WCRF/AICR Systematic Literature Review
Continuous Update Project

The Associations between Diet, Nutrition and Physical Activity and the Risk of Kidney Cancer

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Table of contents

List of abbreviations 4
Characteristics of studies in the Pooling Project of Cohort Studies 5
List of tables 6
List of figures 11
Matrices presented in the WCRF/AICR 2007 Expert Report 15
Modifications to the protocol 16
Notes on figures and statistics used 16
Continuous Update Project: Results of the search 17
1) Randomised controlled trials (RCT) 18
2) Cohort studies 19
2 Foods 23
2.2 Fruit and non-starchy vegetables 23
2.2.1 Non-starchy vegetables 30
2.2.1.2 Cruciferous vegetables 37
2.2.1.5.13 Tomatoes 43
2.2.2 Fruits 48
2.2.2 Citrus fruit 55
2.5.1 Meat 62
2.5.1.2 Processed meat 62
2.5.1.3 Red meat 66
2.5.1.4 Poultry 70
2.5.2 Fish 74
3 Beverages 79
3.6.1 Coffee 79
3.6.2 Tea 86
4 Food production, preservation, processing and preparation 91
4.1.2.7.2 Arsenic 91
5 Dietary constituents 93
5.1.2 Non-starch polysaccharides/dietary fibre 93
5.2 Lipids 98
5.3 Protein 100
5.4.1 Alcohol (as ethanol) 102
5.4.1.1 Beer (as ethanol) 114
5.4.1.2 Wine (as ethanol) 119
5.4.1.3 Spirits (as ethanol) 124
5.5.1.2.1 Dietary alpha-carotene 129

5.5.1.2.2 Dietary beta-carotene 135
5.5.1.2.3 Dietary beta-cryptoxanthin 136
5.5.2.1 Dietary lutein and zeaxanthin 142
5.5.2.2 Dietary lycopene 148
5.5.3.2 Dietary folate 154
5.5.7 Total Pyridoxine - vitamin B6 (food and supplements) 159
5.5.9 Total vitamin C (food and supplements) 164
5.5.9.1 Dietary vitamin C 169
5.5.11 Total vitamin E (food and supplements) 174
5.5.11.1 Dietary vitamin E 179
5.6.3 Total calcium (food and supplements) 184
5.6.3.1 Dietary calcium 189
5.6.3.2 Calcium from supplements 195
6 Physical activity 199
6.1 Total physical activity 199
6.1.1.1 Occupational physical activity 203
6.1.1.2 Recreational physical activity 206
6.1.1.4.1 Walking 210
6.2 Physical inactivity 210
8 Anthropometry 211
8.1.1 BMI 211
8.1.3 Weight 228
8.2.1 Waist circumference 237
8.2.3 Waist to hip ratio 242
8.3.1 Height 247
Annex . Anthropometric characteristics investigated by each study 256
Reference list 258

List of abbreviations

List of Abbreviations used in the CUP SLR

CUP	Continuous Update Project
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
SLR	Systematic Literature Review
2005 SLR	Systematic Literature Review for the WCRF/AICR Second Expert Report
RR	Relative Risk
LCI	Lower Limit Confidence Interval
UCI	Upper Limit Confidence Interval
HR	Hazard Ratio
CI	Confidence Interval

List of Abbreviations of cohort study names used in the CUP SLR

AgHS	Agricultural Health Study
AHS	Californian Seventh Day Adventists
CNBSS	Canadian National Breast Screening Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CPS II	Cancer Prevention Study 2
EPIC	European Prospective Investigation into Cancer and Nutrition
Harward and Pennsylvania Alumni Study	Harward and Pennsylvania Alumni Study 1916-1950
HPFS	Health Professionals Follow-up Study
ICRFS	Icelandic Cardiovascular Risk Factor Study (Reykjavik Study)
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study
JPHC	Japan Public Health Center-based Prospective Study
Kaiser Permanente	Kaiser Permanente Medical Care Program
KNHIC (or KNICH)	Korea National Health Insurance Corporation Study
MEC	Multiethnic Cohort Study or Hawaii Los Angeles Multiethnic Cohort Study
MWS	The Million Women Study
NHS	The Nurses' Health Study
NIH-AARP	NIH-AARP Diet and Health Study
NLCS (or NCS)	The Netherlands Cohort Study
NHSS	Norwegian Health Screening Service
Norway	Norwegian Cohorts (men)
NSHDC	Northern Sweden Health and Disease Cohort Study
NTS (or NTSS)	Norwegian Tuberculosis Screening Study
Reykjavik Study	Icelandic Cardiovascular Risk Factor Study

SCWC	Swedish Construction Workers' Cohort Study
SMC	Swedish Mammography Cohort
Sweden 1970	Sweden 1960-1970
Swedish Twin Cohort	Swedish Twin Cohort 1959-1961
VIP	Västerbotten Intervention Project
VHM&PP	The Vorarlberg Health Monitoring and Promotion Program
WHI	Women's Health Initiative

Characteristics of studies in the Pooling Project of Cohort Studies

Study (sex)	**Country**	**No. of cases**
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (M)	Finland	187
Breast Cancer Detection Demonstration Project Follow-Up Study (F)	US	49
California Teachers Study (F)	US	35
Canadian National Breast Screening Study (F)	Canada	81
Cancer Prevention Study II Nutrition Cohort (M/F)	US	86
Cancer Prevention Study II Nutrition Cohort (M)	US	220
Health Professionals Follow-up Study (M)	US	116
Iowa Women's Health Study (F)	US	117
Melbourne Collaborative Cohort Study (M)	Australia	50
Netherlands Cohort Study (M/F)	The Netherlands	68
New York State Cohort (M)	US	62
Nurses' Health Study (F)	US	86
Swedish Mammography Cohort (F)	Sweden	138
Women's Health Study (F)	US	49

List of tables

Table 1 Number of relevant articles identified during the Second Expert Report and the CUP and total number of cohort studies by exposure. 19
Table 2 Studies on total fruit and non-starchy vegetables identified in the CUP 24
Table 3 Overall evidence on fruit and non-starchy vegetables intake and kidney cancer 24
Table 4 Summary of results of the dose response meta-analysis of total fruit and non-starchy vegetables and kidney cancer 25
Table 5 Inclusion/exclusion table for meta-analysis of fruit and non-starchy vegetables and kidney cancer 26
Table 6 Studies on vegetable intake identified in the CUP 31
Table 7 Overall evidence on vegetables and kidney cancer 31
Table 8 Summary of results of the dose response meta-analysis of vegetables and kidney cancer 32
Table 9 Inclusion/exclusion table for meta-analysis of vegetables and kidney cancer 33
Table 10 Studies on cruciferous vegetables identified in the CUP 38
Table 11 Overall evidence on cruciferous vegetables and kidney cancer 38
Table 12 Summary of results of the dose response meta-analysis of cruciferous vegetables intake and kidney cancer 38
Table 13 Inclusion/exclusion table for meta-analysis of cruciferous vegetables and kidney cancer 39
Table 14 Studies on tomatoes identified in the CUP 44
Table 15 Overall evidence on tomatoes and kidney cancer 44
Table 16 Summary of results of the dose response meta-analysis of tomatoes and kidney cancer 44
Table 17 Inclusion/exclusion table for meta-analysis of tomatoes and kidney cancer 45
Table 18 Studies on total fruit intake identified in the CUP 49
Table 19 Overall evidence on total fruit intake and kidney cancer 49
Table 20 Summary of results of the dose response meta-analysis of total fruits and kidney cancer 50
Table 21 Inclusion/exclusion table for meta-analysis of total fruits and kidney cancer 51
Table 22 Studies on citrus fruit identified in the CUP 56
Table 23 Overall evidence on citrus fruit and kidney cancer 56
Table 24 Summary of results of the dose response meta-analysis of citrus fruit and kidney cancer 57
Table 25 Inclusion/exclusion table for meta-analysis of citrus fruit and kidney cancer 58
Table 26 Results of the Pooling Project of Cohort Studies on processed meat and kidney cancer risk and additional studies identified in the CUP and 2005 SLR 63
Table 27 Overall evidence on processed meat intake and kidney cancer 63
Table 28 Summary of results of the dose response meta-analysis of processed meat and kidney cancer 63
Table 29 Inclusion/exclusion table for meta-analysis of processed meat and kidney cancer 64
Table 30 Results of the Pooling Project of Cohort Studies on red meat and kidney cancer and additional studies identified in the CUP and the 2005 SLR 67
Table 31 Overall evidence on red meat intake and kidney cancer 67
Table 32 Summary of results of the dose response meta-analysis of red meat and kidney cancer 67
Table 33 Inclusion/exclusion table for meta-analysis of red meat and kidney cancer 68
Table 34 Results of the Pooling Project of Cohort Studies and additional studies identified in the CUP and the 2005 SLR on poultry intake and kidney cancer 71

Table 35 Overall evidence on poultry intake and kidney cancer 71
Table 36 Summary of results of the dose response meta-analysis of poultry intake and kidney cancer 71
Table 37 Inclusion/exclusion table for meta-analysis of poultry and kidney cancer 72
Table 38 Studies on fish intake and kidney cancer identified in the CUP 75
Table 39 Overall evidence on fish and kidney cancer 75
Table 40 Summary of results of the dose-response meta-analysis of fish and kidney cancer. 75
Table 41 Inclusion/exclusion table for meta-analysis of fish and kidney cancer 76
Table 42 Studies on coffee identified in the CUP 80
Table 43 Overall evidence on coffee and kidney cancer 80
Table 44 Summary of results of the dose-response meta-analysis of coffee and kidney cancer 81
Table 45 Inclusion/exclusion table for meta-analysis of coffee and kidney cancer 82
Table 46 Studies on tea identified and kidney cancer in the CUP 87
Table 47 Overall evidence on tea and kidney cancer 87
Table 48 Summary of results of the dose-response meta-analysis of tea and kidney cancer .. 87
Table 49 Inclusion/exclusion table for meta-analysis of tea and kidney cancer 88
Table 50 Overall evidence on arsenic and kidney cancer 91
Table 51 Studies on arsenic and kidney cancer identified in the CUP and 2005 SLR 92
Table 52 Studies on dietary fibre intake identified in the CUP 94
Table 53 Overall evidence on dietary fibre and kidney cancer 94
Table 54 Summary of results of the dose response meta-analysis of dietary fibre and kidney cancer 94
Table 55 Inclusion/exclusion table for meta-analysis of dietary fibre and kidney cancer 95
Table 56 Studies on fat intake and kidney cancer 98
Table 57 Meta-analysis of the Pooling Project of Cohort Studies and the additional study identified in the CUP on intake of lipids and kidney cancer 99
Table 58 Results of prospective studies on protein intake by type and kidney cancer identified in the CUP. 100
Table 59 Meta-analysis of the Pooling Project of Cohort Studies and the additional study identified in the CUP on intake of proteins and kidney cancer 101
Table 60 Studies on alcohol (as ethanol) identified in the CUP 104
Table 61 Overall evidence on alcohol (as ethanol) and kidney cancer 105
Table 62 Summary of results of the dose response meta-analysis of alcohol (as ethanol) and kidney cancer 105
Table 63 Inclusion/exclusion table for meta-analysis of alcohol (as ethanol) and kidney cancer 106
Table 64 RRs for nonlinear dose-response analysis 112
Table 65 Studies on beer (as ethanol) identified in the CUP 115
Table 66 Overall evidence on beer (as ethanol) and kidney cancer 115
Table 67 Summary of results of the dose response meta-analysis of beer (as ethanol) and kidney cancer 115
Table 68 Inclusion/exclusion table for meta-analysis of beer (as ethanol) and kidney cancer 116
Table 69 Studies on wine (as ethanol) identified in the CUP 120
Table 70 Overall evidence on wine (as ethanol) and kidney cancer 120
Table 71 Summary of results of the dose response meta-analysis of wine (as ethanol) and kidney cancer 120
Table 72 Inclusion/exclusion table for meta-analysis of wine (as ethanol) and kidney cancer 121

Table 73 Studies on spirits (as ethanol) identified in the CUP Studies on spirits (as ethanol) identified in the CUP 125
Table 74 Overall evidence on spirits (as ethanol) and kidney cancer 125
Table 75 Summary of results of the dose response meta-analysis of spirits (as ethanol) and kidney cancer 125
Table 76 Inclusion/exclusion table for meta-analysis spirits (as ethanol) and kidney cancer 126
Table 77 Studies on dietary alpha-carotene identified in the CUP 130
Table 78 Overall evidence on dietary alpha-carotene and kidney cancer 130
Table 79 Summary of results of the dose-response meta-analysis of dietary alpha-carotene and kidney cancer 130
Table 80 Inclusion/exclusion table for meta-analysis of dietary alpha-carotene and kidney cancer 132
Table 81 Studies on dietary beta-cryptoxanthin identified in the CUP 137
Table 82 Overall evidence on dietary beta-cryptoxanthin and kidney cancer 137
Table 83 Summary of results of the dose-response meta-analysis of dietary beta-cryptoxanthin and kidney cancer 138
Table 84 Inclusion/exclusion table for meta-analysis of dietary beta-cryptoxanthin and kidney cancer 139
Table 85 Studies on dietary lutein and zeaxanthin identified in the CUP 143
Table 86 Overall evidence on dietary lutein and zeaxanthin and kidney cancer 143
Table 87 Summary of results of the dose-response meta-analysis of dietary lutein and zeaxanthin and kidney cancer 144
Table 88 Inclusion/exclusion table for meta-analysis of dietary lutein and zeaxanthin and kidney cancer 145
Table 89 Studies on dietary lycopene identified in the CUP 149
Table 90 Overall evidence on dietary lycopene and kidney cancer 149
Table 91 Summary of results of the dose-response meta-analysis of dietary lycopene and kidney cancer 150
Table 92 Inclusion/exclusion table for meta-analysis of dietary lycopene and kidney cancer 151
Table 93 Studies on dietary folate and kidney cancer identified in the CUP 155
Table 94 Overall evidence on dietary folate and kidney cancer 155
Table 95 Summary of results of the dose response meta-analysis of dietary folate and kidney cancer 155
Table 96 Inclusion/exclusion table for meta-analysis of dietary folate and kidney cancer 156
Table 97 Studies on total vitamin B6 identified in the CUP 159
Table 98 Overall evidence on total vitamin B6 and kidney cancer 160
Table 99 Summary of results of the dose-response meta-analysis of total vitamin B6 and kidney cancer 160
Table 100 Inclusion/exclusion table for meta-analysis of total vitamin B6 and kidney cancer 161
Table 101 Studies on total vitamin C identified in the CUP 164
Table 102 Overall evidence on total vitamin C and kidney cancer 165
Table 103 Summary of results of the dose-response meta-analysis of total vitamin C and kidney cancer 165
Table 104 Inclusion/exclusion table for meta-analysis of total vitamin C and kidney cancer 166
Table 105 Studies on dietary vitamin C identified in the CUP 170
Table 106 Overall evidence on dietary vitamin C and kidney cancer 170

