resistant NTDs has been shown in mouse models (3) and there has been evidence in humans for inositol as an alternative for those not responsive to folic acid (41). This resulted in a pilot clinical trial being conducted at the Institute of Child Health of inositol supplementation in women with a previous NTD affected pregnancy (3).

The importance of B12 in folate metabolism and for further NTD risk reduction has been indicated: a study in Dublin found that women who are deficient in B12 had three times the risk of having an NTD affected pregnancy than those with adequate consumption (42). Professor John Scott, a world authority on vitamin B12 from Dublin, recommended that 2.5 μg of B12 should be taken in addition to folic acid before and during early pregnancy (43). However, although based on clear evidence, this recommendation was reported as a personal communication and additional research is required to further establish the effectiveness of vitamin B12 in preventing NTDs and the optimal dose of B12 required (43).

The importance of other possible environmental causes should also not be ignored, including addressing factors such as maternal diabetes and obesity as part of NTD prevention strategies, in addition to increasing folic acid intake (2). For example, McMahon and colleagues described how even after adjustment for peri-conceptional folic acid use, women who were obese still had double the odds of having an NTD affected pregnancy as women with a normal BMI (44). The biggest NTD risk reduction was observed in those taking folic acid who were overweight/obese when compared to those who were normal/underweight (44).

This is in line with what is previously described about groups with a higher baseline NTD prevalence experiencing a greater reduction in NTD risk when taking folic acid than those with a lower baseline prevalence (20;39).

The effectiveness of various prevention strategies will also vary depending on the type of NTD. For example, there is increased risk of both anencephaly and spina bifida affected pregnancies in diabetic mothers. However, it is specifically for spina bifida affected pregnancies that maternal use of valproic acid has been shown to incur increased risk. The importance of folic acid for prevention of both anencephaly and spina bifida affected pregnancies, has been clearly proven. However, the evidence is less conclusive for encephalocele (5).

Finally, whether an NTD occurs in isolation or in association with other birth defects is an important consideration when targeting prevention strategies. Even after excluding NTD cases occurring as part of known chromosomal, genetic or teratogenic syndromes, the remaining NTDs occurring in association with other defects are thought to be aetiologically distinct from those that are isolated (11;45).Mice studies have shown that a mutation in a single gene necessary for the correct development of more than one body system, can result in non-isolated NTDs (46). It is argued that non-isolated NTDs are unlikely to decline with folic acid usage (47;48).

1.6 Secondary prevention of NTDs: Prenatal detection and TOPFA

In England and Wales, NTDs have a high prenatal detection rate with 99.6% of anencephaly cases and 91.7% of spina cases detected prenatally (49). There is a high TOPFA rate for NTDs and, in line with the clinical picture, TOPFA rates are higher for anencephaly than spina bifida affected pregnancies. In Europe it was reported that 59% of spina bifida cases were terminated in 2007 (2). This figure went up to 71% when countries where TOPFA is illegal were excluded. For anencephaly the TOPFA rate was 83% (2). It is argued that this high prenatal detection and therapeutic termination rate for NTDs could be making NTDs invisible with a consequence that there is less of an impetus behind primary prevention (2).

However, the majority of these cases might be invisible to the public eye but they are not to the families that they affect. It is of critical importance that NTD affected pregnancies that result in a TOPFA are included in prevalence calculations to present an accurate picture.

2 Neural tube defects (NTDs) in different ethnic communities

This chapter starts with a broader global perspective of neural tube defects (NTDs) within different ethnic communities then focuses in on the situation in the U.K. The literature on NTD prevalence and perinatal mortality, prenatal screening and termination of pregnancy for fetal anomaly (TOPFA) and folic acid knowledge and use (including a systematic review published in the early stages of this doctoral thesis) within different ethnic communities in the U.K. is explored.

2.1 A global perspective

Flores and colleagues describe how low and middle-income settings bear the biggest burden of severe birth defects (50). This seems to be particularly the case in South East Asia with 8 countries, India, Sri Lanka, Thailand, Nepal, Indonesia, Bangladesh, Myanmar and Bhutan, reported in the "March of Dimes Global Report on Birth Defects" to have overall birth defect prevalence estimates of between 55 and 65 per 1,000 live births (50;51). The World Health Organisation (WHO) in their strategic framework for the "Prevention and Control of Birth Defects in South-East Asia Region", describe how prevalence estimates from *The March of Dimes Birth Defects Foundation* are generated based on epidemiological modelling and do not allow for exact comparisons between different countries. Nevertheless, congenital heart defects and NTDs are the most common birth defects in the South East Asia region, with the NTD prevalence shown to be particularly marked in Bangladesh, Bhutan, DPR Korea, India and Nepal (52).

As described, one of the factors identified in epidemiological studies as influencing NTD prevalence is ethnicity (10). The relative contribution of genetic and environmental factors to observed differences in NTD prevalence for different ethnic groups is largely unestablished (53). There is also a complex interplay between ethnicity and geography with migration studies indicating that groups with high prevalence do not keep their high risk when they migrate but groups with low risk do (11). However, there are certain groups who seem to have an intrinsically higher or lower risk: A very early study conducted by Leck exploring

the aetiology of NTDs reported that the anencephaly prevalence is high in Sikh communities, regardless of whether they live in areas with an overall high or low prevalence, while those of Black ethnicity have a low prevalence, regardless of where they reside (54).

2.1.1 Indian ethnicity

A high NTD prevalence in the Indian population has been frequently reported in the literature. Early studies reported the NTD rate to be particularly high in the North of India. Rates were as high as 8.8 per 1,000 births in areas where the population was largely Sikh and it was described how the high anencephaly prevalence in Sikhs was maintained after migration to the UK (55). Rates were still high in regions in the North of India that were not predominantly Sikh (55). In 1983, Baird described how the NTD rate was statistically significantly higher in the Sikh population than what was observed in the general population in British Columbia and that a higher proportion of Sikh cases were stillborn (56). In 1995, Millar and colleagues' article exploring the health needs of individuals from different ethnic communities in Canada, describes the particularly marked NTD prevalence in women from India and the need to ensure all pregnant women, but women of Indian ethnicity specifically, take folic acid in the peri-conceptional period (57).

Two recent systematic reviews have been conducted of the birth prevalence of NTDs in India (58;59). Studies in India that include NTD affected pregnancies that result in TOPFA are scarce and both reviews only included NTD birth cases in their calculations. In the first review, the random effects model combined NTD birth prevalence estimate across all the studies was 4.1 per 1,000 births (59). The second review, which included additional larger studies, reported an overall pooled NTD birth prevalence, using a random effects model, of 4.5 per 1,000 births (58). In the latter review, it was described how the highest prevalence was for the Northern region (7.7 per 1,000 births), which was statistically significantly higher than the prevalence for the Southern region (4.2 per 1,000 births). The still marked prevalence in the South was attributed to the inclusion of two studies: one

conducted in Davangere where a high NTD prevalence was reported (11 per 1,000 births) (60) and a study conducted in Pondicherry where the prevalence was 5.7 per 1,000 births (61). Consanguinity was shown to be a significant factor in both studies and argued by the authors of the review to be a potentially important contributor to observed prevalence excesses in the South, a typically lower prevalence area (58). Finally, studies included in two reviews were conducted over a large number of years, with the earliest study in the more extensive review published in 1968 and the most recent in 2013 (58). Allagh and colleagues describe how there is a clear drop in prevalence after 1995 and possible reasons for this could be increased awareness about folic acid and earlier detection of NTDs and subsequent therapeutic abortion (58).

The Indian Council of Medical Research in 1988, five years after the MRC trial was launched, commenced their own double blind randomised controlled trial exploring the impact of folic acid supplementation on NTD recurrence in India. The Indian trial was terminated early in 1991, when the results of the MRC trial were published, for ethical reasons. In the Indian trial, NTD recurrence in the vitamin group was 2.92% and 7.04% in the placebo group, representing a 58.5% reduction in NTD recurrence in those who were taking folic acid. The difference didn't quite reach statistical significance, however, this could have been because the study was slightly under-powered due to its early termination. As the recurrence rate was quite high in both groups, it was argued by the authors that the high NTD recurrence in India is something that needs to be investigated (62).

A recent study conducted in Delhi, in North India, that included both women who did and didn't continue their NTD affected pregnancy, found a significantly increased risk for NTDs in those who didn't take folic acid peri-conceptionally. This was after adjustment for maternal age, occupation, consanguinity, occupation and household income (63). An increased risk of NTDs was also found in those who were vegetarian. When breaking the analysis down into the two main religious groups: Hindu and Muslim, it was described how Hindu women were more likely than Muslim women to follow a vegetarian diet and consanguineous marriages are uncommon among the former but common among the latter in North India (63). Deb and colleagues also found weak evidence of an association between vegetarian

dietary habits and NTD risk in a subsequent case control study conducted in Delhi, again including TOPFA cases (64). The authors described how an increased NTD risk in women who are vegetarian points towards the importance of micronutrients that could be lower in a vegetarian diet; specifically, B12, with low levels in pregnant mothers in India being previously reported (64;65).

Public health action to address the overwhelming burden of NTDs in the Indian population is completely lacking. There is currently no national registry for birth defects in India (58) and, as described, the majority of studies conducted in this setting have only included NTD birth cases. Thus, the burden could be far greater than estimated (50). In 2005 Cherian and colleagues published their research in the Lancet showing that the NTD prevalence in the Balrampur District in Utter Pradesh in the North of India, one of the most underdeveloped areas of India, was one of the highest worldwide (6.57-8.21 per 1,000 live births)(66). As a result of this, Salvi and Damania wrote an article emphasising the critical importance of action being taken in India. They described the difficulties of providing folic acid supplements to all the women that need it and argued for fortification as an important tool to improve folate levels, although an appropriate staple food would need to be identified for fortification. They described how a national NTD prevention campaign, like the current mass campaign for HIV prevention in India, should be a priority (67). Flores and colleagues have described how, to date, in South East Asia, the only countries with current mandatory fortification policies in place are Indonesia and Nepal. They also highlighted the importance of addressing other known risk factors, such as B12 deficiency, in prevention policies (50). It is also of relevance to note the high rate of anencephaly affected pregnancies that were shown to be associated with other malformations (80%) in a study conducted in West India (68). As described, NTDs occurring in association with other defects are unlikely to decrease with folic acid supplementation (47).

2.1.2 Black ethnicity

The majority of the NTD epidemiological studies have been conducted in the United States and it has been shown both before and after fortification that the

highest NTD prevalence is in Hispanics, followed by non-Hispanic Whites and then non-Hispanic Blacks (15). However, many studies have failed to include prenatal diagnoses of NTDs in their prevalence estimates and therefore it is often difficult to ascertain what the "true" ethnic differences are (15). Dunlap and colleagues described how one study which compared the prevalence of NTDs pre and post fortification in the US in different ethnic groups (69) over-estimated the difference between non-Hispanic Whites and Hispanics because only 9 out of the 21 birth defects surveillance systems used included information about prenatal diagnoses (15). A study conducted in Cameroon found that the NTD prevalence was much higher than that reported for Black Americans. This led the authors to conclude that NTDs might not be as rare in sub-Saharan Black Africans as previously thought (70). TOPFA is illegal in Cameroon and none of the mothers involved in the study took folic acid peri-conceptionally (70). However, even after folic acid fortification in the United States, despite absolute gains for all ethnic groups, those of non-Hispanic Black ethnicity still bear the biggest burden of having a low red blood cell (RBC) folate status (15;71). Thus, further research, including pregnancies that result in a termination, is required in the United States to ascertain whether the NTD prevalence is truly as low in Black Americans as current studies suggest. More studies also need to be conducted in Sub-Saharan Africa to ascertain the "true" prevalence among Black Africans and the impact of various environmental and genetic factors on this (70).

2.2 UK focus: What is known about NTDs, specifically how they can be prevented, in ethnic communities in the UK?

2.2.1 NTD Prevalence and Perinatal Mortality

Leck reported in 1969 that the incidence of NTDs did not differ significantly between the local European population in Birmingham and the immigrant Pakistani population (72). Leck and Lancashire subsequently conducted a study over a much longer period (1960-1984) and actually found that there was weak statistical evidence that the birth prevalence of spina bifida is higher in Europeans than those of South Asian origin in Birmingham, although no significant differences were

found for anencephaly (73). It was also argued that terminations were unlikely to unduly affect the results as terminations were very rare in Birmingham before 1979 and the long period studied was largely pre-1979 (73).

Contrastingly, Terry and colleagues described in 1985 that the congenital anomaly and perinatal mortality rates were high in mothers of Pakistani and Indian ethnicity in Birmingham (74). It was described how mothers of Pakistani ethnicity also had the highest rate of consanguinity and increased maternal age, however, in Indian mothers, the rates for both of these factors were low (74). A study by Balarajan and colleagues, published in the same year, but with a much larger sample size, found that the mortality rates for stillbirth and infant deaths attributed to NTDs in England and Wales between 1975 and 1980 were highest in infants born to Indian and Bangladeshi mothers followed by Pakistani and Irish mothers for anencephaly. The ethnic differences were much less marked for spina bifida (75). It was also found in a study published a year previously, conducted in Bradford in the North of England, that the Asian population had higher rates of stillbirth and infant mortality due to congenital malformations than the non-Asian population. The Asian population also had an excess of multiple congenital anomalies (76).

In 1989, Chitty and Winter reported that the NTD incidence was higher in the Pakistani population than the European population in the North West Thames region of England, and that this increased incidence partly accounted for the increased perinatal mortality in the former group (77). Although it is known that consanguinity rates are high in the Pakistani population, terminations were not included in the incidence calculation which makes it difficult to ascertain whether this is a true difference or due to the Pakistani population having fewer terminations (78). Indeed, Alberman in the same year described how data from the Office of Population Censuses and Surveys, showed that there was an excess of deaths due to congenital malformations in babies born to mothers born in Pakistan, followed by mothers born in India. However, they also argued that data, by maternal country of birth, on survivors and TOPFA cases would be important to establish true ethnic differences (79). As a result of this, Chitty and Winter published research the following year that included all NTD cases detected in the prenatal and perinatal period in a London hospital between 1980 and 1987.

However, it was described how routine ultrasound examination was not available until 1984. It was found that the NTD incidence was still statistically significantly higher in Pakistani than White women (80).

More recent data from the "folic acid era" (post 1991) from the North Thames Region in the UK suggests that the rate of NTD affected pregnancies (including terminations) is higher in women of Pakistani or Indian origin (81). The authors also found that red cell folate concentrations were lower in Indian and Pakistani women and argued that further research is required to elucidate whether this is due a lower folic acid intake or genetic mutations in folate metabolising genes, or a combination of the two (81). Preliminary data from the West Midlands congenital anomaly register in 1995 also suggested that Pakistani women have a higher rate of NTD affected pregnancies (82). In 2013, it was reported in the Lancet, using an on-going prospective birth cohort in Bradford, the Born in Bradford study, that congenital anomaly rates were higher in Pakistani mothers than mothers of White British ethnicity. The excess in Pakistani mothers still remained after adjustment for deprivation and consanguinity accounted for almost a third of anomalies to mothers from this ethnic group (83). Although TOPFA cases were not included, the authors described how even after taking termination data into account, there was still an excess of congenital anomalies in mothers of Pakistani ethnicity (83).

Obesity wasn't a risk factor for congenital anomaly in the Born in Bradford cohort and there was little variation in diabetes between different ethnic groups, although numbers were small (83). However, the Health Survey for England, conducted in 2004, found obesity levels were high in those of Pakistani, Black African and Black Caribbean ethnicity (84). The authors argued that poor diet, particularly for South Asians, and lower socio-economic status, are possible reasons for this (84). Women with type 2 diabetes are more likely to come from ethnic minority groups (85) and the risk of having an NTD affected pregnancy is increased in women who are obese or have diabetes (85;86).

2.2.2 *Prenatal Screening and Termination of Pregnancy for Fetal Anomaly (TOPFA)*

Research on ethnic inequalities in the offer and uptake of prenatal screening for NTDs is limited and often comes secondary to research on screening for Down's syndrome (87;88). Rowe and colleagues conducted a review to look at social and ethnic inequalities in the offer, utilisation and uptake of prenatal screening in the UK, clearly recognising the difference between utilisation and uptake, with the latter being dependent on whether women are offered the test in the first place (88). However, results for studies looking at Down's syndrome and NTDs are reported together, despite the fact that only two (89;90) out of the ten studies in this section of the results reported on NTDs. The former found that there was no significant difference between ethnic groups in test acceptance (89) and the latter that less Asian than white women were offered screening (90). Overall it was concluded that South Asian women were less likely to be offered prenatal testing, although it was identified that very few studies actually considered this issue (88). It is difficult to say anything conclusive specifically about screening for NTDs due to limited evidence.

A very insightful study that compared White and Pakistani women's views towards prenatal testing and TOPFA for 30 different conditions found that Pakistani women would have testing for more conditions than White women, but less educated Pakistani women would have terminations for fewer conditions than less educated White women. However, regardless of ethnicity or education level, all women were in favour of terminations for the 4 most serious conditions specified, one of which was anencephaly (91). Although a clear advantage of this study was that conditions were just described and not named to reduce the effect of preconceived ideas, it was identified that in reality more information about individual conditions would be provided and other factors would influence a woman's decision, such as miscarriage risk (91). In another study, it was found that mothers of Pakistani ethnicity were less likely to terminate a pregnancy affected by a serious congenital anomaly than mothers of White or Indian ethnicity (92).

2.2.3 *Knowledge and peri-conceptional use of folic acid: A systematic review and meta-analysis*

A systematic review by Stockley and Lund published in 2008 described how peri-conceptional use of folic acid is still low in the UK, with 48% of women reporting taking folic acid as a best estimate and only 21% as the worst (93). It was argued that the factor most associated with low supplement use is unintended pregnancy, followed by age, socio-economic status and then ethnic group (93). However, while the majority of the UK studies included looked at folic acid knowledge and use in the UK with reference to age or socio-economic status, very few referred to ethnicity. Establishing how peri-conceptional use of folic acid varies by ethnicity is critical in helping to determine whether any "true" ethnic differences in NTD prevalence exist. To develop a better understanding of why women do or do not use folic acid, we need to look to studies assessing women's knowledge of the role of folic acid in NTD prevention, and their sources of information. For ethnic communities, this is essential for the appropriate targeting of health education campaigns and/or for identifying why a fortification policy is so important.

Therefore, a systematic review and meta-analysis was conducted in the early stages of this doctoral thesis to explore how knowledge and peri-conceptional use of folic acid for NTD prevention varies by ethnicity in the UK (22). This work was mainly a literature review with a small amount of original analysis. For this reason, and as the review was conducted so early on and informed key objectives for the later PhD work detailed in Chapter 3, detailed methods and findings are included below as part of this introductory chapter. Discussion from the review is included as part of the wider discussion around what is known about NTDs and how they can be prevented in ethnic communities in the U.K, which can be found at the end of this chapter. There is also further discussion around the merits of mandatory fortification with folic acid in the final discussion of this thesis in Chapter 7. The published manuscript for the review can be found in Appendix A.

2.2.3.1 Methods

2.2.3.1.1 Study selection

Medline, Embase, Pubmed and Cochrane databases were searched by one reviewer as part of a wider literature review looking at NTDs within different ethnic communities (for example, for the wider search in Pubmed, keyword and MESH search terms: neural tube defect* and ethnic* were used). The titles, abstracts and full articles, where necessary, of the approximately 400 studies identified through this wider literature search were scrutinised to identify UK studies that used post-1991 data: i.e. following publication of the Medical Research Council's Vitamin study (17). The full articles of all relevant U.K papers were downloaded and referenced articles from these publications were also assessed for eligibility. Studies that included an assessment of folic acid knowledge or peri-conceptional use in women of non-White or non-Caucasian ethnicity were included in the final review, irrespective of study design. (22). All U.K papers reviewed from the wider literature search were in English and therefore it was not necessary to consider placing any restrictions based on language.

2.2.3.1.2 Study evaluation

Within different ethnic groups, the number of women who knew about the benefits of folic acid use for NTD prevention, and their sources of information, and the number of women who took folic acid pre or peri-conceptionally, was assessed in the relevant studies. The influence of other factors on any observed associations between ethnicity and knowledge of folic acid benefits and whether folic acid was taken pre or peri-conceptionally, was also explored. Findings were evaluated in the context of individual studies' strengths and limitations (22). For example, the number of individuals in the studies from non-White or non-Caucasian ethnic groups was of critical importance.

As for the study selection process, only one reviewer evaluated the studies. However, the Preferred Reporting Items for Systematic reviews and Meta-Analysis

(PRISMA) statement, a 27 item checklist and four phase flow diagram (with slight adaptations to the latter), was utilised to ensure the adequate and appropriate reporting of the systematic review and meta-analysis (94).

2.2.3.1.3 Meta-analysis

Pre-conceptional folic acid use in Caucasians was compared with non-Caucasians across all relevant studies using a random effects model, a model that allows for variation between different studies i.e. the model allows the true effect to vary from one study to another (95). Relevant studies for inclusion were those in which there had been a quantification of pre-conceptional folic acid use in ethnic groupings that could be appropriately categorised as Caucasian and non-Caucasian (22). The analysis was conducted using the *metan* command in Stata (96), which is appropriate to use when conducting a meta-analysis for studies where two groups are compared. Using this method, a suitable summary statistic was estimated for each study and then a weighted average of that statistic was given across the studies. The outcome measure was an odds ratio (the odds of pre-conceptional folic acid use in the Caucasian ethnic group when compared to the non-Caucasian ethnic group) and the results of the analysis were summarised in a forest plot. It was also important to explore any publication or other bias in the meta-analysis and a test to explore the association between the observed effect size and study size was also carried out (22). This was done using the *metafunnel* command in Stata (96), which plots a graph with treatment effects for individual studies on the x axis and study size on the y axis (22).

2.2.3.2 Results

As shown in Figure 3, which summarises the process of selection of studies for inclusion, 49 U.K studies were identified from the wider literature search looking at NTDs within different ethnic communities. Of these, five studies were eligible for inclusion in the review as they assessed folic acid knowledge and/or use in those of non-White or non-Caucasian ethnicity using post-1991 data (22). The main reason for excluding papers was that folic acid knowledge or use was not considered in

those of non-White or non-Caucasian ethnicity (22). One notable example was Tedstone and colleagues' qualitative study which was conducted as part of consumer research, commissioned by the Food Standards Agency (FSA), to further inform the discussion surrounding folic acid fortification policy (97). The study addressed questions around knowledge of the benefits of folic acid for NTD prevention and health practices before and during pregnancy, and minority ethnic participants were included (97). However, no specific results for these research questions, broken down by ethnicity, were reported (22).

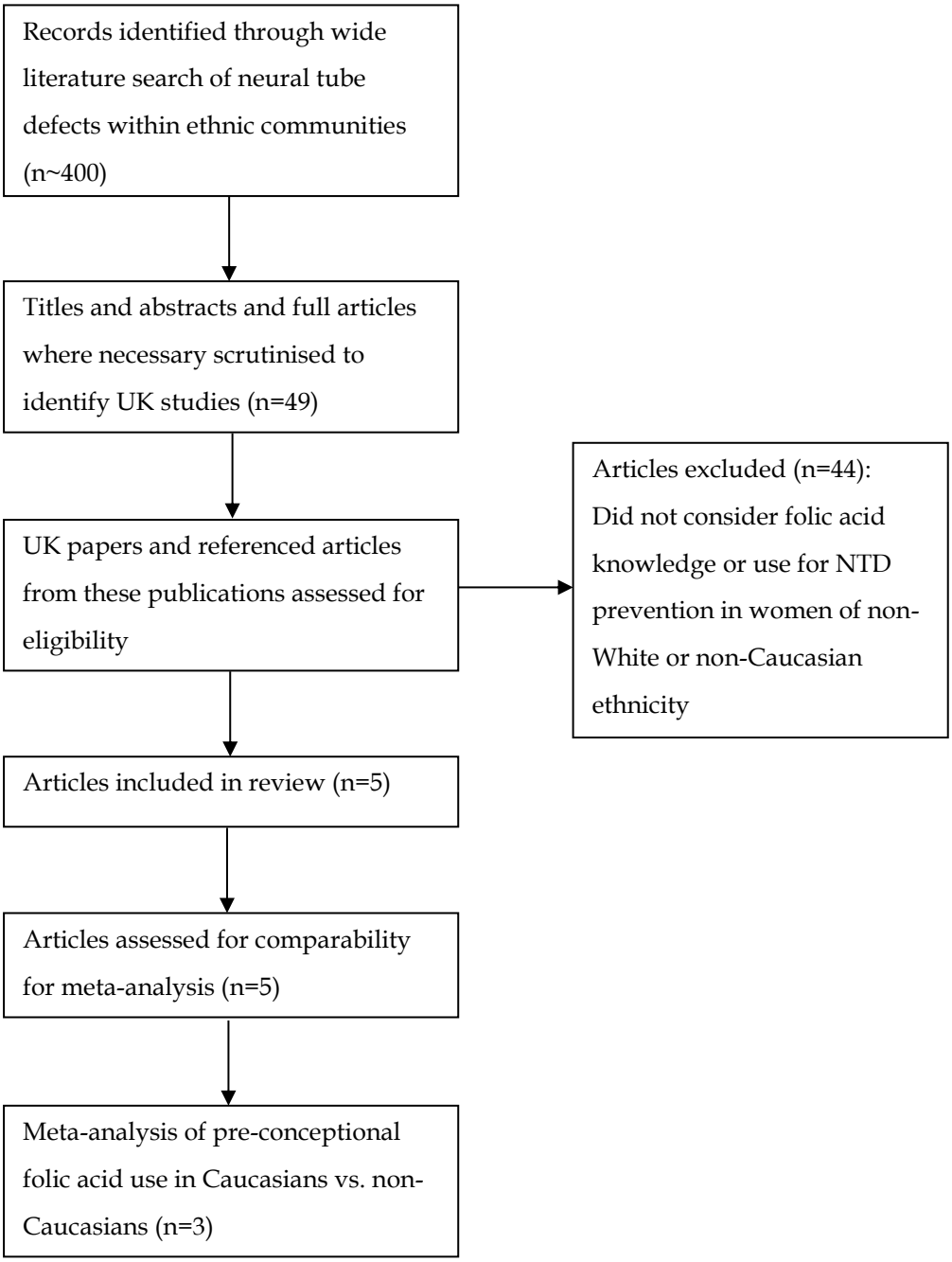

Figure 3: Flow diagram detailing process of selection of studies for inclusion in systematic review and meta-analysis
Source: Peake et al, Birth Defects Research (Part A) (22)

Key information about the five studies, including study design and type of information that was reported, is given in Table 1. In Table 2, a breakdown of the number and proportion of participants in each study by ethnicity, is given.

Table 1: Key information for individual studies included in systematic review

Study	Study setting	Study Population	Study design	Study period	Knowledge of folic acid benefits assessed?	Peri-conceptional folic acid use assessed?	Other Information
Krischer (1997)	2 GP practices (presumed Bristol due to author's location but unspecified)	105 women from inner GP practice and 103 women from suburban GP practice; aged 15-40	Self-completion questionnaire	Inner city GP: Aug 1995 Suburban GP: Dec 1995	Yes	No	Women included whether or not they were attending antenatal appointments. Not stated how ethnicity was defined.
Jessa and Hampshire (1999)	GP antenatal clinics in Nottingham	13 pregnant British Pakistani women attending consecutive antenatal clinics	In-depth interview (in English, Urdu or Punjabi)	Not stated	Yes	Yes	Ethnicity was ascertained using names recorded on antenatal lists.
Howell et al (2001)	Antenatal clinics in Tower Hamlets, London	249 women (120 Bangladeshi and 100 white) attending for first antenatal appointment	Verbally administered questionnaire before appointment	October 1997-July 1998	Yes	Only pre-conceptional folic acid use	Self-described ethnic group.
Brough et al (2009)	Homerton Hospital antenatal clinic or 2 community clinics in Hackney, East London	402 pregnant women attending for first antenatal appointment	Researcher-led questionnaire	June 2002-May 2004	No	Yes. Before 6 weeks gestation was of particular interest.	Self-described ethnic group. Non-English speakers and those taking multi-vitamins (excluding folic acid and iron) excluded.
Lane (2011)	Three South Wales Hospitals' antenatal clinics	386 pregnant women	Anonymous self-completion questionnaire	May 2010	Results were not broken down by ethnicity	Yes	Self-described ethnic group

Source: Peake et al, Birth Defects Research (Part A) (22)

Table 2: Breakdown by ethnicity of the number and proportion of participants in each study

Ethnicity	Number of cases (% of total in each study)				
	Krischer, 1997	**Jessa and Hampshire, 1999**	**Howell et al., 2001**	**Brough et al., 2009**	**Lane, 2011**
White or Caucasian	White: 166 (80)		White: 100 (40)	Caucasian: 155 (39)	White: 307 (80)
Afro-Caribbean	15 (7)				
Asian	18 (9)			42 (10)	32 (8)
Pakistani		13 (100)			
Bangladeshi			120 (48)		
African				111 (28)	
West Indian				66 (16)	
Black					15 (4)
Chinese					2 (1)
Mixed race					5 (1)
Other/ Unknown	9 (4)		29 (12)	28 (7)	25 (6)

Source: Peake et al, Birth Defects Research (Part A) (22)

2.2.3.2.1 Folic acid knowledge

As shown in Table 1, three out of the five studies included in the final systematic review reported knowledge of the benefits of folic acid in women of non-White or non-Caucasian ethnicity. Howell and colleagues reported that in Tower Hamlets, in East London, only 35% of Bangladeshi women knew of the benefits of taking folic acid in comparison to 84% of White women. This was a statistically significant difference ($p<0.001$) (98). Contrastingly, Krischer reported that in an inner-city GP practice, with a multi-ethnic population, there were no key differences in knowledge of the link between folic acid and spina bifida between different ethnic groups (99). However, Krischer's study was underpowered and the inner city practice only had 105 participants. In Jessa and Hampshire's qualitative study, conducted in Nottingham, pregnant women of Pakistani ethnicity were interviewed about their knowledge, health beliefs and attitudes towards folic acid. None of the women interviewed knew exactly why folic acid should be taken (22;100).

The remaining two studies included in the review (101;102) did not report folic acid knowledge in participants, broken down by ethnicity, and it was not possible to infer any differences based on the relationship between knowledge and uptake (22).

2.2.3.2.2 Folic acid use

Four of the five included studies reported data on folic acid use.

Jessa and Hampshire reported that none of the 13 Pakistani women interviewed in their qualitative study took folic acid in the peri-conceptional period (100).

Howell and colleagues described how in a univariate analysis looking at the association between ethnicity and folic acid intake, White women were 5.7 times more likely to take folic acid pre-conception than Bangladeshi women (95% CI: 2.5, 13.2). In the multivariate analysis, where the women's age, school leaving age, social class, parity, planned pregnancy and whether they had heard about folic acid benefits, were adjusted for, White women were still 5.2 times more likely to take folic acid pre-conception than Bangladeshi women (95% CI: 1.1, 25.2) (98).

Brough and colleagues also found ethnic differences in the pre-conception use of folic acid, in their study in Hackney, East London. It was described how pre-conception folic acid use was highest in Caucasians (19%) followed by Asians (12%), West Indians (8%) and Africans (5%). The difference between Caucasians and Africans, was of statistical significance (p=0.038). A further 23% of Caucasians had started to take folic acid after conception but before neural tube closure (6 weeks gestation cut-off in this study). More Caucasian mothers initiated folic acid use before 6 weeks gestation than non-Caucasian mothers (p=0.001). Two key limitations of Brough and colleagues' study were that it was not powered to investigate folic acid use and women who took multivitamins were excluded, which could have potentially biased the study towards participants of lower socio-economic status. Furthermore, although several factors were explored in the study and it was also detailed how mothers from a higher socio-economic group or with higher education levels are more likely to use folic acid, there was no multivariable model: i.e. an exploration of the association between ethnicity and folic acid use,

adjusted for maternal education and socio-economic status (22;101). However, this might not have a huge impact on observed outcomes as there was only a modest difference in the association between ethnicity and folic acid intake between univariate and multivariate models, in Howell and colleagues' study (98).

Finally, Lane and colleagues, in their study including pregnant women from three South Wales Hospitals, reported that there were no ethnic differences in peri-conceptional use of folic acid. However, numbers of participants in ethnic groups other than White British were small, which could have influenced the outcome (22;102).

2.2.3.2.3 Sources of information on folic acid

Advice from health professionals (HPs) (e.g., GPs and midwives) was the main reason given by participants in Lane's study for starting to take folic acid (102). However, it was also reported that 81% of women who took folic acid based on their HPs' advice, only started taking supplements after they became pregnant (102). Participants in Krischer's study stated both the media (including magazines, newspapers, television and radio) and HPs as their sources of information on folic acid (99). In Jessa and Hampshire's qualitative study, none of the Pakistani women interviewed said they could recall their GP giving them any folic acid advice. However, many said they would only take folic acid if their GP advised them to and prescribed it (22;100).

2.2.3.2.4 Meta-analysis

Data on peri-conceptional use of folic acid in Caucasian/White and non-Caucasian/non-White women were assessed in two studies (101;102) and data on pre-conceptional use in three (99;101;102). Therefore, a meta-analysis of the association between ethnicity and whether folic acid was used pre-conceptionally, was carried out. As only two studies assessed knowledge of the benefits of taking folic acid it was not deemed appropriate to also carry out a meta-analysis in this area.

As the three studies assessing pre-conceptional folic acid use varied in the ethnic mix of their participants, and in one study ethnicity was not broken down any further than Caucasian British and Other (102), the comparison in the meta-analysis was between Caucasians/White and non-Caucasians/non-Whites. As shown in Figure 4, the meta-analysis across the three studies, using a random effects model, found that the odds of using folic acid before conception were nearly three times as high in Caucasian/White women as non-Caucasian/non-White women. Thus, when assessed individually, Howell and colleagues (98) and Brough and colleagues (101) found a statistically significant difference between Caucasians and non-Caucasians in pre-conceptional folic acid use and Lane and colleagues did not. However, when the results for the three studies are pooled, there is a clear treatment effect. A test of heterogeneity between different studies was shown to be of borderline statistical significance (p=0.049), lending support to the selection of a random effects model for the analysis. Investigations for bias, found that no individual study unduly influenced the final treatment effect (22).

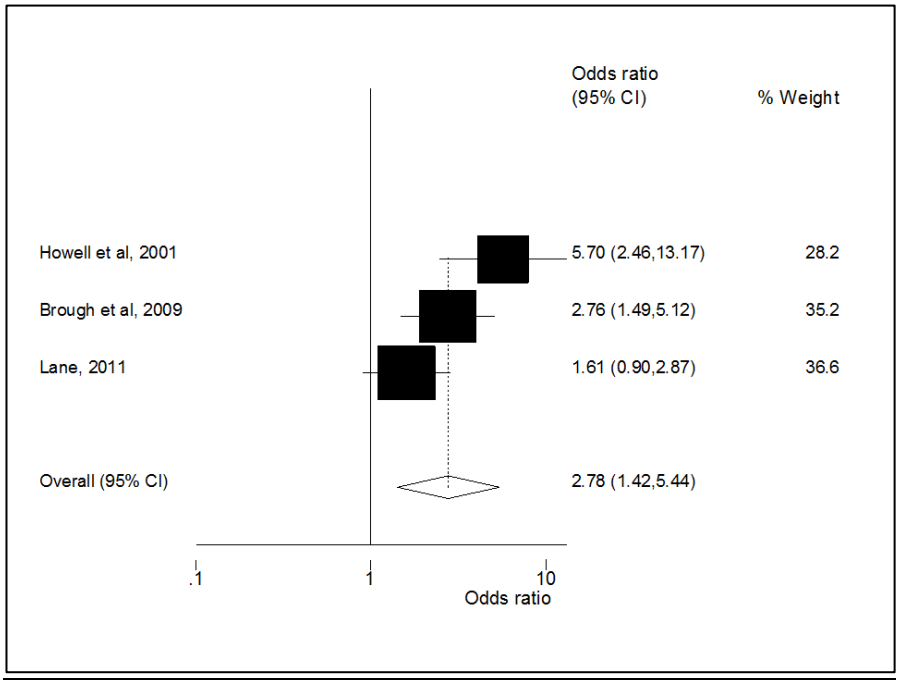

Figure 4: Meta-analysis of pre-conceptional folic acid use in Caucasians/Whites compared to non-Caucasians/non-Whites.
Source: Peake et al, Birth Defects Research (Part A) (22)

2.2.4 *Knowledge and peri-conceptional use of folic acid: Research since the systematic review was published*

In 2014, Bestwick and colleagues reported the results of an audit of the Down's syndrome and NTD screening service at the Wolfson Institute of Preventive Medicine in London, which also collects information on whether folic acid is taken or not (103). It was reported that Caucasians were more likely to take folic acid before pregnancy than non-Caucasians. Specifically, 35% of Caucasians, 18% of Afro-Caribbeans, 20% of South Asians, 22% of Oriental women and 23% of those of "Other" ethnicity took folic acid before pregnancy. This was after adjustment for several factors, including maternal age and diabetes. All differences between the Caucasian and non-Caucasian ethnic groups specified were statistically significant (103).

2.2.5 *Discussion*

As described, data from the "folic acid era" indicates that women of Indian (81) and Pakistani (81;82) ethnicity have an excess NTD prevalence. Data from 1975 to 1980 from England and Wales, also found mortality rates for stillbirth and infant deaths attributed to NTDs were high in the Bangladeshi community (75). Data from the late 1970's and 1980's corroborating what is found in the 1990's is interesting, even when terminations are taken into account in the earlier studies (80). However, it is also of interest that Leck and Lancashire's research including data from an even earlier period (the earliest data year is 1960) found contrasting results: that there was weak statistical evidence that the spina bifida (but not the anencephaly) prevalence was higher in Europeans than South Asians (73). Looking back at Morris and Wald's graph (Figure 2) detailing the change in NTD prevalence between 1964 and 2004, the most marked decline is between the early and late 1980's (32). The authors also previously described how the early 1980's was a time when there started to be an increase in intake of dietary folate (33). It could be argued that Leck and Lancashire's very early study gives a different picture to later research of ethnic differences as it included data from a period when the impact of dietary folate is unlikely to be substantial, pointing towards increased intake of folate or folic acid in the 1980s and 1990s as the reason for observed NTD excesses in mothers of South

Asian ethnicity. However, there were identified limitations with Leck and Lancashire's study, including missing data on ethnicity and them using too broad ethnic groupings (73). Ethnic groupings themselves also change over time making comparisons for specific ethnic groups over long time frames problematic. It is also of importance to take migration history into consideration when interpreting findings. For example, Sikh and Hindu families started to settle in the U.K in the 1960s (104), emphasising how individuals included in the early studies are likely to be immigrants or first generation migrants and those in more recent data, second generation migrants. These individuals cannot be considered as a homogenous group and health behaviours during pregnancy have been shown to differ by generational status (105). Moreover, even when looking at a more restrictive time period, there are clear indications from the literature that ethnic differences are unlikely to be solely explained by discrepancies in folate or folic acid intake.

For mothers of Pakistani ethnicity, recent research from the Born in Bradford study underlined the importance of consanguinity in explaining the excess congenital anomaly rate in Pakistani mothers when compared to those of White British ethnicity (83). This is supported by earlier research which also described maternal age as a possible contributory factor for mothers from this ethnic group (74). For NTD prevalence specifically, the importance of consanguinity in mothers of Pakistani ethnicity has been detailed (77).

Contrastingly, for mothers of Indian ethnicity, consanguinity (74;106) or maternal age (74) does not seem to be a significant factor in congenital anomaly risk in the U.K. In fact, those of Indian ethnicity are a very interesting group with regards to NTD prevalence. As described in section 2.1, those of Indian ethnicity seem to keep their high NTD prevalence, regardless of where they reside (54). Looking at research in India, a high NTD prevalence has been specifically reported in the North (55;58), particularly among the Sikh population, but also among Hindus in certain areas (55). In contrast to the epidemic in the North, consanguinity is likely to be a significant factor in accounting for pockets of increased prevalence in the South (58). The importance of following a vegetarian diet for Hindus and consanguinity in Muslims in the North has also been highlighted (63). Reports of an excess of multiple congenital anomalies in the Asian population in the North of England (76)

and anencephaly affected pregnancies occurring in association with other malformations in a study conducted in the West of India (68), also further highlights the role of factors other than folic acid in explaining ethnic differences in NTD prevalence.

However, the importance of folic acid cannot be ignored and Michie and colleagues described how lower red cell folate concentrations were found in mothers of Pakistani and Indian ethnic origin (81). The results of the systematic review and meta-analysis conducted as part of this thesis, found that Caucasians/Whites are more likely to take folic acid before conception than non-Caucasians/non-Whites (22), which was also shown in a study conducted after the review was published (103). Bestwick and colleagues described how 35% of Caucasians took folic acid before pregnancy, in contrast to 20% of South Asians (103). Findings from the review also indicated that South Asians are less likely to use folic acid. However, there were very few studies included in the final review and this would need to be substantiated with further research (22) .

There are some key limitations of the published systematic review and meta-analysis conducted in the early stages of this doctoral thesis. Included studies were conducted in diverse areas throughout the U.K. and of the three included in the meta-analysis, two were conducted in East London (98;101) and one in Wales (102). The ethnic make-up in Wales is very different to East London and combining the three studies in a meta-analysis could have introduced variation due to the geographical area that was sampled (22). The study periods for the three studies included in the meta-analysis were also diverse, which could have been a potential confounder. However, it is unlikely that variations in study periods would have greatly affected results as all were within the post-1991 "folic acid era" and folic acid usage in the U.K has been consistently low since folic acid supplementation policies were implemented (31;93). It is also a limitation of the available data that comparisons in the meta-analysis could only be made based on broad ethnic categories: Caucasian and non-Caucasian. Although this meant that it was not possible to draw conclusions about specific non-Caucasian groupings, it was very important in revealing whether U.K Caucasian (largely indigenous) women were

more or less likely to take folic acid before conception than non-Caucasians (including many migrant families) (22).

Ethnicity was self-described in all studies included in the meta-analysis, which was a clear strength. All studies included in the meta-analysis were also conducted in antenatal clinics. In Howell and colleagues' (98) and Brough and colleagues' (101) study it was specifically detailed that this was the first antenatal visit, although this was not clearly stated in Lane's (102) study. Conducting the research at the first antenatal visit is important as this is around 12 weeks and it is recommended that women take folic acid supplementation up until this time. Therefore, this is likely to have resulted in clearer recall about folic acid usage (22).

Taking folic acid in the peri-conceptional period is a clear NTD preventative measure and exploring women's knowledge of folic acid, including where they get their information from and whose advice they value, is critical in improving folic acid intake within particular communities. Jessa and Hampshire's qualitative study (100) included in the systematic review was particularly revealing for this and highlighted the importance of more qualitative research being conducted in this area. They highlighted how Pakistani women trusted their GPs most to give them pre-pregnancy advice on folic acid. However, none of the women had received this information from their GP for their current pregnancy (22;100). GPs were also described as important sources of information on folic acid in Krischer's study (99) and as the reason why women started taking folic acid in Lane's study (102). However, critically, it was also detailed how women who took folic acid based on their GPs' advice, were more likely to start late (22;102).

Authors of four out of the five studies included in the systematic review (99-102) argued that fortification of food with folic acid is the most effective method to improve folate intake. Specifically, it was argued that ethnic minority foods such as wheat and chapatti flour need to be fortified to ensure ethnic communities also benefit from fortification (22;99-101). Thus, it was argued that carefully targeted, innovative education campaigns to promote supplement use together with a mandatory fortification policy, including the fortification of ethnic minority foods,

needs to be implemented to improve folic acid intake within different ethnic communities in the U.K. (22).

3 Study design and methodology

In this chapter, the rationale behind conducting the PhD and key aims and objectives are first detailed. Background information to using mixed (quantitative and qualitative) methodology is then given and the decision to use this particular methodology is justified. Information on the study design is given, including an overview of methods, details of the different study phases and how the different components were weighted and integrated. There is a final paragraph with details on information governance.

3.1 PhD rationale

As described in Chapter 1, the increasing "invisibility" of neural tube defects (NTDs), likely due to their high prenatal detection and termination rate, has resulted in there being less of a drive behind their primary prevention in public health policy (2). There are inadequate surveillance systems in many settings which often do not capture termination of pregnancy for fetal anomaly (TOPFA) cases, and therefore the true NTD burden cannot be assessed. In the U.K the importance of pre-conception care as a critical period when intervention can provide long term benefit is being increasingly recognised and there seems to have been a recent shift in attitude towards NTD prevention, with fortification finally being given real consideration. In contrast to the United States, where much of the NTD epidemiological research has been conducted, research in the U.K. is scarce. There is a real paucity of research specifically into NTD prevention within different ethnic communities in the U.K, although, worryingly, based on existing research, there seems to be an increased prevalence within certain ethnic groups. Women of non-White ethnicity, have also been shown to be less likely to take folic acid before pregnancy than women of White ethnicity. Thus, there is a real need for updated prevalence estimates, that include TOPFA cases, by ethnicity in the U.K. (the last study was published in 1998 and included only preliminary data) and to evaluate the importance of other factors, including socio-economic status, which has largely been unrepresented. It is also crucial to better understand how women's views and

knowledge before and during pregnancy shape their pregnancy decisions, to enable the effective targeting of NTD prevention strategies.

3.2 Overall PhD Aim

The overall aim of this doctoral thesis was to gain a better understanding of the NTD epidemiology, natural history and views and practices of women from different ethnic communities in the U.K, before and during early pregnancy, and to use this information to propose appropriate NTD prevention strategies.

3.3 PhD Objectives

1. To calculate accurate NTD prevalence estimates, which include TOPFA cases, for different ethnic groups in the U.K.

2. To explore the impact of other factors e.g. socio-economic status, on any observed association between NTD prevalence and ethnicity.

3. To explore the factors influencing women's decisions of whether to continue an NTD affected pregnancy or not, including variation by ethnic groups.

4. To assess in-depth information from women from ethnic communities about their knowledge, attitudes and health behaviour before and during pregnancy, particularly with regards to folic acid supplementation, and how this impacts on decisions.

3.4 Mixed Methodology

3.4.1 Background

Johnson and Onwuegbuzie describe mixed methods research as a "third research paradigm" with quantitative research at one end of a continuum, qualitative research at the other end and mixed methods research in the middle (107). The same authors, after considering criteria that leaders in the field deem important for defining the methodology, described in 2007 a general definition for mixed methods research. It is stated that it combines quantitative and qualitative elements to enable a depth and breadth of understanding and also for corroboration (108). Similarly, Castro and colleagues argue that using mixed methods can combine confirmatory results from quantitative multivariable analyses with "deeper structure" explorations drawn from the qualitative methods (109). However, that is not to say that mixed methods research is in fact superior to traditional quantitative and qualitative research and, as Johnson and Onwuegbuzie argue, a three paradigm (quantitative, qualitative and mixed methods) world is actually healthy and each has strengths and limitations and places of need (108).

Lingard and colleagues describe the importance of clearly detailing the strategy for mixing methods, including the methods sequence, whether there is equal weighting for qualitative and quantitative components or one is prioritised over the other and how and when methods are integrated (110). Johnson and Onwuegbuzie argue that the lines between the quantitative and qualitative paradigms are less clear than is often presented (108). Therefore, Linguard and colleagues emphasise how good mixed methods research does not dichotomise the values and methods of the two paradigms but clearly articulates how and why there is an integration of the different aspects (110).

3.4.2 Justification for using mixed methods

The focus of this PhD is ethnicity. As Sheldon and Parker rightly highlight, even if ethnicity is self-reported, the ethnic categories which individuals are asked to

identify themselves with in the first place, are socially determined (111). Therefore, although it is of importance to collect this information, there also needs to be a degree of critical engagement with it. Using mixed methods for this PhD was viewed as essential to achieve the appropriate level of insight to enable all research questions to be addressed adequately. Quantitative data were required to calculate up-to-date NTD prevalence estimates for different ethnic groups in the U.K and to start to explore how other key factors might affect these differences. Quantitative data were also important for initial investigations of the factors affecting women's decisions around whether to continue their NTD affected pregnancy or not. However, it was also crucial to understand women's knowledge, attitudes, views, behaviour and cultural influences in relation to folic acid prevention and pregnancy decisions. It was not possible to explore this in the quantitative study and was only possible through the in-depth qualitative interviews. The "why" that could only be explored to a certain extent using the quantitative data was further investigated in the qualitative study and enabled specific recommendations to be made.

3.4.3 Study design

3.4.3.1 Quantitative methods overview

As described in further depth in Chapter 4, the British Isles Network of Congenital Anomaly Registers (BINOCAR), a network of regional congenital anomaly registers across the U.K. and Republic of Ireland, was viewed as the best data source for the quantitative research. Key reasons for this are that all registers are population based, include termination of pregnancy for fetal anomaly (TOPFA) cases and have multi-source reporting, to ensure case ascertainment is as high as possible. There were five BINOCAR registers that neural tube defect (NTD) cases were reported to which both collected ethnicity information and permission was granted to use the data for the study. Therefore, pseudonymised, individual level data was obtained from these five BINOCAR registers for all NTD cases between the years 2006 to 2011 inclusive. Only NTD cases with mothers aged 16 or over were included for ethical reasons. Live and still birth denominator data from the Office for National

Statistics (ONS) were also obtained for the same data years and regions to enable NTD prevalence estimates to be calculated.

Unfortunately, there is not currently a congenital anomaly register that covers any part of London, which, critically, is a very ethnically diverse area. It was, however, possible to obtain termination data, where an NTD was given as a reason for the termination, from the Department of Health (DH) for London. DH termination data were also obtained for the regions covered by two of the BINOCAR registers included in the study for the same data years. Requesting DH termination data from only two regions also covered by BINOCAR registers was viewed as necessary and sufficient to help to validate the completeness of the picture for terminations due to NTDs in the London DH data and also to conduct any other comparative analyses. Termination denominator data were also obtained from the DH. As described in chapter 5, there are both indications of under ascertainment in the DH dataset when an NTD is a reason for the termination and under reporting of terminations to the DH (112). The DH denominator data were used for important sensitivity analyses around NTD prevalence estimates (Chapter 4) and NTD termination cases were linked with NTD TOPFA cases in the BINOCAR dataset for explorations around ethnicity (Chapter 5). However, due to the stated problems, further investigations solely looking at the DH termination data for London were deemed unreliable.

Stata versions 12 and 13 (96;113) were used to clean and analyse the data. To explore NTD prevalence, binomial regression, regression with proportions as the outcome (binomial distribution), was used. To explore the natural history of NTD affected pregnancies, logistic regression, regression with a binary outcome (binary distribution) was used. Statistical methods used in the quantitative research are explored in-depth in chapters 4 and 5.