Table 107 Summary of results of the dose-response meta-analysis of dietary vitamin C and kidney cancer 170
Table 108 Inclusion/exclusion table for meta-analysis of dietary vitamin C and kidney cancer 171
Table 109 Studies on total vitamin E identified in the CUP 175
Table 110 Overall evidence on total vitamin E and kidney cancer 175
Table 111 Summary of results of the dose-response meta-analysis of total vitamin E and kidney cancer 175
Table 112 Inclusion/exclusion table for meta-analysis of total vitamin E and kidney cancer 176
Table 113 Studies on dietary vitamin E and kidney cancer identified in the CUP 180
Table 114 Overall evidence on dietary vitamin E and kidney cancer 180
Table 115 Summary of results of the dose-response meta-analysis of dietary vitamin E and kidney cancer 180
Table 116 Inclusion/exclusion table for meta-analysis of dietary vitamin E and kidney cancer 181
Table 117 Studies on total calcium and kidney cancer identified in the CUP 184
Table 118 Overall evidence on total calcium and kidney cancer 185
Table 119 Summary of results of the dose response meta-analysis of total calcium and kidney cancer 185
Table 120 Inclusion/exclusion table for meta-analysis of total calcium intake and kidney cancer 186
Table 121 Studies on dietary calcium and kidney cancer identified in the CUP 190
Table 122 Overall evidence on dietary calcium and kidney cancer 191
Table 123 Summary of results of the dose response meta-analysis of dietary calcium and kidney cancer 191
Table 124 Inclusion/exclusion table for meta-analysis of dietary calcium intake and kidney cancer 192
Table 125 Studies on supplemental calcium and kidney cancer identified in the CUP and the 2005 SLR 195
Table 126 Overall evidence on supplemental calcium and kidney cancer 196
Table 127 Summary of results of the dose response meta-analysis of supplemental calcium and kidney cancer 196
Table 128 Inclusion/exclusion table for meta-analysis of supplemental calcium intake and kidney cancer 197
Table 129 Studies on total physical activity identified in the CUP 199
Table 130 Overall evidence on total physical activity and kidney cancer 200
Table 131 Inclusion/exclusion table for meta-analysis of total physical activity and kidney cancer 201
Table 132 Overall evidence on occupational physical activity and kidney cancer 203
Table 133 Inclusion/exclusion table for meta-analysis of occupational physical activity and kidney cancer 204
Table 134 Studies on recreational physical activity identified in the CUP 206
Table 135 Overall evidence on recreational physical activity and kidney cancer 207
Table 136 Inclusion/exclusion table for meta-analysis of recreational physical activity and kidney cancer 208
Table 137 Studies on BMI identified in the CUP 212
Table 138 Overall evidence on BMI and kidney cancer 213
Table 139 Summary of results of the dose-response meta-analysis of BMI and kidney cancer 214

Table 140 Inclusion/exclusion table for meta-analysis of BMI and kidney cancer.....215
Table 141 RRs for nonlinear dose-response analysis 227
Table 142 Studies on weight identified in the CUP.....229
Table 143 Overall evidence on weight and kidney cancer 229
Table 144 Summary of results of the dose-response meta-analysis of weight and kidney cancer.....229
Table 145 Inclusion/exclusion table for meta-analysis of weight and kidney cancer 230
Table 146 RRs for nonlinear dose-response analysis 236
Table 147 Studies on waist circumference identified in the CUP 237
Table 148 Overall evidence on waist circumference and kidney cancer.....237
Table 149 Summary of results of the dose-response meta-analysis of waist circumference and kidney cancer 238
Table 150 Inclusion/exclusion table for meta-analysis of waist circumference and kidney cancer.....239
Table 151 Studies on waist to hip ratio identified in the CUP.....242
Table 152 Overall evidence on waist to hip ratio and kidney cancer 242
Table 153 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and kidney cancer 243
Table 154 Inclusion/exclusion table for waist-to-hip ratio and kidney cancer.....244
Table 155 Studies on height identified in the CUP.....247
Table 156 Overall evidence on height and kidney cancer 248
Table 157 Summary of results of the dose-response meta-analysis of height and kidney cancer.....248
Table 158 Inclusion/exclusion table of height and kidney cancer.....249
Table 159 RRs for nonlinear dose-response analysis 255

List of figures

Figure 1 Highest versus lowest forest plot of fruit and non-starchy vegetables and kidney cancer 27
Figure 2 Dose-response meta-analysis of fruit and non-starchy vegetables and kidney cancer - per 100 g/d 27
Figure 3 Funnel plot of total fruit and non-starchy vegetables and kidney cancer 28
Figure 4 Dose-response graph of total fruit and non-starchy vegetables and kidney cancer 28
Figure 5 Dose-response meta-analysis per 100 g /day increase of total fruit and non-starchy vegetables and kidney cancer, stratified by sex 29
Figure 6 Dose-response meta-analysis per 100 g/d increase of fruit and non-starchy vegetables and kidney cancer. Pooling Project of Cohort Studies and EPIC study 29
Figure 7 Highest versus lowest forest plot of vegetables and kidney cancer 34
Figure 8 Dose-response meta-analysis per 100 g/d increase of vegetables intake and kidney cancer 34
Figure 9 Funnel plot of vegetable intake and kidney cancer 35
Figure 10 Dose-response graph of vegetable intake and kidney cancer 35
Figure 11 Dose-response meta-analysis per 100 g /d of total vegetable intake and kidney cancer, stratified by sex 36
Figure 12 Dose-response meta-analysis per 100 g/d increase of vegetable intake and kidney cancer -. Pooling Project of Cohort Studies and CUP. 36
Figure 13 Highest versus lowest forest plot of cruciferous vegetables and kidney cancer 40
Figure 14 Dose-response meta-analysis per 50 g/d increase of cruciferous vegetables intake and kidney cancer 40
Figure 15 Funnel plot of cruciferous vegetables and kidney cancer 41
Figure 16 Dose-response graph of cruciferous vegetables and kidney cancer 41
Figure 17 Dose-response meta-analysis per 50 g/d increase of cruciferous vegetables and kidney cancer -. Pooling Project of Cohort Studies and CUP. 42
Figure 18 Highest versus lowest forest plot of tomatoes and kidney cancer 46
Figure 19 Dose-response meta-analysis per 50 g/d increase of tomato intake and kidney cancer 46
Figure 20 Dose-response graph of tomatoes and kidney cancer 47
Figure 21 Dose-response meta-analysis per 50 g/d of tomato intake and kidney cancer. Pooling Project of Cohort Studies and CUP 47
Figure 22 Highest versus lowest forest plot of total fruits and kidney cancer 52
Figure 23 Dose-response meta-analysis per 100 g/d increase of total fruit intake and kidney cancer 52
Figure 24 Funnel plot of total fruits and kidney cancer 53
Figure 25 Dose-response graph of total fruits and kidney cancer 53
Figure 26 Dose-response meta-analysis per 100 g/d of fruit intake and kidney cancer, stratified by sex 54
Figure 27 Dose-response meta-analysis per 100 g/d of fruit intake and kidney cancer. Pooling Project of Cohort Studies and CUP 54
Figure 28 Highest versus lowest forest plot of citrus fruit and kidney cancer 59
Figure 29 Dose-response meta-analysis per 50 g/d increase of citrus fruit intake and kidney cancer 59
Figure 30 Funnel plot of citrus fruit and kidney cancer 60
Figure 31 Dose-response graph of citrus fruit and kidney cancer 60
Figure 32 Dose-response meta-analysis per 50 g/d increase of citrus fruit intake and kidney cancer, stratified by sex 61
Figure 33 Dose-response meta-analysis per 50 g/d increase of citrus fruit and kidney cancer. Pooling Project of Cohort Studies and CUP 61
Figure 34 Dose-response meta-analysis per 50 g/d increase of processed meat intake and kidney cancer. Pooling Project and CUP. 65

Figure 35 Dose-response meta-analysis for 100 g/d intake increase of red meat intake and kidney cancer. Pooling project and CUP. 69
Figure 36 Dose-response meta-analysis for 100 g/d increase of poultry intake and kidney cancer 73
Figure 37 Highest versus lowest forest plot of fish and kidney cancer 77
Figure 38 Dose-response meta-analysis per 25 g/d increase of fish intake and kidney cancer 77
Figure 39 Funnel plot of fish intake and kidney cancer 78
Figure 40 Dose-response graph of fish intake and kidney cancer 78
Figure 41 Highest versus lowest forest plot of coffee and kidney cancer 83
Figure 42 Dose-response meta-analysis of coffee and kidney cancer, per 1 cup/day 83
Figure 43 Funnel plot of coffee and kidney cancer 84
Figure 44 Dose-response graph of coffee and kidney cancer 84
Figure 45 Dose-response meta-analysis per 1 cup/day increase of coffee intake. Pooling Project and CUP 85
Figure 46 Highest versus lowest forest plot of tea and kidney cancer 89
Figure 47 Dose-response meta-analysis of tea and kidney cancer, per 1 cup/day 89
Figure 48 Dose-response graph of tea and kidney cancer 90
Figure 49 Dose-response meta-analysis per 1 cup/day increase of tea intake and kidney cancer in women. Pooling Project and CUP 90
Figure 50 Highest versus lowest forest plot of dietary fibre and kidney cancer 96
Figure 51 Dose-response meta-analysis per 10 g/d increase of dietary fibre intake and kidney cancer 96
Figure 52 Dose-response graph of dietary fibre and kidney cancer 97
Figure 53 Highest versus lowest forest plot of alcohol (as ethanol) and kidney cancer 107
Figure 54 Dose-response meta-analysis of alcohol intake and kidney cancer - per 10 g/d (as ethanol) 107
Figure 55 Funnel plot of alcohol (as ethanol) and kidney cancer 108
Figure 56 Dose-response graph of alcohol (as ethanol) and kidney cancer 109
Figure 57 Dose-response meta-analysis of alcohol (as ethanol) and kidney cancer, stratified by sex – per 10g /day 110
Figure 58 Nonlinear dose-response analysis of ethanol and kidney cancer 111
Figure 59 Dose-response meta-analysis of alcohol (as ethanol) and kidney cancer - per 10 g/d . Pooling Project of Cohort Studies and CUP 113
Figure 60 Pooling Project of Cohort Studies and CUP: Funnel plot of alcohol (as ethanol) and kidney cancer 113
Figure 61 Highest versus lowest forest plot of beer (as ethanol) and kidney cancer 117
Figure 62 Dose-response meta-analysis of beer (as ethanol) and kidney cancer - per 10 g/d 117
Figure 63 Dose-response graph of beer (as ethanol) and kidney cancer 118
Figure 64 Highest versus lowest forest plot of wine (as ethanol) and kidney cancer 122
Figure 65 Dose-response meta-analysis of wine (as ethanol) and kidney cancer - per 10 g/d 122
Figure 66 Dose-response graph of wine (as ethanol) and kidney cancer 123
Figure 67 Highest versus lowest forest plot of spirits (as ethanol) and kidney cancer 127
Figure 68 Dose-response meta-analysis of spirits (as ethanol) and kidney cancer - per 10 g/d 127
Figure 69 Dose-response graph of spirits/liquor (as ethanol) and kidney cancer 128
Figure 70 Highest versus lowest forest plot of dietary alpha-carotene and kidney cancer 133
Figure 71 Dose-response meta-analysis of dietary alpha-carotene and kidney cancer, per 600 µg/d 133
Figure 72 Dose-response graph of dietary alpha-carotene and kidney cancer 134
Figure 73 Highest versus lowest forest plot of dietary beta-cryptoxanthin and kidney cancer 140
Figure 74 Dose-response meta-analysis of dietary beta-cryptoxanthin and kidney cancer, per 100 µg/d 140
Figure 75 Dose-response graph of dietary beta-cryptoxanthin and kidney cancer 141