3.4.3.2 Quantitative study sample size calculation

One early study conducted in England and Wales found that mortality rates for stillbirth and infant deaths attributed to NTDs for mothers born in

India/Bangladesh were nearly twice as high as to mothers born in the U.K (75). Another early study found that mothers of Pakistani ethnicity in London had a rate of NTD affected pregnancies that was more than double that for White mothers (80). Analyses using data from 1995, from the West Midlands region of the U.K, found that the rate of NTD affected pregnancies to mothers of Pakistani ethnicity was more than five times higher than to mothers of White ethnicity. However, this was conducted using only preliminary data (82).

Using the sampsi command in Stata, the minimum number of mothers from different ethnic groups required in the study population in order to detect a number of different NTD rate differences, were explored. Using this method, it was shown that to detect an NTD rate that is two times higher in mothers of Pakistani than White ethnicity, 11794 mothers would be required in the former ethnic group and 196566 in the latter. To detect an NTD rate that is two times higher in mothers of Indian than White ethnicity, 11493 mothers would be required in the former ethnic group and 287315 in the latter. Finally, to detect an NTD rate that is two times higher in mothers of Bangladeshi than White ethnicity, 11191 mothers would be required in the former ethnic group and 559517 in the latter.

3.4.3.3 Qualitative methods overview

Mothers aged 18 years or older who had a previous NTD affected pregnancy, from ethnic communities, were recruited for in-depth semi-structured interview by advertisements in hospitals, specialist organisations, community and faith-based organisations and social media. Participation in the study was entirely voluntary.

It was decided that grounded theory methodology would be used to both conduct and analyse the qualitative research due to its strongly inductive nature and focus on actions. It was gaining in-depth information from interviewees about their knowledge, attitudes and experiences before and during their pregnancy affected by an NTD that was not unnecessarily forced down a particular direction due to researcher biases or pre-conceived ideas, which was of critical importance. The use of the constant comparative method, constantly comparing data with data, ensured

that the analysis and researcher interpretations were continually challenged and grounded in the data. NVivo 10 software (114) was used to analyse the data. In-depth information about the grounded theory methodology and how it was used in the qualitative research is detailed in Chapter 6.

3.4.3.4 Study Sequence

Although the quantitative research was started first and key information was obtained which informed how the qualitative study was conducted: e.g. which ethnic groups to focus on, the quantitative study was not completed before the qualitative study began. This enabled results from the qualitative study to also shed new light on results from the quantitative study and how later analyses were conducted and interpreted (Figure 5). Therefore, although detailed methodology, findings and key conclusions from the quantitative study are presented first in Chapters 4 and 5 and then methodology, findings (with a stream of discussion throughout) and conclusions for the qualitative study in Chapter 6, this is not exactly the sequence of how things occurred.

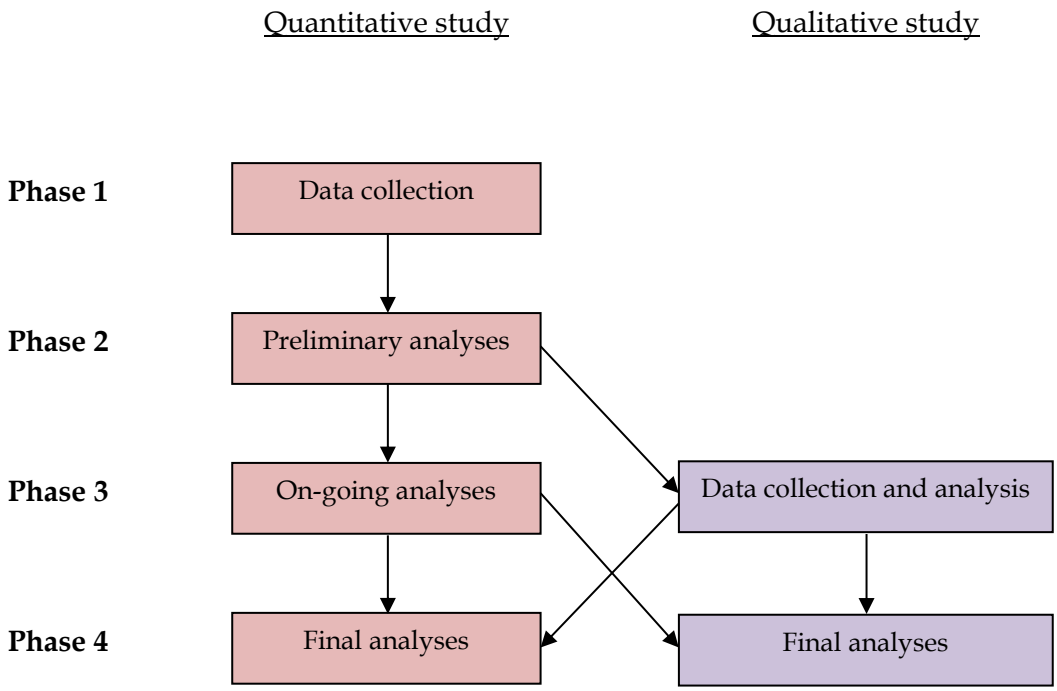

Figure 5: Phases of research in relation to quantitative and qualitative study sequence

3.4.3.5 Study Weighting

Quantitative and qualitative components were essential to enable research questions to be addressed adequately, as detailed, and it was dependent on the research question being addressed as to whether each was given equal weighting or one took precedence over the other. However, overall, there was a stronger weighting for the quantitative study which was the bigger research component.

3.4.3.6 Integration of quantitative and qualitative study components

As shown in Figure 5, analyses of qualitative data in Phase 3 of the research were used to inform final analyses in the quantitative study in Phase 4 of the research. This was particularly apparent for explorations about pregnancy decisions. However, qualitative findings were not explicitly integrated with the quantitative findings around pregnancy decisions in Chapter 5 as it would have been

problematic to do so before the qualitative research had even been detailed. It should therefore be kept in mind when reviewing conclusions for this aspect of the quantitative study that they were not without influence from the qualitative data. For these reasons, a detailed discussion with regards to the quantitative findings is saved for the final discussion (Chapter 7), where the findings from the two study components are more explicitly triangulated.

3.5 Information Governance

NHS Research Ethics Committee (REC) approval was granted for both the quantitative and qualitative study (REC reference: 12/LO/0890). There were also two substantial amendments to the original ethics application, which also received favourable opinions. The approval form for the most recent application can be found in Appendix B. It was also necessary to obtain section 251 approval for the quantitative study, due to the collection of sensitive patient data without explicit patient consent. Both the initial application and a subsequent amendment received approval and the approval form for the latter can be found in Appendix B. As part of this, an NHS Information Governance Toolkit was completed in early 2014 and renewed in 2015. Access to the BINOCAR data was granted by the BINOCAR Management Committee and permission was obtained from the Chief Medical Officer (CMO) for use of the DH termination data (the approval letter from the CMO is included in Appendix B).

4 Introduction to the British Isles Network of Congenital Anomaly registers (BINOCAR) dataset and preliminary epidemiological explorations

In this Chapter the main data source for the quantitative study is introduced and initial investigations of NTD prevalence are carried out using both this dataset and, where appropriate, additional termination data obtained from the Department of Health. These initial explorations were conducted with the aim to inform the main analyses around ethnicity, detailed in Chapter 5.

4.1 BINOCAR data by register

The British Isles Network of Congenital Anomaly Registers (BINOCAR) is a network of regional congenital anomaly registers across the United Kingdom and Republic of Ireland. These regional registers were set up alongside the National Congenital Anomaly System (NCAS) to address both the under-ascertainment and also local research needs (115). Details of all registers included in the study, are given in Table 3. All registers are full members of the European Surveillance of Congenital Anomalies (EUROCAT), the European network of congenital anomaly registers, and are population based, collecting data on all pregnancies affected by congenital anomalies within the region. Although reporting to all registers is voluntary, case finding is active and there is multi-source reporting. Case ascertainment by regional registers is markedly better than the former NCAS, which didn't record terminations of pregnancy for fetal anomaly (TOPFA) cases. However, it was shown that even when looking solely at live and still birth cases, only 60% of the cases that were notified to the regional congenital anomaly registers were also notified to NCAS (115). In addition to multiple source notification, routine audits by regional registers of their data ensure that as many congenital anomaly cases are captured as possible (116;116). High levels of ascertainment have also been confirmed through register comparisons through BINOCAR and EUROCAT (117). However, different regions have been shown to differ in antenatal detection over

time and in the extent to which postnatal cases are notified (117). As shown in Table 3, the East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR) has no upper age limit, for the Northern Congenital Abnormality Survey (NorCAS) it is 12 years, South West Congenital Anomaly Register (SWCAR) 18 years, for the Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB) only cases diagnosed up to 1 year of age are notified and for the Congenital Anomaly Register and Information Service for Wales (CARIS) the upper age limit is also one year (excluding chromosomal and syndromic cases). However, the discrepancy in postnatal notifications is unlikely to be great due to very few postnatal notifications in fact being made to any register (118). Moreover, for congenital anomalies such as neural tube defects (NTDs), which have a high prenatal detection rate (49), this is likely to present less of a problem than for defects such as congenital heart disease (117).

The key data variables obtained from BINOCAR registers specifically for NTD cases notified between 2006 and 2011, is given in Table 4, along with an indication of the missing data for each variable. "NTD cases" were extracted based on International Classification of Diseases (ICD) 10 codes: Anencephaly and similar malformations (Q00); Encephalocele (Q01) and Spina bifida (Q05), with all sub-codes included. The "Anencephaly and similar malformations" group is simply referred to as "Anencephaly" in the rest of this thesis, although Craniorachischisis is also included under this grouping. As shown, completeness for most variables across the registers is consistently high; notable exceptions are body mass index (BMI) of the mother, which has very poor completion in all registers apart from NorCAS, and the sex of baby (although completeness is much better in NorCAS). Critically ethnicity has 13% and 16% missing data in EMSYCAR and SWCAR respectively and 45% missing data in NorCAS.

It is of importance to note the on-going communication that went on with BINOCAR staff and register representatives throughout the duration of this research, to query and further explore obtained data in order to better understand it and interpret results.

Table 3: BINOCAR register description

Register name (short name)	Population coverage	Year established	Annual notification	Case Ascertainment	Minimum and maximum age at diagnosis	Population Characteristics (based on ONS 2011 birth data)
East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR)	All mothers normally resident within South Yorkshire and the counties of Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire, Rutland and Northamptonshire (74,000 births annually)	1997	1,400	Voluntary, multi-source reporting: Includes antenatal clinics, delivery suites, neonatal screening, neonatal and special care baby units, cytogenetics laboratories, clinical genetics, pathology, paediatric surgery and departments of child health.	No lower age limit (all early losses and terminations with anomalies registered). Also, no upper age limit.	82% White; 2% Black/Black British; 6% Asian/Asian British
Northern Congenital Abnormality Survey (NorCAS)	Mothers resident in North East England and North Cumbria (32,000 births annually)	1985	800	Voluntary, multi-source reporting: Includes ultrasonographers, geneticists, midwives, radiographers, obstetricians, paediatricians from a wide range of specialties, pathologists, cardiologists, fetal medicine specialists and surgeons.	No lower age limit (all early losses and terminations with anomalies registered). Upper age limit: 12 years	90% White; 1% Black/Black British; 3% Asian/Asian British

Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)	1991-2004: Oxfordshire only (7,000 births) 2005 onwards: Whole of Oxfordshire, Berkshire and Buckinghamshire (30,000 births annually)	1991	700	Voluntary, multi-source reporting: Includes antenatal clinics, obstetric ultrasound, delivery suites, special care baby units, cytogenetic laboratory, paediatric pathology and the Down's syndrome service.	No lower age limit (all early losses and terminations with anomalies registered). Upper age limit 1 year	74% White; 4% Black/Black British; 11% Asian/Asian British
South West Congenital Anomaly Register (SWCAR)	South West SHA (formerly Avon, Gloucestershire and Wiltshire; Dorset and Somerset and South West Peninsula) (approx 59,000 births annually)	2002	1,500	Includes Ultrasound, Cytogenetics, Pathology (Postmortem Reports), Delivery Suites, Gynae Wards, Neonatal Intensive Care Units, Paediatricians, Physiotherapy, X-ray, Sub specialist consultants e.g. paediatric renal medicine/surgery, orthopaedics, genetics, cardiac databases, fetal medicine.	No lower age limit (all early losses and terminations with anomalies registered). Upper age limit 18 years	87% White; 1% Black/Black British; 2% Asian/Asian British

Congenital Anomaly Register and Information Service for Wales (CARIS)	All of Wales (approx 35,000 births annually)	1998	1,200	Voluntary, multi-source reporting: Includes antenatal clinics, delivery units, paediatric depts., ophthalmology, cytogenetics, pathology, orthopaedics, maxillo-facial and regional centres of paediatric surgery	No lower age limit (all early losses and terminations with anomalies registered). Upper age limit 1 year (excl chromosomal anomalies and syndromes that are included irrespective of age)	86% White; 1% Black/Black British; 2% Asian/Asian British

Table 4: Missing data for key variables by register

Register name (short name)	Number of NTD cases notified between 2006 and 2011 (based on Feb 2014 EUROCAT update)	% missing for key variables										
		Year of outcome	Primary Care Trust of mother's residence at birth outcome	Number of babies/fetuses affected	Number of malformed in multiple set	Multiple malformation code[1]	Sex of baby for cases with gestation length <18 weeks	Sex of baby for cases with gestation length >=18 weeks	Ethnicity of mother[2]	Age of mother at outcome	Maternal BMI at booking	Index of Multiple Deprivation (IMD) 2010 score/quintile of mother's residence at birth outcome[3]
East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR)	511	0	0.39	0	0	0	80.38	22.19	12.92	1.57	100	0.39
Northern Congenital Abnormality Survey (NorCAS)	288	0	13.40	0	0	0	29.37	6.17	45.83	0	23.26	11.81
Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)	216	0	0.47	0	0	0	77.42	30.08	38.43	0.46	96.76	0

South West Congenital Anomaly Register (SWCAR)	326	0	0.31	0.31	0	0	74.14	34.76	7.06	0	94.17	0
Congenital Anomaly Register and Information Service for Wales (CARIS)	303	0	2.02	0	0	0	53.64	21.76	32.01	0	94.06	2.02*

[1]Multiple malformation code gives indication of whether NTD occurs in isolation or in association with other defects.

[2]Broadly based on the ONS 2001 census classification

[3]The IMD score, based on maternal postcode, is calculated in a different way for England and Wales and the two are not directly comparable.

4.2 Twins/Multiple Births

4.2.1 Twins/multiple births in the BINOCAR dataset

Data were obtained from BINOCAR for individual NTD affected babies. Through early explorations of the dataset it was found that there were a number of cases that were part of a multiple set; between 4 and 5% of the cases for each register were multiples, with NorCAS being the exception where nearly 7% of cases were. Overall, there were 78 multiples in the dataset (Table 5). In 63 of the multiple cases only one fetus had a malformation (this included the triplet pregnancy) and in 15 both fetuses were affected. While most registers had more multiple pregnancies in which only one fetus was affected compared with two affected fetuses, the CARIS register had an equal number of both (Table 6).

Table 5: Breakdown of number of NTD affected babies that are singletons or part of a multiple set (twins or triplets), by register

Number of babies/fetuses in pregnancy of affected NTD case	No. (%) in each register					
	EMSYCAR	NorCAS	CAROBB	SWCAR	CARIS	Total
1	489 (96)	268 (93.06)	207 (95.83)	312 (95.71)	289 (95.38)	1565 (95.19)
2	22 (4.31)	19 (6.6)	9 (4.17)	13 (3.99)	14 (4.62)	77 (4.68)
3	0	1 (0.35)	0	0	0	1 (0.06)
Number unknown	0	0	0	1 (0.31)	0	1 (0.06)
Total	511	288	216	326	303	1644

Table 6: Breakdown of the number malformed in multiple set by register

Number malformed in multiple set	No. (%) in each register					
	EMSYCAR	NorCAS	CAROBB	SWCAR	CARIS	Total
1	19 (86.36)	17 (85)	9 (100)	11 (84.62)	7 (50)	63 (80.77)
2	3 (13.64)	3 (15)	0 (0)	2 (15.38)	7 (50)	15 (19.23)
Total	22 (100)	20 (100)	9 (100)	13 (100)	14 (100)	78 (100)

When restricting the dataset to multiples where both fetuses/babies had a malformation, it became very apparent that there were four cases in the dataset that corresponded to only two pregnancies i.e. there were two twin pregnancies where both fetuses had been registered as having an NTD (both of these came from

CARIS). It was not deemed appropriate to include both of these pregnancies twice, as maternal factors would be included twice and the focus of this research is the NTD prevalence in pregnant women from different ethnic communities. Therefore, each pregnancy was defined as an affected pregnancy and one fetus from each of these two pregnancies was excluded from the analysis. For one twin pregnancy both fetuses had the same disease and pregnancy outcome and so either case could be dropped while for the other, the most severe case was kept in the dataset. The result was that each line in the dataset corresponded to an NTD affected pregnancy. When further exploring the dataset to look at previous siblings with an NTD i.e. recurrence in the dataset, it became clear that there were a further two cases which were twin pregnancies but only one from each had been included in the NTD dataset.

4.2.2 Differences between singletons and twins/ multiple births

The dilemma still remained of how to handle multiple pregnancies in the analyses. There is not currently a straightforward solution for this and there is no "standard" approach from the literature. However, a clear excess in non-chromosomal congenital anomalies in multiple births when compared to singletons (119) most commonly in monochorionic twins and specifically anomalies of the central nervous system (120) has been reported; both studies included fetal deaths from 20 weeks gestation and terminations of pregnancy for fetal anomaly in their case definition. Glinianaia and colleagues' (2008) study was focussed on the North of England and was not sufficiently powered to look at differences between different anomalies (120). Previous research has specifically detected an increased prevalence of anencephaly in multiples when compared to singletons (121-123), although all studies were limited by the fact that only live and/or still birth cases were included. Looking at the NTD dataset from BINOCAR, the proportion of anencephaly cases in multiple pregnancies (53%) is higher than in singleton pregnancies (40%) and the difference is of statistical significance (p=0.034). There is no statistically significant difference in the proportion of spina bifida cases in multiples pregnancies (39%) when compared to singletons (48%) (p=0.138).

It has been reported that a fifth of multiple birth non-chromosomal anomaly cases also have a twin with a congenital anomaly (119). In the BINOCAR NTD dataset, if NTD cases rather than NTD pregnancies are included, overall (including chromosomal cases) in 19% of multiples both twins had a malformation (Table 6) and excluding chromosomal cases 18%. It has long been established that discordancy does not mean that genetic factors are not important (124).

It is also known that older mothers are more likely to have multiple pregnancies (125) and using the NTD dataset there was found to be a higher proportion of twins in the 40+ age group (13%) than any of the other age groupings (between 3 and 6%) (p=0.032); this is specific for the spina bifida subgroup where 18% of mothers of affected pregnancies are 40 or over (p=0.002). When chromosomal cases are removed from the analyses, the effect remains very similar (17% of mothers are 40 or over) (p=0.013).

It has been shown that living in an area of lower deprivation, one possible explanation being the better access to Assisted Reproductive Technology (ART), is associated with a higher twinning rate (125). Using only NTD affected pregnancies from the four English registers (NorCAS; EMSYCAR; SWCAR and CAROBB) to compare deprivation of maternal residence between multiples and singletons, there were found to be no statistically significant differences (p=0.914).

The focus of this research is ethnicity, with a key research question being whether the NTD prevalence is higher in certain ethnic communities. Therefore it is relevant to note that, according to the literature, there are high twinning rates in central African countries and low twinning rates in South Asian countries (126). However it was difficult to look at ethnic differences between the singleton and multiples groups in the BINOCAR NTD dataset due to small numbers; although all cases in the multiple with two malformations group were White, this was not statistically significant (p=0.923) and chromosomal cases being excluded made little difference (p=0.995).

Another key research area for this study was to explore the natural history of NTD affected pregnancies within different ethnic communities. The main outcome

measure for this area of research was whether the pregnancy was terminated or not. It has been shown from the literature that twin pregnancies are less likely to be terminated than singleton pregnancies and critically there is a difference in the termination rate between multiple pregnancies where both fetuses have an anomaly and where only one twin is affected (119), as would be expected. In the BINOCAR dataset, multiple pregnancies where both fetuses have a malformation and singleton affected pregnancies have similar termination rates ((10 out of 13 (77%) and 1,253 out of 1,565 (80%) of pregnancies are terminated, respectively)). Termination rates for multiple pregnancies where there is only one affected fetus, are much lower ((32 out of 63 (51%) of pregnancies are terminated)) ($p<0.001$). However, as shown, no association was detected between ethnicity and whether the pregnancy was singleton or multiple and so twin pregnancies are unlikely to have a significant impact on analyses.

In conclusion, taking into consideration whether the pregnancy is singleton, multiple with one malformation or multiple with two malformations is unlikely to affect the study outcomes greatly. However, based on observed differences and reported differences from the literature, it was decided that sensitivity analyses would be carried out after the main analyses, exploring the impact of excluding multiple pregnancies.

4.3 Siblings with anomalies in NTD dataset

A further level of complexity in the dataset that needed to be given due consideration before calculating prevalence estimates was NTD recurrence. The "Siblings with anomalies" variable which designates whether a case has a sibling with a congenital anomaly and whether it is the same defect is poorly completed in all registers except CARIS and therefore, was not used in the analysis (Table 7). This is unfortunate as although it would not have been possible to use this variable to assess the actual recurrence rate, as there is no denominator data for the number of siblings a case has, it would have been useful to link two NTD cases in the dataset with the same mother as the recurrence risk is higher than the first time risk for NTDs (10).

Table 7: Breakdown of siblings with anomalies variable (number and proportion) by register

Siblings with anomalies	No. (%) in each register					
	EMSYCAR	NorCAS	CAROBB	SWCAR	CARIS	Total
Same anomaly[1]	10 (1.96)	0	0	0	10 (3.32)	20 (1.22)
Different anomaly	20 (3.91)	0	0	0	20 (6.64)	40 (2.44)
Same and a different anomaly[2]	7 (1.37)	0	1 (0.46)	0	1 (0.33)	9 (0.55)
No anomaly	7 (1.37)	0	0	0	214 (71.1)	221 (13.46)
Not known	467 (91.39)	288 (100)	215 (99.54)	326 (100)	56 (18.6)	1352 (82.34)
Total	511	288	216	326	301	1,642

[1] NTD

[2] NTD and another congenital anomaly

4.4 NTD subtype and "birth" prevalence

4.4.1 BINOCAR birth prevalence equation

BINOCAR and EUROCAT calculate a "birth" prevalence for congenital anomalies that has the number of cases of congenital anomaly resulting in live births (CA_{LB}), stillbirths (CA_{SB}), late miscarriages (CA_{LM}) and terminations of pregnancy for fetal anomaly (TOPFA) (CA_{TOPFA}) in the numerator and the total number of live births (LB) and still births (SB) in the population, in the denominator. This value is then multiplied by 10,000 to give congenital anomaly birth prevalence per 10,000 births. The "birth" prevalence equation is as follows:

$$p = 10{,}000 \times \frac{CA_{LB}+CA_{SB}+CA_{LM}+CA_{TOPFA}}{LB+SB} \quad (1)$$

For all registers, denominator data (live and stillbirths) is based on Office for National Statistics (ONS) statistics for births over the same time period, which are viewed as robust statistics.

The term "birth" prevalence can be misleading and from the name it might be assumed that only CA_{LB} and CA_{SB} cases are included in the numerator; however, it is so called due to convention with the four "birth" or pregnancy outcomes in the numerator and only births (but not TOPFA or late miscarriages) in the population in the denominator. Moreover, as detailed in the introduction to this thesis in Chapter1, it would be expected that the majority of TOPFA cases would survive to birth if the pregnancy had not been terminated (2). It is only ever possible to calculate a birth prevalence rather than a true incidence for congenital anomalies due to early fetal losses that are not included in any of the data sources.

Figure 6 shows the natural history of NTD affected pregnancies with the blue circle containing cases that will largely be included in the BINOCAR birth prevalence estimates, although there will also be some early losses in this period that wouldn't be included. The diagram is an oversimplification as scans are carried out, and NTDs detected, throughout pregnancy with the earliest prenatal discovery occurring at 8 weeks and the latest at 32 weeks in the dataset. However, the main scans are at 12 and 20 weeks with peaks in NTD detection around these time points. Again, TOPFA are carried out over various weeks in the dataset, ranging from 8 to 37 weeks; however, the majority are carried out within a few weeks of the NTD being detected and there are therefore peaks for this pregnancy outcome just after 12 weeks and just after 20 weeks. The circle in Figure 6 goes beyond birth as there are few cases in the dataset that are detected postnatally.

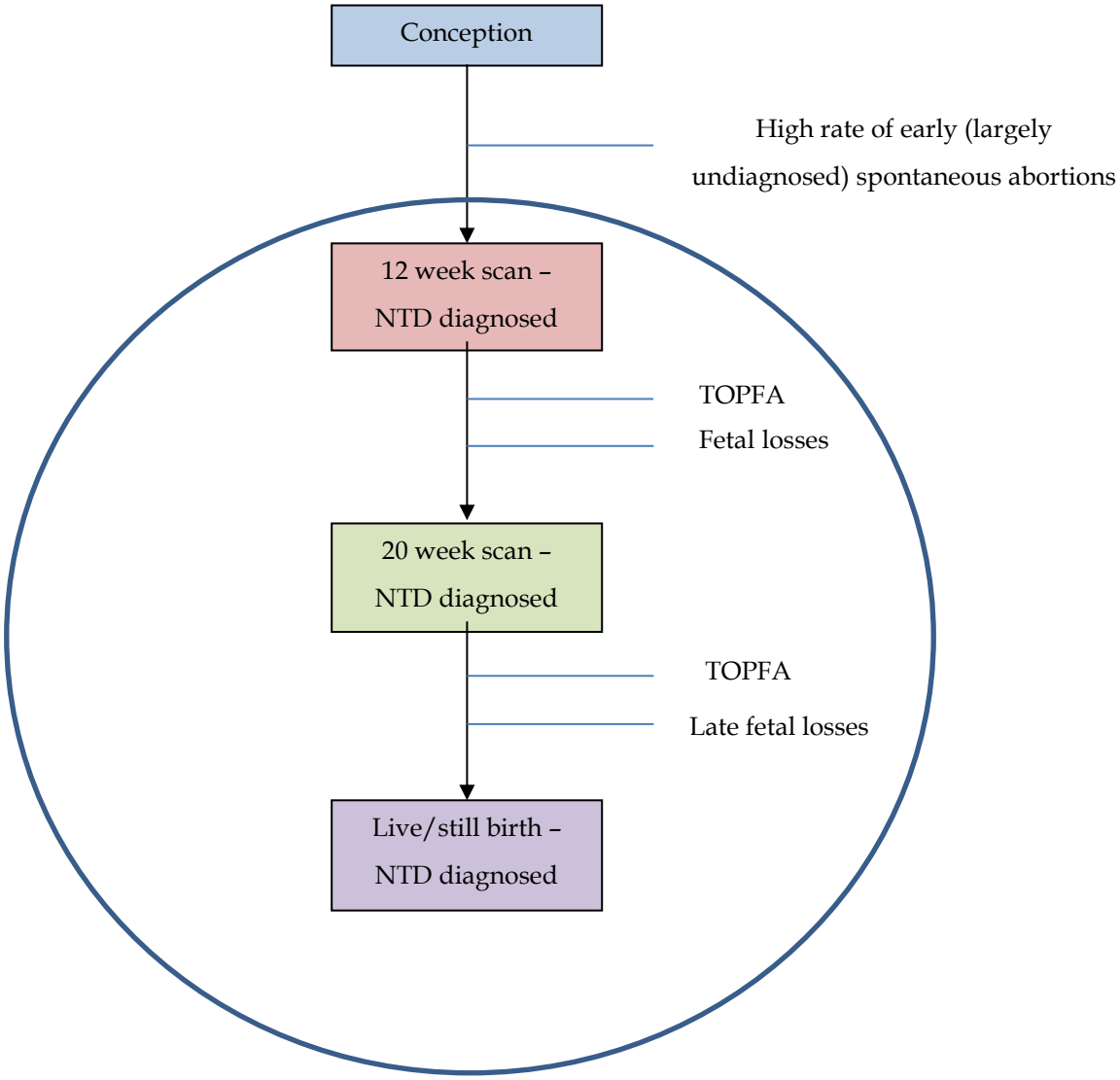

Figure 6: Natural History of NTD affected pregnancies with a focus on "birth" outcomes included in the BINOCAR birth prevalence calculation

As described in the previous section, two cases which had a corresponding case from the same pregnancy, i.e. both twins had an NTD, were dropped from the dataset making the dataset by pregnancy rather than case. Although technically the BINOCAR birth prevalence equation refers to NTD cases, as described, only two cases were dropped and it meant that maternal ethnicity would not be included twice for the same pregnancy.

4.4.2 *Merging numerator and denominator datasets to calculate prevalence*

The BINOCAR NTD (numerator) dataset was collected separately from the ONS denominator (all live and still births within the population) dataset. The former included individual pregnancy level data, whereas the latter only contained aggregated data. For this reason, the NTD dataset had to be transformed into an aggregate format (collapsed) before being merged with the denominator dataset to explore NTD prevalence (Figure 7).

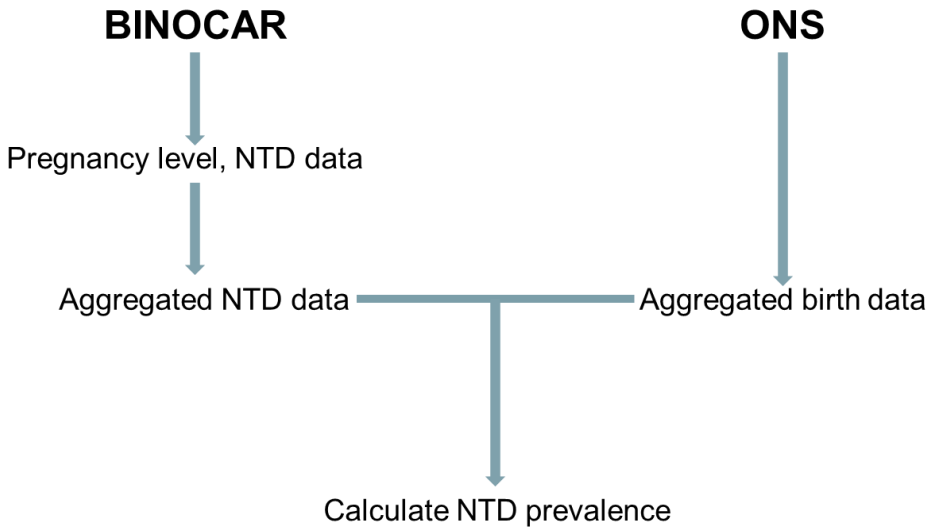

Figure 7: Process of merging pregnancy level and aggregated data to calculated prevalence estimates

4.4.3 *Using binomial regression to estimate NTD prevalence for aggregate binary data*

In order to explore the associations between NTD prevalence and other factors in the dataset, binomial regression was used. For prevalence rate ratios (PRRs), the reference group was always the group with the highest number of births. 95% confidence intervals are usually presented alongside prevalence and PRR estimates, as they give an indication of the possible effect sizes compatible with the data. However, p-values are also sometimes included in tables and often quoted in the text as they give a quantification of the significance level. If confidence intervals for the prevalence estimate for one group does not overlap with those from another

group and if the confidence interval for a PRR does not cross 1, then a statistically significant difference is indicated. Where only summary statistics are available, exact binomial confidence intervals are presented instead, which are comparable to confidence intervals generated using the binomial regression method, using the binreg command, in STATA. All analyses were conducted in STATA.

4.4.4 NTD Prevalence for individual data years

As described in Chapter 1, there are phenotypic and aetiological differences between the different types of NTD. This includes a marked female excess for anencephaly affected pregnancies specifically and there is debate around whether encephalocele should even be considered an NTD due to its distinct genetic, environmental and clinical background (127). Therefore, in addition to calculating an overall NTD birth prevalence for all pregnancies in the dataset, it was important to look at birth prevalence for individual NTD types.

The prevalence for all NTD affected pregnancies and then by NTD type was first calculated for individual years due to several years' data being included in the dataset (2006 to 2011 inclusive). These results are presented in Figure 8.

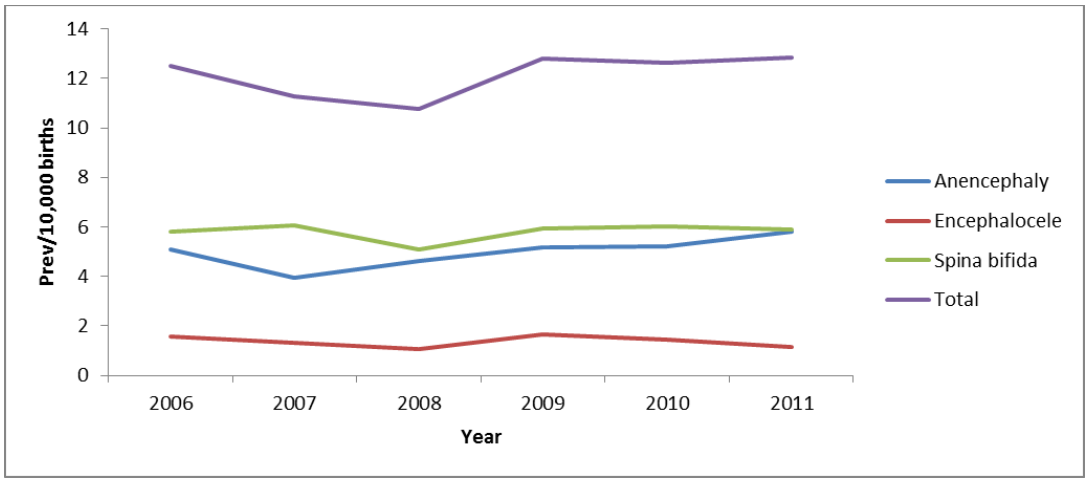

Figure 8: Birth prevalence by year for all NTD affected pregnancies and by NTD type

It is also interesting to compare prevalence estimates for all NTD cases based on the BINOCAR equation with prevalence estimates where only live and still birth cases are included (Figure 9). Many studies on NTD prevalence are based solely on

live/still birth ascertainment, and can be seen to grossly underestimate the true NTD prevalence. As Figure 9 shows, there is a huge discrepancy in the NTD prevalence, across all data years, between estimates that include and exclude TOPFA and late miscarriage cases.

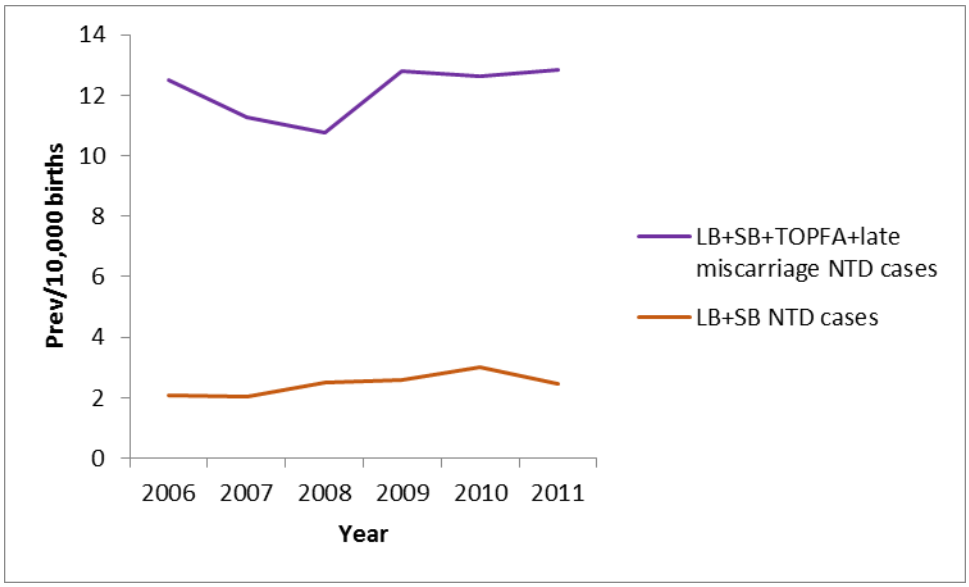

Figure 9: NTD birth prevalence estimates using all NTD cases and only live and still birth cases

Comparing prevalence estimates (for all NTD cases) between individual years, there are shown to no significant differences (Table 8). It was therefore deemed appropriate to combine the data for the different years (2006-2011) in the analysis.

Table 8: Prevalence by year and 95% confidence intervals for all NTD affected pregnancies

Year	Total NTD prev/10,000 births	95% CI
2006	12.51	11.06-14.09
2007	11.29	9.94-12.78
2008	10.75	9.44-12.18
2009	12.81	11.37-14.37
2010	12.64	11.24-14.18
2011	12.85	11.43-14.40

4.4.5 NTD prevalence estimates by region

As described in the introduction to this thesis in Chapter 1, a North/South divide with regards to NTD prevalence in the British Isles, has been reported in the

literature (11). Looking at the NTD prevalence for different regions, across all years, in the BINOCAR NTD dataset, it was found that the overall prevalence was significantly higher in the area covered by CARIS and NorCAS than EMSYCAR and SWCAR (Table 9). This increase was largely driven in both registers by an increase in reported spina bifida cases.

NTDs are listed as one of the anomalies of possible concern on the CARIS website, due to its high prevalence (128). Despite a decline from 115 NTDs per 10,000 births in a 1957 study in South Wales by Laurence (129) to 21 per 10,000 in a study covering part of South Wales in 1992 by Cotter and colleagues (130) to 19 per 10,000 in 1998 when the CARIS register started collecting data, the decline seems to have stopped since 2008 (128).

A study looking at data from NorCAS reported that the NTD prevalence decreased significantly in the period 1984 to 1996, although in 1996 the prevalence was still 14 per 10,000 births (131). In a subsequent study, the overall NTD prevalence across the years 1991 to 1999 inclusive was reported to be 15.6 in the Northern region in comparison to 12.3 in the North West Thames region, 12.6 in Wessex and 11.9 in Oxford (117).

It could be that any observed regional differences are in fact due to natural variation i.e. can be explained by other factors such as deprivation. However, a study exploring localised clustering and geographical variation of congenital anomalies for the same registers included in Rankin and colleagues (117) study found that even after adjusting for maternal age and deprivation, there was still geographical variation at the region and hospital catchment area level (132). Therefore, it was seen as important, in light of these findings, to keep the potential impact of regional differences in mind for future analyses.

Table 9: Prevalence by register and 95% confidence intervals for all NTD affected pregnancies

Register	Total number of NTD affected pregnancies	Total number of births	Total Prev/10,000 births	95% CI
EMSYCAR	511	442057	11.56	10.58-12.61
NorCAS	288	199321	14.45	12.83-16.22
CAROBB	216	181658	11.89	10.36-13.59
SWCAR	326	318251	10.24	9.16-11.42
CARIS	301	210900	14.27	12.71-15.98

Combining all years and regions' data collected in the study, gives an NTD birth prevalence of 12 per 10,000 (Table 10) which is comparable with reports in the literature.

Table 10: Number of NTD affected pregnancies and Birth Prevalence for all NTDs and different subtypes

NTD	Number					Prev/10,000 births
	LB	SB	Late Miscarriage	TOPFA	Total	
All NTDs	298	34	14	1,296	1,642	12.14
Anencephaly	36	17	8	612	673	5.00
Encephalocele	39	*	*	137	185	1.37
Spina bifida	223	11	3	547	784	5.80

*Cells with values less than 5 have been suppressed

4.4.6 Quantifying the difference between including and excluding terminations in NTD birth prevalence denominator

As described, NTD affected pregnancies that result in TOPFA are included in the numerator of the BINOCAR birth prevalence equation but only live and still births, and not terminations in the population studied, are included in the denominator. The reason for this is that births correspond to official ONS statistics and are the most robust estimates. Moreover, for most congenital anomalies that do not have a high TOPFA rate, this is unlikely to distort the outcomes greatly. However, in the BINOCAR dataset for the study, 1296 out of 1642 (79%) NTD affected pregnancies resulted in TOPFA and therefore it was seen as important to quantify the difference between an NTD birth prevalence estimate that includes and excludes terminations in the denominator. Termination denominator data for the regions covered by EMSYCAR and SWCAR for the years 2006 to 2011 inclusive, were obtained from the

Department of Health (DH). Only terminations carried out from 10 weeks gestation were included to exclude early social terminations as, as described, early fetal losses are not captured by BINOCAR and the earliest gestation for a TOPFA case in the NTD dataset is 8 weeks. The NTD birth prevalence was reduced to 10 per 10,000 births (95% CI: 9.54, 10.94) when terminations were included in the denominator from 11 per 10,000 births (95% CI: 10.28, 11.78) when terminations were not included. However, the difference was not statistically significant. It was therefore deemed appropriate to continue to use the BINOCAR birth prevalence calculation, particularly as it was only possible to obtain denominator data for key variables in the study, such as deprivation, for births (and also to enable comparisons with the current literature).

4.4.7 Preliminary epidemiological explorations around NTD prevalence

In the Introduction to this thesis (Chapter 1) it was detailed how several factors are shown to be associated with NTD risk, in addition to ethnicity. It was not possible to obtain information on maternal illness, such as diabetes or epilepsy, any occupational exposures or medication use (questions about these additional factors were asked in the qualitative study detailed in Chapter 6). However, information was collected from BINOCAR on sex of fetus, maternal age, deprivation of maternal residence, maternal body mass index, folic acid use and year and month of outcome (to explore seasonality). It was important to explore the relative impact of each of these factors on NTD prevalence, to ascertain whether any associations as reported in the literature were found, and thus their likely impact on the main analyses around ethnicity.

4.4.7.1 NTD type and whether the NTD is isolated or not

Prevalence estimates for different NTD subtypes for individual data years (Figure 8) and for all years combined (Table 10) have been presented due to detailed aetiological and phenotypic differences in the literature. It is important, therefore, to explore the association between key factors, such as maternal age, on NTD prevalence for individual NTD subtypes, due to expected differences. However, it is

also essential to be critical of the extent to which NTD subtype differences for different factors as described in the literature, are also found in the BINOCAR dataset. Differences were explored for anencephaly and spina bifida subtypes but not for encephalocele, due to the small number of cases. However encephalocele cases were included in analyses of outcomes for all NTDs combined.

As detailed in Chapter 1, in addition to aetiological differences between different NTD subtypes being described in the literature, it is also argued that NTDs that occur in association with other defects are aetiologically distinct from those that are isolated (11;45). This is of particular importance when exploring NTD prevalence as non-isolated NTDs are not expected to decrease with folic acid usage (47;48). However, an early study found that once the type of NTD has been taken into account, the sex ratio and geographic prevalence are similar for isolated and multiple malformation NTD cases. Thus, the authors argued that, after stratifying by NTD subtype, making further distinctions between isolated and non-isolated NTD sub-groups might not be appropriate (133). Despite this, classification systems for congenital anomalies that take aetiology into account have since been developed (134;135). Using one of these classification systems, sex ratio and geographic prevalence differences were first explored in the current dataset, to determine the appropriateness of any further stratification by whether the NTD is isolated or not.

4.4.7.1.1 Classification of isolated and non-isolated cases

A multiple malformation group variable, which gives an indication of whether an NTD occurs in isolation or in association with other defects, was obtained from BINOCAR for all five registers included in the study. The variable is generated using EUROCAT's multiple congenital anomaly algorithm, which designates congenital anomalies to certain categories based on International Classification of Diseases (ICD) 10 coding. As shown in Table 11, NTD cases can be categorised as syndromic, chromosomal, NTD isolated, isolated other or multiple malformations (NTDs associated with other malformations but not recognised conditions). The classification system is hierarchical and only considers one category at a time i.e. the first potential category to be considered is chromosomal. If cases do not have a

chromosomal ICD-10 code, the next potential category is considered. The final category to be considered is the "potential multiple anomalies" if the case does not fit into any of the previous categories (135). Although potential multiples are usually reviewed by clinicians and geneticists, it is likely that some will be missed.

Table 11: Number and proportion of NTD affected pregnancies falling into the different multiple malformation groupings

Multiple Malformation Group	Number	Percent
Syndrome	21	1.28
Chromosomal	81	4.93
Isolated Other	19	1.16
Multiple Malformations	273	16.63
NTD Isolated	1,248	76
Total	1,642	100

Due to small numbers in individual sub-groups and due to the fact that NTD cases designated as multiple malformations may be recognised as syndromes in the future i.e. the grouping is open to change, syndromic, chromosomal, multiple malformations and isolated other cases were grouped as a "non-isolated NTD" category. Isolated other cases were included in the "non-isolated" grouping as babies with isolated other defects have a single congenital defect (the majority in the dataset are amniotic band sequence defects) which is present in addition to the NTD, therefore there is likely to be something else happening to the embryo during development.

An additional classification system for isolated and non-isolated NTD cases, based on a local aetiological variable, exists for CAROBB and EMSYCAR. The aetiological variable has similar sub-groupings to those based on the EUROCAT algorithm, although syndromic cases are simply designated as multiple malformations cases, recognising the difficulty of drawing a distinction between the two. This variable is thought to provide a more accurate representation of whether an NTD is isolated or not as each case is reviewed individually and coded accordingly. However, there is strong agreement between the two classification systems and thus classifications based on the EUROCAT algorithm, which covers all registers, has been used in the majority of analyses (and unless specified). In analyses where there were indications

that the lack of agreement between the two classification systems could impact on observed outcomes, this has been highlighted and discussed.

4.4.7.1.2 NTD prevalence by NTD subtype and malformation type

The overall birth prevalence for non-isolated NTDs (2.91 per 10,000 births) is markedly lower than for isolated NTDs (9.23 per 10,000 births) as it much less common to have the former than the latter (394 and 1248 in the dataset respectively) (Table 12). For non-isolated NTD cases, spina bifida is more likely to be the NTD than anencephaly (Table 12).

Table 12: NTD prevalence by type and whether the NTD is isolated or not

	Prev/10,000 births (95% CI)		
Malformation type (n)	**Anencephaly (n=673)**	**Spina bifida (n=784)**	**Total (n=1642) ***
Isolated NTD (1248)	4.14 (3.81-4.50)	4.30 (3.95-4.66)	9.23 (8.73-9.76)
Non-isolated NTD (394)	0.84 (0.69-1.01)	1.50 (1.30-1.72)	2.91 (2.63-3.22)

*Total does not equal Anencephaly + spina bifida as encephalocele cases are also included.

4.4.7.1.3 Sex ratio

Analyses of sex in the BINOCAR dataset presented problems; if the whole NTD dataset is used (1642 cases) there are 40% of cases that have unknown/indeterminate sex. Calculating NTD prevalence for cases of known sex will therefore be an underestimate as the denominator is live and still births where very few births are of unknown/indeterminate sex. NTD prevalence estimates by sex should therefore only be used to compare the prevalence between males and females within different NTD subtypes in the dataset rather than for looking at absolute figures. Moreover, when unknown/indeterminate sex cases are removed, the proportion of anencephaly cases falls from 41% to 26% as this more severe NTD phenotype is detected earlier in pregnancy, usually around the 12 week scan, when sex determination is more difficult. Therefore, NTD prevalence estimates by sex could also be biased due to under-representation of anencephaly cases.

There is a further level of complexity with exploring sex in the current dataset, which is that although sex determination is much more reliable around the second scan, taken as 18 weeks gestation for the purpose of analyses, 23% of cases with known sex have a gestation length of less than 18 weeks; 39% of these cases come from NorCAS which has the lowest proportion of indeterminate/not known cases (16%) (Table 13). If the dataset is restricted to those cases with a gestation length of 18 weeks or longer, only 29% of anencephaly cases from the original dataset remain due to the early detection and higher termination rate for this more severe phenotype. Overall 91% of anencephaly affected pregnancies are terminated in contrast to 70% of spina bifida cases, and 93% of terminations occur within two weeks of the NTD being discovered.

Table 13: Sex (number and proportion) breakdown for NTD affected pregnancies from different registers

	No (%) in each register					
Sex	EMSYCAR	NorCAS	CAROBB	SWCAR	CARIS	Total
Male	130 (25.44)	112 (38.89)	51 (23.61)	83 (25.46)	97 (32.23)	473 (28.81)
Female	146 (28.57)	129 (44.79)	56 (25.93)	84 (25.77)	103 (34.22)	518 (31.55)
Indeterminate/Not known	235 (45.99)	47 (16.32)	109 (50.46)	159 (48.77)	101 (33.55)	651 (39.65)
Total	511	288	216	326	301	1,642

Based on the limited available data there are significantly more females affected by NTDs than males for all pregnancies with NTD diagnosed at any gestation (female to male PRR = 1.15; 95% CI: [1.02, 1.30]). This sex difference is also significant for those with gestation lengths of 18 weeks or longer for all NTDs combined (1.18; 95% CI: [1.20, 1.36]) and for spina bifida cases (1.19; 95% CI: [1.01, 1.42]); for anencephaly cases there is a greater female predominance but due to the small numbers, the difference doesn't reach significance (1.24; 95% CI: [0.87, 1.79]) (Table 14). The prevalence rate ratios for isolated and non-isolated cases are very similar for both NTD subtypes and for all NTDs combined (Table 15), which is in agreement with what is reported by Dolk and colleagues (133).

Table 14: Female to male prevalence rate ratios by NTD subtype for affected pregnancies of any gestation length and those with gestation lengths of 18 weeks or longer

NTD	Female/Male Prevalence rate ratios (95% CI)	
	Cases of known sex	Cases of known sex with gestation lengths >17 weeks
Anencephaly	1.13 (0.89-1.45)	1.24 (0.87-1.79)
Spina Bifida	1.16 (0.99-1.37)	1.19 (1.01-1.42)
Total	1.15 (1.02-1.30)	1.18 (1.02-1.36)

Table 15: Female to male prevalence rate ratios by NTD type for isolated and non-isolated affected pregnancies of 18 weeks gestation length or longer

NTD	Female/Male Prevalence rate ratios (95% CI)	
	Isolated cases of known sex with gestation lengths >17 weeks	Non-isolated cases of known sex with gestation lengths >17 weeks
Anencephaly	1.24 (0.81-1.90)	1.26 (0.64-2.50)
Spina Bifida	1.20 (0.98-1.47)	1.18 (0.86-1.63)
Total	1.19 (1.00-1.41)	1.15 (0.89-1.49)

4.4.7.1.4 Geographic prevalence

However, from the current analysis of the BINOCAR dataset, it is clear that the significantly higher spina bifida prevalence in NorCAS specifically occurs within isolated cases (Table 16) and in CARIS within non-isolated cases (Table 17). This is not in agreement with the earlier research and it is difficult to disentangle why exactly this might be. Stevenson and colleagues (2004) argue that the focus is on associated anomalies as developmental anomalies occurring with NTDs but this is also the case with twinning (47). Perhaps it is not a coincidence that CARIS has both a higher proportion of non-isolated NTD cases and twins where both have a malformation or that NorCAS has an increased prevalence which is largely driven by isolated cases and also has the highest proportion of twin pregnancies than any other region, the majority of which are twins where only one has an anomaly.