Figure 76 Highest versus lowest forest plot of dietary lutein and zeaxanthin and kidney cancer 146
Figure 77 Dose-response meta-analysis of dietary lutein and zeaxanthin and kidney cancer, per 1000 µg/d 146
Figure 78 Dose-response graph of dietary lutein and zeaxanthin and kidney cancer 147
Figure 79 Highest versus lowest forest plot of dietary lycopene and kidney cancer 152
Figure 80 Dose-response meta-analysis of dietary lycopene and kidney cancer, per 4000µg/d 152
Figure 81 Dose-response graph of dietary lycopene and kidney cancer 153
Figure 82 Highest versus lowest forest plot of dietary folate and kidney cancer 157
Figure 83 Dose-response meta-analysis of dietary folate and kidney cancer - per 100 µg/d 158
Figure 84 Dose-response graph of dietary folate and kidney cancer 158
Figure 85 Highest versus lowest forest plot of total vitamin B6 and kidney cancer 162
Figure 86 Dose-response meta-analyses of total vitamin B6 and kidney cancer, per 1 mg/d 162
Figure 87 Dose-response meta-analysis of total vitamin B6 and kidney cancer 163
Figure 88 Highest versus lowest forest plot of total vitamin C and kidney cancer 167
Figure 89 Dose-response meta-analysis of total vitamin C and kidney cancer, per 200 mg/d 167
Figure 90 Dose-response graph of total vitamin C and kidney cancer 168
Figure 91 Highest versus lowest forest plot of dietary vitamin C and kidney cancer 172
Figure 92 Dose-response meta-analysis of dietary vitamin C and kidney cancer, per 10 mg/d 172
Figure 93 Dose-response graph of dietary vitamin C and kidney cancer 173
Figure 94 Highest versus lowest forest plot of total vitamin E and kidney cancer 177
Figure 95 Dose-response meta-analysis of total vitamin E and kidney cancer, per 5 mg/d 177
Figure 96 Dose-response graph of total vitamin E and kidney cancer 178
Figure 97 Highest versus lowest forest plot of dietary vitamin E and kidney cancer 182
Figure 98 Dose-response meta-analysis of dietary vitamin E and kidney cancer, per 5 mg/d 182
Figure 99 Dose-response graph of dietary vitamin E and kidney cancer 183
Figure 100 Highest versus lowest forest plot of total calcium intake and kidney cancer 187
Figure 101 Dose-response meta-analysis of total calcium intake and kidney cancer - per 200 mg/d 187
Figure 102 Dose-response graph of total calcium and kidney cancer 188
Figure 103 Highest versus lowest forest plot of dietary calcium intake and kidney cancer 193
Figure 104 Dose-response meta-analysis of dietary calcium intake and kidney cancer - per 200 mg/d 193
Figure 105 Funnel plot of dietary calcium intake and kidney cancer 194
Figure 106 Dose-response graph of dietary calcium and kidney cancer 194
Figure 107 Highest versus lowest forest plot of supplemental calcium intake and kidney cancer 198
Figure 108 Meta-analysis of supplemental calcium and kidney cancer – (Use vs. no use) 198
Figure 109 Highest versus lowest forest plot of total physical activity and kidney 202
Figure 110 Funnel plot of total physical activity and kidney cancer 202
Figure 111 Highest versus lowest forest plot of occupational physical activity and kidney cancer 205
Figure 112 Funnel plot of occupational physical activity and kidney cancer 205
Figure 113 Highest versus lowest forest plot of recreational physical activity and kidney cancer 209
Figure 114 Funnel plot of recreational physical activity and kidney cancer 209
Figure 115 Highest versus lowest forest plot of BMI and kidney cancer 219
Figure 116 Dose-response meta-analysis of BMI and kidney cancer - per 5 units 220
Figure 117 Funnel plot of BMI and kidney cancer 221
Figure 118 Dose-response graph of BMI and kidney cancer 222
Figure 119 Dose-response meta-analysis of BMI and kidney cancer, stratified by sex – per 5 units 223
Figure 120 Dose-response meta-analysis of BMI and kidney cancer, stratified by outcome type – per 5 units 224

Figure 121 Dose-response meta-analysis of BMI and kidney cancer, stratified by geographic location – per 5 units....225
Figure 122 Nonlinear dose-response analysis of BMI and kidney cancer....226
Figure 123 Highest versus lowest forest plot of weight and kidney cancer....231
Figure 124 Dose-response meta-analysis of weight and kidney cancer - per 5 kg....232
Figure 125 Funnel plot of weight and kidney cancer....232
Figure 126 Dose-response graph of weight and kidney cancer....233
Figure 127 Dose-response meta-analysis of weight and kidney cancer, stratified by sex – per 5 kg 234
Figure 128 Nonlinear dose-response analysis of weight and kidney cancer....235
Figure 129 Highest versus lowest forest plot of waist circumference and kidney cancer....240
Figure 130 Dose-response meta-analysis of waist circumference and kidney cancer - per 10 cm....240
Figure 131 Dose-response graphs of waist circumference and kidney cancer....241
Figure 132 Highest versus lowest forest plot of waist-to-hip ratio and kidney cancer....245
Figure 133 Dose-response meta-analysis of waist-to-hip ratio and kidney cancer - per 0.1 unit....245
Figure 134 Dose-response graph of waist-to-hip ratio and kidney cancer....246
Figure 135 Highest versus lowest forest plot of height and kidney cancer....250
Figure 136 Dose-response meta-analysis of height and kidney cancer - per 5 cm....250
Figure 137 Funnel plot of height and kidney cancer....251
Figure 138 Dose-response graph of height and kidney cancer....252
Figure 139 Dose-response meta-analysis of height and kidney cancer, stratified by sex - per 5 cm 253
Figure 140 Nonlinear dose-response analysis of height and kidney cancer....254

Matrices presented in the WCRF/AICR 2007 Expert Report

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE KIDNEY

In the judgement of the Panel, the factors listed below modify the risk of cancer of the kidney. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**
Probable		
Limited — suggestive		Arsenic in drinking water[1]
Limited — no conclusion	Cereals (grains) and their products; vegetables; fruits; meat; poultry; fish; eggs; milk and dairy products; total fat; soft drinks; tea; alcoholic drinks (protective effect)[2]; carbohydrate; protein; vitamin A; retinol; vitamin C; vitamin E; beta-carotene; flavonol; Seventh-day Adventist diets; physical activity; body fatness at age 18–20; weight at age 18–20; birth weight; adult attained height; age at menarche; energy intake.	
Substantial effect on risk unlikely	Coffee; alcoholic drinks (adverse effect)[2]	

1 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.

2 The evidence was sufficient to judge that alcoholic drinks were unlikely to have an *adverse* effect on the risk of kidney cancer; but it was inadequate to draw a conclusion regarding a protective effect.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Modifications to the protocol

1. The search team composition was modified. The literature search and data extraction was conducted by Leila Abar (LA). Dagfinn Aune, Deborah Navarro Rosenblatt, LA and Snieguole Vingeliene worked as data analysts and double checked data extraction.
2. In the original protocol, meta-analysis for a particular exposure would be conducted when three or more trials or cohort studies had been published after 2006, and if the total number of studies in the database totalled to more than 3 trials or 5 cohort studies. However, no meta-analysis was conducted in the 2005 SLR for most exposures because cohort studies were not available. For that reason, the CUP team conducted meta-analysis for an exposure when the total number of cohort studies with enough data was 2. The guideline of doing new updates when the total number of studies is more than 3 trials or 5 cohort studies will be implemented in the future reviews.
3. The Pooling Project of Cohort Studies was combined in a dose-response meta-analysis with the studies identified in the 2005 SLR and the CUP.

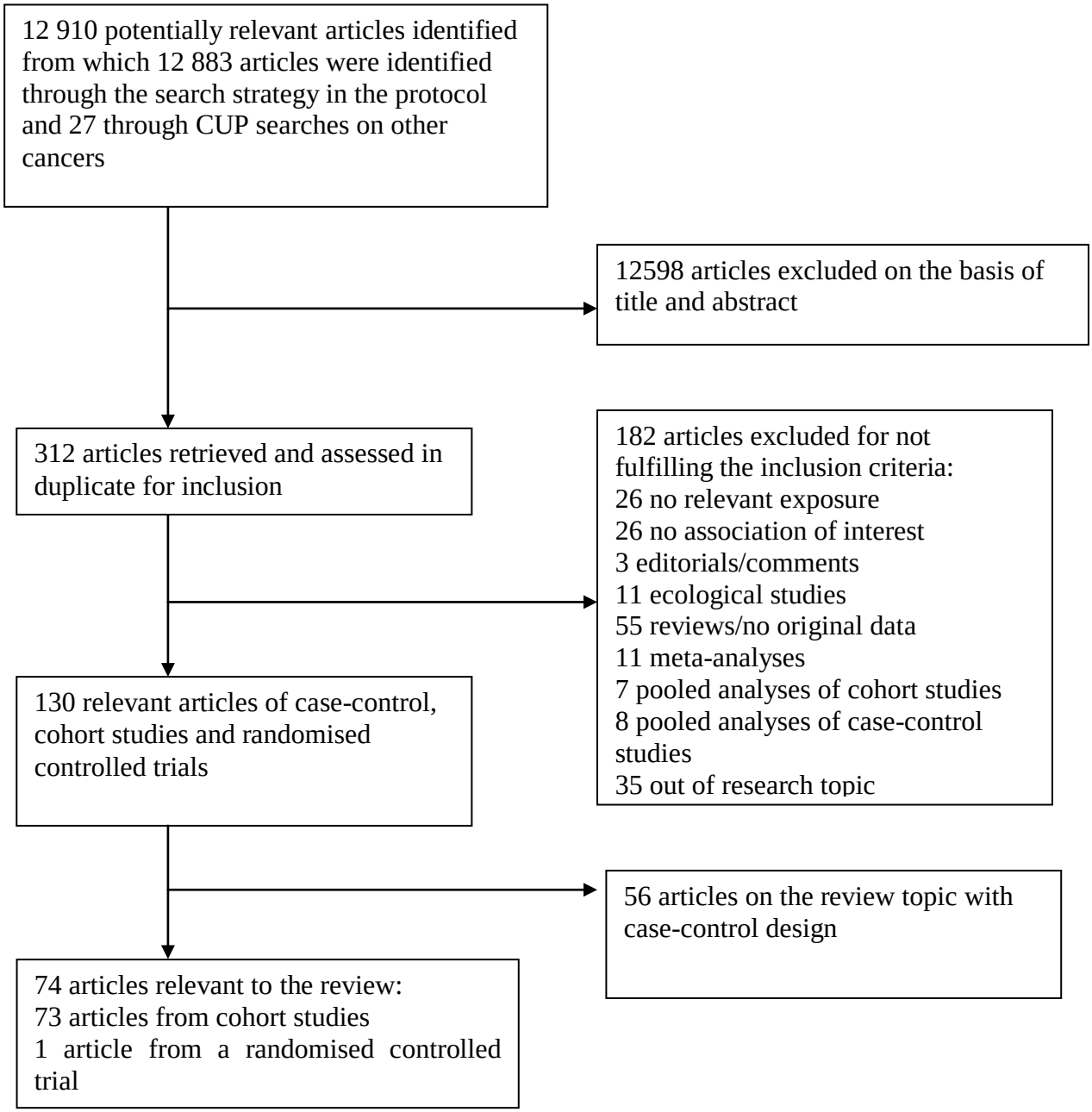
Notes on figures and statistics used

- The statistical methods used are described in the protocol.
- The method by Hamling et al, 2008 was used to convert risk estimates when the reference category was not the lowest category
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins and Thompson, 2002). Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Heterogeneity test and I^2 statistics are shown for a "Highest vs Lowest" meta-analysis when this is the only type of meta-analysis conducted.
- Only summary relative risks estimated with random effect models are shown.
- The dose-response forest plots show the relative risk estimate for each study, expressed per unit of increase. The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and table.
- Highest vs. lowest forest plots show the relative risk estimate for the highest vs the reference category used in each study. The comparisons in each study are shown. The overall summary estimate was not calculated (except for physical activity domains).
- The dose-response plot shows the results for each study included in the review. The relative risks estimates are plotted in the mid-point of each category level (x-axis) and are connected through lines.

Continuous Update Project: Results of the search

The search period is from the 1st of January 2006 until the 31st of March 2013. Relevant papers published before January 1st 2006 were already extracted into the WCRF database

Flow chart of the search for kidney cancer
1 January 2006- 31 March 2013



Results by exposure

1) Randomised controlled trials (RCT)

Only one study was identified.

Low fat dietary pattern

The Women's Health Initiative (WHI) (Prentice et al, 2007) reported no significant effect of dietary modification on kidney cancer risk in postmenopausal women.

The WHI trial was initiated in 1992 with the aim of assessing the risks and benefits of hormone therapy and dietary modification among postmenopausal women. Breast cancer and colorectal cancer were the primary outcomes, and kidney cancer and endometrial cancer were listed as outcomes that may be beneficially influenced by the intervention.

The goals of the dietary modification intervention were to reduce fat intake (20% or less of energy from fat), and increase the intake of vegetables and fruit (5 or more servings/day) and grains (6 or more servings/day). The intervention group experienced an early modest weight loss, with an average weight difference between randomization groups of 1.9 kg at one year from random assignment that diminished to 0.4 kg at 7.5 years.

The average age of the participants was 62.3 years, about three-quarters were overweight or obese (BMI ≥ 25 kg/m2); more than 40% reported a history of hypertension. At 6 years, the intervention group had 8.1% reduction in the percentage of energy from fat, consumed 1.1 servings more of vegetables and fruit and 0.4 servings more of grain than the comparison group.

After 8.1 years of follow-up on average, the incidence of cancer of the kidney did not differ significantly between the intervention and the control groups (HR = 0.78, 95% CI = 0.50-1.20; *P* = 0.92; 91 cases), based on 27629 women (n = 11092 intervention, n = 16537 comparison group).

2) Cohort studies

The Table 1 shows the distribution of articles from cohort studies by exposure included in the WCRF database.
Only exposures updated during the CUP (publication date from 1 January 2006 to 31 March 2013) are shown.

Table 1 Number of relevant articles identified during the Second Expert Report and the CUP and total number of cohort studies by exposure.

The exposure code indicates the code used for the exposure in the WCRF database. The total number of cohort studies is not the sum of the number of articles when some cohort studies published more than one article on the same exposure or one article reported results for more than one cohort study.