Table 16: Prevalence for isolated NTD cases by register and NTD type

Register (n)	Prev/10,000 (95% CI)		
	Anencephaly (n=560)	**Spina bifida (n=581)**	**Total (n=1248)**
EMSYCAR (394)	4.14 (3.56-4.79)	4.14 (3.56-4.79)	8.91 (8.06-9.84)
NorCAS (235)	4.97 (4.04-6.05)	5.72 (4.72-6.87)	11.79 (10.33-13.40)
CAROBB (169)	4.57 (3.64-5.66)	4.07 (3.20-5.11)	9.3 (7.95-10.82)
SWCAR (240)	3.39 (2.78-4.10)	3.58 (2.96-4.30)	7.54 (6.62-8.56)
CARIS (210)	4.13 (3.30-5.09)	4.55 (3.69-5.56)	9.96 (8.66-11.40)

Table 17: Prevalence for non-isolated NTD cases by register and NTD type

Register (n)	Prev/10,000 (95% CI)		
	Anencephaly (n=113)	**Spina bifida (n=203)**	**Total (n=394)**
EMSYCAR (117)	0.86 (0.61-1.18)	1.29 (0.98-1.67)	2.65 (2.19-3.17)
NorCAS (53)	0.85 (0.50-1.37)	1.3 (0.85-1.91)	2.66 (1.99-3.48)
CAROBB (47)	0.88 (0.50-1.43)	1.38 (0.89-2.03)	2.59 (1.90-3.44)
SWCAR (86)	0.72 (0.46-1.08)	1.35 (0.98-1.82)	2.7 (2.16-3.34)
CARIS (91)	0.9 (0.54-1.41)	2.47 (1.84-3.23)	4.31 (3.47-5.30)

4.4.7.1.5 Conclusions

A central research question of this PhD is whether the NTD prevalence is higher within different ethnic communities. Although it will not be possible to make any aetiological conclusions based on this research alone, possible causative factors can be suggested. Based on described differences between isolated and non-isolated NTDs in the literature, regional differences identified in the current dataset, even after stratification by NTD type, and due to feasibility in terms of numbers, it was decided that whether the NTD is isolated or not would be taken into consideration in future analyses, where possible.

4.4.7.2 NTD prevalence estimates by maternal age

In the literature, it has been shown that there is an increased NTD risk for mothers older than 40 years of age and those younger than 19, and that the increase is higher for spina bifida than anencephaly cases (136).

Maternal age from the BINOCAR NTD dataset for this study was found to be roughly normally distributed, following a similar pattern to population level live and still birth data.

As live and still birth data by maternal age was obtained from ONS broken down into different age groups (<20; 20-24; 25-29; 30-34; 35-39; 40+), maternal age for affected pregnancies in the BINOCAR dataset was also broken down into these age groups in the analyses. Table 18 below summarises the maternal age group

breakdown for NTD affected pregnancies from different registers. As shown, there are a higher proportion of older mothers in CAROBB when compared with the other registers, which is a reflection of the underlying population.

Table 18: Maternal age group (number and proportion) breakdown for NTD affected pregnancies from different registers

	No (%) in each register					
Age group	EMSYCAR	NorCAS	CAROBB	SWCAR	CARIS	Total
<20	50 (9.78)	28 (9.72)	10 (4.63)	23 (7.06)	31 (10.3)	142 (8.65)
20-24	106 (20.74)	75 (26.04)	31 (14.35)	62 (19.02)	84 (27.91)	358 (21.8)
25-29	133 (26.03)	86 (29.86)	67 (31.02)	88 (26.99)	76 (25.25)	450 (27.41)
30-34	116 (22.7)	63 (21.88)	50 (23.15)	86 (26.38)	65 (21.59)	380 (23.14)
35-39	78 (15.26)	28 (9.72)	47 (21.76)	55 (16.87)	39 (12.96)	247 (15.04)
40+	20 (3.91)	8 (2.78)	11 (5.09)	12 (3.68)	6 (1.99)	57 (3.47)
Not known	8 (1.57)	0 (0)	0 (0)	0 (0)	0 (0)	8 (0.49)
Total	511	288	216	326	301	1,642

NTD prevalence estimates by maternal age group were calculated initially for all isolated and non-isolated NTD cases combined for spina bifida and anencephaly subtypes, as well as an overall prevalence including all subtypes, to compare outcomes with what has been found in the literature. Isolated and non-isolated NTD cases were then looked at separately to see whether there were any differences between them.

Table 19, which contains absolute prevalence estimates, shows that the NTD prevalence is statistically significantly higher in mothers under 20 years of age (15.08; 95% CI: [12.71, 17.77]) than mothers aged 30-34 (10.55; 95% CI: [9.52, 11.66]). However, although the ONS denominator data contains all mothers under 20 years of age, there are eight NTD affected pregnancies in the BINOCAR data where the mother is under 16 years of age that have not been included in the study for ethical reasons. In a sensitivity analysis, in which these 8 cases are added to the total, the prevalence for the under 20 age group increases to 15.93 (95% CI: [13.49, 18.69]) making the prevalence for this age group now also statistically significantly higher than in the 25-29 (12.20; 95% CI: [11.10, 13.38]) and of borderline significance higher than the 35-39 (11.91; 95% CI: [10.47, 13.49]) age group. No further details are known about these 8 cases, including the NTD type, and therefore it is not possible

to take this any further than to state that the exclusion of under 16s has led to a slight prevalence underestimate in the under 20 age group.

Table 19: NTD prevalence by maternal age group and NTD type

Age group	Prev/10,000 births (95% CI)		
	Anencephaly	Spina Bifida	Total
<20	6.48 (4.96-8.32)	7.33 (5.70-9.27)	15.08 (12.71-17.77)
20-24	5.61 (4.76-6.57)	6.02 (5.13-7.01)	13.05 (11.73-14.47)
25-29	4.88 (4.19-5.65)	5.80 (5.05-6.64)	12.20 (11.10-13.38)
30-34	4.19 (3.55-4.92)	5.19 (4.47-5.99)	10.55 (9.52-11.66)
35-39	4.77 (3.88-5.81)	5.88 (4.89-7.02)	11.91 (10.47-13.49)
40+	5.62 (3.67-8.23)	4.75 (2.98-7.19)	12.31 (9.33-15.95)

Prevalence rate ratios, by maternal age group, are given in Table 20, with the 25-29 age group selected as the reference group due to the highest numbers of births being in this category. As is shown, the overall NTD prevalence is statistically significantly higher in the under 20 group (p=0.028) and statistically significantly lower in the 30-34 age group (p=0.036) when compared to the 25-29 reference group. No statistically significant differences were detected by NTD subtype.

Table 20: NTD prevalence rate ratios by maternal age group and NTD type

Age group	Prevalence Rate Ratios (95% CI)		
	Anencephaly	Spina Bifida	Total
25-29 (ref)	**4.88**	**5.80**	**12.20**
<20	1.33 (0.99-1.77)	1.26 (0.96-1.66)	1.24 (1.02-1.49)
20-24	1.15 (0.93-1.43)	1.04 (0.85-1.27)	1.07 (0.93-1.23)
30-34	0.86 (0.69-1.07)	0.89 (0.74-1.09)	0.86 (0.75-0.99)
35-39	0.98 (0.77-1.25)	1.01 (0.81-1.27)	0.98 (0.84-1.14)
40+	1.15 (0.76-1.74)	0.82 (0.53-1.27)	1.01 (0.77-1.33)

Conducting the analyses separately for isolated and non-isolated NTD affected pregnancies (Table 21), for isolated NTD cases, the NTD prevalence is statistically significantly higher in the under 20 (p=0.054) and lower in the 40+ (p=0.046) age groups, than the 25-29 age group. For non-isolated NTD affected pregnancies, the prevalence is higher in the 40+ age group than the reference group (p<0.001) and this is shown to be specifically for the anencephaly subtype (PRR 3.84; 95% CI: 1.98, 7.43). No other differences by NTD subtype were detected in these sub-analyses. If chromosomal cases are excluded from the non-isolated cases, there is no longer a statistically significant excess in the 40+ group. This may be related to the risk for

three chromosomal conditions in the dataset (Down's syndrome, Patau syndrome and Edward's syndrome) increasing with increasing maternal age. Interestingly, when chromosomal cases are excluded, the prevalence in the 30-34 age group is shown to be statistically significantly lower than the reference group (p=0.009).

Table 21: NTD prevalence rate ratios by maternal age group and whether the NTD is isolated or not

Age group	Prevalence Rate Ratios (95% CI)		
	Isolated	Non-Isolated	Non-isolated minus chromosomal
25-29 (ref)	**9.47**	**2.74**	**2.50**
<20	1.23 (1.00-1.53)	1.24 (0.83-1.85)	1.28 (0.85-1.93)
20-24	1.04 (0.88-1.21)	1.18 (0.89-1.57)	1.20 (0.89-1.61)
30-34	0.89 (0.76-1.04)	0.77 (0.57-1.04)	0.65 (0.46-0.90)
35-39	0.92 (0.77-1.10)	1.18 (0.87-1.61)	0.70 (0.47-1.02)
40+	0.68 (0.47-0.99)	2.13 (1.39-3.26)	0.21 (0.69-2.13)

4.4.7.2.1 Summary

There is an increased NTD prevalence in young mothers, under 20 years of age, in comparison to mothers aged 25-29. This agrees with the published literature. The increased prevalence in the under 20s, was shown to be specifically for isolated NTD cases. An increased NTD prevalence for mothers aged 40+ when compared to those aged 25-29, specifically for anencephaly, is seen for non-isolated NTD cases. This appears to be due to an excess of NTDs occurring in association with chromosomal defects, which becomes more common with increasing maternal age.

4.4.7.3 NTD prevalence estimates by maternal deprivation

An increased risk of NTD affected pregnancies in mothers who live in more deprived areas has been reported in many studies (137). One possibility is that this risk may be mediated by folic acid use, as folic acid use and level of deprivation are highly correlated (101;137).

Both England and Wales have developed an index of multiple deprivation (IMD), at the small area level, based on lower super output area (LSOA) which in turn is created from postcode. It is called multiple deprivation as it recognises a number of

different types of deprivation domains. The English 2010 IMD includes: Income; Employment; Health and Disability; Education, Skills and Training; Barriers to Housing and Services; Crime and Living Environment, and the Welsh 2011 IMD includes: Income; Employment; Health; Education; Geographical Access to Services; Community Safety; Physical Environment and Housing. The domains are made up of different indicators and the overall deprivation score is made up of ranked domain scores for each area; the overall score is then ranked and it is from this ranking that deprivation quintiles, deciles etc. are created. The English and Welsh IMDs are not directly comparable, two key reasons being that they are produced for different areas and there are indicator differences (138;139).

For the English IMD score or Welsh IMD (WIMD) score, a higher score indicates greater deprivation. For the English IMD quintile or WIMD quintile, quintile 5 is the least deprived and quintile 1 the most deprived.

The IMD deprivation quintile rather than score was included in the analyses as live and still birth denominator data were obtained from ONS by deprivation quintile. A breakdown of the number and proportion of affected pregnancies falling into the different quintiles for all English registers is included in Table 22 and a breakdown for the different quintiles for CARIS (Wales) given in Table 23. CAROBB has the highest proportion of cases in the least deprived quintile (quintile 5), as a reflection of the underlying population.

Table 22: Maternal deprivation quintile (number and proportion) breakdown for NTD affected pregnancies for English registers

	No (%) in each register				
Deprivation quintile (IMD)	EMSYCAR	NorCAS	CAROBB	SWCAR	Total
1 (most deprived)	170 (33.27)	92 (31.94)	21 (9.72)	69 (21.17)	352 (26.25)
2	129 (25.24)	57 (19.79)	34 (15.74)	63 (19.33)	283 (21.1)
3	76 (14.87)	49 (17.01)	42 (19.44)	79 (24.23)	246 (18.34)
4	70 (13.7)	35 (12.15)	38 (17.59)	57 (17.48)	200 (14.91)
5 (least deprived)	64 (12.52)	21 (7.29)	81 (37.5)	58 (17.79)	224 (16.70)
Not known	2 (0.39)	34 (11.81)	0	0	36 (2.68)
Total	511 (100)	288 (100)	216 (100)	326 (100)	1341 (100)

Table 23: Maternal deprivation quintile (number and proportion) breakdown for NTD affected pregnancies for Welsh register

Welsh deprivation quintile (WIMD)	No (%)
1 (most deprived)	92 (30.56)
2	61 (20.27)
3	67 (22.26)
4	44 (14.62)
5 (least deprived)	31 (10.30)
Not known	6 (1.99)
Total	301 (100)

To calculate prevalence rate ratios, quintile 1 was chosen as the baseline due to there being the most births within this quintile. It was found that the NTD prevalence was statistically significantly lower in the quintile 4 (0.76; 95% CI: 0.64, 0.91) and quintile 5 (0.80; 95% CI: 0.67, 0.94) than quintile 1. The trend was tested by fitting quintile as a continuous variable. It was found that for each unit increase of quintile, the risk ratio was 0.93 (95% CI: 0.90, 0.96) ($p<0.001$) i.e. the NTD prevalence was shown to be higher in more deprived areas.

When looking at anencephaly and spina bifida subtypes individually, the same outcome is observed for quintile 4 but not quintile 5, where the difference doesn't reach statistical significance ($p=0.06$). Interestingly, the difference between quintile 3 and quintile 1 and quintile 2 and quintile 1 is stronger for spina bifida than anencephaly, although the differences do not reach statistical significance ($p=0.06$ and $p=0.08$ respectively) (Table 24).

Table 24: NTD prevalence rate ratios by deprivation quintile and NTD type for English registers only

Deprivation quintile (IMD)	Prevalence rate ratios (95% CI)		
	Anencephaly	Spina Bifida	Total
1 (most deprived) (ref)	**5.58**	**6.47**	**13.09**
2	0.93 (0.73-1.17)	0.82 (0.65-1.03)	0.90 (0.77-1.05)
3	0.87 (0.68-1.12)	0.79 (0.62-1.01)	0.87 (0.74-1.02)
4	0.72 (0.55-0.94)	0.72 (0.56-0.92)	0.76 (0.64-0.91)
5 (least deprived)	0.78 (0.61-1.01)	0.80 (0.63-1.01)	0.80 (0.67-0.94)

When looking at isolated NTD cases specifically, there is also weak evidence that the difference between quintile 2 and quintile 1 for spina bifida is of statistical

significance (p=0.05) (Table 25). For non-isolated NTDs, there are no statistically significant differences (Table 26).

Table 25: NTD prevalence rate ratios by deprivation quintile and NTD type for NTD isolated cases for English registers only

Deprivation quintile (IMD)	Prevalence rate ratios (95% CI)		
	Anencephaly	Spina Bifida	Total
1 (most deprived) (ref)	**4.76**	**5.02**	**10.19**
2	0.87 (0.67-1.13)	0.76 (0.59-0.99)	0.87 (0.72-1.04)
3	0.84 (0.64-1.11)	0.81 (0.62-1.06)	0.88 (0.73-1.06)
4	0.68 (0.51-0.92)	0.67 (0.50-0.89)	0.73 (0.60-0.89)
5 (least deprived)	0.80 (0.61-1.06)	0.79 (0.60-1.03)	0.81 (0.67-0.98)

Table 26: NTD prevalence rate ratios by deprivation quintile and NTD type for non-isolated NTD cases for English registers only

Deprivation quintile (IMD)	Prevalence rate ratios (95% CI)		
	Anencephaly	Spina Bifida	Total
1 (most deprived) (ref)	**0.82**	**1.45**	**2.90**
2	1.27 (0.72-2.26)	1.00 (0.64-1.59)	1.02 (0.74-1.41)
3	1.02 (0.55-1.89)	0.73 (0.44-1.23)	0.83 (0.58-1.18)
4	0.92 (0.48-1.77)	0.90 (0.55-1.47)	0.88 (0.62-1.25)
5 (least deprived)	0.68 (0.34-1.38)	0.83 (0.51-1.37)	0.75 (0.52-1.08)

Looking at prevalence rate ratios for CARIS and only for total cases within the register and broken down into isolated and non-isolated cases (there was no breakdown by NTD subtype due to small numbers), the NTD prevalence is statistically significantly lower in quintile 5 than quintile 1, and this is shown to be specifically for isolated NTD cases (p=0.011) (Table 27).

Table 27: NTD prevalence risk ratios by deprivation quintile for all NTD cases and broken down by whether the NTD is isolated or not for the Welsh register (CARIS)

Deprivation quintile (IMD)	Prevalence risk ratios (95% CI)		
	Isolated	Non-Isolated	Total
1 (most deprived) (ref)	**11.51**	**5.57**	**17.08**
2	0.82 (0.56-1.22)	0.71 (0.40-1.28)	0.79 (0.57-1.09)
3	1.13 (0.78-1.63)	0.73 (0.40-1.34)	1.00 (0.73-1.37)
4	0.85 (0.56-1.29)	0.52 (0.25-1.05)	0.74 (0.52-1.06)
5 (least deprived)	0.51 (0.30-0.85)	0.76 (0.39-1.45)	0.59 (0.39-0.88)

4.4.7.3.1 Summary

The overall pattern for NTD prevalence by deprivation is in line with what is found in the literature: there is an excess prevalence in quintile 1 (most deprived) when compared to quintile 4 and quintile 5 (least deprived). This excess was shown to be specifically for isolated cases, which is interesting in light of the high correlation that has been described between deprivation and lack of folic acid use, and the fact that non-isolated NTDs are not expected to decline with folic acid usage (47;48). A similar effect is observed for anencephaly and spina bifida subtypes.

4.4.7.4 Maternal body mass index (BMI) in the BINOCAR dataset

An association between obesity and increased risk of NTDs has been reported by several studies (44) and a meta-analysis of eight studies found an almost two-fold increased risk of NTDs in women who were obese; there was a greater increase for spina bifida than anencephaly affected pregnancies (44;140). It has also been shown that the protective effect of folic acid for NTDs is greater in overweight or obese women than underweight or women of normal body mass index (BMI) (44).

BMI values in the NTD dataset were categorised using the International Classification system, as Underweight (<18.50), Normal (18.50-24.99), Overweight (25.00-29.99) and Obese (≥30) (141). As shown in Table 4 previously and Table 28, NorCAS only has 23% of data missing for this variable in comparison to all other registers that have more than 94% of the data missing. Therefore, only data from NorCAS can be used to explore maternal BMI.

Unfortunately, it is only possible to give a descriptive analysis using the BINOCAR dataset rather than to calculate actual prevalence as no denominator data are available.

Table 28: Proportion of mothers in the NTD NorCAS dataset falling into the different BMI categories, including missing cases

Maternal BMI group	No (%)
Underweight	5 (1.74)
Normal	99 (34.38)
Overweight	59 (20.49)
Obese	58 (20.14)
Not known/Missing	67 (23.26)
Total	288 (100)

Despite not having any denominator data, it was found in a study using data from 2007 that the percentage of obese pregnant women in the region covered by NorCAS was almost 16% (142). It is also known from the Centre for Maternal and Child Enquiries (CMACE) report on maternal obesity in the UK that approximately 5% of all women giving birth in the region covered by NorCAS were obese in 2010 (143). This is in contrast to 38% in 2007 and 25% in 2010 of mothers of NTD cases classified as obese (and 26% of mothers across all data years (Appendix C: Table C 1)) in NorCAS where BMI is known, indicating a possible excess for NTD cases. Using the NorCAS data, no significant differences were found in the proportion of mothers falling into the different BMI categories between anencephaly and spina bifida subtypes or between isolated and non-isolated cases (Both tables in Appendix C: Table C 1 and Table C 2).

4.4.7.4.1 Summary

There seems to be an excess of NTD cases among obese mothers in the BINOCAR dataset. However, it would only be possible to conduct further, limited explorations (with no denominator data) of maternal BMI using data from NorCAS.

4.4.7.5 Folic acid use in the BINOCAR dataset

As stated in the Introduction this thesis (Chapter 1), the clear association between folic acid intake and NTD reduction led to the 1992 Department of Health (DH) recommendation that 400 µg of folic acid be taken before conception and for the first twelve weeks of pregnancy. This has resulted in between 21% and 48% of women

taking folic acid peri-conceptionally in the U.K. (93). However, there have been mixed findings as to whether there has been a clear decline in NTDs in the UK during the folic acid era (35) or there has been no change to the existing rate of decrease pre-1992 (34).

Self-reported folic acid usage is only reported by two registers: SWCAR and CARIS. A study assessed the quality of folic acid usage recording in the SWCAR, by comparing recording in SWCAR with computerised and paper prenatal records (144). It was found that when information was reported that any folic acid had been taken in the records, this was transferred correctly to SWCAR in all cases. However, timing of folic acid use was not always transferred correctly. There was found to be no statistically significant difference in the recording of folic acid use in pregnancies affected by NTDs and those not affected by NTDs (144). A breakdown of the folic acid usage data in CARIS and SWCAR is given in Table 29 and Table 30. As shown, the proportion of not known/not recorded is lower in CARIS (32%) than SWCAR (44%).

Table 29: Folic acid use breakdown for CARIS

Self-reported folic acid use	**No (%)**
At least 0.4 mg folic acid supplement taken regularly, started pre-conceptionally	17 (6.85)
Folic acid supplement taken irregularly/post-conceptionally/unknown dose/dose < 0.4 mg	130 (52.42)
No folic acid supplement	22 (8.87)
Folic acid use not recorded for this woman	26 (10.48)
Folic acid use not recorded by this maternity unit/clinician	53 (21.37)
Total	248 (100)

Table 30: Folic acid use breakdown for SWCAR

Self-reported folic acid use	**No (%)**
Folic acid taken pre and post conceptionally	21 (6.44)
Folic acid taken only post conceptionally	7 (2.15)
Folic acid not taken	17 (5.21)
Folic acid taken, timing unknown	139 (42.64)
Not known if folic acid taken	142 (43.56)
Total	326 (100)

Although data are collected differently by CARIS and SWCAR, if the datasets are dichotomised into any use of folic acid or no use of folic acid, then the proportion of

any use is similar for CARIS and SWCAR (87% and 91% respectively). Missing data is ignored in this comparison and timing of folic acid use is not taken into account as this was not always found to be recorded correctly in the SWCAR data in the audit mentioned (144). However, the usefulness of combining the folic acid data in this way is questionable as, looking solely at the CARIS dataset, only 12% of those who take folic acid take it at the correct dose and peri-conceptionally.

Due to the high correlation between folic acid use and deprivation reported in the literature (101), it could be argued that deprivation is a good proxy for folic acid use. However, it is difficult to assess correlation in the current dataset, due to problems with recording timing of folic acid use and missing data, as stated. No attempt has been made to analyse further "folic acid use" using the BINOCAR data, however, this has been explored in the qualitative research (Chapter 6).

4.4.7.5.1 Summary

Peri-conceptional use of folic acid is a critical factor to take into account when exploring NTD prevalence, due to the strong association between folic acid use and NTD risk reduction. However, due to its poor and imprecise recording within the BINOCAR dataset, it cannot be explored further in the quantitative analyses.

4.4.7.6 Month of conception in the BINOCAR dataset

Several studies have reported seasonal variation in the prevalence of NTDs (per conceptions), with a peak in conceptions in the summer months (13;145;146). Castilla and colleagues reported variations for anencephaly specifically (145) and Bound and colleagues only found seasonality for spina bifida in isolated cases and for anencephaly in non-isolated cases (13). It is argued that due to the same conception peak for schizophrenia and NTDs, and also left-handedness and artistic intuition, there might be some underlying process that is common to all of these (147).

Table 31 shows the NTD prevalence per 10,000 conceptions for month pairs e.g. Jan-Feb, for all NTD types combined and then for anencephaly and spina bifida subtypes individually. For the numerator, conception months for NTD affected pregnancies in the BINOCAR dataset were calculated by subtracting the gestation length (in days) from the date of birth outcome (only month and year were obtained due to date of birth outcome being patient identifiable information, so each outcome for each affected pregnancy was designated as occurring on the 15th of the month). Denominator data for all conceptions for the same period (2006-2011) and regions covered by the BINOCAR data were obtained from ONS. ONS calculated an estimated date of conception by subtracting the completed weeks gestation from the birth date and then extracted month of conception from this so it could be used for the analysis. It is known from the literature that there tends to be a peak in conceptions (for all births) around November-December and troughs around March-May and August-September (148), which is mirrored in the obtained conception denominator data from ONS.

There is not shown to be any statistically significant differences in the conception prevalence between any of the month pairs for all NTD subtypes combined and for anencephaly and spina bifida subtypes individually. (Table 31 and visually represented in Figure 10).

Table 31: NTD prevalence per 10,000 conceptions for month-pairs for all NTD affected pregnancies and by NTD subtype

	NTD prevalence/10,000 conceptions (95% CI)		
Month pairs	**Anencephaly**	**Spina Bifida**	**Total (all NTDs)**
Jan-Feb	4.99 (4.09-6.03)	5.73 (4.76-6.84)	12.35 (10.91-13.93)
Mar-Apr	5.13 (4.22-6.17)	5.73 (4.76-6.83)	11.78 (10.38-13.31)
May-Jun	4.49 (3.64-5.48)	5.79 (4.82-6.90)	11.49 (10.10-13.01)
Jul-Aug	4.87 (4.00-5.88)	5.73 (4.78-6.82)	11.91 (10.52-13.44)
Sept-Oct	5.26 (4.35-6.29)	5.75 (4.80-6.83)	12.61 (11.18-14.16)
Nov-Dec	5.61 (4.69-6.67)	6.44 (5.44-7.56)	13.66 (12.19-15.25)

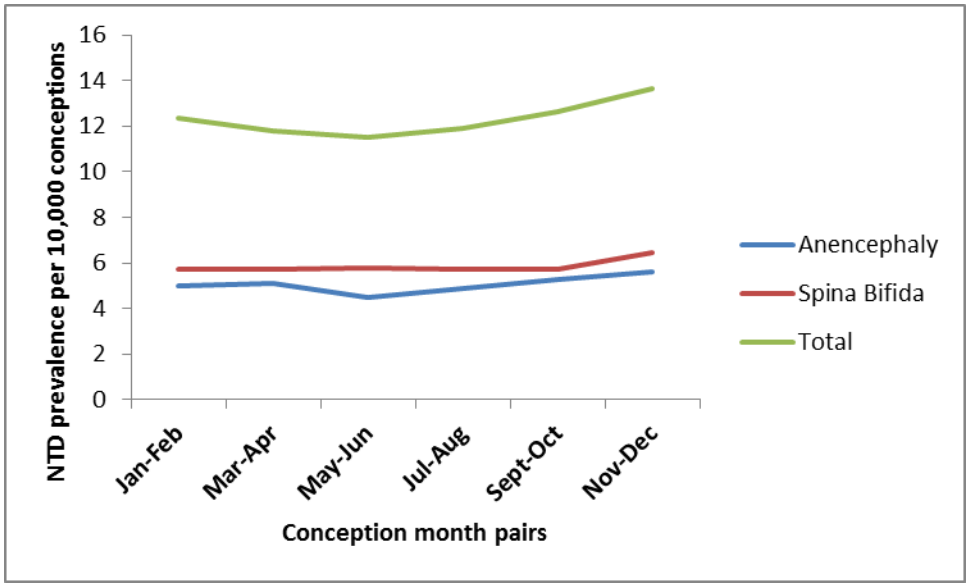

Figure 10: NTD prevalence per 10,000 conceptions by month of conception for all NTDs combined and by NTD subtype

The NTD prevalence per 10,000 conceptions for month pairs for isolated and non-isolated NTD affected pregnancies separately are shown in Table 32 and Table 33 respectively. Again, when stratifying the analyses in this way, there are not shown to be any statistically significant differences in the conception prevalence between any of the month pairs for all NTD subtypes combined and for anencephaly and spina bifida subtypes individually.

Table 32: NTD prevalence per 10,000 conceptions for month-pairs for all isolated NTD affected pregnancies and by subtype

	NTD prevalence/10,000 conceptions (95% CI)		
Month pairs	**Anencephaly**	**Spina Bifida**	**Total (all NTDs)**
Jan-Feb	4.29 (3.46-5.36)	4.38 (3.54-5.36)	9.55 (8.29-10.95)
Mar-Apr	4.39 (3.55-5.36)	4.25 (3.43-5.21)	9.05 (7.83-10.41)
May-Jun	3.52 (2.77-4.41)	4.35 (3.52-5.33)	8.85 (7.64-10.19)
Jul-Aug	3.93 (3.14-4.84)	4.15 (3.35-5.09)	8.93 (7.73-10.27)
Sept-Oct	4.54 (3.71-5.52)	4.41 (3.58-5.37)	9.84 (8.59-11.23)
Nov-Dec	4.65 (3.81-5.62)	4.61 (3.78-5.58)	10.05 (8.79-11.43)

Table 33: NTD prevalence per 10,000 conceptions for month-pairs for all non-isolated NTD affected pregnancies and by subtype

	NTD prevalence/10,000 conceptions (95% CI)		
Month pairs	**Anencephaly**	**Spina Bifida**	**Total (all NTDs)**
Jan-Feb	0.70 (0.39-1.15)	1.35 (0.91-1.94)	2.80 (2.13-3.60)
Mar-Apr	0.74 (0.42-1.20)	1.48 (1.01-2.09)	2.73 (2.07-3.51)
May-Jun	0.97 (0.60-1.49)	1.44 (0.98-2.04)	2.64 (2.00-3.42)
Jul-Aug	0.95 (0.59-1.45)	1.58 (1.10-2.20)	2.98 (2.30-3.79)
Sept-Oct	0.71 (0.41-1.16)	1.34 (0.90-1.91)	2.76 (2.12-3.54)
Nov-Dec	0.96 (0.60-1.45)	1.83 (1.32-2.47)	3.61 (2.88-4.48)

An early study by Bound and colleagues, exploring seasonal variation of congenital anomalies in the Fylde of Lancashire, found that there was significant seasonal variation for NTDs based on month of last menstrual period. Specifically, they found that when the NTD prevalence was high (5.5 per 1000 births), conceptions were higher between the months of December and May (13). NorCAS and CARIS have already been shown to stand out from other registers in previous analyses. Although the prevalence in these two registers is not as high (1.4 per 1000 births) as in the Bound et al study, it seemed worthwhile to ask whether there is a different seasonal pattern in NTD conceptions for these registers when compared to the others. For the higher prevalence registers (NorCAS and CARIS) there was not shown to be any statistically significant differences in the conception prevalence between any of the month pairs and this was also the case for the lower prevalence registers (EMSYCAR, CAROBB and SWCAR) (Table 34). However, it was interesting that it was specifically between September and October that the NTD conception prevalence was statistically significantly higher for the higher prevalence registers (NorCAS and CARIS) (16.86; 95% CI: [13.91, 20.25]) than the lower prevalence registers (EMSYCAR, CAROBB and SWCAR) (10.77; 95% CI: [9.21, 12.52]); between May and June the NTD conception prevalence was also of borderline statistical significance higher in the former (14.62; 95% CI: [11.83, 17.87]) than the latter (10.14; 95% CI: [8.60, 11.88]) (Table 34).

Table 34: NTD prevalence per 10,000 conceptions for month-pairs for all NTD affected pregnancies in NorCAS and CARIS vs. EMSYCAR, CAROBB and SWCAR

Month pairs	NTD prevalence/10,000 conceptions (95% CI)	
	All NTDs for NorCAS and CARIS	**All NTDs for EMSYCAR, CAROBB and SWCAR**
Jan-Feb	11.65 (9.18-14.58)	12.66 (10.92-14.60)
Mar-Apr	14.76 (11.97-18.00)	10.48 (8.91-12.24)
May-Jun	14.62 (11.83-17.87)	10.14 (8.60-11.88)
Jul-Aug	14.24 (11.52-17.40)	10.91 (9.33-12.68)
Sept-Oct	16.86 (13.91-20.25)	10.77 (9.21-12.52)
Nov-Dec	15.74 (12.94-18.96)	12.75 (11.06-14.62)

4.4.7.6.1 Summary

Seasonal differences in conceptions are interesting when looking at higher and lower prevalence registers separately. However, it was not possible to explore this further in subsequent analyses.

4.5 Chapter Summary and Important Points to Take Forward

- 78 multiple pregnancies were recorded in the dataset. As the predisposing pregnancy risk factors for infants from a multiple pregnancy are the same (although they can affect individuals from a multiple set differently), this has been accounted for in the analyses by taking affected pregnancies as the denominator, with the most severe NTD as the outcome of the pregnancy. This leaves 76 multiple pregnancies in the dataset. Sensitivity analyses comparing a dataset with and without multiples have been carried out after the main analyses.

- The NTD prevalence is higher in NorCAS and CARIS than the other three registers, in line with a North/South divide as reported in the literature; this increase is largely due to spina bifida cases and is specifically for isolated NTD cases in NorCAS and non-isolated NTD cases in CARIS.

- Looking at sex in the dataset is difficult as anencephaly cases are often detected and terminated before sex determination is reliable and this variable is of limited usefulness in subsequent analyses.

- The excess prevalence in mothers under 20 years of age is supported by the published literature; this is also shown to be specifically for isolated NTD cases in the dataset. An excess prevalence for mothers aged forty plus is only detected for non-isolated NTDs, specifically chromosomal cases.

- The overall pattern for NTD prevalence by deprivation is in line with the literature; there is an excess prevalence in mothers who live in more deprived areas. This again is shown to be specifically for isolated NTDs.

- Maternal BMI is an important variable but incompletely recorded in all registers except for NorCAS. In comparison with the percentage of all mothers known to be obese in the Northern region, there seems to be an excess of mothers classified as obese in the NTD dataset.

- Folic acid use is poorly completed, particularly with regard to the timing of use. Folic acid use has therefore only been explored further in the qualitative study.

- Although there seems to be an interesting seasonal discrepancy between higher and lower prevalence registers in the dataset, it was not possible to explore this further in subsequent analyses.

- These explorations have highlighted the value of differentiating between isolated and non-isolated NTD cases and NTD subtype, where possible, in analyses.

5 Ethnicity: NTD birth prevalence and the natural history of NTD affected pregnancies

5.1 Introduction

The focus of this chapter is ethnicity and centres in particular on, (a) whether the NTD birth prevalence varies by ethnicity and (b) the natural history of NTD affected pregnancies for different ethnic groups.

There has been wide debate around the usefulness and appropriateness of exploring ethnicity in epidemiological research. A clear distinction must be made between **race**, based on biology and largely discredited as being able to provide biological explanations for disease and **ethnicity**, which is a social construct and informs about cultural or national identity (149;150). Race is something that is defined from the outside whereas ethnicity carries with it a sense of self-identification (149). The two are often used interchangeably with ethnicity sometimes used as a "euphemism" for race (149;150).

Some researchers have been highly critical of the use of ethnicity as an independent variable in epidemiological studies. It has been argued that having ethnicity as the central focus of research can be misleading, due to socio-economic factors being underplayed, and that rather than looking at minority groups per se, we should focus on the social impacts on these groups (149). While others have recognised the limitations of having ethnicity as a variable such as difficulties of measurement; having categories that are too broad and the risk of ethnocentricity, designating a "standard" group, they recognise that ethnicity can be of value beyond social terms. However, a consideration of socio-economic differences should not be secondary to a consideration of cultural and genetic differences when ethnicity is explored (150). Much can be done to improve the value of ethnicity in epidemiological research; collecting the best data possible but also identifying its shortfalls upfront and not drawing conclusions beyond the data at hand. Collecting any additional data that might help to understand why there might be a difference by ethnic group, is essential (150;151).

In the current study, ethnicity is the focus. Ethnicity data reported to BINOCAR registers is self-reported and is broadly based on the ONS 2001 census classification (A breakdown of 2001 census ethnic groupings is given in Appendix D in Table D 1). However, it actually consists of a mixture of higher level and lower level groupings, with those of Mixed ethnicity simply designated as Mixed rather than White and Black Caribbean; White and Black African etc. and those of White ethnicity simply designated as White rather than White British; White Irish etc. Speaking to a representative from EMSYCAR, having different White categories has been found to lead to confusion and for this reason it is simply collected as White. For all other ethnic groups lower level e.g. Pakistani, Black African groupings are used. A breakdown of the number of NTD cases in the BINOCAR dataset with mothers falling into each of the possible ethnic categories collected is given in Table 35. Missing and not stated ethnicity have been combined as 'not known'.

Table 35: Breakdown of number and proportion of NTD cases in the BINOCAR dataset with mothers falling into the different ethnic groups collected by registers

Ethnicity	**NTD cases n (%)**
White[1]	1115 (67.90)
Mixed[2]	5 (0.30)
Indian	31 (1.89)
Pakistani	25 (1.52)
Bangladeshi	10 (0.61)
Other Asian	12 (0.73)
Black Caribbean	5 (0.30)
Black African	15 (0.91)
Other Black	0 (0)
Chinese	0 (0)
Other ethnic group	23 (1.40)
Not known	401 (24.42)
Total	1642 (100)

[1]Contains White British; Irish; Other White background; All White groups

[2]Contains White and Black Caribbean; White and Black African; White and Asian; Other Mixed background

In analyses, Mixed and Other Asian categories are merged with the "Other ethnic group" and simply designated as "Other ethnic group." This is in line with obtained ONS ethnicity denominator data for all live and still births for the same region and

years covered by the BINOCAR dataset in this study (Other Black and Chinese would also be included in the "Other ethnic group" category but there are no cases in the dataset).

It is of importance to note here that ethnicity in the live and still birth denominator data is ethnicity of the baby, as stated by the mother, and ethnicity in the BINOCAR dataset, as detailed, is ethnicity of the mother. This is a limitation of the available data. However, Dattani and colleagues found that when Birth registration and NHS Numbers for Babies (NN4B) data (contains ethnicity of the baby) were linked to Maternity Hospital Episode Statistics (HES) data (contains ethnicity of the mother) there was agreement between the baby's ethnicity and mother's ethnicity in 87% of cases in 2006 (152) and 75% of cases in 2007 (153).

The way in which prevalence data is presented could be argued to be ethnocentric as White is taken as the reference group in prevalence rate ratios, however individual prevalence estimates are also often presented. Moreover, White is not chosen as the reference group as it is seen as the "standard" ethnic group but because the highest number of births (the denominator) are in this group, and it was for this reason, for example, that deprivation quintile 1 (most deprived) was chosen as the reference group in Chapter 4. Additionally, although there is very little existing research on NTD prevalence in different ethnic communities in the UK, a very early study found that still births and infant deaths attributed to NTDs were higher in Indian and Bangladeshi mothers (75). More recent data from the North Thames Region in the UK indicated that the rate of NTD affected pregnancies (including terminations) is higher in women of Pakistani or Indian origin (81) and an increased NTD prevalence in mothers of Pakistani ethnicity has also been reported by Tonks and colleagues in the West Midlands (82). It is therefore hypothesised, based on this very limited evidence, that the NTD prevalence will be higher in mothers of Bangladeshi, Indian and Pakistani ethnic origin than mothers of White ethnicity. The impact of a number of different factors, including deprivation of maternal residence, on any observed association between ethnicity and NTD prevalence is considered in this chapter. However, it is not possible to explore the impact of pre-pregnancy and pregnancy attitudes and experiences, such as folic acid use, diet, any religious observance etc. These factors have been

explored in-depth in a qualitative study of mothers who have had a pregnancy affected by an NTD (Chapter 6).

5.2 Calculating NTD prevalence estimates for different ethnic groups

As in previous analyses, and described in Chapter 4, aggregated denominator data (live and still births) were obtained from ONS and merged with pregnancy level NTD BINOCAR data to form an aggregated dataset for calculating prevalence estimates. Firstly, NTD prevalence was compared by ethnicity for all NTD affected pregnancies in the BINOCAR dataset where ethnicity is not missing (complete cases). Looking at absolute prevalence estimates, for all NTD subtypes combined, the only statistically significant difference observed is that the prevalence is lower for mothers of "Other" ethnicity (4.98 per 10,000; 95% CI: 3.65, 6.79) than mothers of White (10.32 per 10,000; 95% CI: 9.73, 10.94) or Indian (13.45 per 10,000; 95% CI: 9.46, 19.13) ethnicity (Table 36). However, it is very difficult to say anything meaningful about the "Other" ethnic group due to the eclectic nature of this group.

Calculating prevalence rate ratios, with mothers of White ethnicity chosen as the reference group for reasons stated previously, looking at anencephaly affected pregnancies specifically, Indian mothers were shown to be nearly twice as likely to have an NTD affected pregnancy as White mothers (PRR 1.72; 95% CI: 1.05, 2.84) (Table 37); the 95% confidence interval for Indian mothers when compared to White mothers did not include 1, providing evidence to support a statistically significant difference (p=0.032). Although Bangladeshi mothers were shown to be nearly twice as likely as White mothers to have a spina bifida affected pregnancy (Table 37), due to the smaller numbers in this group and the wide confidence interval (PRR 1.83; 95% CI: 0.82, 4.09) this was not a statistically significant difference (p=0.14).

Table 36: NTD birth prevalence estimates by ethnicity for all registers

Ethnicity	Prevalence/10,000 births (95% CI)		
	All NTDs*	Anencephaly	Spina bifida
White	10.32 (9.73-10.94)	4.02 (3.66-4.42)	5.14 (4.73-5.59)
Indian	13.45 (9.46-19.13)	6.94 (4.25-11.32)	4.33 (2.33-8.06)
Pakistani	9.49 (6.41-14.05)	4.17 (2.31-7.54)	3.79 (2.04-7.05)
Bangladeshi	15.69 (8.44-29.18)	4.70 (1.52-14.59)	9.41 (4.23-20.95)
Black Caribbean	10.51 (4.37-25.25)	2.10 (0.30-14.90)	8.40 (3.15-22.40)
Black African	7.66 (4.62-12.71)	3.57 (1.70-7.50)	3.06 (1.38-6.82)
Other ethnic group	4.98 (3.65-6.79)	1.99 (1.22-3.25)	2.24 (1.41-3.56)

*Includes encephalocele

Table 37: NTD birth prevalence rate ratios by ethnicity for all registers

Ethnicity	Prevalence rate ratios (PRR) (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**10.32**	**4.02**	**5.14**
Indian	1.30 (0.91-1.86)	1.72 (1.05-2.84)	0.84 (0.45-1.57)
Pakistani	0.92 (0.62-1.37)	1.04 (0.57-1.89)	0.74 (0.39-1.38)
Bangladeshi	1.52 (0.82-2.83)	1.17 (0.38-3.64)	1.83 (0.82-4.09)
Black Caribbean	1.02 (0.42-2.45)	0.52 (0.07-3.71)	1.63 (0.61-4.37)
Black African	0.74 (0.45-1.24)	0.89 (0.42-1.87)	0.60 (0.27-1.33)
Other ethnic group	0.48 (0.35-0.66)	0.50 (0.30-0.82)	0.44 (0.27-0.70)

Interestingly, when splitting the dataset into isolated and non-isolated cases, with categorisation based on the EUROCAT multiple congenital anomaly algorithm, as detailed in the previous chapter, no effect was observed for isolated cases, apart from the lower prevalence in mothers of "Other" ethnicity (Table 38). However, for non-isolated cases Indian mothers were nearly 3 times as likely (PRR 2.64; 95% CI: 1.57, 4.44) ($p<0.001$) and Bangladeshi mothers more than 3 times as likely (PRR 3.19; 95% CI: 1.32, 7.71) ($p=0.01$) as White mothers to have an NTD affected pregnancy (Table 39). Specifically, the prevalence of anencephaly (as a non-isolated NTD) in Indian mothers was five times higher (PRR 5.43; 95% CI: 2.61, 11.30) ($p<0.001$) and for Bangladeshi mothers, the spina bifida prevalence was more than three times higher (PRR 3.63; 95% CI: 1.16, 11.39) ($p=0.03$) for babies with a non-isolated NTD than in White mothers (Table 38 and Table 39).

Table 38: NTD birth prevalence rate ratio estimates by ethnicity for isolated NTD affected pregnancies for all registers

Ethnicity	Prevalence rate ratios (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**7.85**	**3.38**	**3.85**
Indian	0.88 (0.54-1.45)	1.02 (0.51-2.06)	0.79 (0.37-1.66)
Pakistani	0.87 (0.55-1.39)	0.90 (0.45-1.81)	0.79 (0.39-1.59)
Bangladeshi	1.00(0.41-2.40)	0.93 (0.23-3.72)	1.22 (0.39-3.80)
Black Caribbean	0.80 (0.26-2.49)	0.62 (0.09-4.41)	1.09 (0.27-4.38)
Black African	0.65 (0.35-1.21)	0.90 (0.40-2.03)	0.53 (0.20-1.42)
Other ethnic group	0.48 (0.33-0.68)	0.51 (0.30-0.88)	0.39 (0.22-0.69)

Table 39: NTD birth prevalence rate ratio estimates by ethnicity for non-isolated NTD affected pregnancies for all registers

Ethnicity	Prevalence rate ratios (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**2.46**	**0.64**	**1.29**
Indian	2.64 (1.57-4.44)	5.43 (2.61-11.30)	1.00 (0.32-3.15)
Pakistani	1.08 (0.51-2.29)	1.78 (0.56-5.67)	0.59 (0.15-2.37)
Bangladeshi	3.19 (1.32-7.71)	2.46 (0.34-17.68)	3.63 (1.16-11.39)
Black Caribbean	1.71 (0.42-6.86)	0.00 (0)	3.24 (0.80-13.09)
Black African	1.04 (0.43-2.51)	0.80 (0.11-5.76)	0.79 (0.20-3.18)
Other ethnic group	0.51 (0.27-0.95)	0.39 (0.10-1.59)	0.58 (0.25-1.31)

Simply ignoring missing data can reduce precision and introduce bias into the analyses (154). As shown in Table 4 of Chapter 4 there is huge variability between different registers in the amount of ethnicity data that is missing. Whereas EMSYCAR and SWCAR only have 12.92% and 7.06% of their data missing respectively, the other three registers have more than 32% of their data missing for ethnicity and for NorCAS as much as 45.83% of the data are missing. Registers were dichotomised into those with more than 87% of their ethnicity data complete (SWCAR and EMSYCAR: so-called "complete" ethnicity registers) and the remaining three registers which have less than 68% completeness for ethnicity (NorCAS, CAROBB and CARIS: so-called "incomplete" ethnicity registers). The outcomes of complete case analyses using "complete" (EMSYCAR and SWCAR) ethnicity registers only, as shown in Table 40; Table 41; Table 42 and Table 43 below, can be compared with the outcomes described above for complete case analyses using data from all registers, as shown in Table 36; Table 37; Table 38 and Table 39.

For analyses using "complete" ethnicity registers only, it was found that Indian mothers were nearly twice as likely (PRR 1.86; 95% CI: 1.26, 2.75) (p=0.002) and Bangladeshi mothers more than three times as likely (PRR 3.10; 95% CI: 1.61, 5.97) (p=0.001) as White mothers to have an NTD affected pregnancy (Table 41). For the complete case analyses including data from all registers (Table 37), there was an excess anencephaly prevalence for Indian mothers when compared to White mothers (PRR 2.56; 95% CI: 1.52, 4.31) (p<0.001), however, in this analysis using data only from the "complete" ethnicity registers, the excess is more marked. Additionally, Bangladeshi mothers are shown to have a spina bifida prevalence that is more than four times that for White mothers (PRR 4.29; 95% CI: 1.91, 9.61) (p<0.001) in analyses using only "complete" ethnicity registers (Table 40 and Table 41).

When stratifying by whether or not the NTD is isolated, a similar pattern between the two sets of analyses (complete case analyses for all registers vs. complete case analyses for "complete" ethnicity registers) is observed: For non-isolated NTD cases, there is an excess overall for all NTDs combined for Indian and Bangladeshi mothers when compared to White mothers and specifically anencephaly affected pregnancies are higher in Indian and spina bifida affected pregnancies higher in Bangladeshi mothers (Table 39 and Table 43). However, the excess is much greater in the "complete" ethnicity registers' analyses where anencephaly non-isolated NTD affected pregnancies are more than 7 times as likely in Indian mothers (PRR 7.28; 95% CI: 3.29, 16.15) (p<0.001) and spina bifida non-isolated NTD affected pregnancies more than 8 times as likely in Bangladeshi mothers (PRR 8.45; 95% CI: 2.67, 26.73) (p<0.001) as White mothers (Table 43). There is also shown to be an excess of spina bifida non-isolated NTD affected pregnancies in Black Caribbean mothers when compared to White mothers (PRR 4.10; 95% CI: 1.01, 16.69) in the "complete" ethnicity registers analyses; however, this difference only just reaches statistical significance, and should be treated with caution (Table 42 and Table 43).