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Expert Report	CUP	
1.4	Individual level dietary patterns	1	2	3
1.5	Other dietary patterns	-	1	1
1.7	Other dietary pattern issues	-	2	2
2.1.1.2.2	Refined grain	-	1	1
2.1.1.2.3	Rice	1	1	2
2.1.1.4	Wholegrain	-	1	1
2.1.2	Wheat, barley, oats (other grains)	-	2	2
2.1.2.1	Starchy foods	-	2	2
2.2	Fruits and non-starchy vegetables	4	3	7
2.2.1	Non-starchy vegetables	4	5	8
2.2.1.1	Non-starchy root vegetables and tubers - Carrots	2	1	3
2.2.1.1.1	Starchy roots	1	1	2
2.2.1.2	Cruciferous vegetables	2	3	6
2.2.1.2.2	Chinese cabbage	1	1	2
2.2.1.2.3	Cabbage	2	1	3
2.2.1.4	Green leafy vegetables –not including cruciferous vegetables	3	1	4
2.2.1.4.2	Spinach	2	1	3
2.2.1.4.4	Seaweed	-	1	1
2.2.1.5.13	Tomato	2	1	3
2.2.2	Fruits (general)	5	5	10
2.2.2.1	Citrus fruit	2	4	7
2.2.2.2	Other fruits	-	1	1
2.2.2.2	Apples, pears	-	1	1
2.2.2.2	Berries	2	1	3
2.3	Pulses (legumes)	1	2	3

2.3.1	Soybean, soybean products	-	1	1
2.3.1.1	Miso soup	1	1	2
2.3.2	Lentils	-	1	1
2.3.2.2	Tofu	1	1	2
2.3.4	Peanuts, peanut products	-	1	1
2.5.1	Meat	1	1	2
2.5.1.2	Processed meat	2	3	4
2.5.1.2.9	Sausages	-	1	1
2.5.1.3	Red meat	1	2	3
2.5.1.3.1	Beef	2	1	3
2.5.1.3.3	Pork	1	1	2
2.5.1.4	Poultry	2	2	3
2.5.1.5	Offal and offal products	-	2	2
2.5.2	Fish	2	5	6
2.5.2.3	Fish, processed (dried, salted, smoked)	1	2	3
2.5.2.5	Fatty fish	-	1	1
2.5.2.9	Lean fish	-	1	1
2.5.4	Eggs	-	2	2
2.6	Fats, oils and sugars as foods	-	1	1
2.6.1.1	Butter	1	1	2
2.7	Milk and dairy products	1	1	2
2.7.1	Milk only	2	2	4
2.7.2	Cheese, full fat or unspecified	1	1	2
2.7.3	Yoghurt	-	1	1
2.9	Composite Foods	2	1	3
2.9.13	Confectionery	-	1	1
3.1	Total fluid intake	-	1	1
3.2	Water as beverage	1	1	2
3.4.2	Carbonated beverages	-	1	1
3.5	Fruit juices	1	2	3
3.6.1	Coffee	6	3	7
3.6.2	Tea	4	2	4
3.6.2.1	Black tea	2	1	3
3.6.2.2	Green tea	1	1	2
3.7.1	Alcoholic drinks	3	8	11
4.1.2.7	Heavy metals	-	1	1
4.1.2.7.2	Arsenic	3	1	4
4.1.2.9	Other contaminants	1	2	3
4.2.5.1	Salt, total salt use	-	1	1
4.3.5.4.1	Nitrites and nitrates (as food additives)	1	2	3
4.4.1	Fresh food (as preparation)	-	1	1
4.4.2	Cooked food (as preparation)	-	2	2
4.4.2.5	Frying	-	1	1
4.4.2.6	Grilling (broiling) and barbecuing	-	1	1
4.4.2.7	Heating, re-heating	-	1	1

4.4.2.8	Heterocyclic amines	-	1	1
5.1.1	Polysaccharides	-	1	1
5.1.2	Non-starch polysaccharides/dietary fibre	1	2	3
5.1.2.1	Cereal fibre	-	1	1
5.1.2.2	Vegetable fibre	-	1	1
5.1.2.3	Fruit fibre	-	1	1
5.1.3	Starch	-	1	1
5.1.4	Sugars (as nutrients)	-	3	3
5.1.5	Glycaemic index	-	1	1
5.2	Lipids (as nutrients)	3	1	4
5.2.5	Trans fatty acids	-	1	1
5.2.6	Other dietary lipids, cholesterol, plant sterols	1	1	2
5.3.1	Total protein	3	2	5
5.4	Alcohol (as ethanol)	6	6	8
5.4.1	Alcohol from beer	5	2	7
5.4.2	Alcohol from wine	4	4	7
5.4.3	Alcohol from spirit (hard liquor)	4	2	6
5.5.1	Vitamin A	2	2	4
5.5.1.1	Retinol	3	1	4
5.5.1.2	Dietary alpha-carotene	-	3	4
5.5.1.2	Beta-carotene (food and supplement)	-	1	1
5.5.1.2	Dietary Beta-carotene	-	2	2
5.5.1.2	Serum Beta-carotene	1	1	2
5.5.1.2	Dietary beta-cryptoxanthin	-	3	4
5.5.2	Non-provitamin A carotenoids	-	3	3
5.5.2	Dietary lutein and zeaxanthin	-	3	4
5.5.2	Dietary lycopene	-	3	4
5.5.3.1	Total folate	-	-	1
5.5.3.2	Dietary folate	1	2	3
5.5.5	Thiamin (vitamin B1)	2	1	3
5.5.7	Pyridoxine (vitamin B6)	2	1	4
5.5.8	Cobalamin (vitamin B12)	-	1	1
5.5.9	Vitamin C (food and supplement)	2	1	4
5.5.9	Dietary vitamin C	2	3	6
5.5.11	Vitamin E (food and supplement)	2	1	4
5.5.11	Dietary vitamin E	3	3	6
5.5.13	Other vitamins (including multivitamins)	1	3	4
5.6.2	Iron	2	1	3
5.6.3	Calcium (food and supplement)	2	2	3
5.6.3	Dietary calcium	-	2	2
5.6.3	Supplemental calcium	-	1	1
5.6.3	Serum calcium	-	1	1
5.7	Phytochemicals	-	2	2
5.7.4	Polyphenols	-	2	2
5.8	Other bioactive compounds	2	2	4

6.1	Total physical activity	3	1	4
6.1.1.2	Recreational physical activity	5	2	6
6.1.1.2	Walking	1	1	2
6.1.4	Duration of physical activity	-	1	1
6.1.4.2	Duration of walking	-	1	1
6.2	Physical inactivity	-	2	2
7.1	Energy Intake	3	3	5
7.1.0.1	Energy from fat	-	1	1
7.1.0.2	Energy from protein	-	2	2
7.1.0.3	Energy from carbohydrates	-	1	1
7.1.0.5	Non-alcohol energy	-	1	1
8.1.1	BMI	20	17	28
8.1.2	Other weight adjusted for height measures	2	2	4
8.1.3	Weight	7	3	9
8.1.6	Change in body composition	5	5	10
8.2.1	Waist circumference	-	3	3
8.2.2	Hip circumference	-	2	2
8.2.3	Waist to hip ratio	2	3	4
8.3.1	Height (and proxy measures)	5	6	11
8.4.1	Birth weight	4	1	5

2 Foods

2.2 Fruit and non-starchy vegetables

Methods

A total of 7 articles (7 cohort studies) have been published on fruit and non-starchy vegetables and kidney cancer risk up to 31 March 2013. Four articles were identified during the SLR for the Second Expert Report (2005 SLR) and three articles (4 cohorts) were identified in the CUP. A meta-analysis including 7 cohorts (4 identified during the CUP and 3 during the 2005 SLR) was performed. Intake was rescaled from servings/day (Prineas et al, 1997, Rashidkhani et al, 2005a and Lee et al, 2006) to grams/day using a standard serving size of 80g. The dose-response results are presented for an increment of 100 g/d.

Main results

The summary RR per 100 g/d was 0.99 (95% CI: 0.94-1.04, I^2=21.7%, $p_{heterogeneity}$=0.26). Results were similar in men (3 studies, RR: 0.95 (95% CI: 0.87-1.03) and women (4 studies, RR: 1.03 (95% CI: 0.95-1.11).

The inverse association with fruits and vegetables was restricted to men never smokers in the only study that reported results stratified by smoking status (Lee et al, 2006). Four studies reported no variation of association across categories of smoking (Bertoia et al, 2010; Weikert et al, 2006; Van Dijk et al, 2005; Rashidkhani et al, 2005) and one study reported only age-adjusted associations.

Egger's test for publication bias was not statistically significant (p= 0.09). However, visual inspection of the funnel plot suggests that small studies showing lower than average associations are missing. In influence analysis, the RR did not vary substantially after excluding each study in turn.

The Pooling Project of Cohort Studies (Lee et al, 2009) reported a significant inverse association of fruit and vegetables intake and renal cell cancer (see **Meta-analysis and Pooled studies** below). When the EPIC study (Weikert et al, 2006) -the only study in the CUP that was not included in the Pooling Project of Cohort Studies - was pooled with the overall result of the Pooling Project, the summary relative risk for an increase of 100 g/d of fruits and vegetables was 0.97 (95% CI: 0.92-1.02; I^2=32.2%; pheterogeneity =0.23; 1748 cases).

Heterogeneity

There was low heterogeneity, I^2=21.7%, $p_{heterogeneity}$=0.26.

Comparison with the Second Expert Report

No meta-analysis of cohort studies was conducted in the Second Expert Report. The pooled RR (unadjusted results) of two case control studies for 1 serving increase was 0.93 (95% CI: 0.89-0.98).

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (13 cohort, 1478 cases) reported a pooled RR for >=600 g/d versus <200 g/d of fruit and vegetable intake of 0.68 (95% CI: 0.54-0.87) (Lee et al, 2009). The RR

for a 280 g/d increment of total fruit and vegetables was 0.88 (95% CI: 0.82-0.95). The relationship was consistent with a linear association (P for non-linearity >0.05).The association was not modified by BMI, smoking habits, and history of hypertension. There was no heterogeneity across gender.

Table 2 Studies on total fruit and non-starchy vegetables identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.92	0.63	1.35	425 vs. 86 g/d
Lee, 2006	United States	Both cohorts combined	248		All	0.73	0.28	1.87	>=6 vs. <3 servings/d
		Health Professionals Follow-Up Study	116	14	M	0.45	0.25	0.81	>=6 vs. <3 servings/d
						0.91	0.84	0.99	Per 1 serving/d increase
		The Nurses' Health Study	132	20	F	1.17	0.66	2.07	>=6 vs. <3 servings/d
Weikert, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	306	6.2	All	1.02	0.93	1.11	Per 80 g/d increase
			169		M	1.03	0.92	1.16	
			137		F	0.99	0.86	1.15	

Table 3 Overall evidence on fruit and non-starchy vegetables intake and kidney cancer

	Summary of evidence
2005 SLR	Four articles (three cohort studies) were identified on fruit and non-starchy vegetables and kidney cancer risk. All reported no association.
Continuous Update Project	Four cohorts were identified and included in the meta-analysis. One reported an inverse association. Seven cohorts (six publications) were included in the CUP meta-analysis and no association was observed.

Table 4 Summary of results of the dose response meta-analysis of total fruit and non-starchy vegetables and kidney cancer

	SLR*	Continuous Update Project
Studies (n)	-	7
Cases (n)	-	1215
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.99 (0.94-1.04)
Heterogeneity (I^2,p-value)	-	21.7%, p=0.26
Pooling Project and EPIC		
Studies (n)	-	14
Cases (n)	-	1748
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.97 (0.92-1.02)
Heterogeneity (I^2,p-value)	-	32.2%, p=0.23

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 5 Inclusion/exclusion table for meta-analysis of fruit and non-starchy vegetables and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14812	Bertoia	2010	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person/ years per category	-
KID14793	Lee	2006	Prospective Cohort Studies	The Nurses' Health Study Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Converted servings/d to grams/d Person/ years per category Mid-exposure values Rescale of reported RR for continuous increase in men	-
KID14792	Weikert	2006	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	No	Rescale of reported RR for continuous increase	-
KID14407	Rashidkhani	2005a	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Converted servings/month to grams/d Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale of reported RR for continuous increase	-
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No RR available, Prineas et al, 1997 results used instead
KID01081	Prineas*	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Converted servings/week to grams/d Mid-exposure values	-

*Not adjusted results

Figure 1 Highest versus lowest forest plot of fruit and non-starchy vegetables and kidney cancer

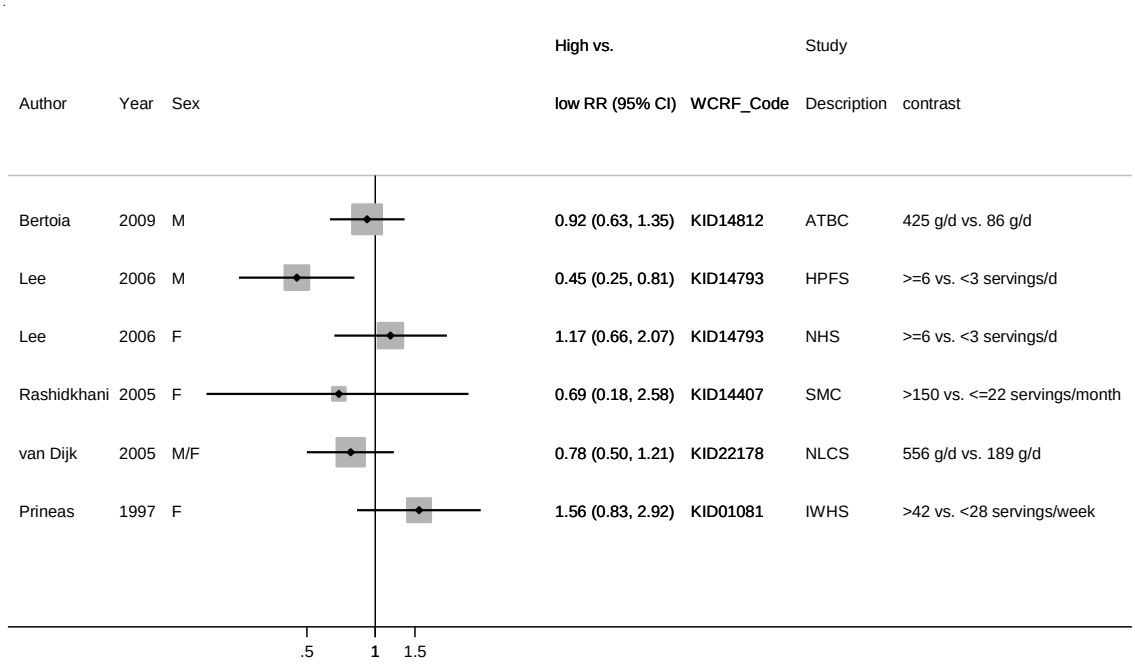


Figure 2 Dose-response meta-analysis of fruit and non-starchy vegetables and kidney cancer - per 100 g/d

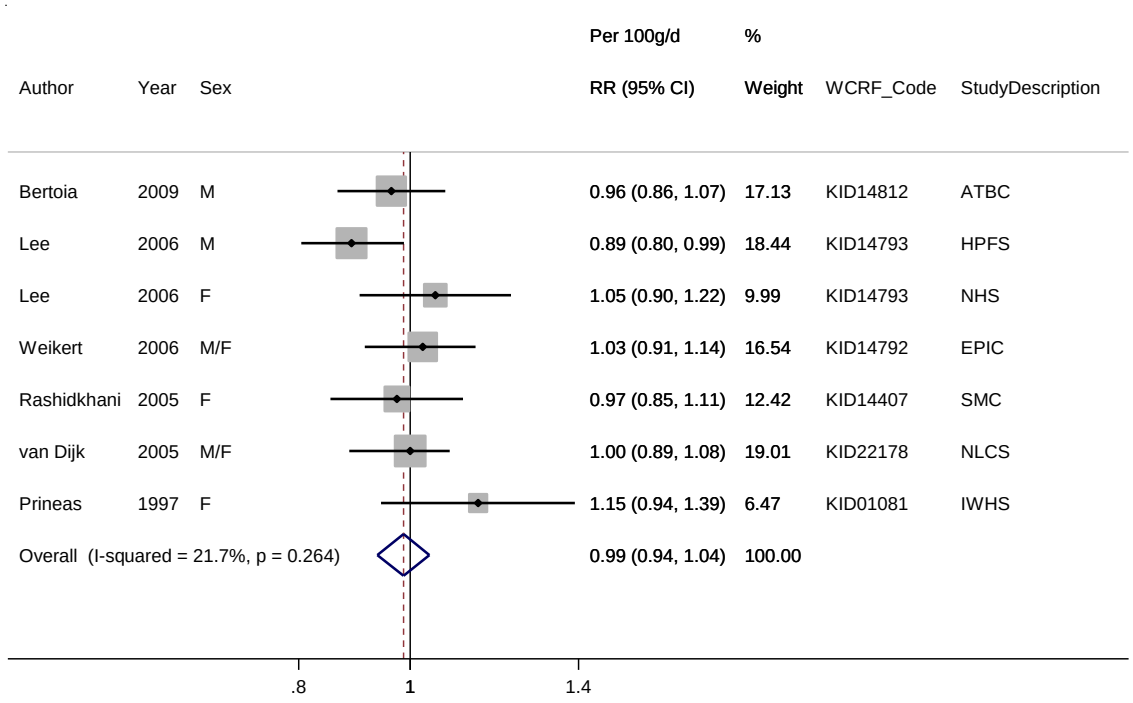


Figure 3 Funnel plot of total fruit and non-starchy vegetables and kidney cancer

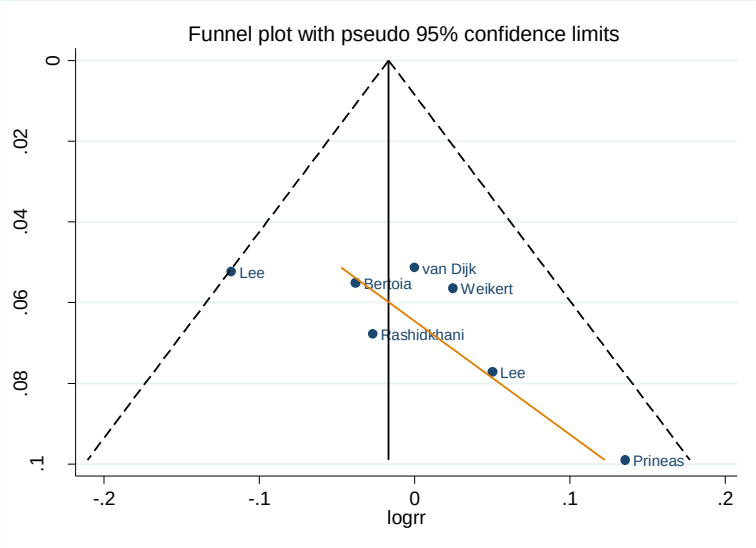
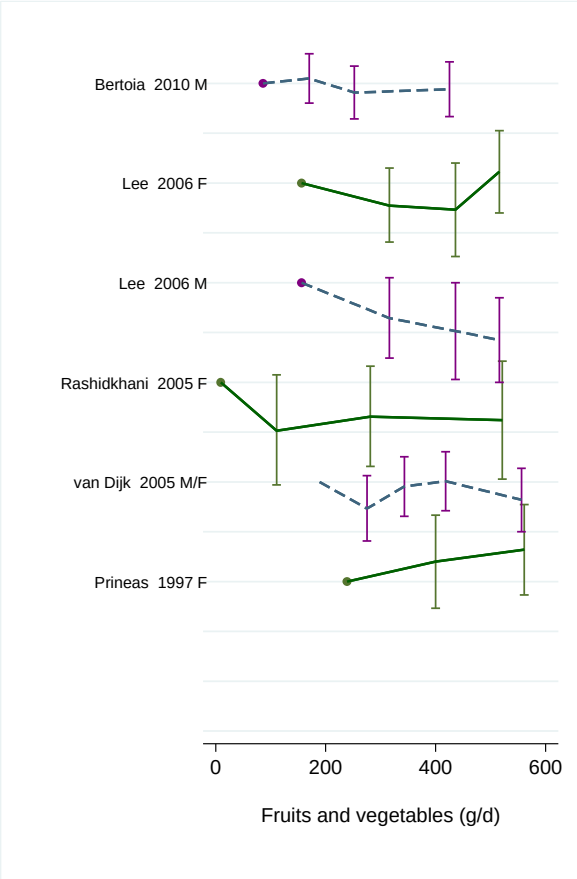


Figure 4 Dose-response graph of total fruit and non-starchy vegetables and kidney cancer



Note: In the EPIC study (Weikert et al, 2006), only continuous results were reported (no association)

.

Figure 5 Dose-response meta-analysis per 100 g /day increase of total fruit and non-starchy vegetables and kidney cancer, stratified by sex

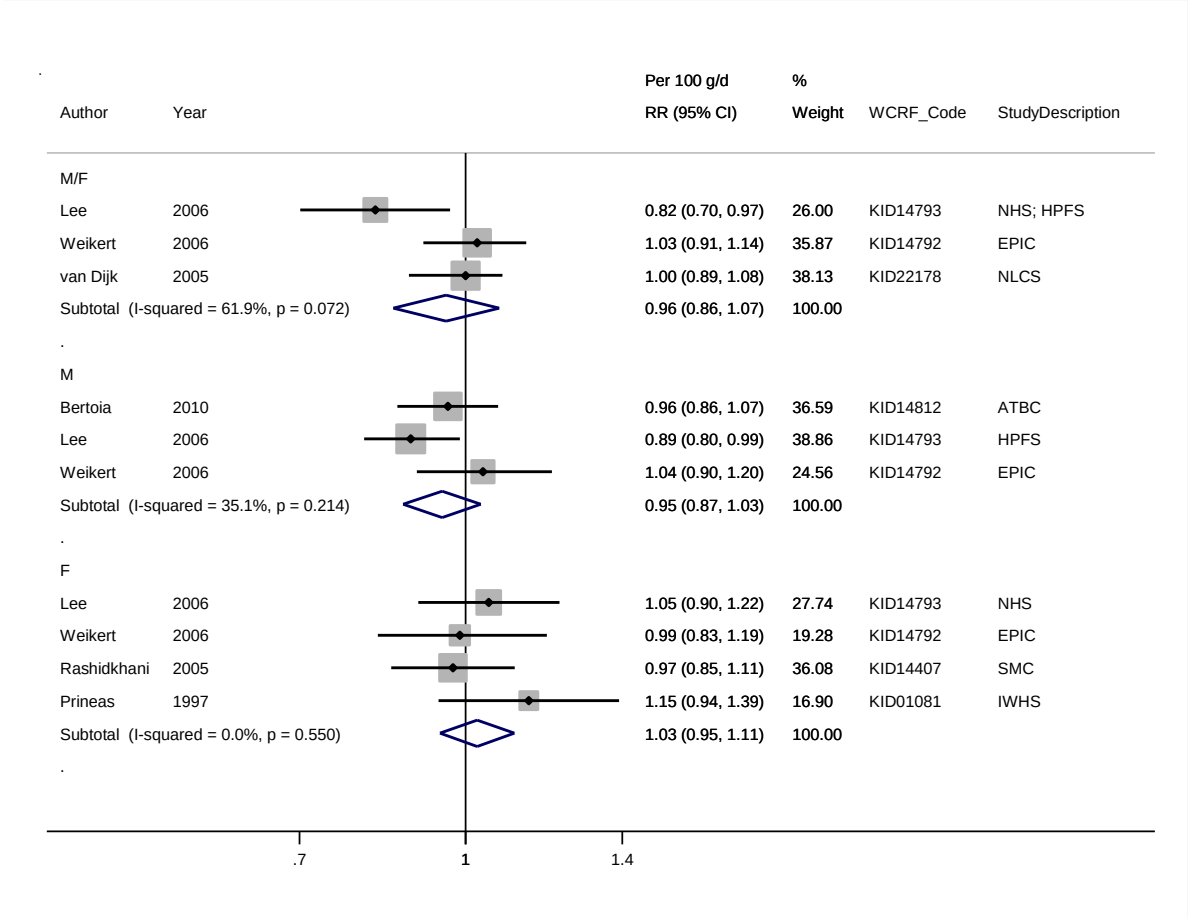
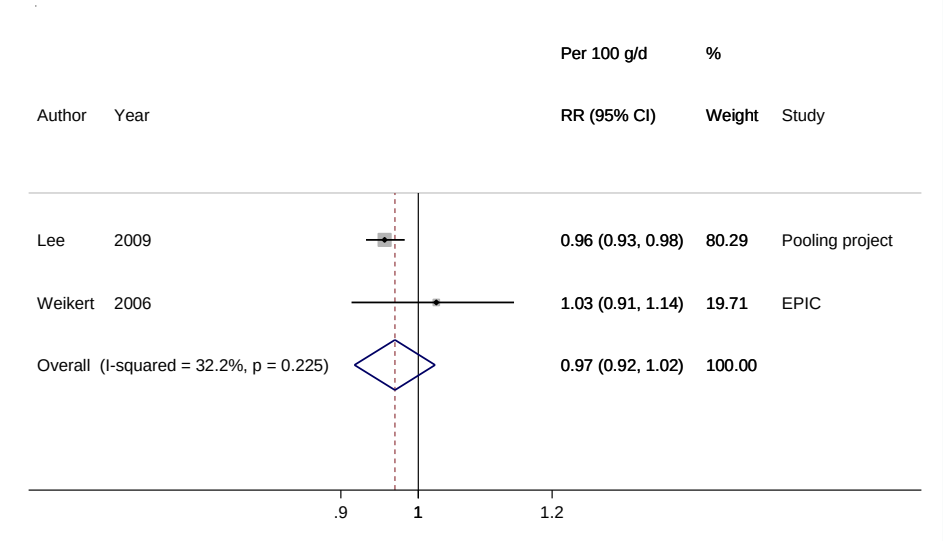


Figure 6 Dose-response meta-analysis per 100 g/d increase of fruit and non-starchy vegetables and kidney cancer. Pooling Project of Cohort Studies and EPIC study



2.2.1 Non-starchy vegetables

Methods

Up to March 2013, 9 articles were identified; 5 articles (5 cohorts) were identified in the CUP.
A meta-analysis including 8 cohort studies (5 identified during the CUP and 3 during the SLR) was performed. Intake was rescaled from servings/day (Prineas et al, 1997, Rashidkhani et al, 2005a Lee et al, 2006) to grams per day using a standard serving size of 80g. In one study (Daniel et al, 2013) vegetable intake was reported as servings/1000 kcal and it was rescaled to grams/day using as approximation the average energy intake per quintile of dietary fibre reported in the article and 225 grams as serving size (MyPyramid Equivalents Database cup equivalents defined as 225g or 237ml of raw or cooked vegetables, 1 cup juice, or 2 cups leafy salad greens). Dose-response analyses were conducted for an intake increase of 100 g/d.

Main results

The summary RR per 100 g/d was 0.99 (95% CI: 0.91-1.09, I^2=44.1%, $p_{heterogeneity}$=0.08). All studies except one (Prineas et al, 1997) controlled for smoking status. Only one study (VanDijk et al, 2005) stratified the analysis by smoking status. No associations were observed in never, former, and current smokers.

Egger's test showed no evidence of publication bias (p= 0.96). Results were similar in men (3 studies, RR: 0.95 (95% CI: 0.69-1.31) and women (4 studies, RR: 1.05 (95% CI: 0.90-1.22). In influence analysis, the RR did not vary significantly excluding each study in turn.

When the Pooling Project of Cohorts (Lee et al, 2009) was combined with two new studies identified in the CUP (EPIC and NIH-AARP) the summary relative risk for an increase of 100g/d of total vegetables was 0.98 (95% CI=0.95-1.01; I^2=0%, $p_{heterogeneity}$=0.69).

Heterogeneity

There was moderate heterogeneity, I^2=44.1%, $p_{heterogeneity}$=0.08. The funnel plot suggests that a study in men showing a strong inverse association (Lee et al, 2006) is an outlier.