Table 40: NTD birth prevalence estimates by ethnicity for EMSYCAR and SWCAR only

Ethnicity	Prevalence/10,000 births (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White	11.49 (10.65-12.41)	4.80 (4.27-5.41)	5.52 (4.95-6.17)
Indian	21.38 (14.55-31.42)	12.33 (7.43-20.45)	5.75 (2.74-12.06)
Pakistani	14.96 (9.30-24.08)	6.16 (2.93-12.92)	6.16 (2.93-12.92)
Bangladeshi	35.66 (18.53-68.61)	7.90 (1.98-31.61)	23.74 (10.66-52.90)
Black Caribbean	14.41 (5.99-34.63)	2.88 (0.41-20.43)	11.52 (4.32-30.71)
Black African	13.50 (7.99-22.80)	5.78 (2.60-12.87)	5.78 (2.60-12.87)
Other ethnic group	5.40 (3.55-8.20)	2.45 (1.32-4.56)	2.21 (1.15-4.24)

Table 41: NTD birth prevalence rate ratio estimates by ethnicity for EMSYCAR and SWCAR

Ethnicity	Prevalence rate ratios (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**11.49**	**4.80**	**5.52**
Indian	1.86 (1.26-2.75)	2.56 (1.52-4.31)	1.04 (0.49-2.20)
Pakistani	1.30 (0.80-2.11)	1.28 (0.61-2.71)	1.11 (0.53-2.36)
Bangladeshi	3.10 (1.61-5.97)	1.64 (0.41-6.60)	4.29 (1.91-9.61)
Black Caribbean	1.25 (0.52-3.02)	0.60 (0.08-4.27)	2.08 (0.78-5.58)
Black African	1.17 (0.69-1.99)	1.20 (0.54-2.70)	1.05 (0.47-2.35)
Other ethnic group	0.47 (0.31-0.72)	0.51 (0.27-0.96)	0.40 (0.21-0.78)

Table 42: NTD birth prevalence rate ratio estimates by ethnicity for isolated NTD affected pregnancies for EMSYCAR and SWCAR

Ethnicity	Prevalence rate ratios (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**8.74**	**4.02**	**4.12**
Indian	1.32 (0.77-2.24)	1.64 (0.81-3.31)	1.00 (0.41-2.42)
Pakistani	1.31 (0.76-2.27)	1.09 (0.45-2.66)	1.28 (0.57-2.88)
Bangladeshi	1.81 (0.68-4.84)	0.98 (0.14-7.01)	2.88 (0.92-8.97)
Black Caribbean	0.99 (0.32-3.07)	0.72 (0.10-5.11)	1.40 (0.35-5.62)
Black African	0.99 (0.51-1.92)	1.20 (0.49-2.91)	0.94 (0.35-2.51)
Other ethnic group	0.51 (0.32-0.81)	0.55 (0.28-1.07)	0.48 (0.24-0.96)

Table 43: NTD birth prevalence rate ratio estimates by ethnicity for non-isolated NTD affected pregnancies for EMSYCAR and SWCAR

Ethnicity	Prevalence rate ratios (95% CI)		
	All NTDs	Anencephaly	Spina bifida
White (ref)	**2.75**	**0.79**	**1.40**
Indian	3.58 (1.99-6.44)	7.28 (3.29-16.15)	1.17 (0.29-4.76)
Pakistani	1.28 (0.47-3.45)	2.23 (0.54-9.19)	0.63 (0.09-4.50)
Bangladeshi	7.17 (2.95-17.46)	5.01 (0.69-36.30)	8.45 (2.67-26.73)
Black Caribbean	2.09 (0.52-8.43)	4.23*e-7 (0)	4.10 (1.01-16.69)
Black African	1.75 (0.72-4.26)	1.22 (0.17-8.85)	1.37 (0.34-5.59)

Other ethnic group	0.36 (0.13-0.96)	0.31 (0.04-2.26)	0.17 (0.02-1.26)

5.2.1 Explorations around missing ethnicity data for different registers

There were discrepancies between a complete case analysis using data from all registers and complete case analysis using data only from "complete" ethnicity registers (those with more than 87% of their ethnicity data complete) when exploring NTD prevalence estimates by ethnicity. Hence, this warranted further investigation before determining whether any subsequent complete cases analyses should include data from all registers or just those with very good ethnicity completion.

5.2.1.1 Exploring whether ethnicity representation in each register reflects the ethnicity of the underlying population

Comparing ethnicity completeness in the NTD dataset with that in the denominator population (all live and still births for the same geographical area) from ONS, 24% of ethnicity data is missing in the NTD dataset, whereas only 8% is missing in the ONS dataset. Therefore, simply ignoring missing ethnicity data for the "incomplete" (less than 68% complete) registers, will reduce precision of prevalence estimates. However, it is also of interest to look at where ethnicity is not missing, to compare the ethnic breakdown in the NTD dataset between different registers and to see whether it is similar to that in the denominator dataset. A breakdown by ethnicity for NTDs and births for EMSYCAR is shown in Figure 11 and Figure 12; for SWCAR in Figure 13 and Figure 14; for NorCAS in Figure 15 and Figure 16 ; for CAROBB in Figure 17 and Figure 18 and for CARIS in Figure 19 and Figure 20.

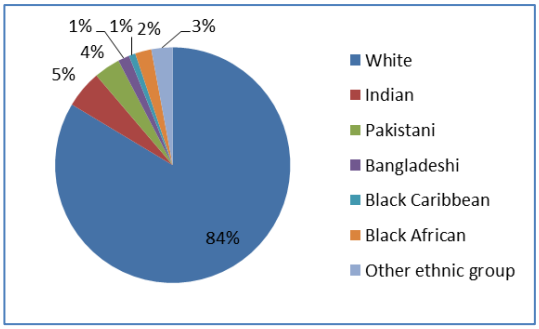

Figure 11: Ethnic breakdown for NTDs in EMSYCAR

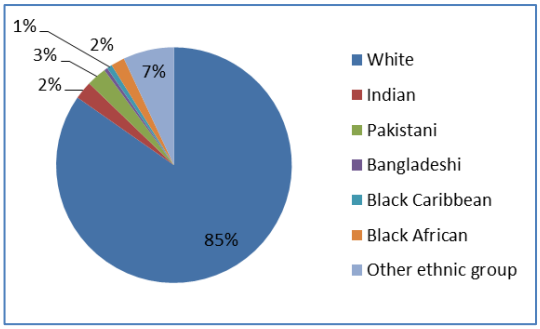

Figure 12: Ethnic breakdown for EMSYCAR births

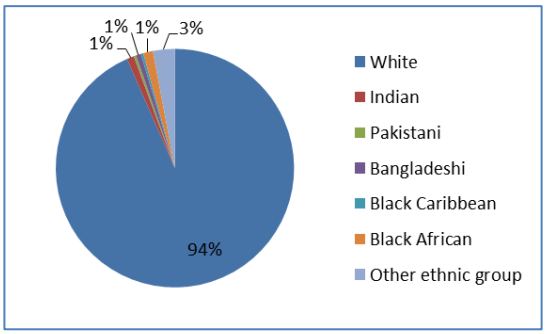

Figure 13: Ethnic breakdown for NTDs in SWCAR

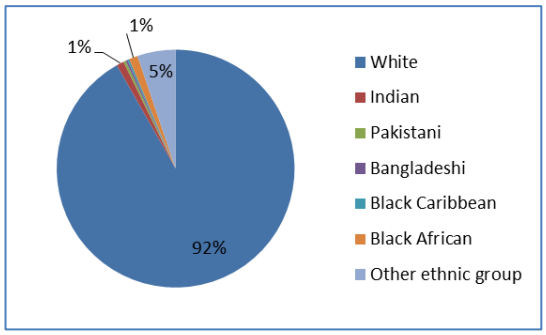

Figure 14: Ethnic breakdown for SWCAR births

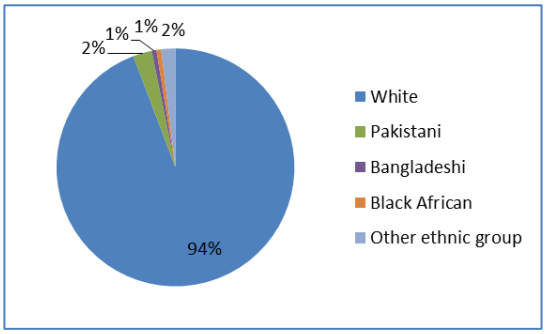

Figure 15: Ethnic breakdown for NTDs in NorCAS

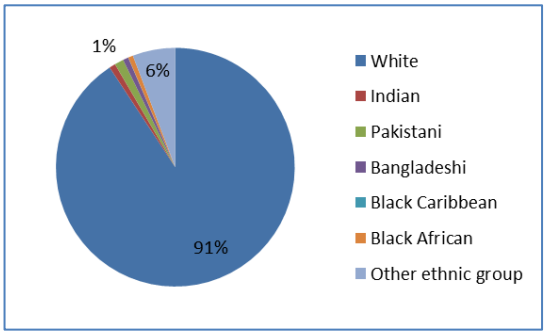

Figure 16: Ethnic breakdown for NorCAS births

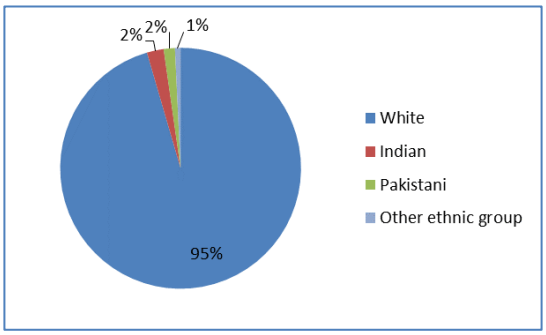

Figure 17: Ethnic breakdown for NTDs in CAROBB

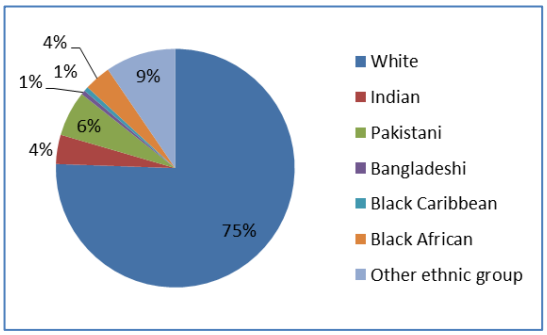

Figure 18: Ethnic breakdown for CAROBB births

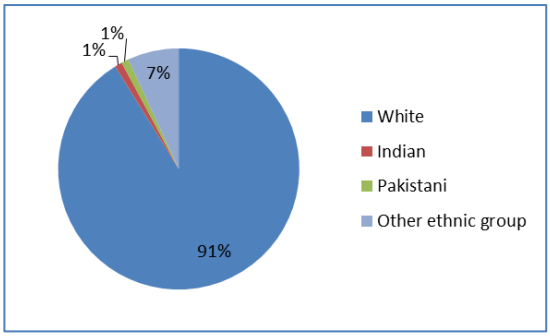

Figure 19: Ethnic breakdown for NTDs in CARIS

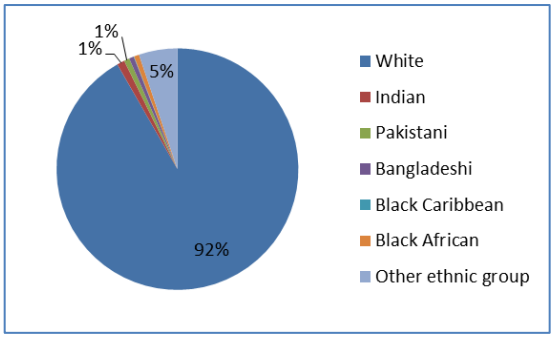

Figure 20: Ethnic breakdown for CARIS births

Of the "complete" ethnicity registers, EMSYCAR covers the most ethnically diverse population with this diversity reflected in the NTD dataset; however, there is a clear excess of Indian and Bangladeshi NTD cases when compared to births to mothers of the same ethnicity. SWCAR covers a much less ethnically diverse area than EMSYCAR, with only 1% of births to Indian mothers in SWCAR when compared to 2.5% in EMSYCAR. The proportion of NTD affected pregnancies to mothers of Bangladeshi ethnicity is more than twice as high as births to mothers from the same ethnic group in the region covered by SWCAR. However, the actual number of affected pregnancies is small (2 to Bangladeshi mothers in SWCAR).

For the "incomplete" ethnicity registers, for NorCAS, the lack of ethnic diversity in the NTD dataset is not very surprising as the underlying population is not very ethnically diverse, with 91% of births to mothers of White ethnicity and the next highest proportion of births after mothers of "Other" ethnicity (6%) is 1% to mothers of Pakistani ethnicity. The same is true of CARIS, which also does not cover a very ethnically diverse area, and is reflected in the NTD dataset. What is surprising, however, is the lack of ethnic diversity in the NTD dataset from CAROBB when compared to the underlying population in which only 76% of births are to mothers of White ethnicity, 6% to mothers of Pakistani ethnicity and 4% to mothers of Indian ethnicity.

5.2.1.2 Comments from register representative about ethnicity completion

As part of the on-going dialogue with BINOCAR staff and register representatives about the data, some important indicators of why ethnicity data might be missing were given. A representative from NorCAS described how completion was poorer

for the earlier years of the data extract before the established proforma that encouraged women to record ethnicity had been developed. This was supported by a review of the NTD dataset as for the first three years of the study (2006 to 2008) 61% of the ethnicity data is missing and for the last three (2009 to 2011) this falls to 32%. Interestingly, the opposite was true for CARIS which had less missing for the first three years of the study (23%) than the last three years (40%). For CAROBB there was no difference between the two data year groups.

Representatives from CAROBB noted that asking about ethnicity was sometimes difficult, due to its sensitive nature, and people are not always sure which ethnic category they fall into. This indicated the potential for bias as ethnicity information might be more likely to be recorded for women from certain ethnic groups than others.

Understanding why ethnicity information reported to registers might be missing is further compounded by the fact that although it should be recorded somewhere in the patient's notes, it can be difficult to find i.e. if it is not recorded well, it may not be reported.

5.2.1.3 NTD subtype

The observed prevalence differences by ethnicity between the two sets of analyses (analyses using data from all registers and analyses using only data from "complete" ethnicity registers) was very interesting when looking at individual NTD subtypes. A breakdown for the missing data for ethnicity by register for different NTD subtypes is shown in Figure 21. This further accentuates the difference in the proportion of missing ethnicity data between EMSYCAR/SWCAR and the other registers; however, importantly, there seems to be an excess of missing data for anencephaly for NorCAS and CARIS. As the excess prevalence in Indian mothers was shown to be specifically for anencephaly cases, the excess missing for anencephaly cases would certainly have an impact on the number of affected pregnancies to Indian mothers that could be observed. This could lead to

an underestimate for the prevalence rate ratio for mothers of Indian when compared to mothers of White ethnicity.

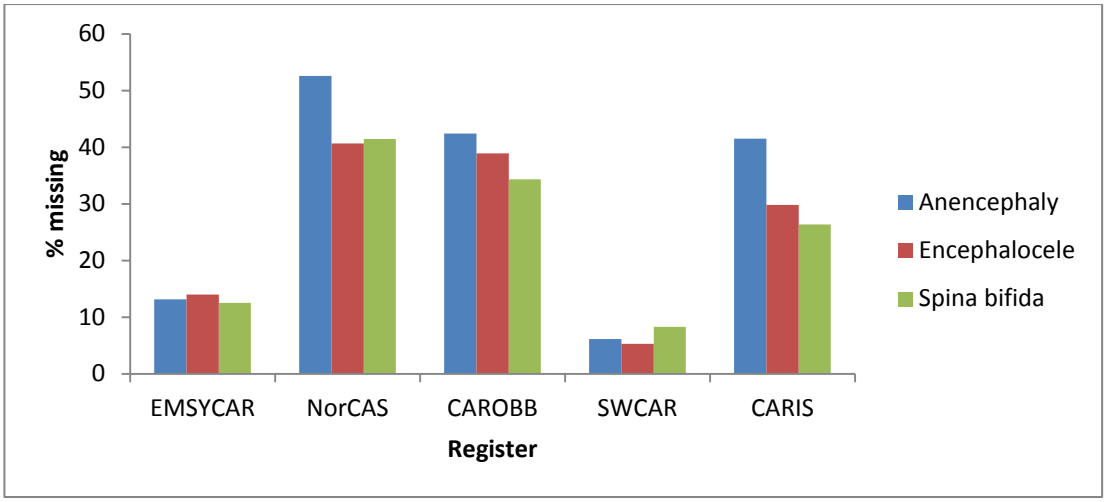

Figure 21: Proportion of missing ethnicity data by NTD type and register

5.2.1.4 Isolated vs. Non-Isolated NTDs

When the analyses were split for isolated and non-isolated cases, a similar pattern was observed for complete case analyses using data from all registers and that only including "complete" ethnicity registers. However, the prevalence excess for Indian and Bangladeshi mothers was more marked in the "complete" ethnicity registers analyses, as described. The proportion of isolated and non-isolated NTD affected pregnancies that occur within each register (total for each register adds up to 100%), is shown in Appendix D in Figure D 1. The pattern is similar for different registers, although the difference between the proportion of isolated cases in CARIS (69.77; 95% CI: 64.24, 74.90) and NorCAS (81.60; 95% CI: 76.63, 85.90) is statistically significant. Looking at the proportion of missing ethnicity data for isolated and non-isolated cases by register, as shown in Figure 22, there is not a huge discrepancy for any of the registers; the difference is greatest for CARIS, where there is an excess of missing data for isolated cases, but this does not reach statistical significance. Therefore, missing ethnicity data does not appear to include an over or under representation of non-isolated cases.

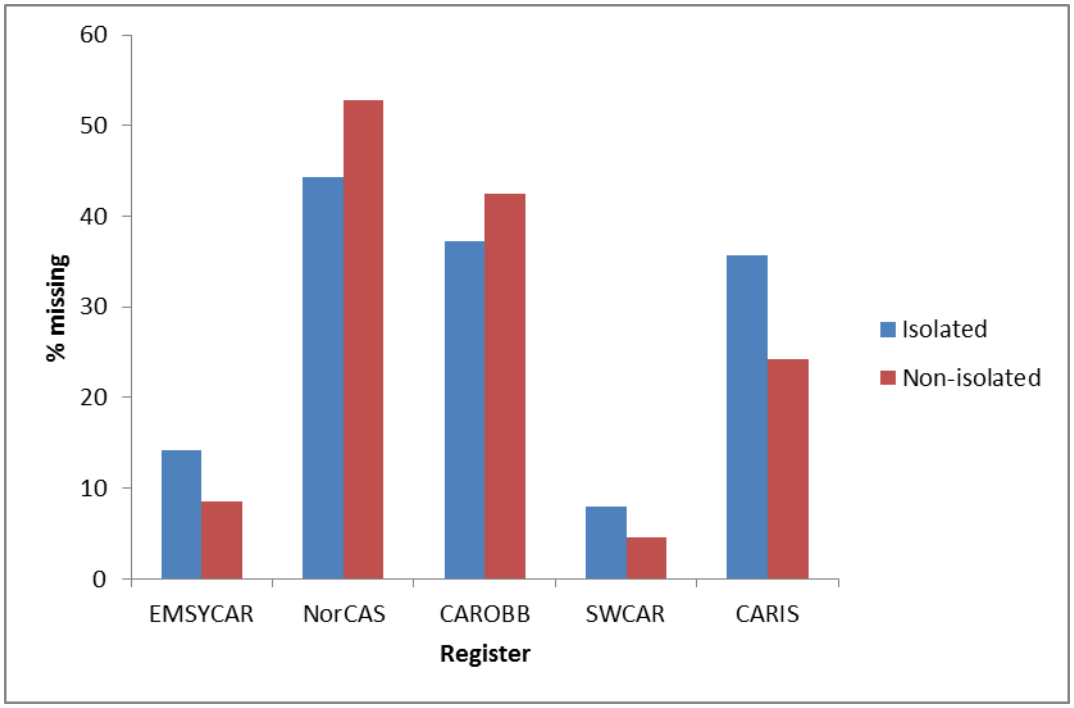

Figure 22: Proportion of missing ethnicity data by whether the NTD is isolated or not and register

5.2.1.5 *Exploration of missing ethnicity through ad hoc data linkage between TOPFA cases in the NTD dataset and termination data from the DH*

As stated, 1296 out of 1642 NTD affected pregnancies in the BINOCAR dataset resulted in TOPFA (79%). Termination data from the DH covering the same regions and years has been obtained where the principal medical condition for the termination is an NTD. Whereas 24% of pregnancies in the BINOCAR NTD dataset have missing ethnicity data, only 4% of cases in the DH termination dataset have ethnicity that is not stated/missing. As the majority of NTDs result in a termination, it was important to link the two datasets to enable further exploration of possible bias in missing BINOCAR ethnicity data. However, information gained from the linkage cannot be extrapolated to affected pregnancies that result in live or still births. There is also some under ascertainment in the DH dataset as an NTD might be the true reason for the termination but this reason is not always given, and there are also indications of under reporting of terminations to the DH (112).

A combination of region (based on register), primary care trust (PCT) of maternal residence, month of termination, year of termination, age of mother and gestation

length were used to uniquely identify affected pregnancies. There were no duplicates (i.e. this combination of variables uniquely identified pregnancies) in the DH dataset but there was one duplicate case in the BINOCAR dataset, when restricting the latter to pregnancies that resulted in a termination. This duplicate was shown to consist of two distinct pregnancies, rather than being a true duplicate as although the two records matched on NTD type in addition to matching on the variables listed above, they didn't match on sex of fetus or age of discovery. The ethnicity of the mother was White in one case and not known in the other. Using this combination of variables to link affected pregnancies common to both the BINOCAR and DH dataset is not perfect and because of this, records had to match on all variables i.e. it was a conservative match. Moreover, the fact that this combination of variables did not uniquely identify every affected pregnancy in the BINOCAR dataset highlights how a match between the two datasets might not be a true match in every case. Therefore, ethnicity data from the DH dataset could not be used to populate missing ethnicity data in the BINOCAR dataset in addition to being used as an exploratory tool for whether there might be any bias in the missing ethnicity data.

After matching and looking at where ethnicity was known in both datasets (n=188), ethnicity matched for merged records in the majority of cases (98%), however there were four instances where they didn't. This supports the argument that the match is correct in most cases. Looking at cases where ethnicity is known in the DH dataset but not known in the BINOCAR dataset (n=54), the majority are White (71%), however there is also a high proportion that are Pakistani (20%). Breaking the data down by register, all of the latter come from CAROBB. In fact, although the numbers are small, as many mothers of White ethnicity have missing data as mothers of Pakistani ethnicity in CAROBB ((11/42 (26%) of White mothers and 11/12 (92%) of Pakistani mothers have missing data)). However, it would be expected that the missing data would mainly be for mothers of White ethnicity, simply because this is the larger ethnic group. This indicates a possible bias for missing ethnicity data in the CAROBB region, which is supported by the anecdotal evidence described in section 5.2.1.2. There is no indication, from this data linkage, that this is the case in the other regions.

5.2.1.6 Exploring whether mothers of Indian and Bangladeshi ethnicity live in more deprived areas in regions covered by "complete" ethnicity registers

As an association between deprivation and NTD prevalence has been reported, an important final consideration is whether it is possible that Indian and Bangladeshi mothers live in areas that are more deprived in the regions covered by "complete" when compared to "incomplete" ethnicity registers. It was found that the proportion of births to mothers of Indian ethnicity in deprivation quintile 1 (most deprived quintile) is significantly higher in NorCAS when compared to all other registers and the proportion in deprivation quintile 1 in CAROBB is significantly lower than in all other registers. Looking at births to Bangladeshi mothers, both the proportion of births in deprivation quintile 1 for CAROBB and SWCAR is statistically significantly lower than the proportion in this quintile for other registers. However, the number of births to mothers of Bangladeshi ethnicity overall is relatively small (A breakdown of proportion of births and confidence intervals for different deprivation quintiles for Bangladeshi and Indian mothers for different registers is given in Table D 2, Table D 3, Table D 4, Table D 5 and Table D 6 in Appendix D). What can be concluded from this comparison is that there does not seem to be any evidence that mothers of Indian or Bangladeshi ethnic origin live in more deprived areas in regions covered by "complete" when compared to "incomplete" ethnicity registers and there is therefore a lack of evidence that the excess prevalence for Indian and Bangladeshi mothers in the former, should be attributed to deprivation.

5.2.2 Conclusions

In a complete case analysis using data from all registers and ignoring missing ethnicity data, there was shown to be an excess anencephaly prevalence in mothers of Indian (PRR 5.43) and an excess spina bifida prevalence in mothers of Bangladeshi ethnicity (PRR 3.63) when compared to mothers of White ethnicity. This excess was found in non-isolated NTDs (other congenital defects are present in addition to the NTD) in women of Indian and Bangladeshi ethnicity. The same was observed but the effect much more marked for Indian (PRR 7.28) and Bangladeshi (PRR 8.45) mothers when compared to mothers of White ethnicity in the complete

case analysis using data only from "complete" (>87% completion) ethnicity registers (EMSYCAR and SWCAR). Through discussions with CAROBB representatives and through linking termination data from BINOCAR with termination data from the DH, there were indications of a potential bias for missing ethnicity data in this register. Specifically, there seemed to be an excess of missing ethnicity data for mothers of Pakistani ethnicity. Although there were no indications of bias for missing ethnicity data in NorCAS and CARIS, from either discussions with register representatives or the data linkage work, the excess of missing ethnicity data for anencephaly cases observed in the NTD dataset could have resulted in an under representation of mothers of Indian ethnicity in the analyses. Additionally, there would be decreased precision in prevalence estimates for registers with "incomplete" (<68% completion) ethnicity information (NorCAS; CAROBB and CARIS), due to there being more missing in the numerator (NTD cases) than the denominator (births). Therefore, because of these identified problems, and due to there being a lack of evidence that Indian and Bangladeshi mothers from "complete" ethnicity registers live in more deprived areas (greater deprivation is associated with a higher NTD prevalence) than mothers of the same ethnicity for the "incomplete" registers, further complete case analyses have been conducted using data only from "complete" ethnicity registers (EMSYCAR and SWCAR). It is also of importance to note that, as shown, the area covered by EMSYCAR is more ethnically diverse than that covered by SWCAR and therefore observed outcomes by ethnicity are unlikely to be over inflated.

Restricting analyses by ethnicity to the "complete" ethnicity registers does have its limitations as there were identified regional differences for NTD prevalence explorations in Chapter 4 and maternal BMI is only recorded with sufficient completeness in NorCAS. An in-depth discussion of this is included in the final chapter of this thesis.

5.3 NTD prevalence in ethnic communities in EMSYCAR and SWCAR

5.3.1 Isolated and Non-Isolated NTDs

As described in section 4.4.7.1.1, a classification system that enables isolated and non-isolated NTDs to be distinguished, based on EUROCAT's multiple congenital anomaly algorithm, has been applied to all NTD affected pregnancies obtained in the BINOCAR dataset. All analyses detailed in this thesis so far that have involved stratification by whether the NTD is isolated or not, have been based on this classification system. However, changing the focus to EMSYCAR and SWCAR only and ethnicity in particular, numbers start to become quite small in some groups.

It was described how there is strong agreement between classification of cases based on the EUROCAT algorithm and a local aetiological variable, only available for CAROBB and EMSYCAR. Comparing the number of NTDs classified as isolated and non-isolated using the two classification systems for EMSYCAR only, 28 cases classified as non-isolated and 7 cases classified as isolated using the EUROCAT algorithm are re-classified as isolated and non-isolated, respectively, using the aetiological classification system (Table 44). Using the kappa statistic, a measure of inter-rater agreement, agreement is shown to be strong (93.15%) ($p<0.001$). However, the strong inter-rater agreement will be influenced by the higher proportion of isolated cases and when looking only at non-isolated cases for groups with small numbers, observed study outcomes could be altered by relatively few categorisation changes.

Table 44: Comparing aetiological vs. EUROCAT algorithm classification for isolated and non-isolated NTD cases in EMSYCAR

Aetiological classification	**EUROCAT algorithm**	
	Isolated	Non-isolated
Isolated	387	28
Non-isolated	7	89

It was described in the previous section (section 5.2) how it was specifically for non-isolated NTDs (determined using the EUROCAT algorithm) that there was found to be an excess NTD prevalence in mothers of Indian and Bangladeshi ethnicity when

compared to mothers of White ethnicity. Anomaly subgroup codes obtained from BINOCAR, which give an indication of what other conditions a fetus might have, were explored for the twelve non-isolated NTDs (based on the EUROCAT algorithm) to Indian mothers and five non-isolated NTDs to Bangladeshi mothers across EMSYCAR and SWCAR. For two of "non-isolated" NTD affected pregnancies to Bangladeshi mothers, club foot was the only condition specified in addition to the NTD. However, club foot is thought to occur as secondary to the NTD, rather than independent of it, and thus, if truly the only other condition in addition to the NTD, the case should be coded as isolated. It was confirmed through both discussions with the BINOCAR database manager and looking at the local aetiological variable, that these two cases should have been categorised as isolated. Furthermore, comparing aetiological and EUROCAT algorithm classification systems for mothers of White, Indian and Bangladeshi ethnicity for both isolated and non-isolated cases in EMSYCAR, 2 out of 7 Bangladeshi mothers; 4 out of 23 Indian mothers and 14 out of 372 White mothers are re-classified using the aetiological system (Table 45). NTD cases are more likely to be re-classified from non-isolated to isolated than the other way round (Table 45).

Table 45: Comparing aetiological and EUROCAT algorithm classification systems for mothers of White, Indian and Bangladeshi ethnicity in EMSYCAR

Ethnicity	Aetiological classification		EUROCAT algorithm	
	Isolated	Non-isolated	Isolated	Non-isolated
White	305	67	291	81
Indian	16	7	12	11
Bangladeshi	4	3	2	5

If prevalence is calculated for non-isolated and isolated NTD affected pregnancies separately, just using EMSYCAR data and the aetiological classification system, the NTD prevalence for Indian mothers when compared to White mothers is more marked for non-isolated NTDs (PRR 3.58; 95% CI: 1.64, 7.79) (p=0.001). However, the difference is also shown to be statistically significant for isolated NTDs (PRR 1.80; 95% CI: 1.09, 2.97) (p=0.022). As described, the inclusion of data from SWCAR is important in order not present an over inflated view for ethnicity outcomes.
It is unfortunate that a local aetiological classification system is not available for SWCAR. However, as detailed, NTD cases are more likely to be re-classified from non-isolated to isolated and there is only 1 mother of Indian ethnicity, and no

mothers of Bangladeshi ethnicity, in the non-isolated category using the EUROCAT algorithm in SWCAR. Any re-classifications for mothers in the White ethnic group in SWCAR are also likely to have little impact due to the size of the population and strong agreement between the two classification systems. It is also of importance to note that the majority of NTD cases re-classified from non-isolated to isolated when going from the EUROCAT algorithm to the aetiological classification system, had no other anomaly subgroup selected in the dataset obtained (17 out of 28). Therefore, to conduct some further exploratory analyses, the aetiological classification system was used for EMSYCAR data and all non-isolated NTD cases in SWCAR where no additional anomaly subgroups had been selected, were re-classified as isolated (to ensure that the NTD prevalence in mothers of White ethnicity for isolated cases in this register is theoretically as high as possible to explore ethnic differences). It was found that although the effect for non-isolated NTD affected pregnancies was more marked: the PRR for non-isolated cases for Indian mothers when compared to mothers of White ethnicity was 2.93 (95% CI: 1.43, 5.98) (p=0.003) and 5.28 for Bangladeshi mothers when compared to mothers of White ethnicity (95% CI: 1.68, 16.58) (p=0.004), an ethnic difference in prevalence was also observed for isolated cases. Specifically, for isolated cases, Indian mothers were 1.60 times more likely (95% CI: 1.00, 2.56) (p=0.05) and Bangladeshi mothers were 2.56 times more likely (95% CI: 1.15, 5.73) (p=0.02) to have an NTD affected pregnancy than mothers of White ethnicity.

5.3.1.1 Conclusions

The EUROCAT multiple congenital anomaly algorithm is an effective and replicable tool for categorising congenital anomaly cases as isolated and non-isolated in analyses with groups unaffected by small numbers. However, when numbers do start to become small in certain groups, analyses using the EUROCAT algorithm categorisation system should be conducted with caution. As shown, analyses based on the EUROCAT algorithm found that it was specifically for non-isolated NTDs that there was an excess NTD prevalence in mothers of Indian and Bangladeshi ethnicity when compared to mothers of White ethnicity. However, this is likely to be a distortion of the true picture, with indications that ethnic differences would

also be observed for isolated cases. As detailed, misclassifications may arise as not all potential multiples will be reviewed by clinicians and geneticists. Dolk and colleagues describe how one of the reasons why cases might be assigned as potential multiples and in fact be isolated is that there is an additional malformation that is not independent of the primary malformation that hasn't been included in the algorithm (135). As shown from the explorations here, a specific example of this is when club foot is the only condition specified in addition to the NTD. Although it could be argued that the way in which the local aetiological variable is generated is less standardised and less widely applicable, its classification of isolated and non-isolated NTD cases is more accurate. It is a shame that a local aetiological variable is not collected by SWCAR and, therefore, in future multivariable analyses around ethnicity, whether the NTD is isolated or not will only be explored in sub-analyses using the EMSYCAR data. There are limitations of this as these sub-analyses will be underpowered and will only be focused on one geographical area, which is very ethnically diverse.

5.3.2 Univariable explorations for ethnicity in the NTD dataset (EMSYCAR and SWCAR)

In preliminary explorations of NTD prevalence using the BINOCAR dataset (Chapter 4) it was found that NTD prevalence was higher in mothers living in more deprived areas and in mothers in the under 20 and 40+ age groups. There were also indications of a discrepancy by sex of fetus, although this is something which is difficult to explore as the majority of anencephaly cases, where specifically a female excess has been previously observed (3), are terminated before sex determination is accurate. Initial univariable explorations around ethnicity and these three variables were conducted primarily in the NTD, pregnancy level, dataset with reference to the denominator dataset where appropriate. Typically, the Chi-Squared Test, and Fischer's Exact Test when cell sizes became too small, were performed in STATA to explore associations.

5.3.2.1 Ethnicity and Deprivation

Results from the 2011 census showed that all ethnic minority groups were more likely to live in more deprived areas than those from the White British ethnic group; deprivation was highest for those of Bangladeshi or Pakistani ethnic origin with more than a third of individuals from these ethnicities living in deprived areas. Those of Indian ethnicity, in contrast, were the least deprived of the ethnic minority groups after White Irish (155). Looking at the birth denominator data obtained from ONS for the study (where deprivation quintile 1 is the most deprived and quintile 5 the least deprived), mothers of Indian ethnicity are concentrated in both quintile 1 and quintile 2 for both the region covered by EMSYCAR and SWCAR. Bangladeshi mothers are concentrated in quintile 1 in the region covered by EMSYCAR; however, for SWCAR, although there are still significantly more births to Bangladeshi mother in the quintile 1 than any other quintile, there is less of a discrepancy between quintile 1, 2 and 3.

Looking just within the BINOCAR NTD dataset, White mothers are more evenly distributed across the different deprivation quintiles in contrast to Pakistani, Bangladeshi, Black Caribbean and Black African mothers who are clearly concentrated in quintile1 (most deprived), although half of White mothers are still within quintile 1 and 2. Indian mothers are concentrated in quintile 1 and 2 ($p=0.004$). No statistically significant differences are detected between maternal ethnicity and deprivation of maternal residence, when breaking the analyses down for anencephaly ($p=0.106$) and spina bifida subtypes ($p=0.193$). However, this could be due to small numbers.

5.3.2.2 Ethnicity and maternal age

Within the NTD dataset, mothers of Indian ethnicity are concentrated in the 25-29 age group and Pakistani mothers in the 25-29 and 30-34 age groups. In contrast, although mothers of White ethnicity aged between 25 and 29 have the highest number of NTD affected pregnancies, there are only slightly less affected

pregnancies in the 20-24 and 30-34 age groups. However, the association between maternal age and ethnicity doesn't reach statistical significance (p=0.09).

Exploring the association between maternal age and ethnicity for anencephaly and spina bifida subtypes separately, for anencephaly affected pregnancies a similar pattern is observed, although the difference still doesn't reach statistical significance (p=0.09). For spina bifida, no statistically significant difference is detected (p=0.27). Despite the fact that there was not found to be a statistically significant association between maternal age and ethnicity, it was still considered an important variable to include in the multivariable model, particularly due to its association with other key variables.

5.3.2.3 Deprivation and maternal age

For NTD affected pregnancies, older mothers are more likely to live in less deprived areas than younger mothers ($p<0.001$). The same effect is observed when looking at anencephaly (p=0.001) and spina bifida affected pregnancies (p=0.001) individually.

5.3.2.4 Ethnicity and sex of baby

A breakdown of the proportion of males and females by maternal ethnicity for pregnancies where the gestation length is eighteen weeks or more in the NTD dataset is given in Table 46. No statistically significant association (p=0.92) between sex and ethnicity is detected, despite the fact that there are equal numbers of males and females born to mothers of White ethnicity in contrast to mothers from most other ethnic groups, where there seems to be a female excess. There is also no statistically significant association for anencephaly affected pregnancies (p=0.67), despite the fact that the sex discrepancy for Indian mothers is more marked, and also for spina bifida affected pregnancies (p=0.66) where the discrepancy for Bangladeshi and Pakistani mothers is more marked. It is a problem that numbers become very small in these analyses. Due to the findings from these explorations and the greatly reduced dataset (particularly for anencephaly affected pregnancy)

that would result from including sex of baby in the analyses, it was not deemed appropriate to include it in the multivariable analyses.

Table 46: Breakdown of sex of baby by maternal ethnicity for NTD affected pregnancies in EMSYCAR and SWCAR, where sex is known and the gestation length is 18 weeks or longer

Ethnicity	Male (%)	Female (%)	Total
White	50.36	49.64	100
Indian	35.71	64.29	100
Pakistani	40	60	100
Bangladeshi	40	60	100
Black Caribbean	33.33	66.67	100
Black African	50	50	100
Other ethnic group	45.45	54.55	100
Total	48.94	51.06	100

5.3.3 Multivariable model exploring the association between ethnicity and NTD prevalence

To explore the mitigating impact of maternal age and deprivation of maternal residence on any observed association between ethnicity (main independent variable) and NTD prevalence (dependent variable) in EMSYCAR and SWCAR, variables were initially added iteratively into a binomial regression model to explore their impact. White, deprivation quintile 1 and maternal age group 25-29 are taken as the reference groups, as in previous analyses. As both deprivation and maternal age were shown to influence observed outcomes, they were adjusted for in the "final" model. To further investigate the complex relationship between ethnicity and deprivation, deprivation quintile was taken out the model as a cofactor and analyses were stratified by deprivation quintile. The model was also stratified by whether the NTD was anencephaly or spina bifida, as the excess NTD prevalence in mothers of Indian ethnicity was shown to be specifically for anencephaly affected pregnancies and in Bangladeshi mothers, for spina bifida affected pregnancies. The model was then further stratified by whether the NTD was isolated or not, in sub-analyses using only the EMSYCAR data (as the aetiological variable is not collected by SWCAR). This analysis was conducted as there were indications that the NTD prevalence discrepancy by ethnicity is more marked for non-isolated cases. Finally, sensitivity analyses were conducted (using EMSYCAR and SWCAR data) to explore

the impact of removing NTD affected pregnancies that occurred as part of a multiple set from the model.

5.3.3.1 Final "all in" model

Table 47 gives both unadjusted prevalence rate ratios e.g. association between ethnicity and NTD prevalence without taking into account other variables and adjusted prevalence rate ratios e.g. the association between ethnicity and NTD prevalence, adjusted for maternal age and deprivation of maternal residence. There is little change to observed associations between ethnicity and NTD prevalence between unadjusted and adjusted models, although there is a slight attenuation of the effect for Bangladeshi mothers in the latter. Specifically, after adjusting for maternal age and deprivation, Indian mothers are still 1.84 times more likely (95% CI: 1.24, 2.73) (p=0.002) and Bangladeshi mothers 2.86 times more likely (95% CI: 1.48, 5.53) (p=0.002) than White mothers to have an NTD affected pregnancy. Holding everything else constant, in the adjusted model, the NTD prevalence in mothers living in deprivation quintile 3, 4 and 5 is statistically significantly lower than mothers living in quintile 1 (most deprived) and deprivation is highly significant in the adjusted model as a whole ($p<0.001$).

Table 47: Binomial regression model to explore the association between ethnicity and NTD prevalence, unadjusted and adjusted for IMD quintile and maternal age for EMSYCAR and SWCAR

Variable	Unadjusted PRR	95% CI	P-value	Adjusted PRR	95% CI	P-value
White (ref)						
Indian	1.86	1.26-2.75		1.84	1.24-2.73	
Pakistani	1.30	0.80-2.11		1.12	0.68-1.85	
Bangladeshi	3.10	1.61-5.97	0.019	2.86	1.48-5.53	0.003
Black Caribbean	1.25	0.52-3.02		1.10	0.46-2.66	
Black African	1.17	0.69-1.99		1.04	0.61-1.77	
Other ethnic group	0.47	0.31-0.72		0.42	0.27-0.66	
IMD quintile 1 (ref)						
IMD quintile 2	0.87	0.72-1.05		0.87	0.71-1.06	
IMD quintile 3	0.74	0.60-0.91	<0.001	0.70	0.56-0.87	<0.001
IMD quintile 4	0.67	0.54-0.83		0.68	0.53-0.85	
IMD quintile 5	0.70	0.56-0.87		0.69	0.54-0.88	
25-29 (ref)						
<20	1.32	1.02-1.72		1.31	0.99-1.74	
20-24	1.03	0.84-1.26		1.01	0.81-1.25	
30-34	0.94	0.78-1.14	0.378	1.04	0.85-1.28	0.367
35-39	1.07	0.87-1.33		1.23	0.98-1.55	
40+	1.14	0.78-1.65		1.32	0.90-1.94	

5.3.3.2 Stratifying by deprivation quintile

When deprivation quintile is removed from the model as a covariate and stratified by, despite births to mothers of Indian ethnicity in the geographical regions covered being concentrated in deprivation quintile 1 and 2, the biggest discrepancy in NTD prevalence between Indian and White mothers is observed in quintile 3 (PRR 2.83; 95% CI: 1.15, 6.93) (Table 48). This accentuates how in order to understand the discrepancy in NTD prevalence between mothers of Indian and White ethnicity,

explorations solely around deprivation are not enough. It is difficult to say anything definitely for Bangladeshi mothers after stratifying by deprivation quintile, due to the small numbers involved.

Table 48: Binomial regression model to explore the association between ethnicity and NTD prevalence, stratified by deprivation quintile and adjusted for maternal age for EMSYCAR and SWCAR

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
	Adjusted PRR (95% CI)	**Adjusted PRR (95% CI)**	**Adjusted PRR (95% CI)**	**Adjusted PRR (95% CI)**	**Adjusted PRR (95% CI)**
White (ref)					
Indian	1.96 (1.00-3.85)	2.29 (1.21-4.36)	2.83 (1.15-6.93)	0.61 (0.09-4.40)	0.52 (0.07-3.76)
Pakistani	1.34 (0.72-2.46)	0.59 (0.15-2.39)	2.32 (0.74-7.31)	0.00	0.00
Bangladeshi	2.91 (1.20-7.08)	2.66 (0.66-10.74)	0.00	9.46 (2.35-38.12)	0.00
Black Caribbean	1.43 (0.53-3.85)	1.10 (0.15-7.87)	0.00	0.00	0.00
Black African	0.98 (0.50-1.92)	0.40 (0.06-2.83)	2.50 (0.62-10.09)	2.02 (0.28-14.45)	1.36 (0.19-9.77)
Other ethnic group	0.18 (0.07-0.49)	0.74 (0.36-1.51)	0.63 (0.23-1.72)	0.60 (0.19-1.88)	0.36 (0.09-1.48)
25-29 (ref)					
<20	1.64 (1.06-2.54)	0.88 (0.47-1.66)	1.58 (0.75-3.34)	1.57 (0.73-3.39)	0.99 (0.30-3.27)
20-24	1.18 (0.82-1.70)	0.87 (0.57-1.34)	1.31 (0.77-2.23)	0.77 (0.41-1.43)	0.95 (0.47-1.91)
30-34	1.07 (0.69-1.64)	1.06 (0.71-1.60)	1.23 (0.76-1.99)	0.82 (0.51-1.32)	0.94 (0.57-1.55)
35-39	2.03 (1.30-3.17)	1.33 (0.83-2.12)	1.17 (0.66-2.05)	0.75 (0.43-1.30)	0.99 (0.57-1.71)
40+	1.13 (0.41-3.13)	1.49 (0.67-3.28)	2.82 (1.41-5.63)	0.67 (0.24-1.88)	0.72 (0.25-2.07)

5.3.3.3 Stratifying by whether the NTD is anencephaly or spina bifida

Carrying out the multivariable binomial regression for anencephaly and spina bifida NTD sub-types separately, as shown in Table 49, after adjusting for deprivation of maternal residence and maternal age, the anencephaly prevalence is still statistically significantly higher in Indian (PRR 2.57; 95% CI: 1.52, 4.34) ($p<0.001$) and the spina bifida prevalence still statistically significantly higher in Bangladeshi (PRR 3.86; 95% CI: 0.72, 8.69) ($p=0.001$) mothers, than mothers of White ethnicity.

Holding everything else constant, deprivation of maternal residence is also highly significant in both the anencephaly and spina bifida models overall (p=0.001). Markedly, for spina bifida affected pregnancies, the prevalence is statistically significantly lower in mothers living in deprivation quintile 2 (PRR 0.70; 95% CI: 0.52, 0.94) (p=0.017), 3 (PRR 0.58; 95% CI: 0.42, 0.81) (p=0.001), 4 (PRR 0.61; 95% CI: 0.44, 0.85) (p=0.004) and 5 (PRR 0.63; 95% CI: 0.45, 0.89) (p=0.008) when compared to quintile 1 (most deprived).

Holding maternal ethnicity and deprivation of maternal residence constant, for anencephaly affected pregnancies, the prevalence is statistically significantly higher in the 40+ age group when compared to those aged 25-29 (PRR 2.02; 95% CI: 1.20, 3.38) (p=0.008) and for spina bifida affected pregnancies, in the 35-39 age group when compared to those aged 25-29 (PRR 1.42; 95% CI: 1.03, 1.97) (p=0.033). It was stated in preliminary analyses (Chapter 4) that an excess NTD prevalence in older mothers is accounted for by chromosomal cases (based on EUROCAT algorithm classification) and when these are removed, an excess is no longer observed. Comparing the aetiological and EUROCAT algorithm classification systems in EMSYCAR specifically for chromosomal cases, there is agreement in all cases. If chromosomal cases from EMSYCAR and SWCAR (n=42) are therefore dropped from the analyses, the excess prevalence in the 35-39 age group when compared to those aged 25-29 for spina bifida affected pregnancies is no longer statistically significant (PRR 1.27; 95% CI: 0.90, 1.78) (p=0.168). This is also true for the excess prevalence in the 40+ age group when compared to those aged 25-29 for anencephaly affected pregnancies (PRR 1.45; 95% CI: 0.81, 2.62) (p=0.213).

Table 49: Binomial regression model to explore the association between ethnicity and NTD prevalence, stratified by whether the NTD is anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR and SWCAR

Variable	Anencephaly			Spina bifida		
	Adjusted PRR	95% CI	P-value	Adjusted PRR	95% CI	P-value
White (ref)						
Indian	2.57	1.52-4.34		1.02	0.48-2.16	
Pakistani	1.00	0.44-2.26		0.98	0.46-2.09	
Bangladeshi	1.50	0.37-6.04	0.037	3.86	0.72-8.69	0.023
Black Caribbean	0.51	0.07-3.63		1.79	0.66-4.81	
Black African	1.06	0.47-2.41		0.87	0.38-1.96	
Other ethnic group	0.43	0.22-0.84		0.37	0.19-0.72	
IMD quintile 1 (ref)						
IMD quintile 2	0.93	0.68-1.26		0.70	0.52-0.94	
IMD quintile 3	0.72	0.51-1.01	0.001	0.58	0.42-0.81	0.001
IMD quintile 4	0.61	0.42-0.88		0.61	0.44-0.85	
IMD quintile 5	0.66	0.45-0.97		0.63	0.45-0.89	
25-29 (ref)						
<20	1.34	0.86-2.09		1.37	0.91-2.05	
20-24	1.20	0.87-1.66		0.95	0.69-1.31	
30-34	1.02	0.74-1.41	0.604	1.15	0.86-1.55	0.383
35-39	1.19	0.83-1.72		1.42	1.03-1.97	
40+	2.02	1.20-3.38		0.86	0.43-1.72	

When deprivation quintile is removed from the anencephaly only model as a cofactor and instead this variable is stratified by, the excess anencephaly prevalence for Indian when compared to White mothers is only observed in quintile 2 (PRR 3.88; 95% CI: 1.77, 8.50) (p=0.001). It is presumably in part a reflection of the underlying population that the excess for Indian mothers is observed in quintile 2, although, as previously detailed, in the ONS birth denominator data mothers of Indian ethnicity were shown to be concentrated in both quintile 1 and 2.

5.3.3.4 *Stratifying by whether the NTD is isolated or not and whether the NTD is anencephaly or spina bifida using only EMSYCAR data*

The multivariable binomial regression models for isolated and non-isolated NTD affected pregnancies in EMSYCAR, which are further stratified by whether the NTD is anencephaly or spina bifida are shown in Table 50 and Table 51. It is difficult to say anything conclusively about the NTD prevalence discrepancy between mothers of Bangladeshi and White ethnicity, particularly for non-isolated NTDs, due to the analyses being underpowered and the very small number of mothers in the former group. The analyses do however indicate an excess of isolated spina bifida affected pregnancies in Bangladeshi mothers when compared to White mothers, after stratifying by maternal age and deprivation of maternal residence (PRR 4.12; 95% CI: 1.52, 11.19) (p=0.005). For mothers of Indian ethnicity, the outcomes in the multivariable model are very interesting: Although for both isolated and non-isolated anencephaly affected pregnancies there is a clear prevalence excess for Indian mothers when compared to White mothers, for the non-isolated group (PRR 7.52; 95% CI: 2.82, 20.09) (p<0.001) the excess is more marked than for the isolated group (PRR 2.44; 95% CI: 1.23, 4.81) (p=0.01).

Holding everything else constant, it is only in the isolated, spina bifida model that deprivation of maternal residence is statistically significant (p=0.002).

Table 50: Binomial regression model to explore the association between ethnicity and NTD prevalence for isolated NTDs, stratified by whether the NTD is anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR

Variable	Anencephaly			Spina bifida		
	Adjusted PRR	**95% CI**	**P-value**	**Adjusted PRR**	**95% CI**	**P-value**
White (ref)						
Indian	2.44	1.23-4.81		0.91	0.34-2.47	
Pakistani	0.69	0.22-2.18		1.11	0.49-2.54	
Bangladeshi	0.00		0.163	4.12	1.52-11.19	0.054
Black Caribbean	0.78	0.11-5.62		1.32	0.33-5.34	
Black African	0.63	0.16-2.57		0.99	0.36-2.71	
Other ethnic group	0.61	0.28-1.30		0.29	0.11-0.79	
IMD quintile 1 (ref)						
IMD quintile 2	0.97	0.64-1.47		0.81	0.55-1.20	
IMD quintile 3	0.66	0.40-1.11	0.166	0.46	0.27-0.77	0.002
IMD quintile 4	0.73	0.44-1.24		0.64	0.40-1.04	
IMD quintile 5	0.78	0.46-1.31		0.54	0.32-0.91	
25-29 (ref)						
<20	2.07	1.17-3.66		1.65	0.95-2.87	
20-24	1.33	0.82-2.15		1.19	0.76-1.85	
30-34	1.25	0.78-2.01	0.965	1.41	0.92-2.17	0.664
35-39	1.86	1.12-3.08		1.59	0.97-2.60	
40+	1.15	0.41-3.26		1.02	0.36-2.86	

Table 51: Binomial regression model to explore the association between ethnicity and NTD prevalence for non-isolated NTDs, stratified by whether the NTD is anencephaly or spina bifida and adjusted for IMD quintile and maternal age for EMSYCAR

Variable	Anencephaly			Spina bifida		
	Adjusted PRR	**95% CI**	**P-value**	**Adjusted PRR**	**95% CI**	**P-value**
White (ref)						
Indian	7.52	2.82-20.09		1.06	0.14-7.80	
Pakistani	2.74	0.63-11.83		0.98	0.13-7.34	
Bangladeshi	7.79	1.03-58.60	0.980	5.70	0.76-42.57	0.382
Black Caribbean	0.00			3.85	0.52-28.68	
Black African	1.91	0.25-14.57		1.33	0.18-10.00	
Other ethnic group	0.51	0.07-3.77		0.00		
IMD quintile 1 (ref)						
IMD quintile 2	1.69	0.69-4.13		0.98	0.39-2.47	
IMD quintile 3	1.25	0.43-3.59	0.186	0.44	0.12-1.59	0.815
IMD quintile 4	1.15	0.37-3.59		0.93	0.33-2.64	
IMD quintile 5	0.47	0.10-2.24		1.09	0.40-2.99	
25-29 (ref)						
<20	0.94	0.20-4.39		0.36	0.05-2.87	
20-24	0.97	0.37-2.58		0.75	0.27-2.08	
30-34	0.59	0.20-1.73	0.102	0.99	0.40-2.47	0.105
35-39	0.70	0.19-2.57		1.40	0.53-3.73	
40+	6.45	2.32-17.93		1.78	0.39-8.20	

5.3.3.5 Removing multiples from the analyses

When the 35 multiple affected pregnancies (22 in EMSYCAR and 13 in SWCAR) are removed from the analyses, there is shown to be very little change to the observed association between ethnicity and NTD prevalence. The NTD prevalence is still statistically significantly higher in Indian (PRR 1.87; 95% CI: 1.25, 2.79) and Bangladeshi (PRR 3.02; 95% CI: 1.56, 5.84) mothers than mothers of White ethnicity, after adjustment for maternal age and deprivation (Appendix D: Table D 7).

5.3.4 Conclusions

Even after adjusting for maternal age and deprivation, the NTD prevalence is still statistically significantly higher in mothers of Indian (p=0.002) and Bangladeshi (p=0.002) ethnicity, than mothers of White ethnicity. This is due to an excess of anencephaly affected pregnancies for Indian mothers and an excess of spina bifida affected pregnancies for Bangladeshi mothers. The small change to the observed association between ethnicity and NTD prevalence after adjustment for deprivation and what is observed after stratifying by, rather than adjusting for, deprivation quintile, suggests that the ethnic discrepancy cannot be explained solely by socio-economic factors.

Sub-analyses conducted, stratifying by whether the NTD is isolated or not, using only the EMSYCAR data (based on the aetiological classification system), indicated that discrepancies in anencephaly prevalence for mothers of Indian and White ethnicity are likely to be attributed more to an increase in non-isolated than isolated cases. It was described in preliminary explorations in Chapter 4 that for non-isolated NTDs there is not shown to be a prevalence discrepancy by deprivation quintile. In the current analyses for ethnicity, stratified by whether the NTD was isolated or not and whether the NTD it was anencephaly or spina bifida, deprivation of maternal residence was only shown to be significant in the isolated, spina bifida model. It has also been reported in the literature that there is a strong correlation between deprivation and folic acid use and that non-isolated NTDs are not expected to decline with folic acid usage (47;48). Thus, although folic acid supplementation is likely to contribute to a reduction in ethnic discrepancies in NTD prevalence, in the population studied, it certainly wouldn't be expected to reduce it entirely.

5.4 Natural History of NTD affected pregnancies in EMSYCAR and SWCAR for mothers from different ethnic communities

5.4.1 Introduction

This section sought to explore whether the proportion of NTD affected pregnancies that result in a termination varies by ethnic group and therefore, how different prevalence estimates might distort the picture by ethnicity. However, the reasons for carrying out these analyses also went beyond this, namely, to form a basis for and complement further exploration, through semi-structured interviews, of why women from different ethnic groups decide to continue their NTD affected pregnancy or not.

As described in the introduction to this thesis (Chapter 2), previous research has shown that mothers of Pakistani ethnicity are less likely than mothers of White and Indian ethnicity to terminate a pregnancy affected by a congenital anomaly (92). It has also been shown that less educated Pakistani mothers would have terminations for fewer conditions than White mothers. However, for anencephaly, all women were in favour of termination regardless of their ethnicity or education level (91).

Key variables in the analyses in this section, but not introduced previously, are detailed in Table 52, with a breakdown of the missing data for each by register. In line with analyses in the previous section of this chapter, this section only includes data from EMSYCAR and SWCAR.

Table 52: Missing data for additional variables by register

Register name (short name)	Number of NTD cases notified between 2006 and 2011 (based on Feb 2014 EUROCAT update)	% missing for NTD cases			
		Birth type	Gestation length in complete weeks	Timepoint of discovery	Gestational age at discovery, if prenatally diagnosed
East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR)	511	0	0.59	2.15	2.49
Northern Congenital Abnormality Survey (NorCAS)	288	0	0.35	0	1.43
Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)	216	0	0.93	0.46	0
South West Congenital Anomaly Register (SWCAR)	326	0	1.84	5.52	9.12
Congenital Anomaly Register and Information Service for Wales (CARIS)	303	0	0.33	0	0.7

5.4.2 Preliminary analyses

5.4.2.1 Birth type

Looking within the BINOCAR NTD dataset, a breakdown of the proportion of pregnancies resulting in each of the different pregnancy outcomes (live birth, still

birth, late miscarriage, TOPFA) is given in Figure 23. Mothers of Indian, Pakistani and Bangladeshi ethnicity have been combined as "Asian" and mothers of Black Caribbean and Black African ethnicity combined as "Black" which is an oversimplification but demonstrates the proportion of pregnancies resulting in still birth or late miscarriage for these aggregated ethnic groups. However, as shown in Table 53, across the EMSYCAR and SWCAR there are only 5 NTD affected pregnancies that result in a late miscarriage and only 22 that result in a stillbirth and so it is not possible to draw definite conclusions about ethnic variation.

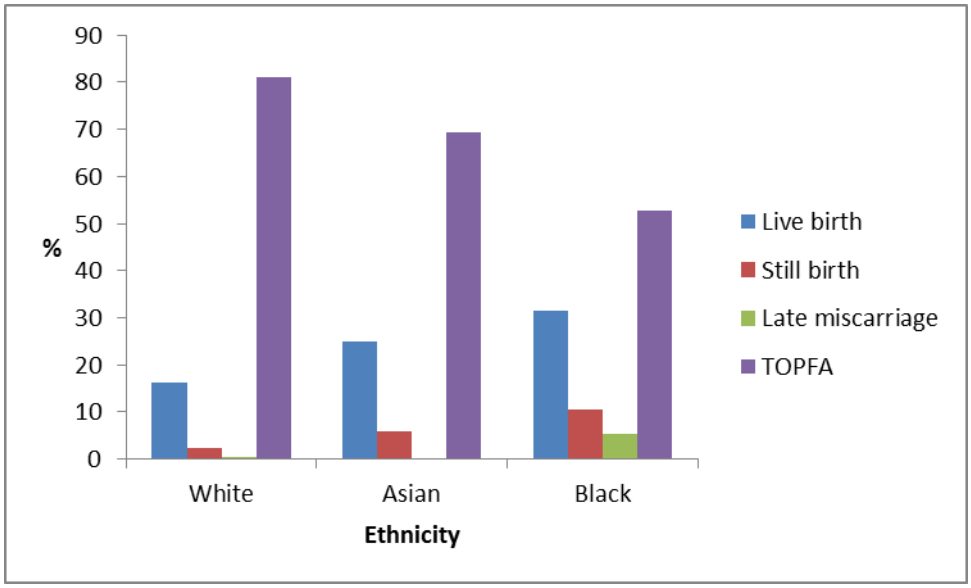

Figure 23: NTD pregnancy outcomes by maternal ethnicity

Table 53: Breakdown for different pregnancy outcomes in the NTD dataset for EMSYCAR and SWCAR

Birth type	Number (%)
Live birth	155 (18.52)
Still birth (24+ weeks)	22 (2.63)
Late miscarriage (20-23 weeks)	5 (0.60)
TOPFA	655 (78.26)
Total	837 (100)

To facilitate further analysis, the NTD dataset was dichotomised into pregnancies that resulted in TOPFA and those that did not. This was due to small numbers for still births and particularly late miscarriages. Moreover, in more than 90% of pregnancies that result in a termination, the NTD has been detected by 21 weeks gestation and since 90% of these are terminated within 2 weeks of being detected, pregnancies that result in a stillbirth (from 24 weeks) are most likely to occur once

the decision has been made to continue the pregnancy. Additionally, although the majority (n=777; 93%) of NTD affected pregnancies are discovered prenatally, there are some that are discovered at birth (n=30; 4%); one postnatally and 29 cases where the time point of discovery is unknown. Therefore, only the 777 discovered prenatally in EMSYCAR and SWCAR have been included in subsequent analyses in this section.

5.4.2.2 NTD type

A breakdown of the number and proportion of different NTD subtypes resulting in TOPFA or not in the BINOCAR dataset is given in Table 54. Anencephaly affected pregnancies are more likely to be terminated than spina bifida affected pregnancies ($p<0.001$). This is not surprising as anencephaly is a more severe phenotype and not compatible with life after birth. Anencephaly also tends to be detected earlier than spina bifida with a peak in detection for the former around the 12 week scan and a peak for the latter around the 20 week scan. However, TOPFA rates for spina bifida affected pregnancies are still high (79% terminated) (Table 54).

Table 54: Number and proportion of prenatally detected NTD affected pregnancies that are terminated or not for different NTD subtypes in EMSYCAR and SWCAR

NTD	Not TOPFA n (%)	TOPFA n (%)
Anencephaly	34 (9.74)	315 (90.26)
Encephalocele	15 (19.48)	62 (80.52)
Spina bifida	73 (20.80)	278 (79.20)
Total	122 (15.70)	655 (84.30)

Therefore, as in previous analyses, primarily, outcomes have been presented for total NTD cases (anencephaly, encephalocele and spina bifida) and then for anencephaly and spina bifida subtypes separately, where appropriate.

5.4.3 Univariable analyses for an exploration of the association between maternal ethnicity and whether an NTD affected pregnancy is terminated or not

In addition to Smith and colleagues finding an ethnic discrepancy in whether individuals terminated a pregnancy affected by a congenital anomaly or not, as detailed in section 5.4.1, they also found that maternal deprivation, maternal age and gestation at which the anomaly is detected affected the outcome (92). Thus, univariable analyses were conducted exploring the association between ethnicity, whether the NTD affected pregnancy was terminated or not and these other factors using the EMSYCAR and SWCAR data, to explore their likely impact in the multivariable model. Explorations around sex of fetus were also conducted using data from both registers and explorations around whether the NTD was isolated or not were conducted using the aetiological variable in the EMSYCAR dataset. As in previous univariable analyses, typically the Chi-Squared Test, and Fischer's Exact Test when cell sizes became too small, were performed in STATA to explore associations.

A breakdown of the proportion of NTD affected pregnancies that result in TOPFA or not for individual ethnic groups is shown in Figure 24. Mothers of Pakistani and Black African ethnicity are statistically significantly less likely to terminate their pregnancy than mothers of White ethnicity ($p<0.001$). Looking at spina bifida and anencephaly affected pregnancies separately, the discrepancy between Pakistani and White mothers is statistically significant for both subtypes but most marked for spina bifida, where 33% of mothers of Pakistani ethnicity terminate an affected pregnancy when compared to 81% of mothers of White ethnicity ($p=0.003$). For anencephaly, 71% of mothers of Pakistani ethnicity and 92% of mothers of White ethnicity terminate an affected pregnancy ($p=0.017$). However, numbers do start to become quite small in these sub-analyses.

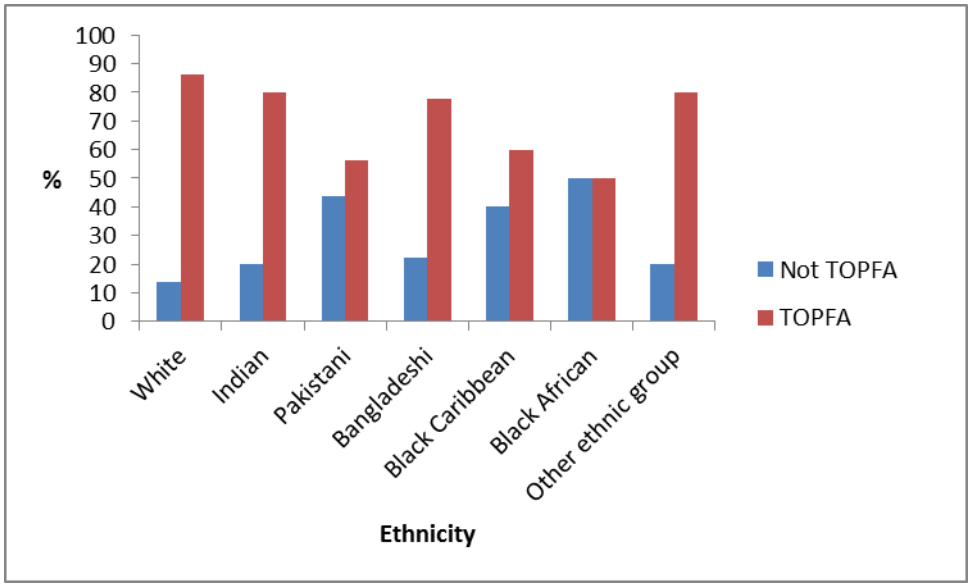

Figure 24: Proportion of NTD affected pregnancies resulting in TOPFA or not for different ethnic groups in EMSYCAR and SWCAR

5.4.3.1 Deprivation

As previously described, there is a strong association between ethnicity and deprivation in the NTD dataset (p=0.005) with mothers of Pakistani and Black African ethnicity clearly concentrated in areas with greater deprivation. No statistically significant differences were detected when looking at anencephaly and spina bifida subtypes specifically; however, as argued, this could be due to small numbers.

The association between deprivation and whether the NTD affected pregnancy is terminated or not, is also statistically significant, with mothers living in areas of greater deprivation less likely to terminate their pregnancy than mothers living in areas of less deprivation (p<0.001); e.g. 93% of mothers living in quintile 5 (least deprived) decided to terminate their NTD affected pregnancy in contrast to 76% of mothers in quintile 1 (most deprived) This pattern is strongly apparent for the spina bifida subtype particularly (p=0.011); for the anencephaly subtype, although there is a statistically significant difference, the difference between mothers living in quintile 5 (least deprived) and quintile 1 (most deprived) is less marked (p=0.041).

5.4.3.2 Gestation, in weeks, at which the NTD is discovered

There are no statistically significant differences in the mean age of discovery, in weeks, between any of the ethnic groups.

However, the mean age of discovery is statistically significantly earlier in pregnancies that result in TOPFA (16.30; 95% CI: 15.99, 16.61) than those that do not (19.94; 95% CI: 19.04, 20.84). This is more pronounced for anencephaly ((TOPFA – 13.77 (95% CI: 13.42, 14.12) and not TOPFA – 17.67 (95% CI: 15.61, 19.73)) than spina bifida ((TOPFA – 19.21 (95% CI: 18.86, 19.56) and not TOPFA – 20.87 (95% CI: 19.93, 21.81)).

5.4.3.3 Gestation, in weeks, at which the NTD is discovered and deprivation of maternal residence

The mean age of discovery, in weeks, is statistically significantly earlier in mothers living in quintile 5 (least deprived) (15.87; 95% CI: 15.08, 16.66) when compared to those living in quintile 1 (most deprived) (17.33; 95% CI: 16.75, 17.91). This statistical difference is observed in anencephaly affected pregnancies only ((Quintile 5 - 13.02 (95% CI: 12.20, 13.84) and Quintile 1 - 14.91 (95% CI: 14.09, 15.73)) and no statistically significant differences are observed for spina bifida.

5.4.3.4 Maternal age

No statistically significant association is detected between maternal ethnicity and age for all NTDs or for anencephaly and spina bifida subtypes separately.

There is also no statistically significant association between maternal age and whether the NTD affected pregnancy is terminated or not (p=0.313)), and this is also observed when looking at anencephaly (p=0.155) and spina bifida (p=0.609) subtypes separately.

5.4.3.5 Maternal age and deprivation of maternal residence

As previously stated, there is a strong association between maternal age and deprivation of maternal residence, with older mothers living in less deprived areas ($p<0.001$); for example, 16% of mothers aged 40+ live in quintile 1 (most deprived) when compared to 52% of mothers under 20. Looking at anencephaly ($p=0.002$) and spina bifida ($p=0.004$) affected pregnancies individually, the same pattern is observed.

5.4.3.6 Sex of baby

As described for previous analyses, sex of baby is very difficult to explore in the current dataset as there is a high proportion of missing data, a disproportionate amount of which is anencephaly due to the earlier detection. No association is detected between ethnicity and sex of baby, in line with what was found previously, in a dataset restricted to cases discovered prenatally and only those of known sex reaching a gestation length of 18 weeks or longer (when sex determination is better) ($p=0.866$). There is also no association detected when looking at anencephaly and spina bifida subtypes individually.

No statistically significant association is detected between sex of baby and whether the pregnancy is terminated or not ($p=0.560$). This is also true when looking at spina bifida ($p=0.338$) and anencephaly affected pregnancies ($p=0.622$) individually. Due to the lack of association and a markedly reduced dataset that would result from including sex, it has not been included in multivariable analyses.

5.4.3.7 Whether the NTD is isolated or not

Using the aetiological classification system within EMSYCAR, there is no statistically significant association between whether the NTD is isolated or not and whether the pregnancy is terminated or not ($p=0.595$). This is also observed when looking at anencephaly ($p=0.299$) and spina bifida ($p=0.554$) subtypes separately. Using this restricted dataset, there is not shown to be any association between

maternal ethnicity and whether the NTD is isolated or not for all NTD subtypes combined (p=0.239). This is also the case for spina bifida affected pregnancies specifically (p=0.977), and there is only 1 Indian mother, 1 Pakistani mother, 1 Bangladeshi mother, 1 Black Caribbean mother and 1 Black African mother in the non-isolated spina bifida group. For anencephaly affected pregnancies, the association is of borderline statistical significance (p=0.062) with 36% of Indian mothers having a non-isolated anencephaly affected pregnancy when compared to 15% of White mothers.

5.4.4 Multivariable analyses exploring the association between ethnicity and whether an NTD affected pregnancy is terminated or not using a logistic regression model

For multivariable analyses, a logistic regression model, with effect sizes expressed as an odds ratio (OR), using the EMSYCAR and SWCAR data, was built up with whether the pregnancy was terminated or not as the binary outcome variable and maternal ethnicity as the main independent variable. To explore the mitigating impact of maternal deprivation, maternal age, NTD type (anencephaly, encephalocele or spina bifida) and gestational age at which the NTD was discovered, on this association, these variables were first added iteratively into the logistic regression model. White maternal ethnicity and maternal age group 25-29 were taken as reference groups as per previous analyses. For NTD type, spina bifida was taken as the reference group as it is the most common NTD. Due to the strong association between maternal deprivation and maternal age and maternal deprivation and gestational age at discovery of the NTD, as described, interaction terms were placed between these two sets of variables and explored. The "final" multivariable model was then built-up, with further stratification by whether the NTD was anencephaly or spina bifida, due to the differences in outcome for the two NTD types observed in the univariable analyses. Sub-analyses using only the EMSYCAR data and stratifying by whether the NTD was isolated or not (based on the aetiological variable) were conducted where it was deemed appropriate and was feasible. Finally, sensitivity analyses were conducted using data from both registers to explore the impact of removing NTD affected pregnancies that occurred

as part of a multiple set from the model (there were 34 multiple pregnancies across EMSYCAR and SWCAR in which the NTD was diagnosed prenatally).

5.4.4.1 An Iterative model

Of importance to note in the iterative explorations, is that the addition of maternal deprivation to a maternal ethnicity and whether the pregnancy was terminated or not only model, was shown to improve it (p=0.007) (based on a likelihood ratio test used to explore model fit with and without deprivation). However, there was only a slight attenuation in the observed association between ethnicity and whether the pregnancy was terminated or not, when maternal deprivation was added. The addition of gestational age at which the NTD was discovered to the model, was also shown to improve it (p<0.001) (again based on a likelihood ratio test comparing model fit with and without this variable). The addition of gestational age of discovery was actually shown to mildly increase the ethnic discrepancy in pregnancy outcome. Although neither NTD type nor maternal age were shown to improve the model fit when added (p=0.780 and p=0.200, respectively, using a likelihood ratio test) both were included in the final model as they are important variables.

5.4.4.2 Exploring variable interactions

The addition of an interaction term between deprivation and maternal age, comparing a model with the interaction term and one without it, using the likelihood ratio test, was not shown to improve it (p=0.583). Doing the same for deprivation and age of discovery, an interaction term is not shown to improve the model in any way (p=0.996).

Putting an interaction term between ethnicity and deprivation (due to the strong association) was not possible as many outcomes are omitted due to the strong collinearity.

Therefore, in the final model, no interaction terms have been included.

5.4.4.3 Final model

Table 55 gives both unadjusted odds ratios e.g. association between maternal ethnicity and whether the pregnancy was terminated or not without taking into account other factors and adjusted odds ratios e.g. the association between ethnicity and whether the pregnancy was terminated or not, adjusted for maternal deprivation, maternal age, NTD type (anencephaly, encephalocele or spina bifida) and gestational age at discovery (in weeks). In the adjusted model, Pakistani (OR 0.16; 95% CI: 0.05, 0.52) (p=0.002) and Black African (OR 0.14; 95% CI: 0.04, 0.49) (p=0.002) mothers are statistically significantly less likely to terminate their pregnancy than White mothers. The effect sizes for Pakistani and Black African mothers differ very little between unadjusted and adjusted models and in fact are slightly stronger in the latter. In the adjusted model, holding everything else constant, mothers living in deprivation quintile 4 are more likely than mothers living in quintile 1 (most deprived) to terminate an NTD affected pregnancy (OR 2.75; 95% CI: 1.18, 6.41) (p=0.019). Maternal deprivation is shown to be highly significant in the adjusted model as a whole (p=0.001). The same is true of gestational age at discovery of the NTD (p<0.001), with pregnancies in which the NTD is discovered earlier being more likely to be terminated (OR 0.82; 95% CI: 0.77, 0.88). Although maternal age is not shown to be significant in the multivariable model overall (p=0.387), there is weak evidence that mothers aged 20-24 are less likely than mothers aged 25-29 to terminate an NTD affected pregnancy (p=0.048).

Table 55: Logistic regression model exploring the association between maternal ethnicity and whether the NTD affected pregnancy is terminated or not, unadjusted and adjusted for NTD type; maternal age; age, in weeks, at which the NTD is discovered; and deprivation of maternal residence for EMSYCAR and SWCAR

Variable	Unadjusted Odds Ratio	95% CI	P-value	Adjusted Odds Ratio	95% CI	P-value
White (ref)						
Indian	0.63	0.23-1.73		1.31	0.32-5.35	
Pakistani	0.20	0.07-0.56		0.16	0.05-0.52	
Bangladeshi	0.55	0.11-2.72	0.001	0.61	0.11-3.36	0.007
Black Caribbean	0.24	0.04-1.44		0.19	0.02-1.74	
Black African	0.16	0.05-0.46		0.14	0.04-0.49	
Other ethnic group	0.63	0.21-1.94		0.81	0.20-3.26	
Spina bifida (ref)						
Anencephaly	2.43	1.57-3.77	<0.001	1.08	0.59-1.96	0.672
Encephalocele	1.09	0.58-2.02		0.77	0.35-1.69	
25-29 (ref)						
<20	0.82	0.39-1.75		1.28	0.49-3.39	
20-24	0.59	0.34-1.03		0.51	0.26-0.99	
30-34	1.02	0.58-1.79	0.114	1.02	0.51-2.02	0.387
35-39	1.14	0.59-2.22		1.04	0.46-2.34	
40+	0.86	0.31-2.41		1.40	0.28-7.02	
Age, in weeks, at discovery	0.82	0.78-0.87	<0.001	0.82	0.77-0.88	<0.001
IMD quintile 1 (ref)						
IMD quintile 2	1.69	1.02-2.81		1.61	0.85-3.05	
IMD quintile 3	1.7	0.98-2.95	<0.001	1.40	0.71-2.76	0.001
IMD quintile 4	2.85	1.46-5.59		2.75	1.18-6.41	
IMD quintile 5	4.05	1.85-8.86		2.49	0.96-6.50	

5.4.4.4 Stratification by NTD type

The multivariable logistic regression outcomes for anencephaly and spina bifida subtypes separately (with NTD type removed as a cofactor) are shown in Table 56.

It is in the anencephaly (p=0.048) rather than spina bifida (p=0.190) only model that ethnicity is shown to be significant overall. However, this is misleading as it is in fact spina bifida affected pregnancies that are statistically significantly less likely to be terminated by mothers of Pakistani (OR 0.15; 95% CI: 0.02, 0.93) (p=0.042) and Black African (OR 0.15; 95% CI: 0.02, 0.93) (p=0.042) ethnicity than mothers of White ethnicity. The effect sizes for Pakistani and Black African mothers are still quite large for anencephaly affected pregnancies, and the OR for Black African mothers for anencephaly (0.13) is actually very similar to that for spina bifida (0.15) affected pregnancies. Again the lack of significance could be due to small numbers, although there are a similar number of affected pregnancies in the anencephaly and spina bifida subgroups and there is a stronger OR for Pakistani mothers in the latter.

Holding everything else constant, pregnancies where the NTD is discovered earlier are more likely to be terminated in both the anencephaly ($p<0.001$) and spina bifida (p=0.007) model. Deprivation of maternal residence is significant only in the spina bifida model (p=0.003), with mothers living in quintile 5 (least deprived) being more likely to terminate their pregnancy than mothers living in quintile 1 (most deprived) (OR 4.16; 95% CI: 1.12, 15.45) (p=0.033). The effect size for age of discovery is greater in the anencephaly (OR 0.79; 95% CI: 0.70, 0.89) than spina bifida (OR 0.88; 95% CI: 0.80, 0.97) model and when adding in variables iteratively to the spina bifida model, it has little impact on the observed association between ethnicity and whether the pregnancy is terminated or not. As previously described, there is no detected association between ethnicity and age at which an NTD is discovered. Also, the mean age of discovery is only statistically significantly earlier in those living in more deprived areas when compared to those living in less deprived areas, for anencephaly and not spina bifida affected pregnancies. Age of discovery, therefore, seems to provide little insight into why Pakistani and Black African mothers are less likely to terminate a spina bifida affected pregnancy than White mothers.

Table 56: Logistic regression model exploring the association between ethnicity and whether the NTD affected pregnancy is terminated or not, stratified by whether the NTD is anencephaly or spina bifida and adjusted for maternal age; age, in weeks, at which the NTD is discovered and deprivation of maternal residence for EMSYCAR and SWCAR

Termination	Anencephaly			Spina bifida		
	Adjusted Odds Ratio	**95% CI**	**P-value**	**Adjusted Odds Ratio**	**95% CI**	**P-value**
White (ref)						
Indian	1.55	0.17-14.34		1.00		
Pakistani	0.23	0.03-1.86		0.15	0.02-0.93	
Bangladeshi	0.18	0.00-13.75	0.048	1.17	0.13-10.92	0.19
Black Caribbean	1.00			0.18	0.01-2.18	
Black African	0.13	0.01-1.54		0.15	0.02-0.93	
Other ethnic group	0.31	0.04-2.29		1.94	0.20-18.48	
25-29 (ref)						
<20	5.19	0.49-55.51		0.82	0.25-2.69	
20-24	0.62	0.20-1.99		0.59	0.23-1.47	
30-34	2.23	0.48-10.33	0.302	0.73	0.30-1.78	0.889
35-39	1.94	0.35-10.71		0.79	0.29-2.16	
40+	3.15	0.25-39.26		1.03	0.11-9.55	
Age, in weeks, at discovery	0.79	0.70-0.89	<0.001	0.88	0.80-0.97	0.007
IMD quintile 1 (ref)						
IMD quintile 2	1.31	0.41-4.18		1.86	0.80-4.33	
IMD quintile 3	1.41	0.38-5.22	0.136	1.57	0.64-3.87	0.003
IMD quintile 4	1.00			2.07	0.80-5.32	
IMD quintile 5	1.45	0.26-8.06		4.16	1.12-15.45	

5.4.4.5 Isolated spina bifida affected pregnancies in EMSYCAR

As described in the univariable analyses, looking at the aetiological variable in the EMSYCAR dataset, there are very few mothers in ethnic groups other than White for the non-isolated spina bifida affected pregnancies. In the multivariable non-isolated spina bifida model all cells for mothers of non-White ethnic groups when compared to mothers of White ethnicity have an odds ratio of 1 and there is no

confidence interval (as there is only 1 mother in each of these non-White ethnic groups). Therefore, only the isolated spina bifida multivariable model is shown in Table 57.

After adjusting for gestational age at discovery, maternal age and deprivation of maternal residence, Pakistani mothers are statistically significantly less likely to terminate an isolated, spina bifida affected pregnancy than White mothers (OR 0.07; 95% CI: 0.01, 0.75) (p=0.028). The difference for Black African and White mothers is not statistically significant, although the effect size is still quite large (OR 0.17). Holding everything else constant in the model, the discrepancy between quintile 5 and quintile 1 in whether the isolated, spina bifida affected pregnancy is terminated or not is only of borderline statistical significance (OR 6.97; 95% CI: 0.80, 60.92) (p=0.079). However, this could be due to small numbers. Interestingly, gestational age at discovery is not statistically significant in this model.

Table 57: Logistic regression model exploring the association between ethnicity and whether the isolated, spina bifida affected pregnancy is terminated or not, and adjusted for maternal age; age, in weeks, at which the NTD is discovered and deprivation of maternal residence for EMSYCAR

Termination	Spina bifida (isolated)		
	Adjusted Odds Ratio	**95% CI**	**P-value**
White (ref)			0.052
Indian	1.00		
Pakistani	0.07	0.01-0.75	
Bangladeshi	1.01	0.09-11.52	
Black Caribbean	1.00		
Black African	0.17	0.01-2.00	
Other ethnic group	0.90	0.06-12.97	
25-29 (ref)			0.317
<20	1.04	0.18-6.11	
20-24	0.38	0.10-1.45	
30-34	0.53	0.14-2.04	
35-39	0.41	0.09-1.80	
40+	0.27	0.02-3.92	
Age, in weeks, at discovery	0.90	0.78-1.03	0.116
IMD quintile 1 (ref)			0.016
IMD quintile 2	2.76	0.90-8.43	
IMD quintile 3	3.95	0.73-21.46	
IMD quintile 4	1.98	0.56-7.07	
IMD quintile 5	6.97	0.80-60.92	

5.4.4.6 Removing multiples pregnancies from final multivariable model using EMSYCAR and SWCAR data

No major changes to the final multivariable model are observed when multiple pregnancies are removed from the analyses, apart from the difference between deprivation quintile 5 and quintile 1 (most deprived) now becomes significant (p=0.046) (Appendix D: Table D 8).

5.4.5 Conclusions

It has been shown in the multivariable logistic regression model, using EMSYCAR and SWCAR data, that Pakistani (OR 0.16; 95% CI: 0.05, 0.52) (p=0.002) and Black African (OR 0.14; 95% CI: 0.04, 0.49) (p=0.002) mothers are less likely than White mothers to terminate their pregnancy, when it is discovered that their child has an

NTD. This is after adjustment for maternal age, NTD type, age of discovery and deprivation quintile of maternal residence. NTD prevalence estimates that do not include terminations are therefore likely to distort the picture for ethnicity, for settings such as the UK, as well as greatly underestimating the "true" prevalence.

When stratifying the analyses by whether the NTD was spina bifida or anencephaly, in line with what was reported by Hewison and colleagues (91), for anencephaly no statistically significant differences on the basis of ethnicity or deprivation were observed. However, Black African mothers had TOPFA rates of a similar magnitude lower than White mothers for both spina bifida and anencephaly affected pregnancies, although only for the former was the difference statistically significant (p=0.042). Although small numbers could play a part in this, it also could indicate that mothers of Black African ethnicity are less likely to terminate a pregnancy affected by a fetal anomaly, regardless of the severity of the condition. For spina bifida affected pregnancies, which have a less severe phenotype and are usually compatible with postnatal survival, TOPFA rates were also statistically significantly lower in Pakistani than White mothers (p=0.042) and in those living in the most deprived when compared to the least deprived quintile (p=0.033).

When stratifying spina bifida affected pregnancies into those that are isolated and non-isolated, using only the EMSYCAR data, although it was not possible to say anything about the non-isolated cases, due to the small numbers, the isolated model was very interesting. Holding everything else constant, it was solely Pakistani mothers who were shown to be statistically significantly less likely to terminate an isolated spina bifida affected pregnancy than mothers of White ethnicity (p=0.028). Additionally, the discrepancy between the most deprived and least deprived deprivation quintile in this model was only of borderline statistical significance (p=0.079) and critically, although highly statistically significant in all previous explored models, in this model gestational age at discovery was not significant. Although strongly associated with whether a NTD affected pregnancy is terminated or not, the timing of provision of information about an NTD diagnosis seems to provide little explanation for ethnic variations in pregnancy outcome. It is difficult to disentangle the complex relationship between ethnicity and deprivation, due to the strong collinearity between the two variables. However, the fact that ethnic

differences in whether a pregnancy is terminated or not are still observed when maternal deprivation is added to the regression model, which is particularly strongly apparent in the isolated spina bifida model, indicates that factors other than maternal deprivation underlie ethnic variations.

The decision around whether to continue an NTD affected pregnancy has been explored in further depth in the qualitative research (Chapter 6).

5.5 Chapter Summary and Important Points to Take Forward

- Due to a high proportion of missing ethnicity data in NorCAS, CAROBB and CARIS, and due to indications of bias/imprecision that would be introduced into the analyses if missing data was simply ignored, complete case analyses were only carried out using EMSYCAR and SWCAR.

- There was shown to be a clear NTD prevalence excess in Indian (anencephaly) and Bangladeshi (spina bifida) mothers when compared to mothers of White ethnicity, after adjusting for maternal age and deprivation of maternal residence. It was also hypothesised, based on the limited available literature, that there would be an excess in Pakistani mothers but this was not detected (and was not attributed to small numbers).

- There were also indications that the anencephaly prevalence excess for Indian mothers was particularly marked for non-isolated NTDs, which are unlikely to decrease with folic acid supplementation.

- Maternal BMI is not collected with sufficient completion by either EMSYCAR or SWCAR and therefore could not be explored further.

- Mothers of Pakistani and Black African ethnicity were shown to be less likely than mothers of White ethnicity to terminate their pregnancy when it was discovered that their child had an NTD, after adjusting for NTD type,

maternal age, gestational age at which the NTD was discovered and deprivation of maternal residence.

- After stratifying by whether the NTD is anencephaly or spina bifida and adjusting for all other factors, it is specifically for spina bifida affected pregnancies that mothers of Pakistani and Black African ethnicity are less likely to terminate their pregnancy. After further stratification, for isolated spina bifida affected pregnancies (those that do not occur in association with other defects), the difference is only statistically significant for Pakistani mothers. Age of discovery does little to explain observed ethnic discrepancies and socio-economic factors are unlikely to be the whole story.

- Explorations around folic acid use and decisions around whether to continue an NTD affected pregnancy or not has been explored further in the qualitative study detailed in Chapter 6.

6 Exploring the pre-pregnancy and pregnancy knowledge, attitudes and health behaviour of South Asian mothers with a previous neural tube defect (NTD) affected pregnancy

6.1 Introduction

Several studies have been conducted exploring the knowledge and peri-conceptional use of folic acid of women of childbearing age in diverse populations. Poor knowledge of the benefits of taking folic acid, specifically its role in NTD prevention, in women of childbearing age is consistently reported in the literature (37;97;102;156). The pregnancy being unintended; young maternal age; being of a low socio-economic status and being of non-White/non-Western ethnicity are typically described as being associated with low knowledge and use (22;37;93;103;157-161). Previous research conducted as part of this doctoral thesis (22), a systematic review exploring knowledge and use of folic acid in women from different ethnic communities in the UK (Appendix A), found, from the limited available evidence, that mothers of South Asian ethnicity have lower knowledge and peri-conceptional use of folic acid than mothers of Caucasian[1]/White ethnicity. A synthesis of results in a meta-analysis found that mothers of Caucasian/White ethnicity are more than three times more likely to take folic acid before conception than mothers of non-Caucasian/non-White ethnicity (22). A further study conducted in the UK after this systematic review was published, also found that mothers of Caucasian ethnicity were more likely to take folic acid before pregnancy than mothers of non-Caucasian ethnicity (103).

No previous research in the UK, or elsewhere based on an extensive literature search, has been conducted into the pre-pregnancy knowledge and health behaviours, particularly with regards to folic acid, of individuals with a previous NTD affected pregnancy. Preliminary findings from a quantitative study, exploring NTD epidemiology in different ethnic communities in the UK and conducted

[1] Caucasian is the term typically used throughout the systematic review and equates to "White" in the British Isles Network of Congenital Anomaly Registers (BINOCAR) data used for the quantitative study for this thesis.

concurrently with this qualitative research (results are described in depth in Chapters 4 and 5) found an increased prevalence in mothers of Indian and Bangladeshi ethnicity when compared to mothers of White ethnicity using data from the East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR) and South West Congenital Anomaly Register (SWCAR) (detailed in Chapter 5). No explorations around folic acid knowledge and use were possible in this study due to insufficient data quality. An increased NTD prevalence in mothers of Pakistani ethnicity has also been previously reported by Tonks and colleagues for another region of the UK (82).

Perceived quality of life/severity of condition (162-167) involvement of the CNS (92;168); religious or personal belief (163;169-171); feeling a strong prenatal attachment ((169;172); gestation at which anomaly is detected (92;173); maternal age (168); maternal education (91); maternal deprivation ((92;165) and maternal ethnicity (92) have all been described as important factors affecting a decision of whether to continue a pregnancy or not when a fetal anomaly is detected. Smith and colleagues (92), when exploring outcomes for pregnancies affected by congenital anomalies using data from the EMSYCAR, found that Pakistani mothers have lower rates of TOPFA than White British and Indian mothers. In the second set of analyses exploring ethnicity in the quantitative study for this thesis (detailed in Chapter 5), it was found that mothers of Pakistani and Black African ethnicity were less likely than mothers of White ethnicity to terminate a spina bifida affected pregnancy. This difference was statistically significant, even after adjusting for maternal age and deprivation and gestation at which the anomaly was detected.

The aim of the qualitative research was to conduct more in-depth explorations around the pre-pregnancy and pregnancy views and experiences of mothers with a previous NTD affected pregnancy. The research was focused specifically on mothers of South Asian (Indian, Bangladeshi and Pakistani) ethnicity. Mothers of Indian and Bangladeshi ethnicity were included in the qualitative study, due to the detected increased NTD prevalence in the quantitative research. Pakistani mothers were included due to the increased NTD prevalence in this ethnic group reported in the literature and the fact that Pakistani mothers were less likely than White mothers to terminate an NTD affected pregnancy in the quantitative study.

Restricting the qualitative study to mothers of South Asian ethnicity meant that in-depth interviews could be conducted with ethnic communities where a high NTD prevalence has been detected and also the importance of specific cultural and dietary factors could be explored.

6.2 Methodology

6.2.1 Background

As stated in Chapter 3, the grounded theory method was used to conduct and analyse the qualitative research. The grounded theory method is inductive, it is routed in the data and everything comes from the data. It is concerned not only with the "how" but also the "why"(174). The method involves being iterative, moving between collecting data and analysis and coding the data in a constant comparative fashion (data are continually compared with data). The development of coding and initial categories are further developed and fine-tuned through going back to the field and collecting more data from existing or new participants. Ultimately, core conceptual categories are raised to a theoretical level (175).

In her book "Constructing Grounded Theory" Kathy Charmaz distinguishes between Objectivist and Constructivist Grounded Theory. Classical objectivist grounded theory is described as adhering strictly to grounded theory steps and erasing the social context underlying the data. The researcher also remains separate and distant from research participants and doesn't take an interpretive stance. Constructivist Grounded Theory, on the other hand, acknowledges that resulting theory is interpretation and depends on the researcher's view; it emphasises the importance of context and reflexivity about own (researcher) interpretations. Charmaz underlines how she draws comparisons for clarity's sake, and that in reality "theorizing means being eclectic, drawing on what works, defining what fits." (175). Mills and colleagues describe a traditional (Glaser) and evolved (Strauss and Corbin) grounded theory, with the latter not believing there is a pre-existing reality, stressing the importance of context and the involvement of the researcher (176). They describe how Constructivist Grounded Theory can be traced from the work of Strauss and Corbin and subsequently through the work of Charmaz. They argue, as Charmaz does, that "all variations of grounded theory exist on a methodological spiral and reflect their epistemological underpinnings"(176).

In their defence of the classical objective stance, Breckenridge and colleagues argue that it is not that participants' perspectives are not important but are incorporated into the research as more data to be analysed and explored with the aim of raising them to a conceptual level (177). It is described how Glaser accuses constructivist grounded theory of making the researcher more important than the participants and that the "objective" stance so often criticised in classical theory is in fact about putting the concerns of the participant over the researcher. He also criticises constructivist theory for always using a pre-defined lens to analyse data (178). The authors conclude by saying that researchers must be clear on the path they decide to take (classical or constructivist) rather than picking and choosing from the two (177). This conclusion seems to be a bit of a contradiction, based on the fact that it is argued that everyone should start a study with an open theoretical perspective. Moreover, as described, and as Charmaz delineates, it is not a one size fits all and she emphasizes the importance of being "eclectic" when theorizing (175). It seems through exploring the literature that many of the criticisms levelled at "classical" or "constructivist" grounded theory are due to misinterpretation.

6.2.2 Aligning research with theory

In the current study, although it is recognised there are multiple truths, multiple voices and perspectives and the importance of looking at context, a key unifying conceptual category was identified in relation to the knowledge and use of folic acid for the prevention of NTDs. A central category was also determined regarding detailed experiences when the spina bifida was detected in interviewees' children and around decisions to continue their pregnancy. These over-arching categories are rendered all the more meaningful and only of practical applicability when all the nuances are taken into account, but it is also believed that they go to the heart of the interviewees detailed experiences.

In line with a constructivist viewpoint, it is believed that searching for assumptions underlying meanings and actions is vital and the researcher is viewed in the current study as an integral part of the research process. Breckenridge and colleagues (177) argue that although in classical grounded theory the importance of an objective

researcher is emphasised, the perspective of the researcher is not ignored but incorporated as more data to be analysed, as described. Here, the researcher is not viewed as simply contributing more data but to a certain extent, influencing the data collected from study participants. I like the idea put forward by Breckenridge and colleagues (177) that in classical theory emphasising researcher objectivity, they are placing the concerns of the participant above the researcher. However, I believe that it is still possible to place the concerns of the participant above the researcher, whilst recognising that it is never possible for a researcher to be wholly objective. The researcher having a certain amount of influence over the data collected is unavoidable, accentuating the importance of being reflexive about potential impact. However, having an influence does not necessarily mean unduly "leading" the data that is generated and arguably, it can actually help to open it up. It is believed that through showing empathy and humanity to participants, as one human being to another and not in the authoritarian figure of researcher over participant, as it is human experience that is being detailed, that the data will be richer and more meaningful.

To conclude, do I ultimately believe that theory is construction and is based on interpretation or do I see it as an objective truth? Perhaps I sit somewhere in the latter half of the methodological spiral with a stronger constructivist leaning. The constant comparative method has been adhered to quite stringently, as detailed below and the main literature review was conducted after writing a first draft of the findings. However, it was not possible (and also would have been undesirable) to start from a completely blank page. Through using grounded theory method I believe the data collected from participants have been placed at the centre, but that it is impossible for such data to be devoid of researcher influence, in line with a constructivist perspective, as a researcher is a human being with their own research leanings and ideologies and not a computer that can be programmed to certain settings. Nevertheless, as stated, I do not believe this reduces the worth or applicability of the outcome and that a researcher with both humanity and reflexivity can be part of research that is meaningful and has depth.

6.2.3 Statement about researcher involvement

I am a 31 year old, White British, PhD student with a background in Infectious Disease epidemiology. During the course of my PhD I have volunteered with the Spina Bifida, Hydrocephalus, Information, Networking, Equality (SHINE) association and spoken to a number of families with children with spina bifida about their experiences. These discussions have not been viewed as extraneous to the research and have been commented on below. I have also been to a number of spina bifida clinics at Great Ormond Street Hospital (GOSH) to recruit women for the study and have again spoken to many families and seen many children living with spina bifida in this setting. I do not believe these experiences have biased me in any way when conducting the research and in fact have helped to open my eyes and enrich it. When conducting the interviews, although a general topic guide was used, this was in no way prescriptive and it was the women's story that was of interest. Some interviewees spoke more openly than others which could have led certain interviewees down a specific path due to the necessity of asking more questions. However, in applying grounded theory methodology, both what was and was not said were considered and the emphasis was on actions.

6.2.4 Participant recruitment

The inclusion criteria for the study were women of South Asian (Indian, Bangladeshi, Pakistani) ethnicity who were 18 years or older and had a previous NTD affected pregnancy. There were no restrictions based on language and materials were translated and an interpreter was present where required. The study was advertised in a variety of different ways, including an advertisement on a spina bifida parent support group on facebook; through SHINE; through GOSH, where the study was introduced to mothers during the spina bifida clinic they attended with their child and through the Asian Parent Carer's project in Manchester. Participation in the study was completely voluntary. Although the study was targeted at both mothers who did and did not continue their NTD affected pregnancy, only mothers of children living with spina bifida took part in the study. This was largely because identifying an effective method for recruiting women who

chose TOPFA proved extremely difficult. SHINE is a charity which helps individuals and families affected by spina bifida, whether the decision is made to continue the pregnancy or not. However, only one interviewee was recruited through this method and she had a child living with spina bifida. The remainder of interviewees were recruited though the spina bifida clinic at GOSH which was attended by children with NTDs and their parents/carers. It would not be expected that not including mothers who chose TOPFA would bias what is observed about pregnancy behaviours and attitudes before diagnosis. However, it did mean that the second part of the analysis was focused specifically on mothers deciding to continue their pregnancy. There were also no anencephaly affected pregnancies included. However, this is an in-depth qualitative study and is not intended to be representative. Moreover, what was revealed specifically about spina bifida affected pregnancies where the decision was made to continue the pregnancy, was very striking.

Individuals who expressed an interest in taking part in the study and who met the inclusion criteria, were given an information sheet about the study (a copy of the information sheet can be found in Appendix E). The contact details of potential interviewees were also taken at this time and they were contacted after a week to see whether, after taking some time to consider the information they had been given, they would like to take part. It was emphasised throughout that participation in the study was completely voluntary and that women did not have to answer any questions they did not want to and were free to withdraw from the study at any time.

Recruitment took place over twelve months, between December 2013 and December 2014, and eight women took part in the study. Interviews were in-depth and having a sample size of eight was viewed as both sufficient and necessary to enable an exploration of the pre-pregnancy and pregnancy views and experiences of South Asian mothers who had a child with spina bifida using grounded theory methodology as part of a mixed methods study.

Key self-reported information for the eight interviews of South Asian ethnicity (four of Bangladeshi ethnicity and two of Pakistani and Indian ethnicity) is given in Table

58. It was not the purpose of the qualitative research to quantify certain outcomes; however, it was useful to underline certain key factors e.g. reports of previous miscarriage/TOPFA.

Table 58: Key self-reported participant characteristics

Patient ID	Country of Birth	Ethnicity	Religion	Age group	Maternal health conditions	Planned/un-planned pregnancy	Pre-pregnancy folic acid use	Previous miscarriage/TOPFA reported	Older siblings (n)
1	UK	Indian	N/A	35-39	Gestational diabetes; blood clotting issue	Planned	Yes	Yes	N/A
2	UK	Bangladeshi	Muslim	25-29	Vitamin D deficiency	Unplanned	No	No	2
3	UK	Bangladeshi	Muslim	25-29	Anaemia	Semi-planned	No	Yes	2
4	Unknown	Bangladeshi	Muslim	30-34	Vitamin D and iron deficiency*	Unplanned	Yes	No	4 (1 with congenital condition)
5	Pakistan	Pakistani	Muslim	30-34	Anaemia; brain tumour	Unplanned	No	No	1
6	UK	Bangladeshi	Muslim	20-24	Vitamin D and iron deficiency	Unplanned	No	Yes	1
7	Pakistan	Pakistani	Muslim	25-29	Vitamin D deficiency and on aspirin	Planned	Yes	Yes	1
8	UK	Indian	N/A	30-34	Beta thalassemia trait; UTI and exposed to rotavirus during pregnancy*	Unplanned	Yes	Yes	2

*Severe morning sickness also reported

6.2.5 Interview procedure

At the beginning of each interview the study aims, confidentiality, the voluntary nature of participation and the participant's right to withdraw from the study at any time were again described and emphasised. Written informed consent was obtained prior to each interview (A copy of the consent form is included in Appendix E). Interviews were in-depth and a topic guide was followed (the original topic guide is included in Appendix E) but were flexible and the interviews were participant led. The topic guide was adapted after each interview in line with the constant comparative method, as detailed below. All interviews were audio-taped and lasted between 22 and 70 minutes.

6.2.6 Data collection and analysis

6.2.6.1 Summary

All interviews were transcribed verbatim and coded using NVivo software. Analysis consisted of informal coding and memoing (reflective notes) during the interview stage, then line-by-line coding (with an emphasis on actions), memoing, development of focused codes and initial conceptual categories from interviews then theoretical sampling and further coding, memoing and raising focused codes to conceptual categories and raising conceptual categories to a theoretical level in the final stage.

6.2.6.2 Using the constant comparative method: Coding and memoing

Preliminary coding and memoing was conducted after each interview which dictated the direction of subsequent interviews and the topic guide was adapted accordingly. After all interviews had been carried out, analyses were conducted in a constant comparative fashion i.e. line-by-line coding was conducted for the first interview, then line-by-line coding was carried out for the second interview, a memo was then used to examine codes within and between the two interviews and

more focused codes started to be developed. Line-by-line coding was then conducted for the third interview, which was then examined and compared with coding in the first two interviews etc. The process of developing focused codes was described to two supervisors and there was discussion around this.