Comparison with the Second Expert Report

No meta-analysis of prospective studies was conducted in the Second Expert Report. An inverse association between intake of vegetables and kidney cancer risk was found in a dose-response analysis of case-control studies. The combined RR per serving/day was 0.94 (95% CI: 0.89-0.99, I^2=0%, $p_{heterogeneity}$=0.49, n=3).

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (13 cohorts, 1478 cases) reported a summary RR of 0.72 (95% CI: 0.48-1.08), for >=400 g/d versus <100 g/d vegetable intake (Lee et al, 2009) that was slightly attenuated to 0.75 (95% CI: 0.49-1.14) after further adjustment for fruit intake. The RR for a 130 g/d increment of total vegetables was 0.95 (95% CI=0.87-1.03).

Table 6 Studies on vegetable intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2013	United States	NIH-AARP Diet and Health Study	1816	9	M/F	0.97	0.84	1.12	1.83 vs. 0.52 servings/1000 kcal
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	1.23	0.85	1.79	202 g/d vs. 39 g/d
George, 2009	United States	NIH-AARP Diet and Health Study	973	8	M	0.95	0.78	1.17	Q5 vs. Q1
			363		F	0.80	0.56	1.15	
Lee, 2006	United States	Both cohorts combined	248		All	0.71	0.27	1.86	>=6 vs. <3 servings/d
		Health Professionals Follow-Up Study	116	14	M	0.44	0.25	0.77	
		The Nurses' Health Study	132	20	F	1.17	0.62	2.20	
Weikert, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	306	6.2	All	0.97	0.85	1.11	Per 40 g/d increase
			169		M	1.03	0.85	1.24	
			137		F	0.91	0.74	1.11	

Table 7 Overall evidence on vegetables and kidney cancer

	Summary of evidence
2005 SLR	Four cohort studies were identified on vegetable intake and kidney cancer risk. All reported no association.
Continuous Update Project	Five cohorts were identified; four were included in the meta-analysis. Overall, 8 cohorts (seven articles) were included in the CUP meta-analysis. No association was observed.

Table 8 Summary of results of the dose response meta-analysis of vegetables and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	8
Cases (n)	-	3031
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.99 (0.91-1.09)
Heterogeneity (I^2,p-value)	-	44.1%, p=0.08
Pooling Project, EPIC and NIH-AARP		
Studies (n)	-	15
Cases (n)	-	3600
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.99 (0.96-1.01)
Heterogeneity (I^2,p-value)	-	0%, p=0.65

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 9 Inclusion/exclusion table for meta-analysis of vegetables and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14858	Daniel	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Converted servings per 1000 kcal to grams per day Person/ years per category	-
KID14842	George	2009	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	No	No	-	Superseded by Daniel et al., 2013
KID14812	Bertoia	2010	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person/ years per category	-
KID14793	Lee	2006	Prospective Cohort Study	The Nurses' Health Study; Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Converted servings per day to grams per day Person/ years per category Mid-exposure values	-
KID14792	Weikert	2006	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	No	Rescale of reported RR for continuous increase	-
KID14407	Rashidkhani	2005a	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Converted servings per month to grams per day Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale of reported RR for continuous increase	-
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	No RR available
KID01081	Prineas*	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Converted servings per week to grams per day Mid-exposure values	-

* Not adjusted results

Figure 7 Highest versus lowest forest plot of vegetables and kidney cancer

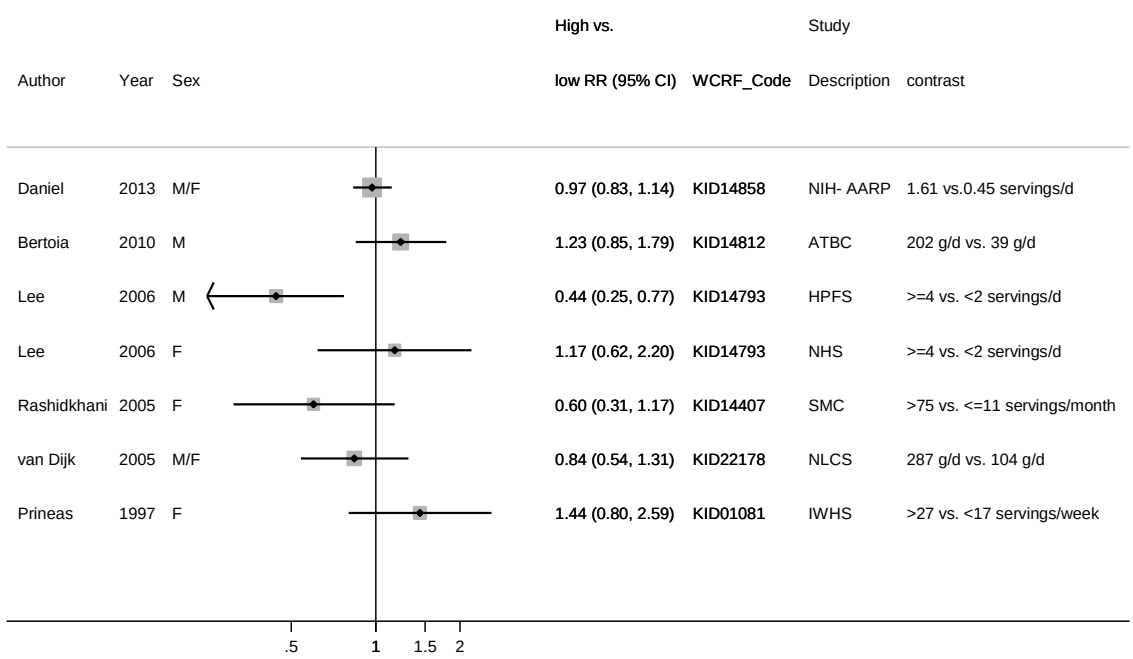


Figure 8 Dose-response meta-analysis per 100 g/d increase of vegetables intake and kidney cancer

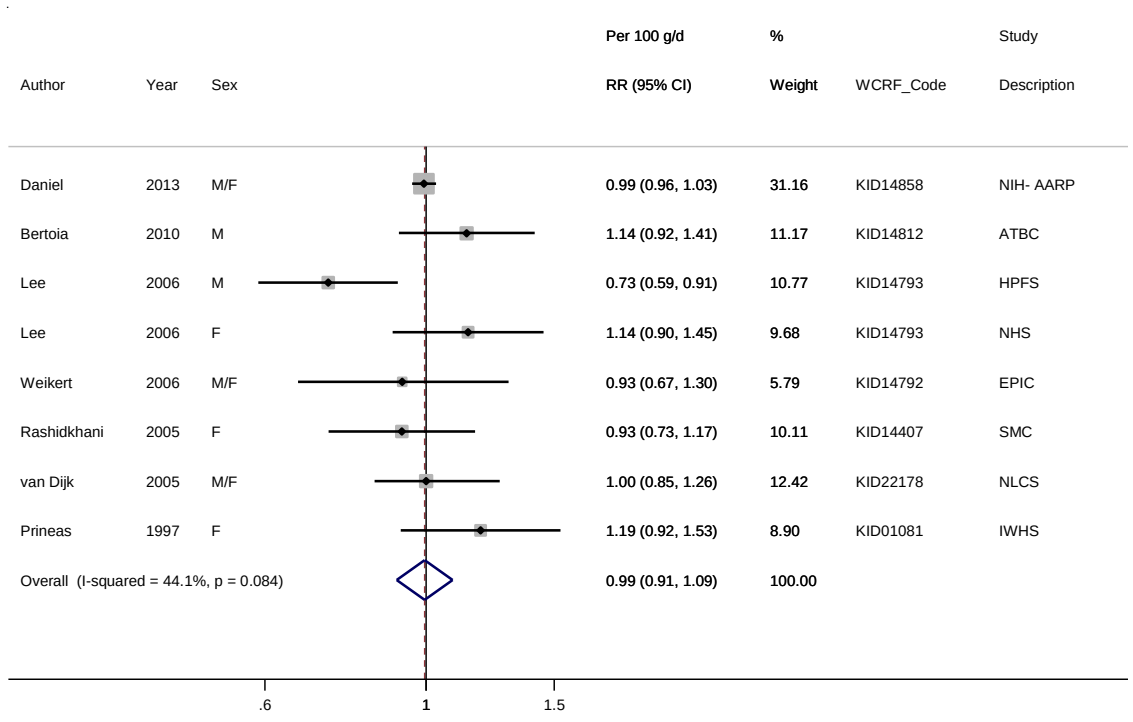


Figure 9 Funnel plot of vegetable intake and kidney cancer

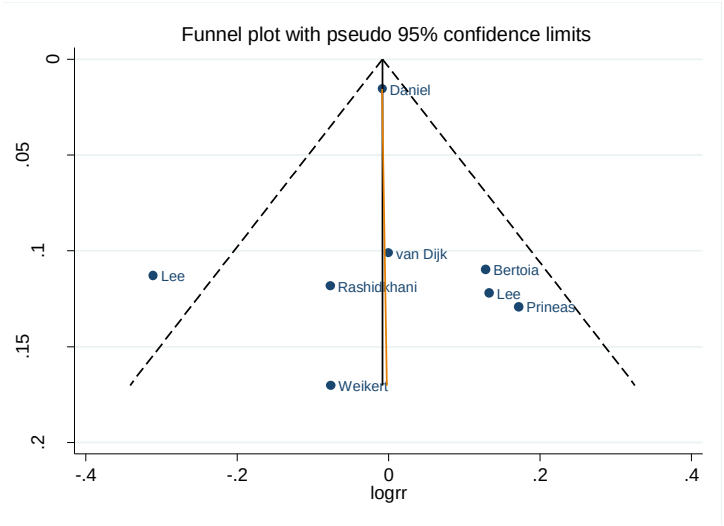


Figure 10 Dose-response graph of vegetable intake and kidney cancer

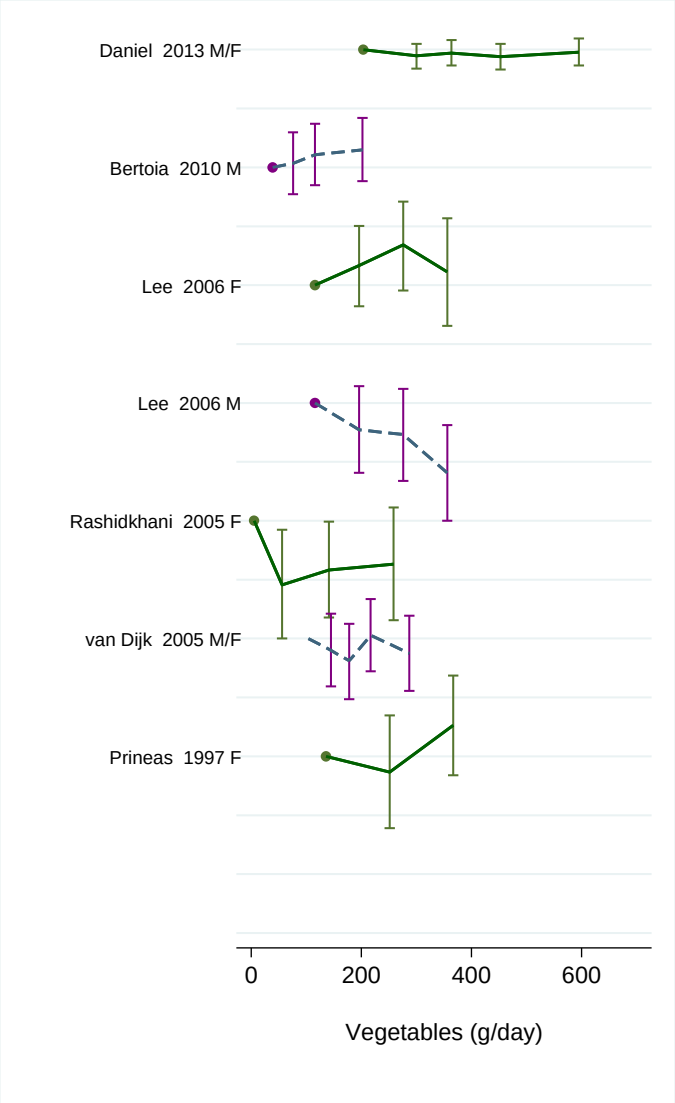


Figure 11 Dose-response meta-analysis per 100 g /d of total vegetable intake and kidney cancer, stratified by sex