Focused codes were raised to preliminary conceptual categories through constant comparison and reflection through further memo writing and diagramming. The process of developing a core conceptual category for the study, based on interviewees' detailed accounts, using the constant comparison method is described in section 6.2.6.4.

6.2.6.3 Theoretical sampling

Following later interviews which identified some health professionals (HPs) as giving a bleak picture for spina bifida when the condition was detected, in line with the inductive process of grounded theory, I went back to previous interviewees. These further interviews were then coded and constantly compared with data already collected, in the same way as described above. Through doing this, it emerged that only those who did not routinely see children with spina bifida or indicated they had little understanding of the complexity of the condition tended to give a worst case scenario as inevitability.

6.2.6.4 Emergence of giving meaning through detail and emphasis vs. gaining meaning through experience as a core conceptual category

After coding and constantly comparing the first four interviews, key focused codes that seemed to be emerging centred on timing: Investing time; the limiting nature of time; the torturing nature of time. However, it kept bothering me that these codes somehow fell short, or at least were insufficient on their own, at getting to the heart of what was happening. Something said by one interviewee when asked what pre-pregnancy care means to her, kept resonating in my mind:

After #child's name# it means a lot. Before #child's name# nothing. It didn't occur to me, I didn't even, I'd heard about it but didn't think it was important. So after #child's name# it's a lot (Interviewee 2).

After going back to this statement several times and this particular interview, it was detailed in a memo how although timing was of course important here, it was through the particular circumstance of having a baby with spina bifida that pre-pregnancy care now meant so much. This lead to the development of two further focused codes: Meaning through circumstance and meaning through emphasis, with the two being interlinked and a tension existing between gaining meaning through learning; through being told and gaining meaning through a lived experience. These codes were further scrutinised and developed in the process of coding subsequent interviews and going, of course, back over previous ones in a constant comparative fashion and were ultimately raised as a core conceptual category.

6.2.7 Presentation of findings

In-line with the grounded theory methodology, reference to the literature and discussion is interspersed throughout the findings section. There are two main sub-sections presented: The first surrounds the core conceptual category identified regarding folic acid knowledge and use and the second around the decision to continue a spina bifida affected pregnancy. There is further discussion with a stronger researcher overview towards the end of each sub-section.

6.3 Findings

6.3.1 Pre-pregnancy knowledge and health behaviours, particularly with regards to folic acid: Giving meaning through detail and emphasis vs. gaining meaning through experience

A sense of information being given and understood in sufficient detail and with sufficient emphasis in contrast to a sense of learning through a lived experience is at the heart of the analysis. The fact that information about the benefits of taking folic acid has been given in sufficient detail and with sufficient emphasis, does not necessarily mean this information will be acted on, as there are several factors involved. Even if this health message is adhered to before and during pregnancy, it does not mean that the pregnancy will not be affected by an NTD as their aetiology is complex and poorly understood. A pregnancy where folic acid is taken, can still be affected by an NTD and of course, one where it isn't will usually not be affected by an NTD (approximately 1 in a 1000 pregnancies are affected(4)) (Figure 25).

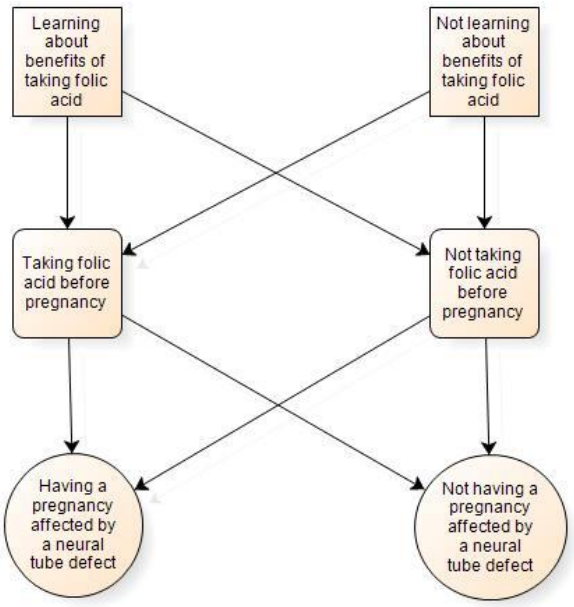

Figure 25: Possible pathways for "knowing" and "not knowing" about folic acid benefits and pregnancy outcomes

However, folic acid is a clear prevention tool for NTDs and it would be difficult to dispute the importance of informing all prospective mothers of its benefits. Sadly, all mothers in this study only fully appreciated the importance of peri-conceptional

folic acid use for NTD prevention through their lived experience of having an NTD affected pregnancy. This was brought into sharp focus by what one mother said when asked what the term pre-pregnancy care means to her:

After #child's name# it means a lot. Before #child's name# nothing. It didn't occur to me, I didn't even, I'd heard about it but didn't think it was important. So after #child's name# it's a lot (Interviewee 2).

Meaning failed to be imbued previously due to inadequate information that lacked emphasis; when she had been told about folic acid in her previous pregnancies she described how it was just said as "a passing comment." It hadn't even been mentioned at all when she went to see the GP after finding out she was pregnant with her child who was later discovered to have spina bifida. Meaning couldn't fail to be imbued through her experience of having a child with spina bifida.

One mother had been trying to get pregnant for ten years, had six previous miscarriages and her pregnancy with her daughter who had spina bifida was fully planned. Despite taking folic acid for many years, she only found out that neural tube closure occurs early in pregnancy when her daughter was born and the condition was detected. She described the importance of receiving more information on why folic acid should be taken:

And even maybe a bit more information on why you should take folic acid. I mean yeah it says to avoid spina bifida but it doesn't, it wasn't until after she was born that they explained that that condition happens so early on and that's why you have to take it before pregnancy (Interviewee 1).

This interviewee also emphasised the importance of enough information being given but not too much:

It's the amount of information and what information and obviously generally a lot of people don't need to know the ins and outs, the background, they just need to know you need to take this because it avoids this (Interviewee 1).

Another interviewee also spoke about the importance of emphasising how taking folic acid can help your baby but not 'overdoing' the advice:

They should explain why. I'm not talking that you show them the difficult picture – at least you should tell them that 'Look this is very important for your baby'. Yeah (Interviewee 5).

6.3.1.1 Knowing in time

As described, interviewee 1, despite taking folic acid for many years, was only fully aware of the benefits of taking folic acid before pregnancy once it was discovered that her daughter had spina bifida. When advice is given, is critical to this concept of gaining knowledge through detail and emphasis rather than through a lived experience. Folic acid is a prevention tool for NTDs and can only be of benefit if taken before pregnancy as neural tube closure will occur by about day 28 of pregnancy, before many women know they are pregnant (4). The most important time to be aware of its benefits is therefore before pregnancy. For all mothers in the current study, the spina bifida was detected in their children at the 20 week scan at the earliest. One mother described how it was when the spina bifida was detected in her child that she learnt when folic acid needs to be taken:

I think during that time when I found out spina bifida, that you're supposed to take folic acid 3 months before and 3 months after (Interviewee 6).

Another mother detailed how it was the first time that she heard the word spina bifida when it was discovered that her child had the condition:

When I was pregnant with her and the doctors told me about her, I just heard first time that word 'spina bifida' I didn't heard before (Interviewee 7).

Interviewee 8 also stated that when she was told her daughter had spina bifida at the 20 week scan, she had "no idea what neural tube defects were."

As shown in Table 58, 4 out of the 8 interviewees started taking folic acid before they became pregnant with their child who had spina bifida, however in no case were they sufficiently aware of why until the condition had been detected.

6.3.1.2 Respecting/emphasising responsibility of Health Professionals (HPs) to advise

Interviews were only conducted with mothers and not with HPs and so the perspective of the HP cannot be taken into account here. However, all mothers described how it was the GP/Midwife (in most cases the GP) who they respected and trusted most to give them pre-pregnancy health advice. This supports previous research conducted with pregnant British Pakistani mothers, where pregnancies were unaffected by an NTD, who emphasised the important role of the GP in giving them pre-pregnancy advice (100). In the current study one mother said she would prefer to receive advice from the GP "because they're more experienced, they know about it (Interviewee 2)." Another mother described the doctor as "knowing everything (Interviewee 5)" and one mother described getting information from the GP as being far superior to getting information through a leaflet:

Cos people, if people give leaflet, some people they won't bother innit. They will just say I will read it and they don't read it. They forget about it. If the doctor talks, the information will go through to them. They can take something in and it's better like that (Interviewee 3).

They not only respected GPs as informers, but thought they had a responsibility to inform. One mother stated that:

Because new mums who are having the baby first time, so it has to be the doctor's responsibility to tell them, inform them at the GP's (Interviewee 7).

6.3.1.3 Not seeking/not receiving pre-pregnancy care from health professionals

It has been reported by previous studies how the majority of women who are advised by their GP to take folic acid, go on to take it (37;102). However, it is also reported that the majority of women taking folic acid based on a HPs advice, don't start until after they become pregnant (102). It was interesting in the current study how the role of the GP/midwife was largely discussed by mothers with regards to when they became pregnant. The GP was seen as the person you go and see when you find out you are pregnant and not before. However, it was assumed by one

interviewee that GPs would give the same advice before pregnancy as they do when you go and see them when pregnant. She said:

If you go and see your GP I assume they will give you a whole load of paperwork to look through cos they give you wads and wads of stuff when you are pregnant so it would be the same before you are trying to get pregnant (Interviewee 1).

As stated, interviews were only conducted with mothers and so the perspective of the HP cannot be given. However, some very interesting research conducted by Stephenson and colleagues involved interviewing HPs, including GPs and midwives, about their views on pre-pregnancy guidelines and whether they thought it was their responsibility to offer pre-pregnancy care. It was found that knowledge was hazy and many of the interviewees did not see it as their responsibility to offer this service. It was described how one GP said "I don't do pre-pregnancy care – I tend to leave that for the antenatal appointments" (179). Another GP described that, "We often get people saying do I need to see a Gynaecologist about having a baby and you say well no, go and get pregnant and then come back to me" (180).

6.3.1.4 Planning pregnancy vs. not planning pregnancy

GPs might not regard it as their responsibility to provide pre-pregnancy care and it seems to be the "norm" for mothers to visit the GP once they are pregnant, therefore even for the pregnancy "planners" this presents a bit of a predicament. In Stockley and colleagues (93) systematic review of research specifically encouraging women who were young and of lower socio-economic status to take peri-conceptional folic acid, it was reported that the biggest factor associated with low folic acid use was the pregnancy being unintended. However, use is still low in the pregnancy "planners" and a European wide survey exploring awareness and use of folic acid by women of reproductive age (37) found that only 28% of those who described their pregnancy as planned, took folic acid. Interestingly, most of the women planning their pregnancy did not consult a HP before stopping their method of contraception, which probably impacted the low rate of use in the planners as the majority of women who were advised to take folic acid by a HP, as previously

reported, went on to take it (37). This is supported by previous research that found that whether the HP was consulted before planning, predicted awareness and use of folic acid (157). However, it is very difficult to dichotomise pregnancies into those that are planned/intended and those that are not planned/unintended and doing so is probably over simplistic. Described limitations of many studies exploring pregnancy intendedness include that the terms planned and intended can mean different things to different women (181) and that there is not necessarily a congruence between intentions and behaviour (182).

As stated previously, it is not the purpose of the qualitative research to quantify certain outcomes and only eight mothers were interviewed. However, two mothers in the current study described how their pregnancy with their child who had spina bifida was planned; four that the pregnancy definitely wasn't; one said it wasn't planned but in less definite terms, "I wasn't so much planning" (Interviewee 6) and one mother that it was "sort of like planned" (Interviewee 3). For the two mothers who described their pregnancy as planned, both took folic acid before pregnancy. One of these mothers had had six previous miscarriages and had researched extensively in order to have a successful pregnancy. She had built up knowledge and gradually adopted health behaviours over a significant period of time. For the other mother, she had to have a termination for her previous pregnancy as her baby's brain hadn't formed properly and she had been consistently taking folic acid since that point:

They just give me folic acid. I was taking folic acid when I've got … you know the abortion before her pregnancy … I was taking folic acid from that time to when she born on that time (Interviewee 7).

In two of the "non-planners" folic acid was already being routinely taken before pregnancy, in one case due to an absorption problem and in another due to pregnancy vitamins being taken routinely for beta-thalassemia trait. In the mother whose pregnancy was "sort of like planned" she didn't take folic acid until she went to see her GP after she found out she was pregnant and he advised her to, as was the case with her previous pregnancies. She described how she didn't take folic acid before she became pregnant as she wasn't sure when it was going to happen:

Cos I didn't know when I was gonna fall pregnant so I didn't know when to take folic acid (Interviewee 3).

6.3.1.5 Previous pregnancies setting norms

A sense of earlier pregnancies setting norms and impacting practices during later pregnancies, was very striking in the study. Interviewee 3 also described how:

Afterwards, when I find out, doctor prescribed me and then I take it straight away. It's like normal pregnancy isn't it, when you go to the doctor they give you folic acid (Interviewee 3).

A "normal pregnancy" for this mother, and what had occurred for her previous pregnancies, was that the doctor was visited once pregnant and it was then that folic acid was given. It was very interesting in this study that every mother interviewed had a gravidity of at least one before becoming pregnant with their child who had spina bifida i.e. they all had previous pregnancies. A few of the mothers in the study who hadn't planned the pregnancy where their baby had spina bifida also indicated that at least one of their previous pregnancies had been planned and that they had taken folic acid. It is reported how the second pregnancy to a mother that results in a birth is likely to be the most planned and the third pregnancy and any subsequent pregnancies that result in a birth are likely to be least planned (182). In the current study, out of the six "un-planned" pregnancies where the child had spina bifida, four mothers had two or more older children. The importance of receiving advice from the GP/midwife was strongly emphasised by mothers during the interviews; yet it does not seem to be routine, in the case of a pregnancy being planned, for women to visit their GP or the GP to give them pre-pregnancy advice. Even if they did visit their GP before pregnancy and were given pre-pregnancy advice to take folic acid, which is a strong motivator for use, their knowledge of the benefits of taking folic acid are likely to be low. Women are likely to take folic acid if their GP advises them to, even if they don't have a full understanding of the benefits (37). However, it has been shown that those who do not know about the benefits of taking folic acid are less likely to initiate folic acid use pre-conception (102).

6.3.1.6 Wanting to have a healthy pregnancy

In the current study it was strongly apparent that all mothers interviewed loved their children and didn't want them to suffer. Interviewees spoke of their deep shock and distress when they found out that their baby had spina bifida and the very difficult time that followed for their family. One mother described how depressed she became:

When she was born actually I was in deep shock – every night I start crying, because I don't know what's this ... why it's happened to me, and why she is like this ... I was so depressed (Interviewee 5).

Another mother described how she couldn't cope and veered between two states:

And then literally I had two states, either sleeping or crying – I had no in between, I just couldn't cope with anything else (Interviewee 8).

Mothers also described how when you become pregnant you do everything you can to ensure the baby will be healthy:

If they're not thinking about theirself they should have to think about the baby, something little inside. Yeah. Yeah it's alive something inside (Interviewee 7).

You have more fruit, you have more yoghurt and have more milk and you know you're trying to take care of them, because ... that's the way I am, I just think this is my responsibility just going to try and make sure that they come out healthy (Interviewee 8).

As detailed in Figure 25, some women who take folic acid before and during pregnancy will still go on to have an NTD affected pregnancy. Indeed, 4 out of the 8 interviewees in this study reported starting taking folic acid before getting pregnant. Despite the uncertainty, however, in all cases, when mothers knew what the harm might be, they weighed up the simple act of taking a supplement against the small but important risk of an NTD. All mothers interviewed, took folic acid for

subsequent pregnancies after their pregnancy with their child who had spina bifida. Interviewee 1 described how, despite not planning a subsequent pregnancy, she had been taking the high dose folic acid since she had given birth to her daughter:

So at the moment we're not planning but in case I was to fall pregnant without knowing or when I do start planning to fall pregnant. Since she's been born I've just been taking the high dose (Interviewee 1).

Semi-structured interviews were conducted by Tedstone and colleagues (97) with mothers, including those from Black and Minority Ethnic (BME) communities, to explore knowledge of NTDs and folic acid. It was interesting that avoiding harm to their baby was described as a strong motivator for making lifestyle changes but promoting general health was not. Not smoking and drinking was seen as preventing harm but taking folic acid wasn't, as there was very little awareness of the association between folic acid and NTD prevention (97). Information that folic acid can help to prevent harm to your baby, like not smoking and not drinking, and details of exactly what it could prevent and when it needs to be taken to be effective, is information that no mother with a strong protective instinct for her child, would take lightly. If the benefits were more clearly explained when seeking and receiving pre-pregnancy advice when this occurs, or failing this, when a mother goes to visit a GP once she is pregnant, in the latter scenario it might not be able to help the current pregnancy but it could help subsequent pregnancies.

It is therefore theorized that giving sufficient information about the benefits of taking folic acid, including when it needs to be taken and with sufficient emphasis is important before pregnancy. "Before pregnancy" also encompasses "before subsequent pregnancies" and information given in an earlier pregnancy could help to protect a later one. However, it was also emphasised in this study that there are key misconceptions and situational factors that need to be addressed; taken into consideration or utilised as further opportunities to improve peri-conceptional use of folic acid.

6.3.1.7 Healthy eating is not enough

It was indicated by some mothers in the current study that we can slip into thinking that healthy eating is enough linked to a lack of awareness of the greater bioavailability of folate in its synthetic form, folic acid. One interviewee whose GP didn't even mention folic acid to her once she became pregnant, said how she didn't go back to check with her GP as she thought she was probably getting enough of what she needed from her food:

I mean that's in one sense that's what I was thinking where cos we have a lot of spinach, we have a lot of the vegetables so I think that's another reason why I didn't go back to the GP thinking I'm having enough anyway (Interviewee 2).

Another interviewee in the current study described how time was a big barrier for her to go out and get more vitamin supplements and that due to the fact that she had a healthy diet, and would think this is enough, she probably would not do so:

Because for me to try and get the time to go and get some more vitamins for myself because these ones are not given out anymore would be a bit difficult – I probably wouldn't do it. I think you know what, I'm okay, I'm a healthy person, I don't need it (Interviewee 4).

When asked what the term pre-pregnancy care means to her, as previously stated, interviewee 2 said "After #child's name# it means a lot. Before #child's name# nothing." Many mothers described pre-pregnancy care as including both healthy eating and taking folic acid supplements at the time of the interview and after their experience of having a child with spina bifida:

That would mean eating lots of healthy food, vegetables, fruits and taking folic acid and tablets and things, yeah vitamins (Interviewee 4).

You have to eat healthy food and … yeah. And folic acid specially (Interviewee 7).

In the study by Prue and colleagues (183) one of the reasons given by mothers for not taking folic acid, was that they believed healthy eating was enough. This is also

a misconception that has previously been reported to be held by HPs and after a training programme that aimed to disseminate information about folic acid, it was found the knowledge of the fact that getting enough folate from diet is extremely difficult, was increased (184).

6.3.1.8 Having a previous healthy pregnancy

A sense of previous pregnancies setting norms for current pregnancies and individuals having a strong motivation to have a healthy pregnancy, was described in previous sections. It was also described how it is essential that earlier pregnancies are utilised as opportunities for relaying important information for later pregnancies. However, if earlier pregnancies are healthy it could impact the perceived importance of any health information that is given. One of the interviewees in the study described how she really struggled to eat well during a previous pregnancy:

Yeah the first one I wasn't even eating properly. It's like I would get up and have a crisp, I would go to bed having a crisp ... just living on crisps. But she came out healthy. She did (Interviewee 6).

The mother struggled to eat properly in her previous pregnancy and everything was fine and so healthy eating was not significant to her. It was really striking that out of the 4 mothers who took folic acid before pregnancy, one had multiple "non-healthy" previous pregnancies that resulted in miscarriage; one had to have a termination due to a congenital anomaly and one interviewee had an older child with a congenital condition.

It has been reported by some studies that use of folic acid is lower among mothers who have had a previous healthy pregnancy (183;185). Prue and colleagues (183) described how mothers who believed that they didn't need to take folic acid gave the fact that they had had a previous healthy child as their reason. It is reported that knowledge of the benefits of taking folic acid are higher in mothers who have given birth to a child when compared to those who haven't; however, specific knowledge that folic acid can reduce NTDs, is currently very low in both groups (19% in the

former and 13% in the latter). Moreover, these findings must be treated with caution as information on benefits of taking folic was also given at the end of the questionnaire, which could have biased results (37).

6.3.1.9 Reporting a previous miscarriage

The number of mothers in the study (four out of eight) who reported having at least one miscarriage before they had their child with spina bifida, was striking. A high spontaneous abortion rate has previously been reported in pregnancies preceding a NTD affected pregnancy (186). However, as described, none of the mothers in the study were fully aware of the benefits of taking folic acid until the spina bifida was detected in their child. Interviewee 1 who had six previous miscarriages, was only put on the higher (5mg) dose folic acid once she gave birth to her daughter who had spina bifida. Interviewee 8, who was taking folic acid as part of a pregnancy vitamin she had been routinely taking for beta thalassemia trait, described how she had lost one twin in her previous pregnancy. For the two interviewees, interviewee 3 and 6, who were carrying singletons when they miscarried and both reported one miscarriage, both became pregnant again soon afterwards. Neither received counselling about folic acid at this point and neither were taking folic acid in the peri-conceptional period when pregnant with their child who had spina bifida. Interviewee 7 who had to terminate her previous pregnancy as the baby's brain "hadn't formed properly" (suspected anencephaly), was only placed on the normal dose (400 μg) folic acid at the time of the termination. Six months later, she became pregnant with her daughter who had spina bifida.

6.3.1.10 Considering higher dose (5mg) folic acid

As stated, interviewee 7 was only taking the normal dose folic acid when she fell pregnant with her daughter who had spina bifida. It was only at this point that she was put on the high dose (5mg) folic acid for her subsequent pregnancy with her son who didn't have an NTD:

they said continue this whatever you're taking, they didn't give me on that time 5mg, no. The normal I was taking, that's it I was taking yeah… They didn't give me on her time, but when the boy was … so then they increased the dose (Interviewee 7).

This sense of folic acid dose is really critical and another striking factor in the research was the number of mothers (seven out of the eight interviewees) who reported some form of vitamin absorption problem (this included vitamin D and iron deficiency as shown in Table 58). Interviewee 1 was the only mother who didn't report an absorption problem and after being placed on the high dose folic acid once her daughter with spina bifida was born, she still went on have another miscarriage and ectopic pregnancy. One of the mothers (interviewee 4) who reported an absorption problem described how she had routinely been taking the high dose folic acid before and whilst pregnant with her daughter who had spina bifida:

Yeah cos I was low so I was on 5mg ... just generally I was on that. And when I found out I was pregnant I was still on that as well. Like it didn't increase or anything, it just stayed on the same level (Interviewee 4).

Folic acid is very clearly not everything, yet, as described, interviewee 7 had a healthy pregnancy when she was taking the high dose folic acid and interviewee 6 who hadn't been taking folic acid and then was put on the higher dose, went on to have two subsequent healthy pregnancies.

6.3.1.11 Religious observance during pregnancy

As shown in Table 58 above, for the two mothers of Indian ethnicity, interviewee 1 stated that she would not describe herself as following any particular religion but would participate in things due to tradition:

Well obviously I don't follow it, don't practise it but I participate in things when I go to my parents' house but not really on an everyday basis (Interviewee 1).

Interviewee 8 did not state that she followed any particular religion. All mothers of Pakistani (n=2) and Bangladeshi (n=6) ethnicity described themselves as Muslim. Fasting during Ramadan is one of the five pillars of Islam and involves not eating or drinking between dawn and dusk. Islamic law states that pregnant women do not have to fast, although many still choose to do so (187). The impact of fasting during pregnancy on fetal outcomes is inconclusive (188). From the mothers who described themselves as Muslim, two detailed that they had fasted during pregnancy and three that they didn't (with one mother it was not discussed). For the two interviewees that did fast, it fell towards the end of their pregnancy. One of these mothers stated:

I can't remember but yeah I'm sure cos it fell in the month so and I usually fast in my pregnancies. So yeah I must have fasted...It would have been late pregnancy, late as in 6 months. It was 6 months (Interviewee 2).

One of the mothers who didn't fast described how "even when you're pregnant during Ramadan you don't fast anyway." However, she went on to clarify that "it depends on yourself … cos I get light headed quite quickly" (Interviewee 6). Another mother detailed how she couldn't fast as the fasts were long and she had bad morning sickness:

I would have, but they were like really long fasts, because at that time the fasts finished at 9pm. And also I was very sick (Interviewee 4).

6.3.1.12 NTDs being an act of God

Mothers spoke about how they found support through their faith in God. One mother described how she prayed during her pregnancy with her daughter with spina bifida and her gratitude to God that she was ok:

Yeah and I was praying over my pregnancy about her and I was thinking I don't know what will happen… But she is all right, I thank God all the time. She's all right, she's doing very well (Interviewee 7).

Another mother spoke about her belief that everything happens for a reason:

I mean I do believe everything is, what we believe is everything is planned by God anyway so if it was gonna happen it was gonna happen (Interviewee 2).

However, she also stated that the GP "didn't do her job" by not mentioning folic acid to her. There were also indications by interviewees that they felt a certain degree of guilt about their child having spina bifida and they feared being blamed. Although the GP didn't do her job by not informing her about folic acid when she was pregnant, it was very sad as no-one had explained to interviewee 2 that it would have been too late for her to take folic acid anyway by that point, and she had ongoing guilt that she should have gone back and asked or just started taking it. Interviewee 1, who had been taking folic acid for many years, felt a sense of guilt that there was something she had done wrong to result in her child having spina bifida as her friends hadn't taken folic acid and their children didn't have an NTD:

Cos I've had friends obviously when we were discussing things that obviously I feel guilty that you know we've taken the folic acid and they say ooh I didn't even know I was pregnant so I didn't start taking folic acid until after and their child's completely fine. Obviously you're just in that lucky, yeah (Interviewee 1).

Husain (189) conducted semi-structured interviews with mothers of children with spina bifida, focusing on coping and stress in the period after birth and argued that HPs have an important role in addressing mothers' beliefs that they are to blame. In the current study, in some cases, rather than addressing feelings of blame, HPs seemed to reinforce it. Despite the fact that none of the interviewees had been sufficiently informed of the benefits of taking folic acid before the NTD was detected in their child, when the NTD was detected, the link with folic acid seemed to be readily stated; guidance was given by HPs in "diagnosis" rather than "prevention" mode. One mother's response when she was asked if she was taking folic acid when the NTD was detected was:

I said yes I was because a lot of people say, people with her condition is because they haven't realised they are pregnant and haven't being taking the folic acid cos it happened so early on (Interviewee 1).

Another mother was told:

Continuously I was taking but they said to me in your body is folic acid less, that's why it's happened (Interviewee 7).

NTDs seemed to be attributed to people "failing" to take folic acid or having lower levels in their body. In one case, a strong sense of ignorance about the condition and presumption was emphasised:

oh the midwife there said 'Oh spina bifida ... so you weren't taking any folic acid then? (Interviewee 8)'

Al-Gailani (190) in his article tracing the history of folic acid in Britain makes a very interesting point:

If epidemiology in the tradition of social medicine encouraged NTDs to be understood in relation to social problems of poverty and malnutrition, by the end of the century they were more likely to be attributed to individual women's failure to respond appropriately to expert guidance

As stated, folic acid is a prevention tool for NTDs, but it is not the complete picture. NTDs are never caused by a "failure" on the part of the mother, even if "expert guidance" is given in a timely manner, which was not the case here. From the comments of the interviewees, it seemed that in some cases there was ignorance on the part of the HPs about the complexity of NTDs. It was actually quite striking that one of the doctors who had a better understanding of the condition, emphasised that the mother was not at fault:

He said 'Are mum and dad related?' and we're like 'No'. And he's like 'Any family history?' I'm like 'No. And then he just went through and said it's just an act of God.' And that's the way I liked it to be referred to - it's an act of God. You weren't at fault (Interviewee 8).

6.3.1.13 Targeting education campaigns

After conducting a systematic review exploring the knowledge and peri-conceptional use of folic acid by mothers from different ethnic communities, as part of this doctoral thesis, it was recommended that carefully targeted and innovative campaigns need to be implemented in combination with a mandatory fortification programme for different ethnic communities (22). For mothers of South Asian ethnicity who were interviewed in the current study, it was GPs/midwives who were most commonly stated as the people they respect/feel they have a responsibility to give them pre-pregnancy health advice. It was also detailed how none of the interviewees were sufficiently aware of the benefits of taking folic acid, until it was discovered that their child had spina bifida. It cannot be assumed that GPs will play such a vital role for all South Asian mothers, with the term ethnicity itself being a social construct (149;150). However, it is striking that both South Asian mothers interviewed by Jessa and Hampshire (100) and South Asian mothers in this study, emphasised GPs/midwives as their preferred information source. Moreover, across different ethnic groups, both the media, such as newspapers and television, and HPs are the most commonly cited desired sources of information on folic acid (22). It was theorized based on the responses of interviewees that giving sufficient information about the benefits of taking folic acid with sufficient emphasis is essential for impacting early and later pregnancies. It would therefore seem that the best initial stage to try to increase the likelihood that South Asian mothers receive this information is targeting culturally sensitive education campaign at HPs.

Interviewees detailed how some HPs had a real lack of understanding of the complexity of NTDs and thus increasing awareness about the condition and its complex aetiology should be a crucial part of the campaign. Giving sufficient information on why folic acid should be taken, whilst giving information in a sensitive way that helps to lessen rather than perpetuate any ensuing sense of self-blame, should also be addressed. Based on the responses of interviewees, there were also further factors which need to be understood by HPs and addressed when giving individuals pre-pregnancy health advice. A key factor is the misconception that we can get sufficient folate from diet alone. Folate is far more bioavailable in its synthetic form, folic acid, and emphasising the importance of both eating healthily

and taking folic acid supplements, is critical. In addition to describing the benefits of taking folic acid in combination with having a healthy diet, based on the responses of interviewees, it is also important to emphasise that having an earlier healthy pregnancy that is unaffected by an NTD, does not necessarily mean this will be the case for subsequent pregnancies. Seven out of the eight interviewees reported some form of vitamin absorption problem: It is also recommended that this is taken into account when counselling mothers, including a consideration of the added therapeutic benefits of being on the high dose folic acid (5mg). One of the mothers reported she had Beta thalassemia trait and the National Institute for Health and Care Excellence (NICE) guidelines currently recommends that those with thalassemia take the higher dose folic acid (191). Finally, it is striking that four of the eight interviewees reported at least one previous miscarriage and one reported a previous TOPFA. This strongly suggests that another potentially vital time to inform about the benefits of taking peri-conceptional folic acid, is soon after a miscarriage or after a pregnancy is terminated due to fetal anomaly.

As described, a European wide survey found that the majority of women planning their pregnancy did not consult a HP before stopping their method of contraception, which probably impacted the low rate of folic acid use (28%) in the planners. Therefore, ensuring that women planning their pregnancy visit the GP in the first place is problematic. Two mothers in the current study suggested that another important way to inform about folic acid benefits, which would ensure individuals are made aware before pregnancy, is through sex education in schools. One mother said:

But then before that, even school. Bringing out all the sex education and this, that and the other, surely that should be a part of it. I don't think that comes into it at all. I don't think, you know. Yeah because we learn a lot in school and it gets drummed in at that time so surely this, having the folic acid when you're pregnant or this will happen, could happen (Interviewee 2).

This emphasises the high degree of receptivity of young people at school and the amount of information that is absorbed and retained during this period of life. To increase awareness about NTDs as early as possible, an additional future targeted

education campaign could therefore be at those providing sex education classes at schools. Consequently, sex education classes could be extended to describe NTDs and prevention by folic acid in sufficient detail to young women. The importance of visiting the GP for tailored advice when planning pregnancy could also be emphasised.

6.3.1.14 Further discussion

There has been a real paucity of qualitative research into the peri-conceptional knowledge and use of folic acid by different ethnic communities and, as described in the Introduction to this chapter, this qualitative study was the first to specifically explore the pre-pregnancy and pregnancy knowledge and behaviours of individuals with a previous NTD affected pregnancy in the UK. Jessa and Hampshire (100) in their qualitative research with pregnant mothers of Pakistani ethnicity from Nottingham in the UK, found that none of the mothers had been informed by the GP about the benefits of taking folic acid but they stated that they believed it was the duty of the GP to give them this advice. This was also the case for the South Asian mothers interviewed in this study, as described. However, this research with mothers with a child with spina bifida, went beyond looking at mothers' knowledge and peri-conceptional use of folic acid and was concerned with mothers' experiences both before and after the condition was detected in their child. It was thus underlined by mothers how HPs did not sufficiently detail the benefits of folic acid in "prevention" mode, before pregnancy, but stated its association with NTDs in "diagnosis" mode, when the spina bifida had been detected. The over assertion of the link between NTDs and folic acid, by some HPs, as described, could indicate a lack of understanding about the condition. This could be linked to the "invisibility" of NTDs. One mother in the study described how she felt a responsibility to tell other prospective mothers about the importance of taking folic acid:

I told whoever I know. Whoever I know now, even when they've just got married or whatever I'm like make sure when you're planning your pregnancy, have your folic acid and I do tell people, I do tell them (Interviewee 2).

She had a child who had spina bifida, who was wonderful, but the condition was very far from being invisible for her and she felt a duty to inform others. It is believed that making NTDs less invisible for HPs could only be a good thing.

Additionally, further situational factors were discussed, or brought to light through the in-depth discussions, which could impact whether individuals receive sufficient folate/folic acid in the peri-conceptional period. It was the practices and views of South Asian mothers that were specifically explored here and this enabled specific recommendations to be generated for both information received by GPs and other HPs through education campaigns and the mothers themselves when learning of the benefits of folic acid. Valuing an individual's religious belief is of paramount important, including recognising the support and strength this might give them, whilst also, with great sensitivity, considering the impact that certain practices, such as fasting early in pregnancy, might have on them and their baby. The high proportion of interviewees who reported some form of vitamin absorption problem was very striking. None of the interviewees specifically reported that they were B12 deficient, and all self-reported that they were not vegetarian. However, evidence suggests that those who are vegetarian might be at higher risk of B12 deficiency (192) and there has been shown to be an increased risk of NTDs in mothers who are B12 deficient (42). This should be taken into consideration when counselling communities where vegetarianism is more common.

The generated theory from this analysis, being given sufficient information, with sufficient emphasis, about the benefits of folic acid to impact current and future pregnancies, focuses on the strong protective effect of folic acid: the 1991 Medical Research Council (MRC) double blind randomised controlled trial showed an approximately 70% reduction in NTD recurrences in women taking folic acid supplements (17). However, the fact that taking folic acid before and during early pregnancy will not prevent all NTDs, introduces uncertainty into the equation. As described, some mothers in this study reported that they had started taking folic acid before they became pregnant with their child who had spina bifida. And, as described in the Introduction to this chapter, a key reason for this research being conducted with mothers of South Asian ethnicity was that the NTD prevalence was shown to be particularly elevated in mothers of Indian and Bangladeshi ethnicity in

the quantitative study (Chapter 5). However, there were indications that this elevation was most marked for Indian mothers for non-isolated NTDs, NTDs occurring in combination with other defects, which are unlikely to decrease with folic acid usage (47).

Coupled with this uncertainty about the benefits of taking folic acid is a consideration of the risk of having an NTD affected pregnancy in the first place. Approximately 1 in a 1000 pregnancies in the UK are affected by NTDs (4). However, as findings from the quantitative study showed, the NTD prevalence can be as high as 2 in a 1,000 for Indian mothers and 3 in a 1,000 for Bangladeshi mothers. In the current study, when aware of the potential harm, despite the uncertainty of benefit, all mothers weighed up the simple act of taking a supplement against a small but important risk of an NTD. It is described how information that folic acid can help to prevent harm to your baby is information that no mother with a strong protective instinct for her child would take lightly. However, in no way does this indicate that a mother who does routinely take folic acid when aware of its benefits is any better or loves her child any more than a mother who does not. In previous studies, other stated reasons by mothers for not taking folic acid include busy lives, competing priorities for concern and poor memory (193). We all have a multitude of life demands competing for our attention and the routine of taking tablets is something that is not necessarily easy to stick to. One interviewee described the problem of sticking to the routine of tablet taking:

I don't know. It's just the routine of taking tablets. Yeah you can't keep up with it (Interviewee 6).

Moreover, having a child with spina bifida was something that was very real and tangible for all mothers interviewed in the current study. Hearing about the risk of NTDs, and being given details of what the condition is, is very different to having a direct experience of it. Therefore, it cannot be automatically assumed that as all mothers in the current study took folic acid after they had a child with spina bifida that mothers who have not had an NTD affected pregnancy, will take folic acid when aware of the benefits. Although not explored in this study, it was very interesting that in the qualitative study conducted by Jessa and Hampshire (100)

with pregnant British Pakistani women, individuals stated that they preferred their GP to prescribe folic acid rather than to simply buy it over the counter. This supports earlier research comparing the views of Asians and non-Asians towards certain medications being made available over the counter, with the former group showing much less desirability for this than the latter (194). Higher dose (5mg) folic acid is currently prescribed by GPs but the normal dose (400 μg) is not. If the normal dose was also prescribed by GPs for those who have a preference for it, then they would be further "endorsing" its use: it would not just be a vitamin bought across the counter but something with the stamp of approval from the doctor, like a medicine, to take.

6.3.1.15 Key conclusions and recommendations

In conclusion, mothers of South Asian ethnicity interviewed in this study only fully appreciated the benefits of taking folic acid when it was discovered that their child had spina bifida; they found out in "diagnosis" rather than "prevention" mode. However, all mothers indicated that it was their GP/midwife who they respected most/felt they had a responsibility to give them adequate advice about folic acid benefits. It does not seem routine for many women to visit a HP before they get pregnant when planning their pregnancy and HPs do not necessarily view it as their role to provide pre-pregnancy counselling. Yet what was striking was that for all women interviewed, their pregnancy with their child who had spina bifida was not their first. Half of the interviewees reported previous miscarriages and one mother a previous TOPFA. There was also a sense in the study of previous pregnancies setting norms for current ones. Therefore, although it is best to inform mothers of the benefits of taking folic acid before pregnancy to protect that pregnancy, if this is not possible or does not occur, giving information about benefits as early as possible within that pregnancy could help to protect future pregnancies. Moreover, the information does not just need to be given once as mothers can be informed again at antenatal clinics and soon after a miscarriage or TOPFA occurs is also a critical point to provide information. It is recommended that a culturally sensitive education campaign is targeted at HPs to ensure they have an adequate understanding of NTDs and their complexity, to tailor counselling for

South Asian mothers for specific circumstances and to ensure that information is given in a sensitive way that helps to lessen rather than perpetuate any ensuing sense of self-blame. Another suggested method to inform young women before they become pregnant is through sex education classes at school.

6.3.2 Deciding to continue a spina bifida affected pregnancy: Seeing the whole picture (with human eyes)

In the current study, for two interviewees the spina bifida was not detected in their child until birth (interviewee 1 and 3) and in two detection was late (for interviewee 6 this was at 36 weeks and in interviewee 5 this was at 24 weeks; the latter was detected and the child was born in Saudi Arabia where termination is only permitted up until 120 days after conception (164)). For three interviewees the NTD was detected at 20 weeks (interviewee 2; 7 and 8) and the parents made the decision to continue the pregnancy and in one interviewee (interviewee 4), it was unknown when the NTD was detected.

Therefore, when exploring around decisions to continue a spina bifida affected pregnancy only data from interviewee 2, 7 and 8 can be included. Although the number of interviewees was limited, the in-depth interviews resulted in a rich dataset for qualitative analysis. Many of the points raised were striking and are important to detail here. Comments from discussions with parents of children with spina bifida are also included where necessary and where appropriate, in accordance with the grounded theory methodology, regardless of ethnic background. Ahmed and colleagues (163), in their research exploring the views of parents from different ethnic backgrounds towards prenatal testing and termination of pregnancy for sickle cell disorders and thalassemia major, found that even for those mothers who believed that termination was prohibited by their religion, many would consider termination to avoid their child suffering. Therefore, regardless of ethnicity or religious belief, it was perceived severity of the condition/quality of life of the child that was shown to be the most important factor when deciding to continue the pregnancy or not. This led the authors to conclude that there is a real need to move away from stereotypical views based on faith and ethnicity, towards looking at the beliefs of individuals (163). This has been strongly apparent in the

current study and has been key to how this second part of the qualitative study has evolved.

The importance of seeing the whole picture is central to this part of the analysis. It was described towards the end of the last section how the "invisibility" of NTDs could contribute towards breeding ignorance about their complexity. From discussions with mothers about their experiences when the spina bifida was detected in their child, it seems that this invisibility could affect HPs perceptions of the severity of the condition and what is consequently communicated to parents about it. However, based on the detailed experiences, this seems to go further than not seeing and communicating the whole picture, in some cases, to a lack of humanity and recognition that the decision of whether to continue the pregnancy or not, lies with the parents.

6.3.2.1 Giving a worst case picture and driving TOPFA

From the responses of some interviewees (and discussions with mothers more widely) it seemed that not routinely seeing children living with spina bifida, inclined HPs towards presenting a much bleaker picture of the condition. Interviewee 2 and 8 spoke about how the doctors they saw prenatally and scanned them during their pregnancy gave them a worst case picture when the spina bifida was detected in their child as how things would be; not as a possibility. One mother described how the doctor said:

He'll be blind, deaf, dumb. He won't be able to talk, he'll have bowel problems (Interviewee 2)

Such a bleak picture was given despite the fact that it could be detected at the 20 week scan that the defect was lower down. For interviewee 8 a similarly bleak picture was presented:

So they were talking about the brain, and basically made out that the whole life was just going to be one surgery after another, too much suffering, many disabilities (Interviewee 8).

Being given such a bleak picture by some HPs came simultaneously with what was perceived as a strong drive behind terminating the pregnancy. Several parents of children living with spina bifida from SHINE, also commented on this. Interviewee 8 described how she felt "badgered" to terminate her pregnancy. After one scan with a doctor who didn't allow her to ask questions, she described how she "had 45 minutes of grilling and badgering" by another doctor who subsequently told her "Do you understand what the effects of this is. Your baby is going to be completely retarded," which again appeared to reflect ignorance about the condition. This mother emphasised that these were the exact words used, and her experience was not dissimilar to other mothers. One mother I spoke to who was not of South Asian ethnicity said that the same term, "mentally retarded" had been used when describing how her child would be.

The same doctor who "badgered" interviewee 8 to terminate her pregnancy also said "We don't have many cases of spina bifida nowadays." Interviewee 2 described how she felt pressurised to end her pregnancy and despite her decision to continue after the condition was detected at 20 weeks, on every subsequent scan (approximately monthly) termination was discussed:

he'd say you know you've still got the option to have an abortion. We could set it up now, we could do this, we could do that (Interviewee 2).

This mother also described how the doctor who carried out each of her scans, and spoke about termination on every one, cared for her until birth but didn't see her son again after that:

this doctor he was, right through from the beginning till the end. The end meaning he gave birth, cos I had a caesarean. After the operation he disappeared, I didn't see him after that. He didn't see #child's name# (Interviewee 2).

6.3.2.2 The paradox of choice

This sense of feeling "badgered (Interviewee 8)" by HPs to terminate their pregnancy accentuated how even if they did believe the outcome to be the worst

case scenario that they presented, based on this limited picture, they were not completely leaving the decision of whether to continue the pregnancy or not to the parents. When discussing their experiences of TOPFA, women describe how it is never a real choice as their agency is restricted and with either decision, no-one really "wins" (195). Parents emphasise the importance of being supported in their decision to continue their pregnancy when a congenital anomaly is detected, if this is the decision they come to (170;196;197). A qualitative study exploring around parents' pregnancy decisions when holoprosencephaly was detected in their child, found that many women felt unsupported to continue their pregnancy and that the emphasis was very much on termination (171).

In the current study, in addition to feeling pressurised to end their pregnancy, mothers felt unsupported by HPs when they decided to continue and were even made to feel guilt for doing so. Both interviewee 2 and 8 described how they were made to feel guilty for the impact having a child with spina bifida would have on their relationship with their husband and other children:

He was basically talking about my family, how we wouldn't have a family structure, how my other kids would be affected, that I wouldn't have any time for them (Interviewee 2).

I'm going to ruin my marriage, I'm going to ruin my life, I'm going to ruin my kids' life, and I'm also being incredibly cruel by bringing in such you know an unworthy life into this world (Interviewee 8).

Interviewee 2 described how she felt completely unsupported to continue the pregnancy and that she would have felt much more support if she had decided to end it:

I found a lot of support through, if you want an abortion, we're here, we're gonna help you. We've got this, we've got that to support you. Yeah there was a lot of support through that way. Which was traumatic (Interviewee 2).

Interviewee 8 also described how she felt unsupported to continue her pregnancy by some HPs and in one instance was asked over and over again whether she was sure:

So the baby's got spina bifida, and I hear that you're planning to go ahead with the pregnancy'. I was like 'Yes'. And he asked me so many times if I was sure 'Do you know what it involves? Are you absolutely sure? Have you thought about it? Are you sure?' Like how many times do I have to say 'sure'? (Interviewee 8)

She also emphasised how there seemed to be little appreciation of and sensitivity towards the multitude of factors that can affect the decision of whether or not to continue a pregnancy. Spina bifida is typically detected around the 20 week scan and therefore, in some cases, feticide will be necessary to end the pregnancy. It has been shown by previous research that the psychological pain associated with terminating a pregnancy due to fetal anomaly, is difficult to overcome and this is particularly the case when feticide is involved (195). Interviewee 8 described how when the process of feticide was described to her, she was horrified and she couldn't even contemplate doing it:

there's no way I can go into a room and watch them inject her heart, I just can't do that (Interviewee 8)

She described how having to take a pill would be less traumatic but having the late termination was completely inconceivable. Despite the mother's reaction, she was still subsequently "grilled and badgered" to end the pregnancy.

It was also automatically assumed that interviewee 8 was deciding to continue the pregnancy because of religion:

And then she said can I ask are you saying no for religious reasons. I was like no, I'm saying no because it's my baby and I actually love her (Interviewee 8).

Her reason for continuing was for love not religion and she went on to describe how she had loved her baby since her pregnancy was known:

even though I haven't met her, I actually love this baby, because she's my child (Interviewee 8).

She stated that as soon as she knew she was pregnant "it's like it's my baby." Mothers have reported already loving their baby and feeling a strong bond with them as reasons for continuing their pregnancy affected by a fetal anomaly in previous research (169;172). There is little evidence to support an assumption that mothers of a particular ethnicity will choose to continue their pregnancy for religious reasons. As stated, work by Ahmed and colleagues (163) exploring the views of parents towards prenatal testing and termination of pregnancy for sickle cell disorders and thalassemia major found that perceived severity of the condition was shown to be a more important factor than religion or faith when deciding to continue the pregnancy or not (163). This was supported by subsequent work by the same authors (162) conducted in Yorkshire comparing the views of European and Pakistani women who either had a child with a congenital anomaly or terminated their pregnancy because of one, towards prenatal testing and termination for 30 different fetal conditions. It was found overall that there were more similarities than differences between the two groups and that the most important factor in the decision was a perception of the child's quality of life. Again, although Pakistani women said that Islam didn't allow termination, they came to the personal decision that TOPFA is justified for serious conditions as it would be wrong to bring a child into the world that isn't going to have any quality of life (162).

Every situation is different and each individual unique. Interviewee 7 described how she had to have a termination for her previous pregnancy as her baby's brain hadn't formed properly and how when it was detected that her daughter had spina bifida in her subsequent pregnancy and she was offered a termination, she said no:

And when they told me about her condition which the baby maybe can't walk and maybe have lots of operations and this and that. My husband was with me also, the doctors told me about terminate the pregnancy, but I said no. Because before her I've got a miscarriage and that baby was also not good. They said … when the first scan they said its brain not proper make and something … I don't know what they were saying after that. And they said you

have to terminate the pregnancy because the baby can die inside maybe 6 months pregnancy or 7 months … but that time you get more difficulties (Interviewee 7).

This mother didn't speak further about her decision to continue her pregnancy and this wasn't probed further due to the mother having had to have a previous termination and it being a very sensitive situation.

6.3.2.3 Taking off the clinical mask

HPs having sensitivity and compassion when giving information about a fetus with a congenital anomaly has previously been described as essential by parents, with one parent remarking that the HP should "take off the clinical mask and see the person as a person" (197). In the current study interviewee 8 described how there was a real lack of empathy, realisation that it was a human that they were speaking about and humans that they were speaking to, when the condition was described. She remarked how "you know you need to realise that this life's over here, it's not just a picture on a scanner," and how "I think its routine for them, they don't realise that there's emotions attached." It was also quite poignant what she subsequently said:

I think over here there's that lack of humanity, there really is. When it comes to doctors, there really is a lack of humanity (Interviewee 8).

In addition to feeling unsupported and guilty for continuing her pregnancy and pressurised to end it, interviewee 2 commented on how everything "was just so negative. It was horrible." It was very interesting as this mother spoke about how when the condition had been detected she went away to research on the internet and to look on YouTube and that it tended to be the "good things" that were on there:

Yeah I think on youtube parents put the videos up when they reach a goal; when they're happy about something. It's the good things I could see that were on youtube (Interviewee 2).

She then described that there would "be the negative parts or the medical parts" on websites. Remarks from interviewee 2 about the negative/medical things she saw on websites and negativity of some of the HPs point to an interesting point about a too medicalised picture being presented. Although interviewee 2 described how being given such a bleak picture was beneficial for her:

I actually benefited from having a bleak picture cos then I woke myself up, I got myself prepared for the worst (Interviewee 2).

For her husband the opposite was true and she described how "he didn't deal with that part, the negativity." It was also really sad what she described what she expected to see when her child was born:

So when I gave birth I couldn't even look at him, I was scared. Cos I was imagining this monster (Interviewee 2).

This contrasted sharply with what she actually saw:

And then when I saw him I was like, oh, he's normal. He looks fine (Interviewee 2).

In previous research exploring parents' experiences when a fetal anomaly is detected, individuals have emphasised the importance of the HP providing them with detailed and unbiased information about the condition, including giving both a best and worst case picture; for them to acknowledge uncertainty where this is the case and to give information through a variety of methods, including verbal, written and using visual illustration (170;171;195-198). Based on interviewees' responses in the current study, some HPs in fact gave biased information, only a worst case picture and didn't acknowledge uncertainty.

6.3.2.4 A few angels

Receiving conflicting views from different HPs (196) and different HPs holding different views towards TOPFA (199), has been reported in the literature. Interviewees in the current study did not describe all doctors as driving termination

so strongly and as interviewee 8 said, "if you come across so many awful … you need a few angels as well." She described how a doctor early on advised her of her pregnancy options but did not pressurise her in any way:

he said look I'm not suggesting you do this, it's entirely your decision, but legally I'm obliged to tell you that if you want a termination then you can have one. So there was no pressure on me to do that (Interviewee 8).

This was the same doctor discussed in the section above who seemed to have a better understanding of spina bifida (and did not immediately attribute it to folic acid not being taken) and described it as just being "an act of God", having no clear cause.

Interviewee 2 described how the neurosurgeon at GOSH gave a much more balanced view and how this resulted in it being a much less traumatic experience:

She was A's neurosurgeon from the beginning. They referred, when I was pregnant they referred me to go to GOSH. And she, when I spoke to her, she gave both sides…I remember that appointment not being so traumatic (Interviewee 2).

6.3.2.5 Dispelling ignorance

As previously described, it is the views of mothers of children with spina bifida that have been explored here and so everything detailed is from their perspective. Also, no individuals were interviewed who decided to end their pregnancy and so it is specifically the views of those that decided to continue that have been included. Nevertheless, the discrepancies in mothers' detailed experiences about consultations with doctors who do not routinely see children with spina bifida when compared to those that do, was striking. The perceived "negative", over medicalised picture with a strong onus on termination seemed to come from the prenatal team and the more "positive", less traumatic and balanced view came from the neurosurgical team. It was also those who seemed to know more about the condition that had the most sensitivity about it and as one mother said, "when people do know (about the condition), they're just so much more different"

(Interviewee 8). It was described at the end of the last section how targeting education campaigns at HPs to improve their knowledge about NTDs was essential; explorations throughout this section have shown that this should also include HPs who routinely scan and counsel mothers about their pregnancy options. Previous research has shown that although the probability of TOPFA tended to be associated with the severity of the condition, at similar levels of severity, CNS anomalies were more likely to result in a termination (168). This is a very interesting finding and a possible postulated reason for this was that the impact of having a CNS anomaly is being communicated to parents differently (168). This needs to be addressed.

A lack of exposure to individuals living with NTDs might not be the whole picture here. Interviewee 2 spoke about how she thought that money was the reason that termination is driven so hard:

I know a lot is to do with money. Cos these kids, there's a lot of money behind them, the NHS. So I think that's more why, you know why they try to push towards a termination cos there is a lot of money behind them (Interviewee 2).

However, what is strongly apparent is that there are women who are not receiving the complete picture about spina bifida when it is detected that their child has the condition, which means that they do not have sufficient information in order to be able to make an informed decision. In some cases the decision women come to is not being respected, including reports of them being treated with very little humanity.

It has been observed in other qualitative research, involving both parents and clinicians, that neonatal surgeons can sometimes be over optimistic when counselling mothers when a fetal anomaly is detected (200). However, it has been shown that neurosurgical teams working more closely with fetal medicine specialists can help to ensure that parents receive a more balanced picture about a fetal anomaly from the outset (201). It is recommended that this setup is strongly considered more widely.

6.3.2.6 Further discussion

Numerous studies have been conducted exploring mothers' experiences when a fetal anomaly is detected. Lafarge and colleagues conducted a systematic review of qualitative research exploring women's experiences of TOPFA. The authors described how mothers who had a TOPFA went through the experience of their world being shattered; a sense of losing control and re-gaining it again. They also described how the women emphasised the importance of HPs giving them detailed and unbiased information. However, above all else, women valued their HP showing them empathy and compassion (195). The current study was the first qualitative study in the UK to focus specifically on the experiences of South Asian mothers who have had a previous pregnancy affected by an NTD. As described in the Methodology section of this Chapter, it was only mothers who had a child living with spina bifida that decided to take part. Yet it is striking how the views of mothers who decided to continue their NTD affected pregnancy in this study, and mothers who had a TOPFA across 14 studies synthesised in a meta-ethnography by Lafarge and colleagues, coalesced: All went through a process of their world falling apart and then went through a cycle of regaining a sense of control again. And critically, all emphasised the importance of being given clear and unbiased information from their HPs whilst also being treated with humanity and supported in the decision that they come to.

The described over-clinical way in which mothers felt the information about their child's condition was relayed to them by some HPs was quite poignant. As one mother said, their child is "not just a picture on a scanner (Interviewee 8)." The 'clinical' approach that the women described did not recognize their baby as a "person" but the mothers did. When a fetus becomes a human is a contentious issue, however, it might be missing the point slightly to focus too heavily on this and instead look at the emotional bond that mothers described as having with their baby when they were 20 weeks pregnant. For the past five months their child had been growing inside of them and they had grown to love them, whether they were technically a "person" or not. An over-clinical picture was not described as being given by the neurosurgical team, people who would routinely see children with the condition. Perhaps this reflects different priorities and previous research conducted

in the US, comparing the views of maternal fetal medicine and fetal paediatric care specialists, has shown that the latter were more likely to see the well-being of the fetus and the former the well-being of the mother, as their primary responsibility (199). However, based on described accounts in this study for mothers who decided to continue their pregnancy, in overlooking the fetus, HPs are hurting the mother as they already see the fetus as their baby.

In the previous section for this qualitative research it was detailed how mothers interviewed in the study didn't know about the benefits of taking folic acid and many heard the word spina bifida for the first time when it was discovered that their child had the condition. In the quantitative study for this thesis, it was described how there is a peak in the detection for spina bifida around the 20 week scan and for mothers who make the decision to have a TOPFA, they often make the decision quite quickly, with 90% of NTDs terminated within 2 weeks of the condition being detected. Thus, at the time when the spina bifida is detected and the mother is unlikely to know very little about the condition, it is crucial to also provide mothers with a positive view of a future with a child with spina bifida so they make the decision that is "right" for them. The bleak view of the condition that was described as being presented by some HPs, contrasted sharply with many of the interviewees descriptions of their child's life. One mother described how her child is doing everything as normal:

No as far as I'm concerned she's doing everything like a normal child. Nobody can tell anything's wrong with her until I say something (Interviewee 3).

Another mother described how her daughter still has the same mentality as everyone else:

They still have that normal mentality ... still same feelings as everyone else (Interviewee 6).

One interviewee also described how well her daughter was doing:

But she is all right, I thank God all the time. She's all right, she's doing very well (Interviewee 7).

There will also be children with the worst case spina bifida presented by HPs and one interviewee described how this was the case for the daughter of someone she knew:

Yeah well she had an awful time and she lived until she was about 8 I think (Interviewee 2).

However, based on the interviewees' detailed experiences, there will also be individuals for whom this will be very far from the truth and parents need to be given all possibilities.

It is argued that not understanding the complexity of spina bifida sufficiently and not routinely seeing children with spina bifida, might not be the sole reason for HPs presenting such a bleak picture of the condition. However, one has to ask whether it would be morally and legally permissible to present the condition in such a bleak light if it was not believed this is how things will be. As described, one mother said she thought it had more to do with monetary reasons that termination was driven so strongly; however, again, when would this ever be an ethically acceptable reason? Furthermore, regardless of other factors, it is troubling that termination is perceived to be driven at all as it at best reflects a lack of regard for the parents' right to decide whether to continue the pregnancy or not.

6.3.2.7 Key conclusions

In conclusion, based on detailed experiences of mothers who have a child with spina bifida, those HPs who do not routinely see many children living with spina bifida seem to be more inclined to give a worst case picture as the diagnosis, rather than appreciating the complexity of the condition. Consequently, mothers may not be presented with a balanced picture in order to be able to make an informed decision about whether to continue the pregnancy or not. It appears that some HPs place more of an onus on TOPFA in their counselling and do not respect the mothers' decision to continue their pregnancy when it is discovered that their child has spina bifida. The inhumane way in which some women described that they were treated, was shocking. HPs that routinely see children with spina bifida were

described by interviewees as giving a more balanced and "positive" view of the condition. It is therefore recommended that neurosurgical teams work more closely with fetal medicine specialists to ensure a more balanced view of fetal anomalies is given from the outset and it is seriously considered the types of individuals that are permitted to scan and counsel vulnerable women.

6.4 Chapter summary and important points to take further

Grounded theory methodology was used to explore the pre-pregnancy and pregnancy views and experiences of South Asian mothers of children with spina bifida. Being inductive in nature, grounded theory methodology ensures the study outcomes are routed in the data; it is from the mother's detailed experiences that theory is generated.

All mothers interviewed in the current study were only fully aware of the benefits of taking folic acid during the peri-conceptional period, when the spina bifida was detected in their baby. They both respected and thought GPs/midwives have a responsibility to inform them about folic acid benefits. However, many did not visit their GP until they were pregnant and, as indicated from previous research, GPs do not necessarily see it as their responsibility to provide pre-pregnancy advice. All mothers in the study had previous pregnancies before having their child with spina bifida and it was therefore theorised that even if health advice will not be able to help current pregnancies, it could help future ones. Targeting culturally sensitive education campaigns at the HPs themselves is a crucial first stage in ensuring information about the benefits of taking folic acid is more effectively communicated to mothers or mothers to be of South Asian ethnicity: Based on interviewees accounts, many HPs seemed to be unaware of the complexity of the condition and to broach the subject with little sensitivity in "diagnosis" rather than "prevention" mode.

A sense of the "invisibility" of NTDs, due to the high prenatal detection and termination rate, impacting GPs/midwifes knowledge and sensitivity towards the condition, also seemed to impact the way HPs counselled mothers about their pregnancy choices when the condition was detected. Typically, HPs who didn't

routinely see children with spina bifida, only gave a worst case picture and the emphasis was very much on termination. Some of the detailed consultations denoted a real lack of humanity. As neurosurgeons were described as giving a more positive view, it is recommended that the paediatric team work more closely with the fetal medicine team to ensure a more complete picture about potential outcomes for the condition is understood and communicated, in the right way.

7 Discussion

7.1 Why is an ethnic discrepancy in neural tube defect (NTD) prevalence observed?

In the introductory chapters to this doctoral thesis (Chapter 2 and Chapter 3), it was described how there is a lack of robust and up-to-date NTD prevalence estimates by maternal ethnicity in the U.K. and a general paucity of epidemiological research in this area. Therefore, a central research aim of this PhD was to calculate accurate and up-to-date NTD prevalence estimates by ethnicity and to explore the impact of key factors, such as socio-economic status. As detailed in Chapter 5, it was shown that mothers of Indian and Bangladeshi ethnicity have a statistically significantly higher NTD prevalence than mothers of White ethnicity. This was based on data from two congenital anomaly registers in the U.K: the East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR) and the South West Congenital Anomaly Register (SWCAR) for the years 2006 to 2011 inclusive. The excess prevalence in Indian mothers was shown to be specifically for anencephaly affected pregnancies and in Bangladeshi mothers for spina bifida affected pregnancies. No excess was detected in Pakistani mothers, and this was not due to a small sample size. The region covered by EMSYCAR is much more ethnically diverse than that covered by SWCAR and thus, most of the NTD cases in Indian and Bangladeshi mothers are from the EMSYCAR register. Apart from the "Other" ethnic group, the highest proportion of births, in the region covered by EMSYCAR, are to mothers of Pakistani ethnicity after mothers of White ethnicity, and it is unclear why a similar NTD excess in Pakistani mothers is not observed.

Variations in classifications systems for isolated and non-isolated NTDs can affect results, as discussed under limitations below. However, using only the EMSYCAR data, it was still indicated that the anencephaly prevalence discrepancy between mothers of Indian and White ethnicity was likely to be attributed more to an increase in non-isolated than isolated cases. This is important as it has been argued in the literature that non-isolated NTDs are aetiologically distinct from those that are isolated (11;45) and that the former are unlikely to decline with folic acid usage

(47). From both preliminary explorations (Chapter 4) and explorations around ethnicity (Chapter 5) in the quantitative study key differences between non-isolated and isolated NTDs were indicated, even after taking NTD type into account. Folic acid usage couldn't be explored in the quantitative research as discussed in more detail below.

Both specifically a high rate of anencephaly affected pregnancies (55) and anencephaly affected pregnancies occurring in association with other defects (non-isolated) (68) have been reported for Indian mothers in the literature. In fact, mothers of Indian ethnicity are a very interesting group when it comes to NTD prevalence and, as stated in the Introduction to this thesis (Chapter 2), a high NTD prevalence is observed in Indian mothers, regardless of where they reside (54). Early research in the U.K. found an increased congenital anomaly and perinatal mortality rate in mothers of Indian ethnicity in Birmingham (74) and mortality rates for stillbirth and infant deaths attributed to NTDs, throughout England and Wales, which were higher in Indian (and Bangladeshi) mothers (75). More recent research from the North Thames region (which includes London) found an increased NTD rate in mothers of Indian ethnicity (81) and this study found an increased prevalence in Indian mothers for the region covered by EMSYCAR and SWCAR.

It has previously been reported that it is mainly in the North of India that a high NTD prevalence is observed, however, there have also been shown to be pockets of increased prevalence in the South (55;58). In the North, the marked NTD prevalence is particularly among the Sikh population but also among Hindus in certain areas (55). It was not possible to explore religion in the quantitative study for this PhD. However, the majority of Indian mothers with an NTD affected pregnancy in the study came from Leicester. The largest non-Christian religious group in Leicester is Hindu (202). Young and Clark in their analysis of lethal malformations and perinatal mortality in Leicestershire demonstrated that consanguinity is rare in Sikh and Hindu mothers (106). It was also reported in a study conducted in Birmingham that although the congenital anomaly and perinatal mortality rate was high in mothers of Indian ethnicity, the consanguinity rate was low (74). Therefore, although it was not possible to explore either religion or consanguinity in the

current dataset, it would not be expected that consanguinity would have a significant impact on the excess NTD prevalence to Indian mothers observed.

For Bangladeshi mothers, consanguinity might have been a bigger contributory factor (and is discussed further below). There is little existing literature on NTD prevalence within Bangladeshi mothers. Only one study has described an excess of deaths due to NTDs in Bangladeshi mothers in the U.K (75), however, this study presents data for Indian and Bangladeshi mothers as a group and there are no data broken down by subgroup (75). Nevertheless, the World Health Organisation has reported that Bangladesh is one of the countries in South East Asia (in addition to Bhutan, DPR Korea, India and Nepal) with a particularly marked NTD prevalence (52) and therefore the NTD excess observed in the current study is not wholly unexpected.

It was demonstrated in preliminary explorations in the quantitative study for this thesis that there is an excess NTD prevalence in younger mothers for isolated NTD cases and in older mothers for non-isolated (specifically chromosomal) cases. The addition of maternal age to the regression model was shown to have little impact on the observed association between ethnicity and NTD prevalence. This is in support of previous research that found that maternal age was not a significant factor in congenital anomaly risk for Indian mothers (74).

It was also demonstrated in preliminary analyses that there was an excess NTD prevalence in mothers living in more deprived areas, specifically for isolated cases. It is known that there is a strong collinearity between maternal ethnicity and deprivation which to a certain extent impedes disentangling the complex relationship between the two factors. However, after adjustment for maternal deprivation, ethnicity remains an independent predictor of NTD prevalence. This further accentuates the importance of factors other than maternal deprivation in explaining observed discrepancies in NTD prevalence by maternal ethnicity. Moreover, the ESRC Centre on Dynamics of Ethnicity (CoDE) briefing, based on the 2011 Census, reported that those of Indian (and White Irish) ethnicity live in the least deprived neighbourhoods of all ethnic minority groups (155).

7.1.1 Quantitative Study Limitations

7.1.1.1 Classification systems

The ONS 2001 census classification on which the ethnic groupings in this study are based are quite broad and may not capture relevant aspects of ethnicity associated with the aetiology of NTDs. As described as part of the justification for using mixed methodology in this study in Chapter 3, ethnic categories will always be socially determined, with classifications changing over time, depending on the social or political contexts (111). Ethnic groupings also fail to take into account crucial cultural factors. However, a critical aim in this thesis, further enabled through the qualitative research, was to investigate the ethnocultural factors influencing why a particular difference was observed, including a consideration of the impact of socio-economic factors, which are often under reported.

As detailed in Chapter 5, for NTD prevalence calculations by ethnicity, in the numerator (BINOCAR data) it is ethnicity of mother and in the denominator (ONS data) it is ethnicity of the baby. Although there is shown to be strong agreement between the two (152;153), this is definitely a limitation of the data that was available for the analysis.

Investigations in Chapter 5 emphasised that differences between coding systems designating whether an NTD is isolated or not become apparent when groups in analyses start to become small, for example in analyses involving ethnicity. Therefore, although for preliminary explorations for the quantitative study, analyses stratified by whether the NTD was isolated or not produced reliable outcomes, when looking at ethnicity, outcomes had to be interpreted with caution and analyses were more restrictive.

7.1.1.2 Ethnicity completeness

Analyses of NTD prevalence in relation to ethnicity could only be conducted using EMSYCAR and SWCAR due to a high proportion of missing ethnicity data in the

other registers and indications of bias or imprecision that would be introduced into analyses if missing data were simply ignored (Chapter 5). As detailed in chapter 5, ethnicity should be recorded somewhere in the patient's notes. However, if it is difficult to find, it might not be reported to the register. SWCAR retrospectively completed all their ethnicity data using patient notes and they had the most complete ethnicity data of all the registers, although there will always still be a proportion with not stated/not known ethnicity. It would have been important to explore whether an ethnic discrepancy was observed in Bangladeshi mothers in regions other than those covered by EMSYCAR and SWCAR in the U.K, as this was more unexpected (based on the literature) than the observed excess in Indian mothers in this study. It also would have been interesting to see whether an NTD excess was observed in Pakistani mothers for other geographical regions as an increased NTD prevalence in mothers from this ethnic group has been reported in regions including London (80;81) and the West Midlands (82), whereas this was not detected using data from EMSYCAR and SWCAR.

7.1.1.3 Lack of routine data on important co-factors

Folic acid usage couldn't be explored in the quantitative study as it was poorly and imprecisely recorded in the BINOCAR dataset. This is both due to inaccuracies during the data extraction process (144) and a high proportion of missing data in the computerised and paper prenatal records themselves. The lack of such data in routine records is a barrier to understanding the role and impact of folic acid use in the U.K in preventing NTDs. However, maternal deprivation, which seemed to have little attenuating effect on the observed association between ethnicity and NTD prevalence, has been described as being highly correlated with folic acid usage in the literature (101). It was also observed in preliminary analyses (Chapter 4) conducted before the main analyses centred around ethnicity, that there was no discrepancy in NTD prevalence by maternal deprivation for non-isolated NTD cases. Therefore, adjusting for folic acid use in the regression model exploring the association between ethnicity and NTD prevalence might have had little impact.

Dietary habits, specifically vegetarianism, could not be explored in the study. However, it has been reported that in the North of India there is an increased risk of NTDs in Hindu mothers who follow a vegetarian diet (63) and this could have been a contributory factor in the study.

As described in Chapter 4, it was not possible to explore NTD recurrence in the quantitative study, which is a limitation of the current research as the recurrence risk is higher than the first time risk for NTDs (10). This could have been of particular consequence for mothers of Indian ethnicity due to the high NTD recurrence rate in India that has been reported in the literature (62). However, it is unlikely to have had a major attenuating effect on the observed NTD prevalence excess observed in Indian mothers.

Again, detailed in the preliminary explorations for the quantitative study (Chapter 4), maternal body mass index (BMI) was only recorded well within NorCAS where there were indications that there were an excess of NTD cases for mothers who were obese (in accordance with the literature (44)). Maternal BMI would be recorded in all prenatal records, however it was only NorCAS that was routinely collecting this information for all data years included in the study (2006 to 2011). It is a limitation of the current study that the impact of maternal BMI on the association between ethnicity and NTD prevalence, could not be explored, particularly as obesity levels have been shown to be high in certain ethnic groups (84) and the risk of having an NTD affected pregnancy is increased in women who are obese (140). However, it is argued that BMI is not always a good measure of body fat composition and that mothers of South Asian ethnic origin are more likely to have a higher body fat composition than mothers of African ethnic origin for the same BMI level (84).

Finally, information on consanguinity could not be collected. This is unlikely to be a significant factor for Indian mothers but could influence risk for mothers of Bangladeshi ethnicity. In the literature, the importance of consanguinity as a risk factor for NTD prevalence in Pakistani mothers has been described (77) and it is arguable that this is likely to also be the case for other populations that are

predominantly Muslim and who favour first-cousin marriages, such as individuals of Bangladeshi ethnicity (203).

7.1.1.4 No congenital anomaly data for London

There was no congenital anomaly register covering any part of London, which has significant ethnic and socio-economic diversity. Such data would therefore have contributed invaluable information to the analysis.

7.1.2 Conclusions

Based on data from EMSYCAR and SWCAR, including TOPFA cases, with a denominator of over half a million births, robust NTD prevalence estimates by ethnicity were calculated. The increased NTD prevalence in Indian mothers was shown to be specifically for anencephaly affected pregnancies and in Bangladeshi mothers for spina bifida affected pregnancies, when compared to mothers of White ethnicity. Looking solely at the EMSYCAR data, it was also indicated that the anencephaly prevalence discrepancy for Indian and White mothers was likely to be attributed more to an increase in non-isolated than isolated cases, which is strongly indicative of the involvement of genetic factors. The persistently high NTD prevalence in the Indian population, regardless of where they reside, also points towards genetics. Although in analyses stratified by whether the NTD was isolated or not, numbers became very small for Bangladeshi mothers and no conclusions could be drawn, the likely importance of consanguinity for Bangladeshi mothers, also suggests the involvement of genetic factors.

Mothers of Indian ethnicity retain their high NTD prevalence wherever they reside and previous research in the U.K has reported an increased NTD prevalence in mothers from this ethnic group in several geographical areas, therefore it would be expected that the excess NTD prevalence observed in Indian mothers in this study would be applicable beyond the geographical area studied. For Bangladeshi mothers, the findings would be extrapolated to other geographical areas with more caution, although it is possible that it is due to small sample sizes and lower

precision of estimates that a specific excess in mothers from this ethnic group has not been more commonly described in previous studies. An excess NTD prevalence in Pakistani mothers was not observed in this study but has been described in studies conducted in other regions of the U.K. This could indicate that there is geographical variation in NTD prevalence for certain ethnic groups.

Despite the absence of data on dietary habits and folic acid use, it would be unlikely that they would be able to explain entirely ethnic discrepancies in NTD prevalence observed. For folic acid use, this is further reinforced by there being little change to the observed association between ethnicity and NTD prevalence, when maternal deprivation is taken into account. The latter observation also highlights the critical importance of looking at maternal deprivation when exploring ethnicity in epidemiological research, but also the value of including ethnicity as an independent variable, beyond a consideration of socio-economic factors.

7.2 What are the best prevention strategies for NTDs in ethnic communities?

Increasing folic acid use is a highly effective NTD prevention strategy and it is estimated that folic acid can prevent between 50 and 70% of NTDs (15). It has been described how pre-conceptional folic acid use is low in mothers of non-White ethnicity, with indications that this was particularly true for mothers of South Asian ethnicity, when compared to mothers of White ethnicity. However, use is still low within White mothers (22;103). Therefore, all populations are seriously lacking in suitable folic acid supplementation and increasing its usage would have a beneficial effect in all groups, including ethnic groups with a high NTD prevalence, even if it is not a key reason for the ethnic discrepancy observed.

The qualitative research was conducted with South Asian mothers, in whom an NTD prevalence excess has been described in this thesis and previously. Two Indian mothers, four Bangladeshi mothers and two Pakistani mothers who had a child with spina bifida were interviewed. Four out of the eight mothers reported

that had taken folic acid before pregnancy. However, two of the mothers were taking folic acid routinely for a vitamin absorption problem.

The qualitative study enabled explorations that went beyond a simple quantification of whether South Asian mothers took folic acid or not to gaining in-depth information about why they might not have adequate knowledge of supplementation and how both folic acid knowledge and use can best be improved. The qualitative research emphasised that although it is important to give information about the benefits of taking folic acid before pregnancy, there are also benefits in providing such information during pregnancy as this could help to protect a future pregnancy. This was particularly striking as all mothers interviewed had a previous pregnancy before their NTD affected pregnancy and there was a strong sense of earlier pregnancies setting norms for later ones. It was emphasised that GPs or other health professionals (HPs) giving advice on prenatal prevention was likely to have the greatest impact as South Asian mothers said that they both respected and thought their GP/midwife had a responsibility to provide this information. Therefore, it is argued that a culturally sensitive education campaign should be targeted at HPs to first improve their understanding about NTD prevention, including key situational factors that need to be taken into account and misconceptions that need to be addressed (based on responses from interviewees). This would be a crucial first stage in increasing knowledge and use of folic acid among women from minority ethnic groups, in particular those with high rates of NTDs or congenital anomalies.

In the discussion of findings for the qualitative research in Chapter 6 the difficulty of the routine of tablet taking was emphasised. It was also detailed that it cannot be assumed that mothers who have not had an NTD affected pregnancy will take folic acid when aware of its benefits based on the fact that all mothers interviewed in the study took folic acid for subsequent pregnancies after having a child with spina bifida.

As detailed in Chapter 2, four out of the five studies included in the systematic review conducted in the early stages of this doctoral thesis, exploring knowledge and peri-conceptional use of folic acid by women from different ethnic communities

in the U.K, argued that fortification of food with folic acid is the most effective method to improve folate intake (22).A study by Morris and colleagues (204) using congenital anomaly data from England and Wales found that if mandatory fortification had been adopted between 1998 and 2012 in the U.K at the same level as in the USA, 2014 fewer pregnancies would have been affected by an NTD. This equates to an approximately 21% reduction in NTD prevalence (204).

It is therefore very strongly recommended that in addition to the targeting of culturally sensitive education campaigns at HPs in order to improve their understanding of NTDs that, as a matter of urgency, a mandatory fortification policy be implemented in the U.K, including the fortification of ethnic minority foods. The reality of the situation in the U.K, as described in Morris and Wald's earlier study, published in 2007, that there has been little change in NTD prevalence since the late 1980s (32) when compared to the projected impact on prevalence if mandatory fortification had been introduced, as detailed in Morris and colleagues recent study (204), is stark and shocking. Mandatory fortification is both a safe and cost effective method to increase folic acid intake and it is argued that it is a public health failure that it has not been implemented in the U.K (204).

7.2.1 Qualitative study limitations

This study was targeted at mothers of South Asian ethnicity with a previous NTD affected pregnancy, however, only mothers of children living with spina bifida came forward to be interviewed, as described, due to women mainly being recruited through Great Ormond Street Children's Hospital (GOSH). In particular, no mothers of Indian ethnicity with a previous anencephaly affected pregnancy were interviewed. However, it should be kept in mind that this was a qualitative study that was not intended to be representative of all NTD subtypes but rather to explore in-depth the pregnancy experiences and decisions of mothers with affected babies.

It was stated on the participant information sheet that pre-pregnancy knowledge, attitudes and health behaviour would be explored and folic acid wasn't specifically

mentioned as several factors were explored. However, when asked what the term pre-pregnancy means to them, all mothers spoke about folic acid. Therefore, knowing that folic acid knowledge and use was something that was likely to be discussed, could have affected how women recalled information about this in the interview. It is also of importance to note that although for the majority of mothers interviewed, their child who had spina bifida was a baby or a young child, for two interviewees the children were older. The time since their pregnancy with their child could have affected recall. However, due to this being a very difficult and distressing time for all interviewees, the memory of that time period seemed to be very clear and vivid. A further important final consideration is how an individual's current situation might have affected the interpretation of previous events. All women interviewed had a child living with spina bifida who they loved very much and any previous discussions around termination might have seemed all the more horrifying because of this. However, specific details of previous conversations around termination still, in some cases, clearly denoted a lack of respect for the mother's decision to continue the pregnancy.

7.2.2 Conclusions

At the end of the systematic review conducted in the early stages of this doctoral thesis it was argued that innovative education campaigns should be targeted at ethnic communities to improve folic acid use together with a mandatory fortification policy. Based on in-depth interviews with mothers of South Asian ethnicity with a previous NTD affected pregnancy, this recommendation is altered slightly to argue for the targeting of culturally sensitive education campaigns at HPs, as these are the individuals from whom women are willing to receive information. The recommendation for mandatory fortification still remains.

7.3 Why do women decide to continue a spina bifida affected pregnancy and how can we ensure it is a fully informed decision

As detailed in Chapter 5, it was shown that mothers of Pakistani and Black African ethnicity were statistically significantly less likely to terminate an NTD affected pregnancy than mothers of White ethnicity using data from EMSYCAR and SWCAR. It has previously been reported in the literature how mothers of Pakistani ethnicity are less likely to terminate a pregnancy affected by a congenital anomaly than White mothers (92). Also in line with previous research around termination of pregnancy for fetal anomaly (TOPFA) for congenital anomalies in general (92), it was shown that mothers living in less deprived areas and mothers in which the condition is detected earlier are more likely to terminate an NTD affected pregnancy. There was also some evidence that TOPFA was less likely in younger mothers. However, even after adjustment for all of these factors, an ethnic difference in TOPFA rates in the quantitative study was still detected. Ethnic differences in TOPFA rates identified are important, however, it is of critical importance not to make assumptions beyond the data at hand. One of the mothers of South Asian ethnicity in the qualitative study described how a HP counselling her automatically assumed she was deciding to continue her pregnancy for religious reasons, whereas she stated that in fact she continued because she already loved her baby.

Ahmed and colleagues described how the perceived severity of the condition/quality of life of the child is the most important factor when deciding whether to continue a pregnancy affected by a fetal anomaly or not. They therefore argued that there is a real need to move away from stereotypical views based on faith and ethnicity, towards looking at the beliefs of individuals (162;163). Ensuring a distinction is drawn between perceived severity and actual severity is critical. Looking at the quantitative data, the fact that it was specifically for spina bifida (and not anencephaly) affected pregnancies that there was an ethnic discrepancy in TOPFA rates, could lead to the argument that severity of the NTD is a key factor affecting a mothers decision of whether to continue the pregnancy or not. However, looking more closely at the data, this argument is inadequate. Although not statistically significant, Black African mothers had TOPFA rates of a similar

magnitude lower than White mothers for both spina bifida and anencephaly affected pregnancies and again, although not statistically significant, the effect size for Pakistani mothers in the anencephaly model was also quite strong. Moreover, looking at overall TOPFA rates for anencephaly and spina bifida affected pregnancies in the BINOCAR dataset, although 90% of anencephaly affected pregnancies are terminated, there are still 79% of spina bifida affected pregnancies (the less severe phenotype) that are terminated.

The inadequacy of looking at severity of the condition and importance of looking at perceived severity of the condition, in a consideration of the factors affecting a decision of whether to continue a spina bifida affected pregnancy or not, was strongly accentuated through the qualitative research. South Asian mothers who were interviewed described how the picture they got of spina bifida was often bleak and didn't emphasise that the prognosis for the condition is actually quite varied. It was typically those HPs who do not routinely see children living with spina bifida that were described as giving a one-sided view and they were also perceived as driving TOPFA quite strongly. It was for this reason that it was argued that the invisibility of NTDs could be affecting HPs perceptions of the condition, which is something which was also evident in explorations around how and when HPs give information about folic acid in the earlier part of the qualitative research. To ensure that mothers are able to make a fully informed decision about whether to continue their spina bifida affected pregnancy or not, it was therefore recommended that those who routinely see children with spina bifida work more closely with those who counsel women about the condition but only rarely see affected children, to increase both their understanding and sensitivity towards it.

7.3.1 Conclusions

The quantitative research for this thesis was important for highlighting an ethnic discrepancy in TOPFA rates for spina bifida affected pregnancies, even after taking into account gestational age at discovery and maternal deprivation. However, it is important to be cautious when interpreting the results and not taking the interpretation beyond the data at hand i.e. assuming that religion is an important

factor because of the ethnic difference. This was accentuated through the qualitative research and has also been described previously (162;163). Moreover, indicators in the quantitative research that severity of condition was inadequate in explaining differences in outcomes for anencephaly and spina bifida affected, was further developed in the qualitative research which accentuated the critical importance of **perceived** severity. Based on detailed accounts, mothers seem to be given a worst case picture of spina bifida as how things will be, rather than as a possible outcome by HPs who do not routinely see children with spina bifida. Therefore, it is recommended that the prenatal team counselling mothers when a fetal anomaly is detected work more closely with the clinical teams who care for children with NTDs to ensure mothers are given a more balanced picture from the outset in order to be able to make a fully informed decision.

7.4 Appropriateness of using mixed methodology

The outcomes of this doctoral thesis have accentuated the appropriateness of using mixed methodology (both quantitative and qualitative) as opposed to solely quantitative or qualitative methods to address the research questions. Through the quantitative study it was possible to calculate robust NTD prevalence estimates for different ethnic groups with a clear indication of the involvement of genetic factors in explaining the difference. However, it was only through the qualitative study that in-depth information could be obtained to understand the views, knowledge, behaviour and attitudes of ethnic groups where a high NTD prevalence has been described, before and during their pregnancy affected by an NTD. This enabled a clear, informed prevention strategy to be recommended surrounding the best prevention tool for NTDs that we have: folic acid supplementation.

Moreover, the integration of qualitative and quantitative components for the research exploring women's decisions to continue an NTD affected pregnancy or not, were very revealing and essential to more fully understand the complexity of the issue. The ethnic discrepancy in TOPFA rates reported in the quantitative study identified important differences, however, the in-depth interviews accentuated that there was a need to look beyond simple categories of ethnicity to understand what

these represent. Individuals' detailed experiences constantly challenged a view which it is very easy adhere to without being consciously aware, of ethnic distinctions as natural and unchanging. Particularly with regards to the question around pregnancy decisions, findings from the qualitative study brought a different perspective to the results from the quantitative study and affected interpretation as the quantitative study, to a certain extent, affected the focus of the qualitative research.

The decision was made to focus on mothers of South Asian ethnicity in the qualitative research due to an increased NTD prevalence (Indian and Bangladeshi) and lower TOPFA rates (Pakistani) in mothers from this ethnic grouping found in the quantitative research (as well as the excess NTD prevalence for Pakistani mothers described in the literature). This meant that specific cultural factors could be explored and culturally sensitive recommendations proposed to form part of an NTD prevention strategy. It also meant that no restrictions needed to be placed based on language and that no-one needed to be excluded because on this, which could have biased who was interviewed. However, it did mean that the number of women interviewed was relatively small and recruitment took place over several months. It also meant that the views of women from other ethnic communities could not be represented, for example, in the quantitative analysis it was found that mothers of Black African ethnicity had low TOPFA rates yet their views could not be explored within the scope of this thesis.

7.5 Implications for practice and prevention

The identified problems of using existing coding systems for exploring isolated and non-isolated congenital anomalies in analyses, accentuates the need for an aetiological-based coding system that is more robust. EUROCAT's multiple congenital anomaly algorithm is an effective and replicable tool for categorising congenital anomaly cases that could be implemented across all registers. However, it needs further refinement with a greater emphasis on the recording and classifying of multiple malformations, before it can be used with confidence in all epidemiological analyses.

It is also of critical importance that information governance processes for key data providers, such as ONS and HES, are more seamless and transparent for researchers. Section 251 approval was obtained for the PhD research to enable linkage between the HES and ONS data, which was of particular importance in matching baby's ethnicity to mother's ethnicity. However, due to information governance changes, no data could be obtained in the study time frame, which spanned several years. This is something that really needs to be addressed to ensure that the best possible data are used for analysis.

As shown by the missing ethnicity data, BMI data being only available for one register and folic acid usage data that was poorly and imprecisely recorded, there is significant room for improving reporting to registers. This is important not only for in-depth epidemiological studies but also for routine monitoring. Implementation of the new National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) began in April 2015 and could help to harmonise reporting across all geographical areas. Also, the fact that the NCARDRS will cover the whole of England, will mean that London data will also be included. However, the rigorous, multi-source reporting to registers that has been built up over several years and through the hard work of many individuals is not something that it will be easy to replicate overnight at a national scale. Therefore, the quality of data output could actually be diminished in the early stages of the national registration service being implemented.

Looking to prevention, it is proposed based on the responses of interviewees in the qualitative research that culturally sensitive education campaigns should be targeted at HPs to ensure they have adequate understanding of the complexity of NTDs and can relay information effectively to mothers from ethnic communities about the benefits of folic acid. However, considerations also need to be given to gaining funding for such an initiative and the allocation of time for GPs, who have busy schedules, for the different sessions.

It is also recommended that the fetal medicine team work more closely with the neurosurgical team to ensure the former have adequate understanding about spina

bifida and give a balanced picture about prognosis when counselling families. This is not an untested recommendation and has actually been shown to be highly effective in Leicester (201). There seems to be a real need, particularly in London based on the responses of the interviewees, to strongly consider this setup.

7.6 Further research

As the impact of obesity on the observed association between ethnicity and NTD prevalence could not be explored in the quantitative study, this would be an important area for future research. This is of particular importance due to the described association between obesity and NTD prevalence and the fact that obesity levels have been found to be high in mothers from certain ethnic communities (84).

It would also be important to conduct the study in other geographical areas of the U.K. to explore whether an excess in NTD prevalence for the same ethnic groups is observed. This might be possible using NCARDRS data once this system is well-established.

There is also a real need to better characterise the non-isolated NTDs in Indian mothers, where a clear excess is indicated. This includes gene studies to explore genetic causation. This research is a crucial first stage before being able to implement effective prevention strategies for this particular malformation type.

As described, only South Asian mothers of children with spina bifida were interviewed in the qualitative study. There are a number of broader hard-to-reach groups whose views would contribute to a better understanding of women's decisions during pregnancy and so to the prevention and management of NTDs. These include bereaved mothers and women who decided to terminate the pregnancy (including mothers who have an anencephaly affected pregnancy). It also would be of importance to explore the views of women from other cultural/ethnic groups.

7.7 Summary

The described increased NTD prevalence in mothers of Indian (anencephaly) and Bangladeshi (spina bifida) ethnicity when compared to mothers of White ethnicity, with an indication that the difference is more marked for non-isolated NTDs in Indian mothers, is strongly indicative of the involvement of genetic factors. However, increasing folic acid supplementation in all populations for NTD prevention is essential and a crucial first stage in increasing knowledge and use among South Asian mothers, where supplementation seems to be worryingly low, is by targeting a culturally sensitive campaign at HPs. Increasing understanding among HPs about spina bifida, a largely invisible condition due to the high TOPFA rate, in particular is also of critical importance to ensure HPs give a balanced view about the condition when counselling mothers about their pregnancy choices.

Reference List

(1) Kurinczuk JJ, Hollowell J, Boyd PA, Oakley L, Brocklehurst P, Gray R. The contribution of congenital anomalies to infant mortality. National perinatal epidemiology unit, university of Oxford Inequality in infant mortality project briefing paper 2010;1-13.

(2) Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol 2010;686:349-64.

(3) Copp AJ, Greene ND. Neural tube defects--disorders of neurulation and related embryonic processes. Wiley Interdiscip Rev Dev Biol 2013 Mar;2(2):213-27.

(4) Greene ND, Stanier P, Copp AJ. Genetics of human neural tube defects. Hum Mol Genet 2009 Oct 15;18(R2):R113-R129.

(5) Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol 2013 Aug;12(8):799-810.

(6) Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, Shaw GM. Spina bifida. Nature Reviews Disease Primers 2015 Apr 30;15007.

(7) Record RG, McKeown T. Congenital Malformations of the Central Nervous System: I-A Survey of 930 Cases*. British Journal of Social Medicine 1949;3(4):183.

(8) Obladen M. Cats, frogs, and snakes: early concepts of neural tube defects. J Child Neurol 2011 Nov;26(11):1452-61.

(9) Carter CO. Clues to the aetiology of neural tube malformations. Developmental Medicine & Child Neurology 1974 Dec;16(6:Suppl 32):Suppl-15.

(10) Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. [Review] [63 refs]. DEV DISABIL RES REV 2010;16(1):6-15.

(11) Frey L, Hauser WA. Epidemiology of neural tube defects. [Review] [82 refs]. Epilepsia 2003;44:Suppl-13.

(12) Xiao KZ, Zhang ZY, Su YM, Liu FQ, Yan ZZ, Jiang ZQ, et al. Central nervous system congenital malformations, especially neural tube defects in 29 provinces, metropolitan cities and autonomous regions of China: Chinese Birth Defects Monitoring Program. Int J Epidemiol 1990 Dec;19(4):978-82.

(13) Bound JP, Harvey PW, Francis BJ. Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J EPIDEMIOL COMMUNITY HEALTH 1989 Dec;43(4):330-42.

(14) Tanoshima M, Kobayashi T, Tanoshima R, Beyene J, Koren G, Ito S. Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis. Clin Pharmacol Ther 2015 Jun 5.

(15) Dunlap B, Shelke K, Salem SA, Keith LG. Folic acid and human reproduction-ten important issues for clinicians. Journal of Experimental & Clinical Assisted Reproduction 2011;8:2.

(16) Bower C, Stanley FJ. Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. Med J Aust 1989 Jun 5;150(11):613-9.

(17) Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet 1991 Jul 20;338(8760):131-7.

(18) Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992 Dec 24;327(26):1832-5.

(19) Daly S, Mills JL, Molloy AM, Conley M, Lee YJ, Kirke PN, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. Lancet 1997 Dec 6;350(9092):1666-9.

(20) Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet 2001 Dec 15;358(9298):2069-73.

(21) Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med 1999 Nov 11;341(20):1485-90.

(22) Peake JN, Copp AJ, Shawe J. Knowledge and periconceptional use of folic acid for the prevention of neural tube defects in ethnic communities in the United Kingdom: systematic review and meta-analysis. Birth Defects Res A Clin Mol Teratol 2013 Jul;97(7):444-51.

(23) Centers for Disease Control and Prevention (CDC. Spina bifida and anencephaly before and after folic acid mandate--United States, 1995-1996 and 1999-2000. MMWR Morbidity and mortality weekly report 2004;53(17):362.

(24) De WP, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med 2007 Jul 12;357(2):135-42.

(25) Bower C. Prevention of neural tube defects with folate. J Paediatr Child Health 2013 Jan;49(1):2-4.

(26) Brown RD, Langshaw MR, Uhr EJ, Gibson JN, Joshua DE. The impact of mandatory fortification of flour with folic acid on the blood folate levels of an Australian population. Med J Aust 2011 Jan 17;194(2):65-7.

(27) Bower C, Maxwell S, Hickling S, D'Antoine H, O'Leary P. Folate status in Aboriginal people before and after mandatory fortification of flour for bread-making in Australia. Aust N Z J Obstet Gynaecol 2015 Dec 10.

(28) Bower C, Eades S, Payne J, D'Antoine H, Stanley F. Trends in neural tube defects in Western Australia in Indigenous and non-Indigenous populations. Paediatr Perinat Epidemiol 2004 Jul;18(4):277-80.

(29) Clark NA, Fisk NM. Minimal compliance with the Department of Health recommendation for routine folate prophylaxis to prevent fetal neural tube defects. Br J Obstet Gynaecol 1994 Aug;101(8):709-10.

(30) Raats MM, Thorpe L, Hurren C, Elliott K. Changing Preconceptions. Volume 2. The HEA Folic Acid Campaign 1995-1998. Summary Report Trevelyan House, London: London Health Education Authority 1998.

(31) Neill AM, Laing RJ, Perez P, Spencer PJ. The 'Folic Acid Campaign': has the message got through? A questionnaire study. J Obstet Gynaecol 1999 Jan;19(1):22-5.

(32) Morris JK, Wald NJ. Prevalence of neural tube defect pregnancies in England and Wales from 1964 to 2004. J Med Screen 2007;14(2):55-9.

(33) Morris JK, Wald NJ. Quantifying the decline in the birth prevalence of neural tube defects in England and Wales. J Med Screen 1999;6(4):182-5.

(34) Botto LD, Lisi A, Robert-Gnansia E, Erickson JD, Vollset SE, Mastroiacovo P, et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working? Br Med J 2005 Mar 12;330(7491):571.

(35) Busby A, Abramsky L, Dolk H, Armstrong B, Addor MC, Anneren G, et al. Preventing neural tube defects in Europe: a missed opportunity. Reprod Toxicol 2005 Sep;20(3):393-402.

(36) Centers for Disease Control and Prevention (CDC). Folate status in women of childbearing age, by race/ethnicity--United States, 1999-2000, 2001-2002, and 2003-2004. MMWR - Morbidity & Mortality Weekly Report 2007 Jan 5;55(51-52):1377-80.

(37) Bitzer J, von SA, Bannemerschult R. Women's awareness and periconceptional use of folic acid: data from a large European survey. Int J Womens Health 2013;5:201-13.

(38) Amorim MR, Lima MA, Castilla EE, Orioli IM. Non-Latin European descent could be a requirement for association of NTDs and MTHFR variant 677C > T: a meta-analysis. American Journal of Medical Genetics Part A 2007 Aug 1;143A(15):1726-32.

(39) Heseker HB, Mason JB, Selhub J, Rosenberg IH, Jacques PF. Not all cases of neural-tube defect can be prevented by increasing the intake of folic acid. British Journal of Nutrition 2009 July;102(2):173-180.

(40) Kirke PN, Molloy AM, Daly LE, Burke H, Weir DG, Scott JM. Maternal plasma folate and vitamin B12 are independent risk factors for neural tube defects. Q J Med 1993 Nov;86(11):703-8.

(41) Cavalli P, Copp AJ. Inositol and folate resistant neural tube defects. J Med Genet 2002 Feb;39(2):E5.

(42) Molloy AM, Kirke PN, Troendle JF, Burke H, Sutton M, Brody LC, et al. Maternal vitamin B12 status and risk of neural tube defects in a population with high neural tube defect prevalence and no folic Acid fortification. Pediatrics 2009 Mar;123(3):917-23.

(43) Hoffbrand AV. Professor John Scott, folate and neural tube defects. Br J Haematol 2014 Feb;164(4):496-502.

(44) McMahon DM, Liu J, Zhang H, Torres ME, Best RG. Maternal obesity, folate intake, and neural tube defects in offspring. Birth Defects Res A Clin Mol Teratol 2013 Feb;97(2):115-22.

(45) Khoury MJ FAU, Erickson JD FAU, James LM. Etiologic heterogeneity of neural tube defects: clues from epidemiology. Am J Epidemiol 1982 Apr;115(4):538-48.

(46) Greene ND, Massa VF, Copp AJ. Understanding the causes and prevention of neural tube defects: Insights from the splotch mouse model. Birth Defects Res A Clin Mol Teratol 2009 Apr;85(4):322-30.

(47) Stevenson RE, Seaver LH, Collins JS, Dean JH. Neural tube defects and associated anomalies in South Carolina. Birth Defects Res A Clin Mol Teratol 2004 Sep;70(9):554-8.

(48) Stoll C, Dott B, Alembik Y, Roth MP. Associated malformations among infants with neural tube defects. Am J Med Genet A 2011 Mar;155A(3):565-8.

(49) Boyd PA, Tonks AM, Rankin J, Rounding C, Wellesley D, Draper ES. Monitoring the prenatal detection of structural fetal congenital anomalies in England and Wales: register-based study. J Med Screen 2011;18(1):2-7.

(50) Flores AL, Vellozzi C, Valencia D, Sniezek J. Global Burden of Neural Tube Defects, Risk Factors, and Prevention. Indian J Community Health 2014 Nov;26(Suppl 1):3-5.

(51) Christianson A, Howson CP, Modell B. March of Dimes: global report on birth defects, the hidden toll of dying and disabled children. March of Dimes Birth Defects Foundation. 2005.

(52) World Health Organisation. Prevention and Control of Birth Defects in South-East Asia Region: Strategic Framework 2013-2017. 2013. Available

from: http://apps.searo.who.int/PDS_DOCS/B4941.pdf [Accessed 19th August 2015]

(53) Mitchell LE. Epidemiology of neural tube defects. American Journal of Medical Genetics - Seminars in Medical Genetics 135 C (1) (pp 88-94), 2005 Date of Publication: 15 May 2005(1):15.

(54) Leck I. Causation of neural tube defects: clues from epidemiology. Br Med Bull 1974 May;30(2):158-63.

(55) Verma IC. High frequency of neural-tube defects in North India. Lancet 1978 Apr 22;1(8069):879-80.

(56) Baird PA. Neural tube defects in the Sikhs. American Journal of Medical Genetics 1983 Sep;16(1):49-56.

(57) Millar J, Etches DJ, Diaz S. Ethnic groups. Primary Care - Clinics in Office Practice 22 (4) (pp 713-730), 1995 Date of Publication: 1995(4):1995.

(58) Allagh KP, Shamanna BR, Murthy GV, Ness AR, Doyle P, Neogi SB, et al. Birth prevalence of neural tube defects and orofacial clefts in India: a systematic review and meta-analysis. PLoS One 2015;10(3):e0118961.

(59) Bhide P, Sagoo GS, Moorthie S, Burton H, Kar A. Systematic review of birth prevalence of neural tube defects in India. Birth Defects Res A Clin Mol Teratol 2013 Jul;97(7):437-43.

(60) Kulkarni ML, Mathew MA, Reddy V. The range of neural tube defects in southern India. Arch Dis Child 1989 Feb;64(2):201-4.

(61) Mahadevan B, Bhat BV. Neural tube defects in Pondicherry. Indian J Pediatr 2005 Jul;72(7):557-9.

(62) Central Technical Co-ordinating Unit ITCUI. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. Indian J Med Res 2000 Dec;112:206-11.

(63) Deb R, Arora J, Meitei SY, Gupta S, Verma V, Saraswathy KN, et al. Folate supplementation, MTHFR gene polymorphism and neural tube defects: a community based case control study in North India. Metabolic Brain Disease 2011 Sep;26(3):241-6.

(64) Deb R, Arora J, Saraswathy KN, Kalla AK. Association of sociodemographic and nutritional factors with risk of neural tube defects in the North Indian population: a case-control study. Public Health Nutr 2014 Feb;17(2):376-82.

(65) Pathak P, Kapil U, Yajnik CS, Kapoor SK, Dwivedi SN, Singh R. Iron, folate, and vitamin B12 stores among pregnant women in a rural area of Haryana State, India. Food Nutr Bull 2007 Dec;28(4):435-8.

(66) Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least-developed area of India: a population-based study. Lancet 2005 Sep 10;366(9489):930-1.

(67) Salvi VS, Damania KR. Neural tube defects in India--time for action. Lancet 2005 Sep 10;366(9489):871-2.