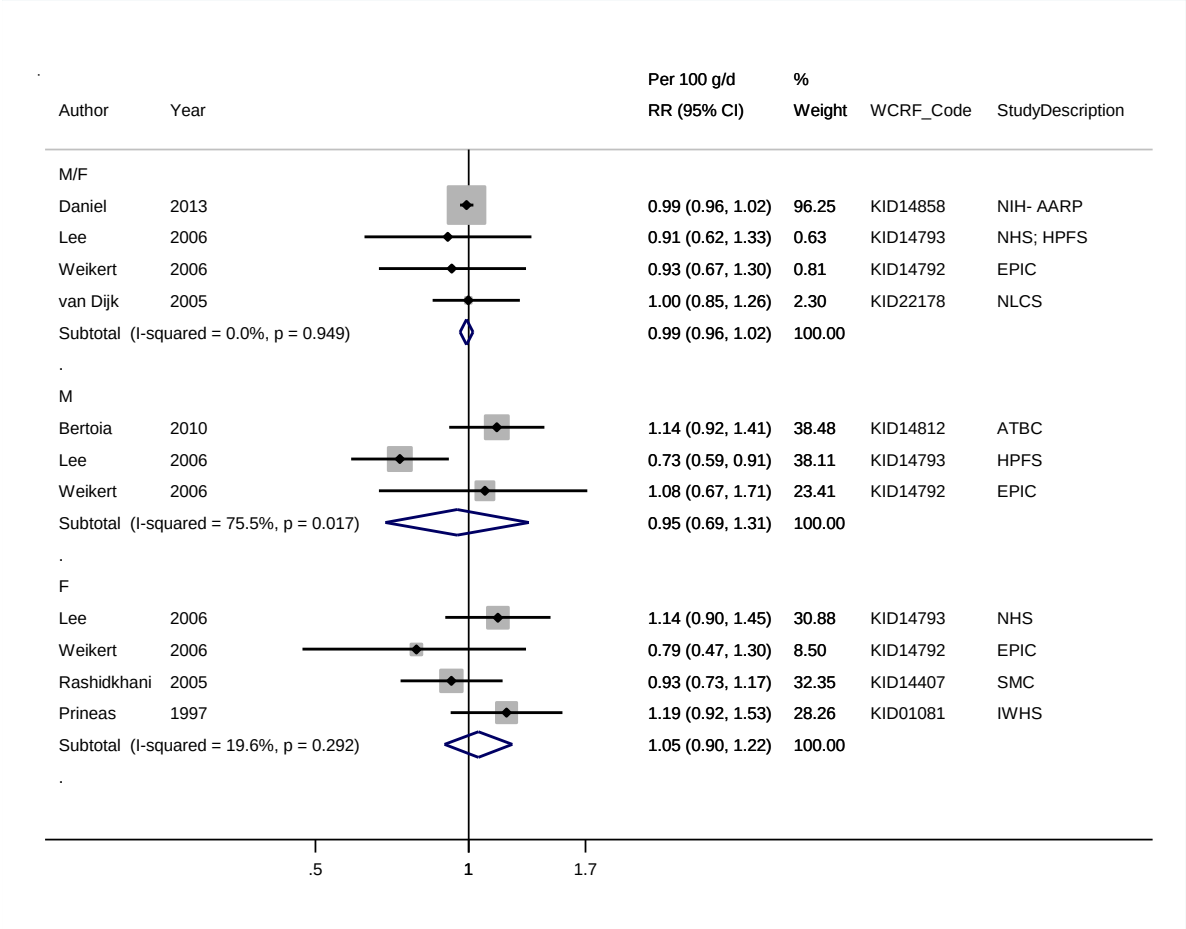
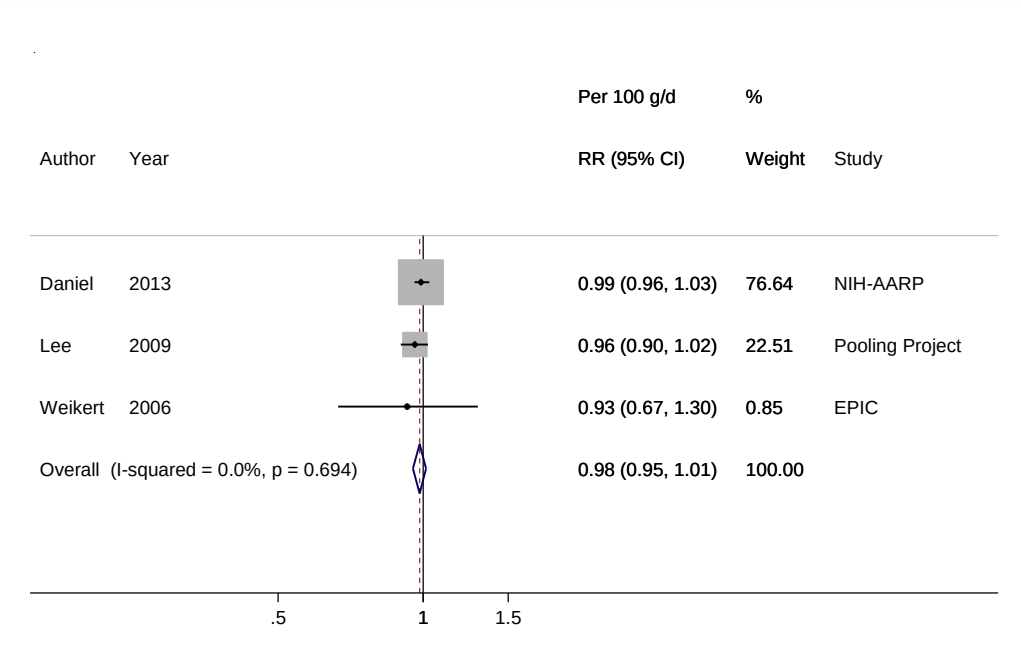


Figure 12 Dose-response meta-analysis per 100 g/d increase of vegetable intake and kidney cancer -. Pooling Project of Cohort Studies and CUP.



2.2.1.2 Cruciferous vegetables

Methods

Up to March 2013, 5 articles were identified; 3 articles (4 cohorts) were identified in the CUP. A meta-analysis including 5 cohorts (4 identified during the CUP and 1 during the SLR) was performed. In two studies (Lee et al, 2006 study and Bertoia et al, 2010) servings/week and times/week were converted to grams per day using a conversion unit of 80g as 1 serving or 1 time. One study (Daniel et al, 2013) reported cruciferous vegetable intake in servings/1000 kcal that was approximated to grams/day using the average energy intake by quintile of fibre reported in the fibre as approximation. Dose-response analyses were conducted per 50 g/d increase.

Main results

The summary RR per 50 g/d was 0.93 (95% CI: 0.81-1.08, I^2=18.5%, $p_{heterogeneity}$=0.30). Egger's test showed no evidence of publication bias (p= 0.91).

When the results of the only study identified in the CUP (NIH-AARP, Daniel et al, 2013) not included in the Pooling Project of Cohort Studies was pooled together with the Pooling Project, the overall results were similar. The summary relative risk of renal cell cancer for an increase of 50 g/d of cruciferous vegetables was 0.95 (95% CI: 0.90-1.00, I^2=0%; $p_{heterogeneity}$ =0.96; 3294 cases)

Heterogeneity

Low heterogeneity was observed, I^2=18.5%, $p_{heterogeneity}$=0.30

Comparison with the Second Expert Report

No meta-analysis of cohort studies was conducted in the Second Expert Report. A meta-analysis of 3 case-control studies reported a RR for one serving/week of 0.94 (95% CI: 0.90-0.97). The CUP found no association between cruciferous vegetable consumption and kidney cancer risk.

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (13 cohort studies) reported RR of 0.97 (95% CI: 0.91-1.03), for an increase of 30 g/d of intake of cruciferous vegetables (e.g., broccoli, cabbage) (Lee et al, 2009). The only study identified in the CUP that was not included in the Pooling Project was the NIH-AARP study (Daniel et al, 2013).

Table 10 Studies on cruciferous vegetables identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2013	United States	NIH-AARP Diet and Health Study	1816	9	M/F	0.83	0.72	0.97	0.33 vs. 0.02 servings/1000 kcal
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	1.24	0.87	1.79	0.33 vs. 0.01 times/day
Lee, 2006	United States	Both cohorts combined	248		All	0.82	0.54	1.26	>=5 vs. <2 servings/week
		Health Professionals Follow-Up Study	116	14	M	0.67	0.39	1.16	
		The Nurses' Health Study	132	20	F	1.04	0.58	1.86	

Table 11 Overall evidence on cruciferous vegetables and kidney cancer

	Summary of evidence
2005 SLR	Two cohort studies were identified on cruciferous vegetable consumption and kidney cancer risk; both reported no association.
Continuous Update Project	Four cohorts were identified. Overall, 5 cohorts (4 articles) were included in the CUP meta-analysis. Overall, no association was observed.

Table 12 Summary of results of the dose response meta-analysis of cruciferous vegetables intake and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	2551
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	0.93 (0.81-1.08)
Heterogeneity (I^2,p-value)	-	18.5%, p=0.30
Pooling Project and NIH-AARP		
Studies (n)	-	14
Cases (n)	-	3294
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	0.95 (0.90-1.00)
Heterogeneity (I^2,p-value)	-	0%, p=0.96

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 13 Inclusion/exclusion table for meta-analysis of cruciferous vegetables and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14858	Daniel	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Converted servings/1000 kcal to grams/day Person/ years per category	-
KID14812	Bertoia	2010	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Converted times per day to grams/day Person/ years per category	-
KID14793	Lee	2006	Prospective Cohort Study	The Nurses' Health Study; Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Converted servings/week to grams/day Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes	RR for continuous increase was rescaled	-
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No RR available

Figure 13 Highest versus lowest forest plot of cruciferous vegetables and kidney cancer

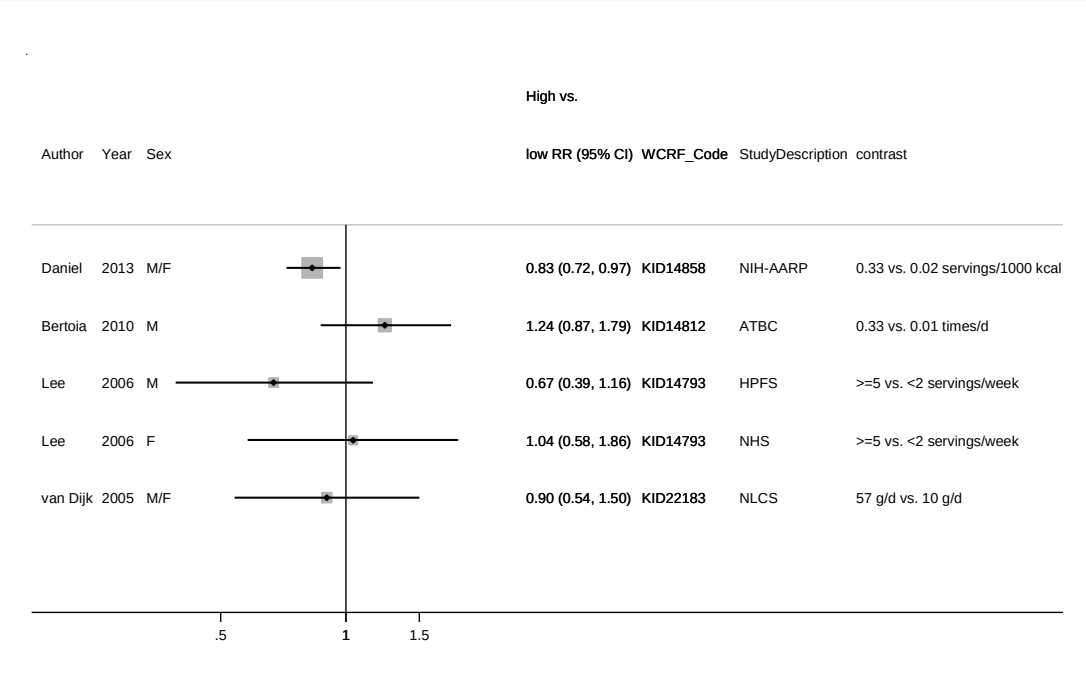


Figure 14 Dose-response meta-analysis per 50 g/d increase of cruciferous vegetables intake and kidney cancer