(68) Gole RA, Meshram PM, Hattangdi SS. Anencephaly and its associated malformations. J Clin Diagn Res 2014 Sep;8(9):AC07-AC09.

(69) Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics 2005 Sep;116(3):580-6.

(70) Njamnshi AK, Djientcheu VP, Lekoubou A, Guemse M, Obama MT, Mbu R, et al. Neural tube defects are rare among black Americans but not in sub-Saharan black Africans: the case of Yaounde - Cameroon.[Erratum appears in J Neurol Sci. 2009 May 15;280(1-2):135]. J Neurol Sci 2008 Jul 15;270(1-2):13-7.

(71) Dowd JB, Aiello AE. Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? Int J Epidemiol 2008 Oct;37(5):1059-66.

(72) Leck I. Ethnic differences in the incidence of malformations following migration. British Journal of Preventive & Social Medicine 1969 Aug;23(3):166-73.

(73) Leck I, Lancashire RJ. Birth prevalence of malformations in members of different ethnic groups and in the offspring of matings between them, in Birmingham, England. J Epidemiol Community Health 1995 Apr;49(2):171-9.

(74) Terry PB, Bissenden JG, Condie RG, Mathew PM. Ethnic differences in congenital malformations. Arch Dis Child 1985 Sep;60(9):866-8.

(75) Balarajan R, McDowall M. Mortality from congenital malformations by mother's country of birth. J Epidemiol Community Health 1985 Jun;39(2):102-6.

(76) Gillies DR, Lealman GT, Lumb KM, Congdon P. Analysis of ethnic influence on stillbirths and infant mortality in Bradford 1975-81. J Epidemiol Community Health 1984 Sep;38(3):214-7.

(77) Chitty LS, Winter RM. Perinatal mortality in different ethnic groups. Arch Dis Child 1989 Jul;64(7):1036-41.

(78) Chitty LS, Winter RM. Perinatal mortality in different ethnic groups. Arch Dis Child 1989 Jul;64(7):1036-41.

(79) Alberman E. Congenital malformations. Br Med J 1989 Dec 9;299(6713):1416.

(80) Chitty L, Winter RM. Congenital malformations. Br Med J 1990 Jan 13;300(6717):121-2.

(81) Michie CA, Chambers J, Abramsky L, Kooner JS. Folate deficiency, neural tube defects, and cardiac disease in UK Indians and Pakistanis. Lancet 351 (9109) (pp 1105), 1998 Date of Publication: 11 Apr 1998(9109):11.

(82) Tonks A, Wyldes M, Whittle M. Neural Tube Defects 1995: Report of Incidence, Detection and Outcome. West Midlands Congenital Anomaly Register. Report No: 5, 1995

(83) Sheridan E, Wright J, Small N, Corry PC, Oddie S, Whibley C, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. Lancet 2013 Jul 3.

(84) Gatineau M, Mathrani S. Ethnicity and obesity in the UK. Perspect Public Health 2011 Jul;131(4):159-60.

(85) Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. Br Med J 2006 Jul 22;333(7560):177.

(86) Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, et al. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med 2007 Aug;161(8):745-50.

(87) Watt HC, Wald NJ, Smith D, Kennard A, Densem J. Effect of allowing for ethnic group in prenatal screening for Down's syndrome. Prenatal Diag 1996 Aug;16(8):691-8.

(88) Rowe RE, Garcia J, Davidson LL. Social and ethnic inequalities in the offer and uptake of prenatal screening and diagnosis in the UK: a systematic review. [Review] [33 refs]. Public Health 2004 Apr;118(3):177-89.

(89) Marteau TM, Johnston M, Shaw RW, Slack J. Factors influencing the uptake of screening for open neural-tube defects and amniocentesis to test for Down's syndrome. Br J Obstet Gynaecol 1989 Jun;96(6):739-41.

(90) Hamilton SM, Maresh MJ. Antenatal screening by history taking--a missed opportunity. J Obstet Gynaecol 1999 Jan;19(1):10-4.

(91) Hewison J, Green JM, Ahmed S, Cuckle HS, Hirst J, Hucknall C, et al. Attitudes to prenatal testing and termination of pregnancy for fetal abnormality: A comparison of white and Pakistani women in the UK. Prenatal Diagnosis 2007 May;27(5):419-430.

(92) Smith LK, Budd JL, Field DJ, Draper ES. Socioeconomic inequalities in outcome of pregnancy and neonatal mortality associated with congenital anomalies: population based study. Br Med J 2011;343:d4306.

(93) Stockley L, Lund V. Use of folic acid supplements, particularly by low-income and young women: a series of systematic reviews to inform public health policy in the UK. Public Health Nutrition 2008 Aug;11(8):807-21.

(94) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Br Med J 2009;339:b2535.

(95) Borenstein M, Hedges L, Rothstein H. Meta-analysis: fixed effect vs. random effects. Meta-Analysis com 2007.

(96) StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP. 2011

(97) Tedstone A, Browne M, Harrop L, Vernon C, Page V, Swindells J, et al. Fortification of selected foodstuffs with folic acid in the UK: consumer research carried out to inform policy recommendations. J PUBLIC HEALTH 2008 Mar;30(1):23-9.

(98) Howell SR, Barnett AG, Underwood MR. The use of pre-conceptional folic acid as an indicator of uptake of a health message amongst white and Bangladeshi women in Tower Hamlets, east London. Fam Pract 2001 Jun;18(3):300-3.

(99) Krischer J. Knowledge about folic acid and the prevention of neural tube defects in two general practice populations. Br J Gen Pract 1997 Apr;47(417):231-2.

(100) Jessa F, Hampshire AJ. Use of folic acid by pregnant British Pakistani women: a qualitative pilot study. Health Education Journal 1999 Jun 1;58(2):139-45.

(101) Brough L, Rees GA, Crawford MA, Dorman EK. Social and ethnic differences in folic acid use preconception and during early pregnancy in the UK: effect on maternal folate status. J HUM NUTR DIET 2009 Apr;22(2):100-7.

(102) Lane IR. Preventing neural tube defects with folic acid: Nearly 20 years on, the majority of women remain unprotected. Journal of Obstetrics and Gynaecology 2011 Oct;31(7):581-585.

(103) Bestwick JP, Huttly WJ, Morris JK, Wald NJ. Prevention of neural tube defects: a cross-sectional study of the uptake of folic acid supplementation in nearly half a million women. PLoS One 2014;9(2):e89354.

(104) Peach C. South Asian migration and settlement in Great Britain, 1951-2001. Contemporary South Asia 2006;15(2):133-46.

(105) Hawkins SS, Lamb K, Cole TJ, Law C. Influence of moving to the UK on maternal health behaviours: prospective cohort study. Br Med J 2008 May 10;336(7652):1052-5.

(106) Young ID, Clarke M. Lethal malformations and perinatal mortality: a 10 year review with comparison of ethnic differences. Br Med J (Clin Res Ed) 1987 Jul 11;295(6590):89-91.

(107) Johnson RB, Onwuegbuzie AJ. Mixed methods research: A research paradigm whose time has come. Educational researcher 2004;33(7):14-26.

(108) Johnson RB, Onwuegbuzie AJ, Turner LA. Toward a definition of mixed methods research. Journal of mixed methods research 2007;1(2):112-33.

(109) Castro FG, Kellison JG, Boyd SJ, Kopak A. A Methodology for Conducting Integrative Mixed Methods Research and Data Analyses. J Mix Methods Res 2010 Sep 20;4(4):342-60.

(110) Lingard L, Albert M, Levinson W. Grounded theory, mixed methods, and action research. Br Med J 2008;337:a567.

(111) Sheldon TA, Parker H. Race and ethnicity in health research. J Public Health Med 1992 Jun;14(2):104-10.

(112) Morris JK, Grinsted M, Springett AL. Accuracy of reporting abortions with Down syndrome in England and Wales: a data linkage study. J Public Health (Oxf) 2015 Mar 4.

(113) StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. 2013

(114) QSR International Pty Ltd. NVivo qualitative data analysis software: Verson 10. 2012.

(115) Boyd PA, Armstrong B, Dolk H, Botting B, Pattenden S, Abramsky L, et al. Congenital anomaly surveillance in England--ascertainment deficiencies in the national system. Br Med J 2005 Jan 1;330(7481):27.

(116) BINOCAR. British Isles Network of Congenital Anomaly Registers (BINOCAR): Data Quality. 2011. Available from: http://www.binocar.org/methods/dataquality [Accessed 22nd April 2014]

(117) Rankin J, Pattenden S, Abramsky L, Boyd P, Jordan H, Stone D, et al. Prevalence of congenital anomalies in five British regions, 1991-99. Arch Dis Child Fetal Neonatal Ed 2005 Sep;90(5):F374-F379.

(118) BINOCAR. British Isles Network of Congenital Anomaly Registers (BINOCAR): Data Collection. 2011. Available from: http://www.binocar.org/methods/datacollection [Accessed on 22nd April 2014]

(119) Boyle B, McConkey R, Garne E, Loane M, Addor MC, Bakker MK, et al. Trends in the prevalence, risk and pregnancy outcome of multiple births with congenital anomaly: a registry-based study in 14 European countries 1984-2007. BJOG 2013 May;120(6):707-16.

(120) Glinianaia SV, Rankin J, Wright C. Congenital anomalies in twins: a register-based study. Hum Reprod 2008 Jun;23(6):1306-11.

(121) Doyle PE, Beral V, Botting B, Wale CJ. Congenital malformations in twins in England and Wales. J EPIDEMIOL COMMUNITY HEALTH 1991 Mar;45(1):43-8.

(122) Li SJ, Ford N, Meister K, Bodurtha J. Increased risk of birth defects among children from multiple births. Birth Defects Res A Clin Mol Teratol 2003 Oct;67(10):879-85.

(123) Tang Y, Ma CX, Cui W, Chang V, Ariet M, Morse SB, et al. The risk of birth defects in multiple births: a population-based study. MATERN CHILD HEALTH J 2006 Jan;10(1):75-81.

(124) Bryan E, Little J, Burn J. Congenital anomalies in twins. Baillieres Clin Obstet Gynaecol 1987 Sep;1(3):697-721.

(125) Smith LK, Manktelow BN, Draper ES, Boyle EM, Johnson SJ, Field DJ. Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: population-based cohort study. BMJ Open 2014;4(4):e004514.

(126) Smits J, Monden C. Twinning across the Developing World. PLoS One 2011;6(9):e25239.

(127) Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol 2013 Jun 18.

(128) CARIS. Anomalies of Possible Concern: Neural Tube Defects. 2014. Available from: http://www.caris.wales.nhs.uk/anomalies-of-possible-concern. [Accessed 5th August 2014]

(129) Laurence KM. The apparent declining prevalence of neural tube defects in two counties of South Wales. Z Kinderchir 1985;supplement I(40):58-60.

(130) Cotter M, Elder S, Lawrence KM. Wales participation in the EUROCAT surveillance of congenital abnormalities: a report of the study in South Glamorgan and Gwent during 1992 (draft). WHCSA. 1994.

(131) Rankin J, Glinianaia S, Brown R, Renwick M. The changing prevalence of neural tube defects: a population-based study in the north of England, 1984-96. Northern Congenital Abnormality Survey Steering Group. Paediatr Perinat Epidemiol 2000 Apr;14(2):104-10.

(132) Armstrong BG, Dolk H, Pattenden S, Vrijheid M, Loane M, Rankin J, et al. Geographic variation and localised clustering of congenital anomalies in Great Britain. Emerg Themes Epidemiol 2007;4:14.

(133) Dolk H, De WP, Gillerot Y, Lechat MF, Ayme S, Cornel M, et al. Heterogeneity of neural tube defects in Europe: the significance of site of

defect and presence of other major anomalies in relation to geographic differences in prevalence. Teratology 1991 Nov;44(5):547-59.

(134) Wellesley D, Boyd P, Dolk H, Pattenden S. An aetiological classification of birth defects for epidemiological research. J Med Genet 2005 Jan;42(1):54-7.

(135) Garne E, Dolk H, Loane M, Wellesley D, Barisic I, Calzolari E, et al. Paper 5: Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases. Birth Defects Res A Clin Mol Teratol 2011 Mar;91 Suppl 1:S44-S50.

(136) Vieira AR, Castillo TS. [Maternal age and neural tube defects: evidence for a greater effect in spina bifida than in anencephaly]. Rev Med Chil 2005 Jan;133(1):62-70.

(137) Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Dev Disabil Res Rev 2010;16(1):6-15.

(138) Welsh Government. Welsh Index of Multiple Deprivation 2011: Summary Report. 2011. Available from: http://gov.wales/docs/statistics/2011/110831wimd11summaryen.pdf [Accessed 13th August 2014]

(139) Communities and Local Government. The English Indices of Deprivation 2010. 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/6320/1870718.pdf [Accessed 13th August 2014].

(140) Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009 Feb 11;301(6):636-50.

(141) World Health Organisation. World Health Organization (WHO) BMI classification. 2006. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html& 11-8-2014. [Accessed 11th August]

(142) Heslehurst N, Rankin J, Wilkinson JR, Summerbell CD. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989-2007. Int J Obes (Lond) 2010 Mar;34(3):420-8.

(143) Centre for Maternal and Child Enquiries. Maternal obesity in the UK: Findings from a national project. CMACE London. 2010

(144) Mytton J, Harrison V, McLoughlin A, Thompson R, Overton T. An evaluation of the recording of folic acid use in the South West Congenital Anomaly Register. Prenat Diagn 2008 Aug;28(8):722-6.

(145) Castilla EE, Orioli IM, Lugarinho R, Dutra GP, Lopez-Camelo JS, Campana HE, et al. Monthly and seasonal variations in the frequency of congenital anomalies. Int J Epidemiol 1990 Jun;19(2):399-404.

(146) de l, V, Lopez-Cepero R. Seasonal variations in the incidence of some congenital anomalies in Puerto Rico based on the timing of conception. P R Health Sci J 2009 Jun;28(2):121-5.

(147) Marzullo G, Fraser FC. Similar rhythms of seasonal conceptions in neural tube defects and schizophrenia: a hypothesis of oxidant stress and the photoperiod. Birth Defects Res A Clin Mol Teratol 2005 Jan;73(1):1-5.

(148) Darrow LA, Strickland MJ, Klein M, Waller LA, Flanders WD, Correa A, et al. Seasonality of birth and implications for temporal studies of preterm birth. Epidemiology 2009 Sep;20(5):699-706.

(149) Sheldon TA, Parker H. Race and ethnicity in health research. J Public Health Med 1992 Jun;14(2):104-10.

(150) Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. Br Med J 1994 Jul 30;309(6950):327-30.

(151) McKenzie K, Crowcroft NS. Describing race, ethnicity, and culture in medical research. Br Med J 1996 Apr 27;312(7038):1054.

(152) Dattani N, Datta-Nemdharry P, Macfarlane A. Linking maternity data for England, 2005-06: methods and data quality. Health Stat Q 2011;(49):53-79.

(153) Dattani N, Datta-Nemdharry P, Macfarlane AJ. Linking maternity data for England 2007: methods and data quality. Health Statistics Quarterly 2012;53:4-21.

(154) Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Br Med J 2009;338:b2393.

(155) ESRC Centre on Dynamics of Ethniciity (CoDE). Ethnicity and Deprivation in England: How likely are ethnic minorities to live in deprived neighbourhoods? 2013. Available from: http://www.ethnicity.ac.uk/medialibrary/briefingsupdated/ethnicity-and-deprivation-in-england-how-likely-are-ethnic-minorities-to-live-in-deprived-neighbourhoods%20%281%29.pdf. Accessed on 25th April 2014].

(156) Bener A, Al Maadid MG, Al-Bast DA, Al-Marri S. Maternal knowledge, attitude and practice on folic acid intake among Arabian Qatari women. Reproductive Toxicology 2006 Jan;21(1):21-5.

(157) Berg LTW, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Trends and predictors of folic acid awareness and periconceptional use in pregnant women. AM J OBSTET GYNECOL 2005;192(1):121-8.

(158) Fauzi NAM, McKenna D, Yusoff A, Rahman NA. Awareness and use of folic acid among Malaysian women of childbearing age. International Medical Journal 2009 Sep;16(3):201-9.

(159) Mannien J, de JA, Cornel MC, Spelten E, Hutton EK. Factors associated with not using folic acid supplements preconceptionally. Public Health Nutr 2013 Oct 10;1-7.

(160) Rosenberg KD, Gelow JM, Sandoval AP. Pregnancy intendedness and the use of periconceptional folic acid. Pediatrics 2003 May; 111(5 Pt 2):1142-5.

(161) Timmermans S, Jaddoe VW, Mackenbach JP, Hofman A, Steegers-Theunissen RP, Steegers EA. Determinants of folic acid use in early pregnancy in a multi-ethnic urban population in The Netherlands: the Generation R study. Prev Med 2008 Oct;47(4):427-32.

(162) Ahmed S, Hewison J, Green JM, Cuckle HS, Hirst J, Thornton JG. Decisions about testing and termination of pregnancy for different fetal conditions: a qualitative study of European White and Pakistani mothers of affected children. J Genet Couns 2008 Dec;17(6):560-72.

(163) Ahmed S, Atkin K, Hewison J, Green J. The influence of faith and religion and the role of religious and community leaders in prenatal decisions for sickle cell disorders and thalassaemia major. Prenatal Diag 2006 Sep;26(9):801-9.

(164) Ahmed S, Green JM, Hewison J. Attitudes towards prenatal diagnosis and termination of pregnancy for thalassaemia in pregnant Pakistani women in the North of England. Prenat Diagn 2006 Mar;26(3):248-57.

(165) Arif MO, Fatmi Z, Pardeep B, Ali T, Iqbal H, Bangash HK, et al. Attitudes and perceptions about prenatal diagnosis and induced abortion among adults of Pakistani population. Prenatal Diag 2008 Dec;28(12):1149-55.

(166) Evans MI, Sobiecki MA, Krivchenia EL, Duquette DA, Drugan A, Hume RF, Jr., et al. Parental decisions to terminate/continue following abnormal cytogenetic prenatal diagnosis: "what" is still more important than "when". Am J Med Genet 1996 Feb 2;61(4):353-5.

(167) France EF, Locock L, Hunt K, Ziebland S, Field K, Wyke S. Imagined futures: how experiential knowledge of disability affects parents' decision making about fetal abnormality. Health Expect 2012 Jun;15(2):139-56.

(168) Schechtman KB, Gray DL, Baty JD, Rothman SM. Decision-making for termination of pregnancies with fetal anomalies: analysis of 53,000 pregnancies. Obstet Gynecol 2002 Feb;99(2):216-22.

(169) Hurford E, Hawkins A, Hudgins L, Taylor J. The decision to continue a pregnancy affected by Down syndrome: Timing of decision and satisfaction with receiving a prenatal diagnosis. [References]. Journal of Genetic Counseling 2013 Oct;(5):587-93.

(170) Maijala H, Astedt-Kurki P, Paavilainen E, Vaisanen L. Interaction between caregivers and families expecting a malformed child. J Adv Nurs 2003 Apr;42(1):37-46.

(171) Redlinger-Grosse K, Bernhardt BA, Berg K, Muenke M, Biesecker BB. The decision to continue: the experiences and needs of parents who receive a prenatal diagnosis of holoprosencephaly. Am J Med Genet 2002 Nov 1;112(4):369-78.

(172) Hedrick J. The lived experience of pregnancy while carrying a child with a known, nonlethal congenital abnormality. J Obstet Gynecol Neonatal Nurs 2005 Nov;34(6):732-40.

(173) Rauch ER, Smulian JC, DePrince K, Ananth CV, Marcella SW. Pregnancy interruption after second trimester diagnosis of fetal structural anomalies: the New Jersey Fetal Abnormalities Registry. AM J OBSTET GYNECOL 2005 Oct;193(4):1492-7.

(174) Foley G, Timonen V. Using Grounded Theory Method to Capture and Analyze Health Care Experiences. Health Serv Res 2014 Dec 18.

(175) Charmaz K. Constructing Grounded Theory. 2nd ed. London: Sage Publications Ltd; 2014.

(176) Mills J, Bonner A, Francis K. The development of constructivist grounded theory. International journal of qualitative methods 2008;5(1):25-35.

(177) Breckenridge J, Jones D, Elliott I, Nicol M. Choosing a methodological path: Reflections on the constructivist turn. Grounded Theory Review 2012;11(1):64-71.

(178) Glaser BG. Constructivist grounded theory? Forum Qualitative Sozialforschung/Forum: Qualitative Social Research 2002;3(3), Art.12

(179) Stephenson J, Patel D, Barrett G, Howden B, Copas A, Ojukwu O, et al. How do women prepare for pregnancy? Preconception experiences of women attending antenatal services and views of health professionals. PLoS One 2014;9(7):e103085.

(180) Stephenson J, Patel D, Barrett G, Howden B, Copas A, Ojukwu O, et al. Department of Health Policy Research Programme Project Ref: 006/0068: "Pre-Pregnancy Health and Care in England: Exploring Implementation and Public Health Impact". 2013.

(181) Barrett G, Wellings K. What is a 'planned' pregnancy? Empirical data from a British study. Soc Sci Med 2002 Aug;55(4):545-57.

(182) Barrett G, Smith SC, Wellings K. Conceptualisation, development, and evaluation of a measure of unplanned pregnancy. J Epidemiol Community Health 2004 May;58(5):426-33.

(183) Prue CE, Flores AL, Panissidi P, Lira A. But I've already had a healthy baby: folic acid formative research with Latina mothers. Journal of Women's Health 2008 Oct;17(8):1257-69.

(184) Edwards L, Wyles D. The folic acid messageGÇôcan training make a difference? Journal of human nutrition and dietetics 1999;12(4):317-26.

(185) Bakker MK, Cornel MC, de Walle HE. [Awareness and periconceptional use of folic acid among non-western and western women in the Netherlands following the 1995 publicity campaign]. [Dutch]. Nederlands Tijdschrift voor Geneeskunde 2003 Dec 6;147(49):2426-30.

(186) Carmi R, Gohar J, Meizner I, Katz M. Spontaneous abortion--high risk factor for neural tube defects in subsequent pregnancy. American Journal of Medical Genetics 1994 Jun 1;51(2):93-7.

(187) Kridli SA. Health beliefs and practices of Muslim women during Ramadan. MCN Am J Matern Child Nurs 2011 Jul;36(4):216-21.

(188) Petherick ES, Tuffnell D, Wright J. Experiences and outcomes of maternal Ramadan fasting during pregnancy: results from a sub-cohort of the Born in Bradford birth cohort study. BMC Pregnancy Childbirth 2014;14:335.

(189) Husain T. Improving the health and well-being of women at risk for neural tube defect recurrence. US: U Texas School of Public Health; 2009.

(190) Al-Gailani S. Making birth defects 'preventable': pre-conceptional vitamin supplements and the politics of risk reduction. Stud Hist Philos Biol Biomed Sci 2014 Sep;47 Pt B:278-89.

(191) NICE. Antenatal Care. 2014. Available from: https://www.nice.org.uk/guidance/CG62 1-2-2014. 30-7-2015. [Accessed on 30th June 2015]

(192) Piccoli GB, Clari R, Vigotti FN, Leone F, Attini R, Cabiddu G, et al. Vegan-vegetarian diets in pregnancy: danger or panacea? A systematic narrative review. BJOG 2015 Apr;122(5):623-33.

(193) Barbour RS, Macleod M, Mires G, Anderson AS. Uptake of folic acid supplements before and during pregnancy: focus group analysis of women's views and experiences. J Hum Nutr Diet 2012 Apr;25(2):140-7.

(194) Rashid A, Jagger C, Goodyer L. Views of Asians and non-Asians on sources of drug information and the desirability for medication to be made available over the counter. Br J Gen Pract 1996 Oct;46(411):609-10.

(195) Lafarge C, Mitchell K, Fox P. Termination of pregnancy for fetal abnormality: a meta-ethnography of women's experiences. Reprod Health Matters 2014 Nov;22(44):191-201.

(196) Asplin N, Wessel H, Marions L, Georgsson OS. Pregnant women's experiences, needs, and preferences regarding information about

malformations detected by ultrasound scan. Sex Reprod Healthc 2012 Jun;3(2):73-8.

(197) McCoyd JL. What do women want? Experiences and reflections of women after prenatal diagnosis and termination for anomaly. Health Care for Women International 2009 Jun;30(6):507-35.

(198) Aite L, Trucchi A, Nahom A, Casaccia G, Zaccara A, Giorlandino C, et al. Antenatal diagnosis of diaphragmatic hernia: parents' emotional and cognitive reactions. J Pediatr Surg 2004 Feb;39(2):174-8.

(199) Brown S, Donelan K, Martins Y, Sayeed S, Mitchell C, Buchmiller T, et al. Does professional orientation predict ethical sensitivities? Attitudes of paediatric and obstetric specialists toward fetuses, pregnant women and pregnancy termination. Journal of Medical Ethics 2014 Feb;40(2):117-22.

(200) Lotto R. PhD Researcher. Personal communication. 25th February 2015.

(201) Cartmill M. Neurosurgeon. Personal communication. 16th March 2015.

(202) Leicester City Council. The Diversity of Leicester - A Demographic Profile. 2008. Available from: http://www.publicspirit.org.uk/assets/LeicesterDiversityOfLeicester.pdf [Accessed 26th September 2015].

(203) Bittles AH, Black ML. The impact of consanguinity on neonatal and infant health. Early Hum Dev 2010 Nov;86(11):737-41.

(204) Morris JK, Rankin J, Draper ES, Kurinczuk JJ, Springett A, Tucker D, et al. Prevention of neural tube defects in the UK: a missed opportunity. Arch Dis Child 2015 Dec 17.

(205) Office for National Statistics (ONS). National Statistics interim standard classifications for presenting ethnic and national groups data. 2014. Available from: http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/guide-method/classifications/archived-standard-classifications/ethnic-group-interim-classification-for-2001/presenting-ethnic-and-national-group-data/index.html [Accessed 10th November 2014].

9 Appendix B

NHS
Health Research Authority

NRES Committee London - Central
Skipton House
80 London Road
London
SE1 6LH

Tel: 020 797 22560

06 November 2012

Miss Jordana Peake
PhD student
UCL (Grand Challenge studentship)
Room 342, Medical School Building
IfWH University College London
74 Huntley Street, London
WC1E 6AU

Dear Miss Peake

Study title:	**Prevention of neural tube defects (NTDs) in ethnic communities in the UK: NTD epidemiology and pre-pregnancy knowledge, attitudes and health behaviour**
REC reference:	**12/LO/0890**
Protocol number:	**version 1.8**
Amendment number:	**IRAS Version 3.4**
Amendment date:	**16 October 2012**

The above amendment was reviewed at the meeting of the Sub-Committee held on 05 November 2012.

Ethical opinion

There were no ethical issues discussed.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	Version 2.1	11 September 2012
Notice of Substantial Amendment (non-CTIMPs)	IRAS Version 3.4	16 October 2012
Covering Letter	Email from Jordana Peake to Julie Kidd 22/10/2012	22 October 2012

Jordana Peake PhD Amendments: Peer Review (Email)		16 October 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

12/LO/0890:	**Please quote this number on all correspondence**

Yours sincerely
PP

[redacted]

Dr John Keen
Chair

E-mail: NRESCommittee.London-Central@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Philip Diamond, University College London Hospitals NHS Foundation Trust*
Mr Dave Wilson
NIGB Ethics & Confidentiality Committee Secretariat

NRES Committee London - Central

Attendance at Sub-Committee of the REC meeting on 05 November 2012

Name	*Profession*	*Capacity*
Dr Andrew Hilson	Consultant in Nuclear Medicine	Expert
Dr John Keen	General Practitioner	Expert

NHS
Health Research Authority
Confidentiality Advisory Group

Skipton House
80 London Road
London
SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net

Jordana Peake
University College London
Room 236
Medical School Building
74 Huntley Street
London
WC1E 6AU

j.peake@ucl.ac.uk

12 November 2013

Dear Ms Peake

Study title:	**Prevention of neural tube defects in ethnic communities in the UK**
CAG reference:	**ECC 5-05(d)/2012**
IRAS Project ID:	**95331/352022/4/606**
REC number:	**12/LO/0890**

Thank you for your amendment request to the above research application, submitted for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality, although other relevant legislative provisions will still be applicable.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. Following recent legal advice, please note that research applications covering data generated within England and Wales require an approval decision to be made jointly by the Health Research Authority and the Secretary of State for Health. This amendment was considered via proportionate review under criteria 8, amendments to approved applications.

Secretary of State for Health and Health Research Authority approval decision

The Secretary of State for Health and the Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, have determined the following:

1. The amendment is approved, subject to compliance with the standard and specific conditions of approval.

Context

This research application from University College London detailed a study which aimed to calculate the prevalence of neural tube defects (NTDs) within different ethnic groups, to map the natural history of NTD pregnancies and to assess pre-pregnancy knowledge, attitudes and behaviour of women with a previous NTD affect pregnancy. Confidential patient information including name, NHS number, date of birth and postcode was requested to allow the Health and Social Care Information Centre (HSCIC) to access data from BINOCAR registers in order to link HES, BINOCAR and ONS data and provide pseudonymised data only to the applicant.

The HSCIC would provide the Department of Health (DH) Abortion Statistics Manager with identifiable demographic data in order to allow them to identify the cohort and provide pseudonymised data to the applicant.

Amendment request

An amendment request was received on 12 September 2013 for inclusion of 2011 data, which was not yet available at the time of the original application, and inclusion of a consanguinity field which was already collected by one of the congenital anomaly registers. The request cited a link between consanguinity and birth defects which had not been extensively explored in relevant literature to date. It was also clarified that identifiable patient data from BINOCAR registers would not be linked to HES, ONS and DH datasets, and that all identifiable data would be destroyed at the end of the study rather than archived as had been originally proposed.

Confidentiality Advisory Group advice

The amendment requested was considered by the Confidentiality Advice Team as there was no significant increase in the identifiability of the data, and a recommendation of approval was submitted to the Health Research Authority and the Secretary of State for Health.

Specific conditions of support

1. Confirmation of a favourable opinion from a Research Ethics Committee. **Received 11/09/2013.**

As the above conditions have been met this letter confirms final approval for this amendment.

Reviewed documents

The documents reviewed by the Confidentiality Advice Team were:

Document	*Version*	*Date*
Amendment request letter dated 12/09/2013		12/09/2013
Favourable opinion letter from NRES Committee – London Central dated 11/09/2013		11/09/2013
IRAS amendment form dated 22/08/2013		22/08/2013

Please do not hesitate to contact me if you have any queries following this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
Deputy Confidentiality Advice Manager

Email: HRA.CAG@nhs.net

Enclosures: Standard conditions of approval

Copy to: NRES Committee London – Central
nrescommittee.london-central@nhs.net

Standard conditions of approval

The approval provided by the Health Research Authority is subject to the following standard conditions.

The applicant will ensure that:

1. The specified patient identifiable information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant.
4. All staff with access to patient identifiable information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to patient identifiable information have received appropriate ongoing training to ensure they are aware of their responsibilities.
6. Activities are consistent with the Data Protection Act 1998.
7. Audit of data processing by a designated agent is facilitated and supported.
8. The wishes of patients who have withheld or withdrawn their consent are respected.
9. The Confidentiality Advice Team is notified of any significant changes (purpose, data flows, data items, security arrangements) prior to the change occurring.
10. An annual report is provided no later than 12 months from the date of your final confirmation letter.
11. Any breaches of confidentiality / security around this particular flow of data should be reported to CAG within 10 working days, along with remedial actions taken / to be taken.

Department of Health

From the Chief Medical Officer,
Professor Dame Sally C Davies

Richmond House
79 Whitehall
London
SW1A 2NS

T +44 (0)20 7210 5150-4
F +44 (0)20 7210 5407
sally.davies@dh.gsi.gov.uk
www.dh.gov.uk

3 October 2013

Jordana Peake
Room 236, Medical School Building
IfWH University College London
74 Huntley Street
London WC1E 6AU

Dear Ms Peake

Request for agreement to use abortion data in a linkage project looking at neural tube defects in ethnic communities.

Thank you for your letter asking for permission to use abortion data for your proposed linkage project investigating neural tube defects in ethnic communities to get a true estimate of prevalence.

I have seen the research study's background and objectives and I understand you have REC approval. I am therefore content for you to use abortion data for this study.

To progress your request, please would you ring Ms Grinsted on [redacted] or email her at [redacted] and she will send you a confidentiality agreement document. On receipt of a fully completed and signed copy, the data held by the Abortion Statistics Team can be used for the purposes of the research as outlined. The confidentiality agreement states: the data released should be kept secure and only up to a maximum 12 months and then it must be destroyed; the data must be used only for the approved research; the data must not be forwarded to any third party; and that you must seek agreement from DH before publishing any resulting tables or articles. There will be no charge for the data.

Yours sincerely

[redacted]

PROFESSOR DAME SALLY C DAVIES
CHIEF MEDICAL OFFICER
CHIEF SCIENTIFIC ADVISER

10 Appendix C

Table C 1: Proportion of mothers in the NTD NorCAS dataset falling into the different BMI categories, by NTD subtype and excluding missing cases

Maternal BMI group	Anencephaly (%)	Spina Bifida (%)	Total (%)
Underweight	2.47	1.72	2.26
Normal	41.98	48.28	44.8
Overweight	29.63	24.14	26.70
Obese	25.93	25.86	26.24
Total	100	100	100

Table C 2: Proportion of mothers in the NTD NorCAS dataset falling into the different BMI categories, broken down by whether the NTD is isolated or not and excluding missing cases

Maternal BMI group	Isolated (%)	Non-Isolated (%)
Underweight	2.78	0
Normal	43.89	48.78
Overweight	27.78	21.95
Obese	25.56	29.27
Total	100	100

11 Appendix D

Table D 1: ONS 2001 Census Ethnic grouping

Ethnic group	
Level 1	Level 2
White	White British Irish Other White background All white groups
Mixed	White and Black Caribbean White and Black African White and Asian Other mixed background
Asian or Asian British	Indian Pakistani Bangladeshi Other Asian background All Asian groups
Black or Black British	Caribbean African Other Black background All Black groups
Chinese or Other Ethnic Groups	Chinese Other ethnic group All Chinese or Other groups
All ethnic groups	All ethnic groups

Source: ONS, 2014 (205)

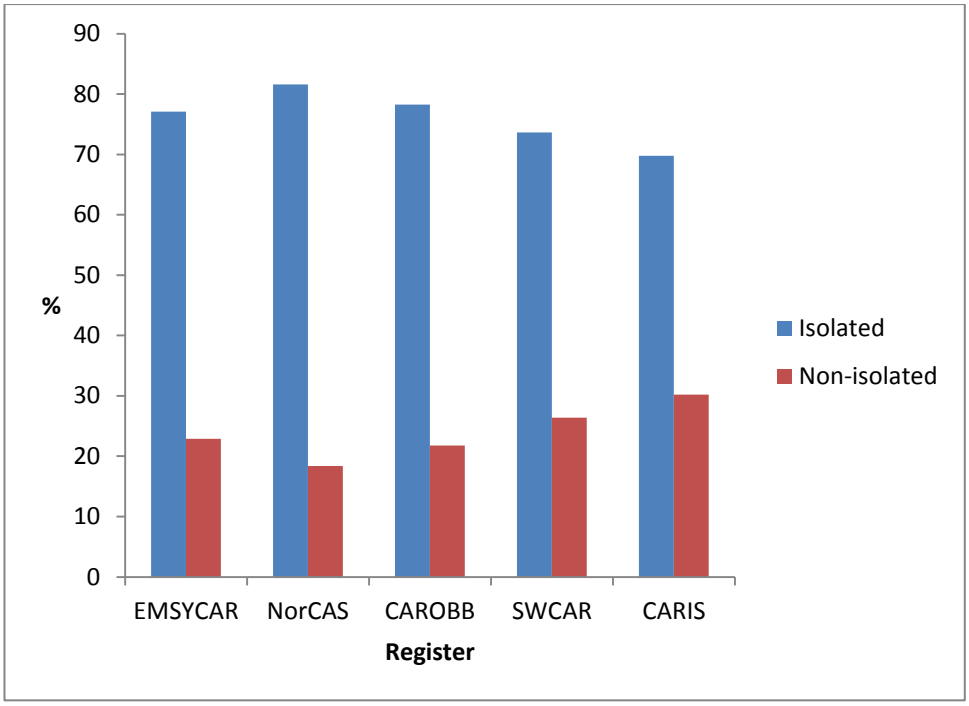

Figure D 1: Proportion of isolated and non-isolated NTD affected pregnancies within each register

Table D 2: Proportion of births falling into the different deprivation quintiles for Indian and Bangladeshi mothers in EMSYCAR

Deprivation quintile (IMD)	% births (95% CI)	
	Indian	Bangladeshi
1	27.20 (26.31-28.10)	56.83 (54.53-59.11)
2	28.99 (28.08-29.92)	25.48 (23.50-27.53)
3	14.77 (14.06-15.50)	8.55 (7.31-9.92)
4	13.79 (13.11-14.50)	5.50 (4.50-6.64)
5	15.24 (14.53-15.98)	3.65 (2.84-4.61)

Table D 3: Proportion of births falling into the different deprivation quintiles for Indian and Bangladeshi mothers in NorCAS

Deprivation quintile (IMD)	% births (95% CI)	
	Indian	Bangladeshi
1	35.66 (33.40-37.96)	55.55 (53.00-58.07)
2	23.85 (21.86-25.92)	28.47 (26.21-30.81)
3	12.33 (10.82-13.97)	7.40 (6.13-8.83)
4	10.71 (9.30-12.26)	4.36 (3.39-5.51)
5	17.45 (15.70-19.32)	4.23 (3.27-5.37)

Table D 4: Proportion of births falling into the different deprivation quintiles for Indian and Bangladeshi mothers in CAROBB

Deprivation quintile (IMD)	% births (95% CI)	
	Indian	Bangladeshi
1	6.26 (5.70-6.85)	15.71 (13.55-18.06)
2	27.53 (26.49-28.59)	37.26 (34.32-40.27)

3	25.74 (24.72-26.77)	22.41 (19.92-25.07)
4	16.66 (15.80-17.56)	10.25 (8.48-12.25)
5	23.82 (22.82-24.83)	14.37 (12.30-16.64)

Table D 5: Proportion of births falling into the different deprivation quintiles for Indian and Bangladeshi mothers in SWCAR

	% births (95% CI)	
Deprivation quintile (IMD)	Indian	Bangladeshi
1	27.22 (25.53-28.97)	29.17 (25.81-32.70)
2	26.88 (25.20-28.62)	21.55 (18.55-24.80)
3	19.96 (18.45-21.54)	20.69 (17.74-23.89)
4	12.55 (11.30-13.87)	16.09 (13.44-19.04)
5	13.38 (12.11-14.75)	12.50 (10.13-15.19)

Table D 6: Proportion of births falling into the different deprivation quintiles for Indian and Bangladeshi mothers in CARIS

	% births (95% CI)	
Welsh Deprivation quintile (WIMD)	Indian	Bangladeshi
1	29.67 (27.66-31.75)	52.97 (50.17-55.75)
2	20.63 (18.86-22.49)	20.27 (18.08-22.59)
3	14.23 (12.71-15.85)	12.35 (10.59-14.29)
4	13.01 (11.55-14.57)	6.73 (5.41-8.25)
5	22.46 (20.63-24.37)	7.68 (6.27-9.29)

Table D 7: Binomial regression model to explore the association between ethnicity and NTD prevalence, adjusted for IMD quintile and maternal age, with multiples removed

Variable	Adjusted PRR	95% CI	P-value
White (ref)			
Indian	1.87	1.25-2.79	
Pakistani	1.19	0.72-1.96	
Bangladeshi	3.02	1.56-5.84	0.009
Black Caribbean	1.17	0.48-2.82	
Black African	1.10	0.65-1.88	
Other ethnic group	0.45	0.29-0.69	
IMD quintile 1 (ref)			
IMD quintile 2	0.88	0.72-1.09	
IMD quintile 3	0.72	0.57-0.90	0.000
IMD quintile 4	0.71	0.56-0.90	
IMD quintile 5	0.70	0.55-0.90	
25-29 (ref)			
<20	1.35	1.01-1.80	
20-24	1.04	0.84-1.30	0.681
30-34	1.05	0.85-1.29	
35-39	1.22	0.97-1.55	
40+	1.20	0.79-1.81	

Table D 8: Logistic regression model, with multiple pregnancies removed, exploring the association between maternal ethnicity and whether the NTD affected pregnancy is terminated or not, adjusted for NTD type; maternal age; age, in weeks, at which the NTD is discovered and deprivation of maternal residence

Termination	Adjusted Odds Ratio	95% CI	P-value	Overall p-value
White (ref)				
Indian	1.16	0.27-4.95	0.837	
Pakistani	0.13	0.04-0.43	0.001	
Bangladeshi	0.53	0.10-2.94	0.469	0.003
Black Caribbean	0.15	0.02-1.51	0.108	
Black African	0.11	0.03-0.40	0.001	
Other ethnic group	0.75	0.18-3.13	0.694	
Spina bifida (ref)				
Anencephaly	1.33	0.70-2.54	0.391	0.367
Encephalocele	0.85	0.37-1.95	0.706	
25-29 (ref)				
<20	1.30	0.46-3.69	0.625	
20-24	0.50	0.25-1.00	0.051	0.343
30-34	1.06	0.51-2.21	0.877	
35-39	1.19	0.49-2.91	0.698	
40+	1.08	0.21-5.67	0.926	
Age, in weeks, at discovery	0.80	0.74-0.86	<0.001	<0.001
IMD quintile 1 (ref)				
IMD quintile 2	1.57	0.80-3.10	0.191	
IMD quintile 3	1.29	0.64-2.63	0.479	0.001
IMD quintile 4	2.52	1.06-6.02	0.037	
IMD quintile 5	3.16	1.02-9.80	0.046	

12 Appendix E

UCL INSTITUTE OF CHILD HEALTH

UCL Elizabeth Garrett Anderson Institute for Women's Health

Birth Defects Research Centre
UCL Institute of Child Health
30 Guilford Street
London
WC1N 1EH

Prevention of neural tube defects (NTDs) in ethnic communities (student research project)

Participant Information Sheet

We would like to invite you to take part in our study which is being supported by Dominic Thompson, Consultant Paediatric Neurosurgeon and Clinical Lead and Lindy May, Neurosurgical Nurse Consultant at Great Ormond Street Hospital. Before you decide we would like you to understand why the research is being done and what it would involve for you. You can talk to others about the study if you wish and you can take as long as you like to decide whether to take part or not.

What is the purpose of the study?
The study is being carried out, as part of a PhD, to explore the pre-pregnancy knowledge, attitudes and health behaviour of women from different ethnic communities with a previous neural tube defect (NTD) affected pregnancy.

Why have I been invited to take part?
This study has been advertised through Great Ormond Street Hospital, specialist organisations such as SHINE, community and faith-based organisations and through social media to recruit women of Bangladeshi, Pakistani or Indian ethnicity who have previously had an NTD affected pregnancy, and are happy to be interviewed, about their pre-pregnancy views and practices.

Do I have to take part?

No. Your participation in the study is entirely voluntary and you are free to withdraw from the study at any time. If you decide you do not want to be interviewed, or you want to stop the interview part way through you are completely free to do so without giving a reason and this will not affect the usual standard of care you receive in any way.

What will happen to me if I take part?
Before the interview we will discuss the study with you and answer any questions you may have. If you are happy to take part, we will ask you to sign a consent form agreeing to take part in the interview. The interview should last about 45 minutes and tea, coffee and biscuits will be provided during this time. We would like to record the interview so we have an accurate record of what you tell us. The recording will be transcribed and anonymised and then the data will be analysed by the study lead.

Expenses and payments
You will not be paid for taking part in the study but all your travel expenses will be reimbursed to you.

What are the possible benefits of taking part?
It is hoped that findings of the study will provide us with a better understanding of potential barriers to NTD prevention in ethnic groups at high risk, and how we can overcome them. This will enable us to generate new information that will lead to the development of future studies of preventive pre-pregnancy interventions and to target NTD prevention interventions to promote the health of women and their children.

What are the disadvantages of taking part?
45 minutes will need to be set aside to complete the interview. However, the interview will be conducted at your convenience. Some women may find it distressing to discuss pre-pregnancy knowledge and health behaviour when they have previously had an NTD affected pregnancy. Remember that you don't have to answer any questions that you don't want to and are free to withdraw from the study at any point without giving a reason and this will not affect your normal care. If you feel you need someone to talk to after the interview process, support is available.

Will my participation in the study be confidential?
Yes. Any information provided by you will be kept strictly confidential. Only those at UCL directly involved in the study will have access to any personal details or contact details you provide as part of the study, and these will be locked in a filing cabinet in a securely locked office environment at UCL. If any of the information you have contributed to the study is presented in project reports, publications and in the PhD thesis, it will have all identifiers removed to ensure you remain anonymous.

Who is funding the research?
The study is being funded by the UCL Grand Challenges Scheme studentships.

Who has reviewed the study?

The study has been reviewed by the NHS Research Ethics Committee—London Central. The reference for this study is 12/LO/0890.

What if there is a problem?
Should you have any complaints about the way in which the study is being conducted or you have any queries please discuss with Jordana Peake who is leading the study (contact details below).

You can get independent advice from a Hospital's PALS team and further information about NTDs, such as spina bifida, and the support services available from SHINE (all contact details are below).

Thank you for taking the time to read this information. If you are satisfied that you understand what the study involves and wish to participate we will now ask you to complete the consent form.

Contact information
Study lead: Jordana Peake
Institute of Child Health Tel: 020 7905 2612
Email: j.peake@ucl.ac.uk
Mobile: 07792113211

Independent Advice: Patient advice and liaison service (PALS)
University College London Hospital
Tel: 020 7691 5834 Email: PALS@uclh.nhs.uk

Great Ormond Street Hospital
Tel: 020 7829 7862 Email: pals@gosh.nhs.uk

Central Manchester University Hospitals
Tel: 0161 276 8686 Email: pals@cmft.nhs.uk

SHINE
Tel: 01733 555988 Email: info@shinechairty.org.uk

UCL Project number: 11/054

REC Ref: 12/LO/0890

Patient Identification Number

Prevention of neural tube defects (NTDs) in ethnic communities

(Student research project)

INTERVIEW CONSENT FORM

Name of Principal Investigator: Jordana Peake

		Please initial boxes
1.	I confirm that I have read and understand the information sheet dated 27.09.13 version 1.3 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I agree to take part in the above study with the understanding that my right to confidentiality will be protected at all times, including only anonymised information from the study being included in project reports, PhD thesis and publications.	
4.	I agree to take part in an interview of about 45 minutes about my health and my pre-pregnancy knowledge, attitudes and health behaviour.	
5.	I agree for the interview to be audio recorded with a digital device. Any recordings will be held confidentially and will be stored on secure servers at UCL.	
6.	I understand that data collected during the study may be looked at by individuals from UCL for audit purposes, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	

7. I agree to be contacted by the study lead if necessary. | |

Name of Patient	Signature of Patient	Date
Name person taking consent	Signature of person taking consent	Date
Role of person taking consent		

When completed: 1 copy for patient; 1 copy for researcher

Topic Guide for In-Depth Interviews

Aims and objectives

The overall aim of this study is to explore the pre-pregnancy knowledge, attitudes and health behaviour of women from ethnic communities with a previous neural tube defect (NTD) affected pregnancy.

Key objectives to explore:

- Definition of pre-pregnancy care
- Knowledge of pre-pregnancy health advice, such as the benefits of taking folic acid for NTD prevention.
- Pre-pregnancy health behaviours
- Pre-pregnancy views and attitudes
- Suggestions to improve both knowledge of pre-pregnancy interventions, such as taking folic acid, and women acting on this advice.

Introduction

Aim: To introduce the research and reassure of confidentiality

- Introduce self, including role at UCL
- Explain the aims of the research
- The length of interview
- Voluntary nature of participation and right to withdraw at any time
- Introduce audio recorder
- Stress confidentiality
- Any questions

1. Background

Aim: To introduce the respondent and any background information that might be of relevance to the study

- Age
- Ethnicity
- Religion
- Household composition
- Main daytime activity – whether working or not or occupation of partner

- Any chronic illnesses such as diabetes or epilepsy

2. Definition of pre-pregnancy care

Aim: To start with a broader question and explore what pre-pregnancy care means for them

- What does the term "pre-pregnancy care" mean to them
    - What does pre-pregnancy care include i.e.
        - Folic acid for NTD prevention
        - Avoidance of alcohol, smoking
        - Healthy eating
        - Screening for infectious diseases
        - Immunizations
        - Genetic screening

3. Health advice before pregnancy

Aim: To establish what pre-pregnancy information was received, specifically the benefits of taking folic acid, and by who

- Any advice given before pregnancy
    - Who gave this advice
- Were they told about folic acid and what were they told about it i.e.:
    - Its' role in NTD prevention
    - When it should be taken
    - Dose
- Any advice given when they became pregnant and when was this advice given
    - Who was this advice given by

4. Health behaviours before and during early pregnancy

Aim: To establish any health behaviours/practices adopted in preparation for or during early pregnancy

- Any particular health behaviour/ practices adopted before getting pregnant e.g.:
    - Visiting GP
    - Types of food consumed i.e. vegetarian or not
    - Folic acid use - when started and for how long
    - Other vitamin use such as B12
    - Ceasing caffeine consumption
    - Ceasing smoking
    - Screening for infectious diseases
    - Immunizations

- Genetic screening

- Any particular health behaviour/ practices adopted during pregnancy (see list above)
  - At what time point in pregnancy

- Reasons for health behaviours being adopted

- Were particular health behaviours stopped at any point before/during early pregnancy and for what reason i.e.
  - Religious reasons

- Febrile illness during early pregnancy
  - Antibiotic and antipyretic use for this

5. Pre-pregnancy views and attitudes

Aim: To explore barriers and enablers to women accessing and acting on pre-pregnancy information

- Importance of pre-pregnancy period
  - Is pre-pregnancy care something that should be invested in
  - Views on pre-pregnancy health interventions
- Who they most trust to give pre-pregnancy advice
- Barriers vs. Enablers to women getting pre-pregnancy health advice
  - Unplanned vs. planned pregnancy
  - Information sources
  - Money

6. Suggestions

Aim: To explore suggestions of how dissemination and uptake of pre-pregnancy health advice can be improved

- What should be done to improve the dissemination of pre-pregnancy health messages, such as folic acid use, and women following this advice.

Close

- Thank participant and ask whether they have any further questions
- Reassure participant again about confidentiality
- Reimburse travel expenses
- Ask if they would like to be informed of the study outcomes (and take email address if this is how they would like to be informed)