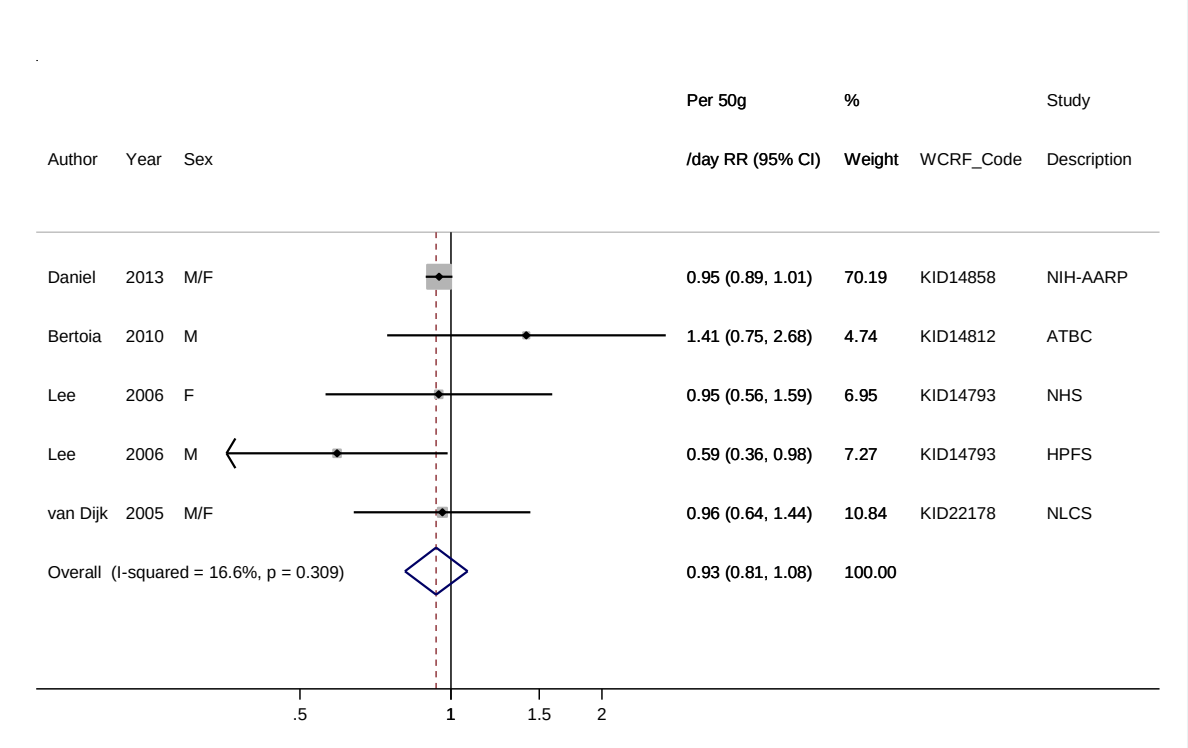


Figure 15 Funnel plot of cruciferous vegetables and kidney cancer

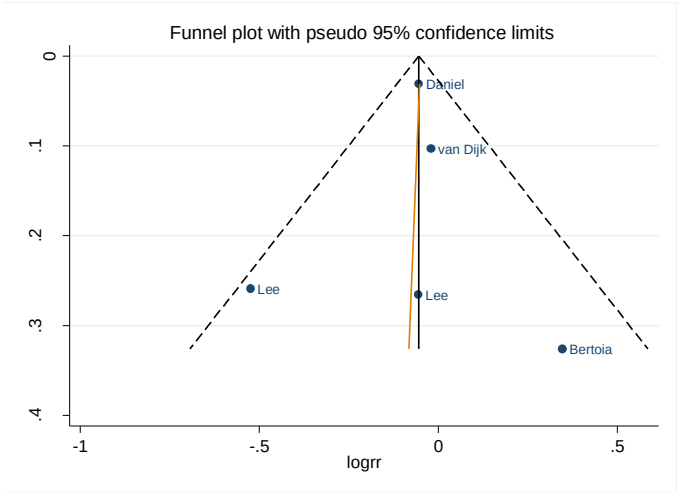


Figure 16 Dose-response graph of cruciferous vegetables and kidney cancer

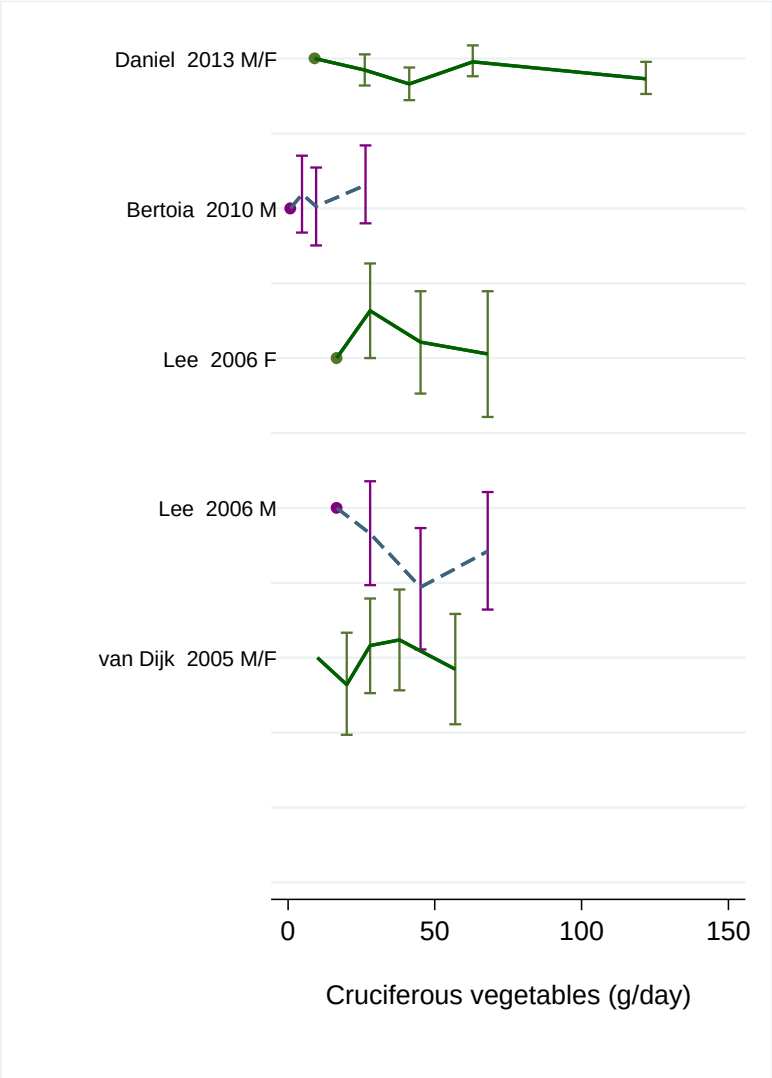
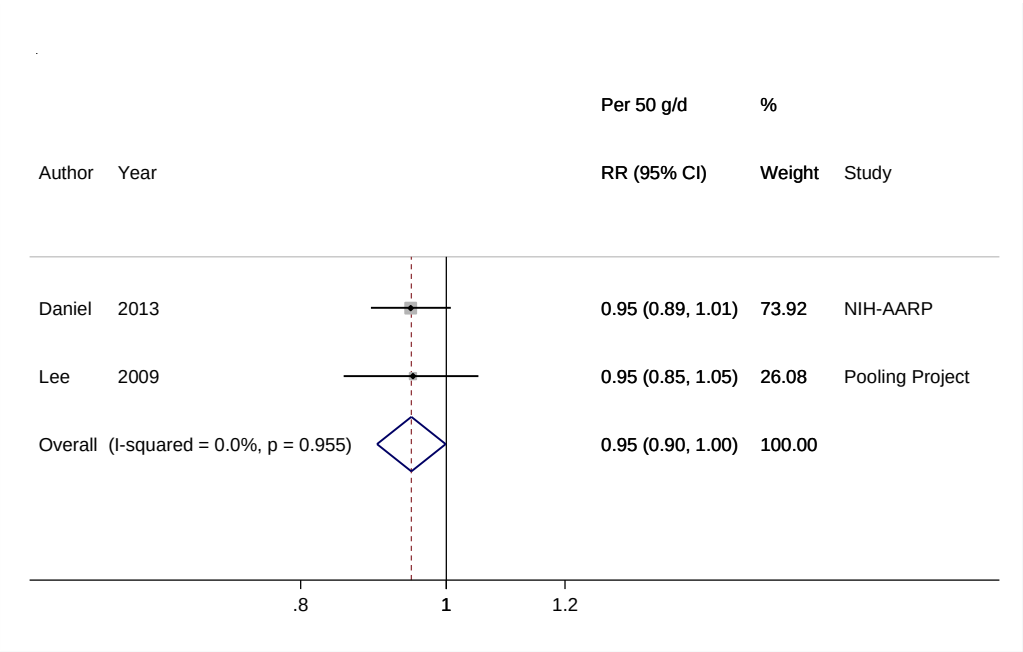


Figure 17 Dose-response meta-analysis per 50 g/d increase of cruciferous vegetables and kidney cancer -. Pooling Project of Cohort Studies and CUP.



2.2.1.5.13 Tomatoes

Methods

Up to March 2013, 3 articles (3 cohort studies) were identified from which one was identified in the CUP. The three cohort studies were included in the meta-analysis. In two studies (Rashidkhani et al, 2005a and Iso et al, 2007) servings were converted to grams using 80g as one standard serving. Dose-response analyses were conducted per 50g/d.

Main results

The summary RR per 50 g/d increase was 1.11 (95% CI: 0.93-1.34, I^2=0.0%, $p_{heterogeneity}$=0.62). Egger's test showed no evidence of publication bias (p= 0.85) but only three cohorts were included.

Heterogeneity

No heterogeneity was observed, I^2=0.0%, $p_{heterogeneity}$=0.62.

Comparison with the Second Expert Report

No meta-analysis of cohort or case-control studies was conducted in the Second Expert Report. The CUP found no association between tomato consumption and kidney cancer risk

Meta-analysis and Pooled studies

In the Pooling Project of Cohort Studies of 13 cohort studies reported pooled RR of 1.12 (95% CI: 0.92-1.37), for an increment of 122 grams of tomato intake per day (Lee et al, 2009).
When the Pooling Project (Lee et al, 2009) was combined with the studies identified in the CUP (JACC, Iso et al, 2007), the RR per 50g/d increment was 1.05 (95% CI: 0.97-1.14).

Table 14 Studies on tomatoes identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Iso, 2007	Japan	Japan Collaborative Cohort Study	41	12	M	1.35	0.55	3.29	>=3-4 vs. <1 times/week
			15		F	0.89	0.25	3.16	

Table 15 Overall evidence on tomatoes and kidney cancer

	Summary of evidence
2005 SLR	Two cohort studies were identified on tomatoes' consumption and kidney cancer; both reported no association.
Continuous Update Project	One cohort was identified. Overall, 3 cohorts were included in the CUP meta-analysis.

Table 16 Summary of results of the dose response meta-analysis of tomatoes and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	427
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	1.11 (0.93-1.34)
Heterogeneity (I^2,p-value)	-	0.0%, p=0.62
Pooling Project and JACC		
Studies (n)	-	14
Cases (n)	-	1534
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	1.05 (0.97-1.14)
Heterogeneity (I^2,p-value)	-	0%, p=0.81

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 17 Inclusion/exclusion table for meta-analysis of tomatoes and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14841	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Converted times per week to grams per day Mid-exposure values	-
KID14407	Rashidkhani	2005a	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Converted servings per week and day to grams per day Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort Study	Incidence	Yes	Yes	No	Rescale of reported RR for continuous increase	-

Figure 18 Highest versus lowest forest plot of tomatoes and kidney cancer

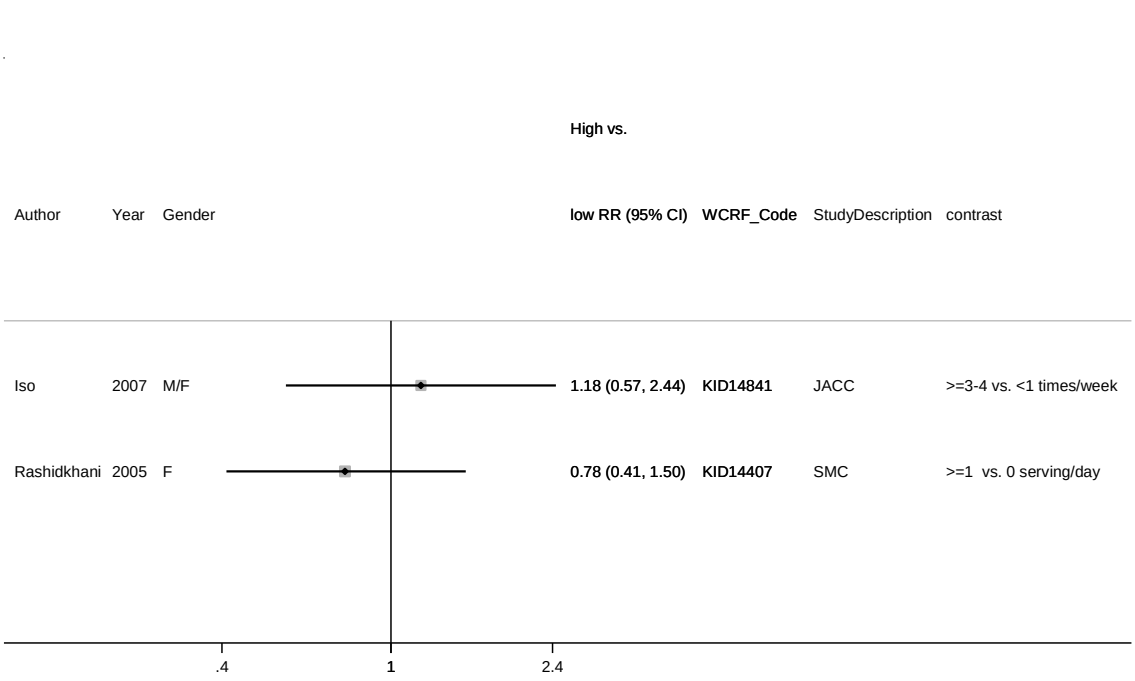


Figure 19 Dose-response meta-analysis per 50 g/d increase of tomato intake and kidney cancer

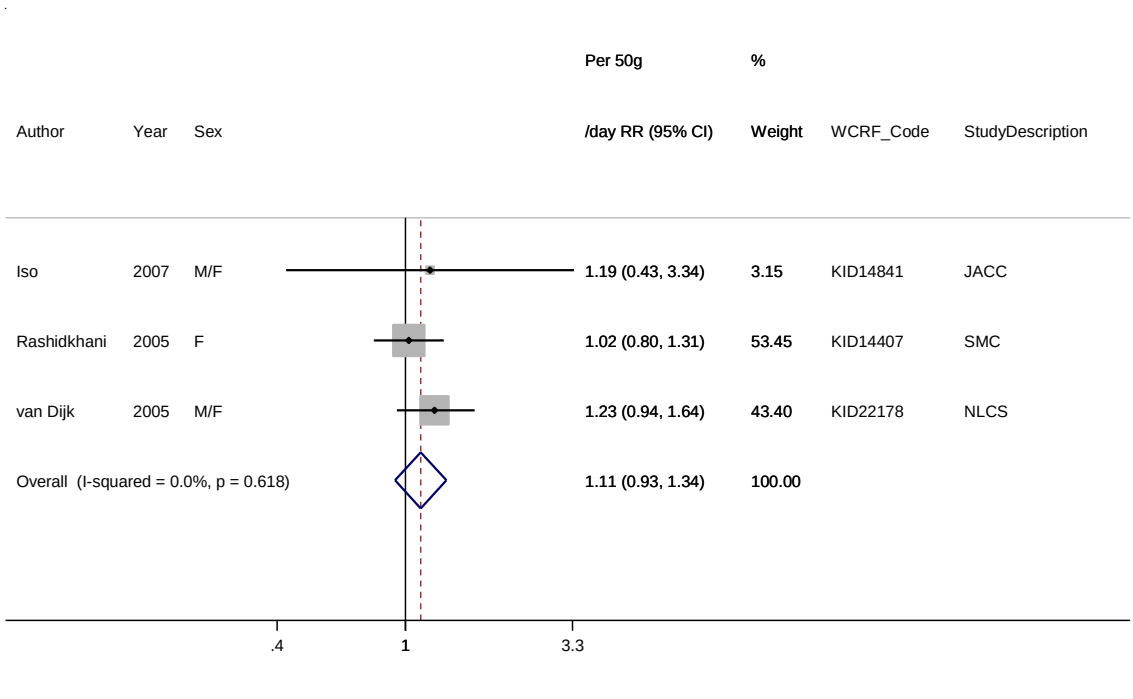


Figure 20 Dose-response graph of tomatoes and kidney cancer

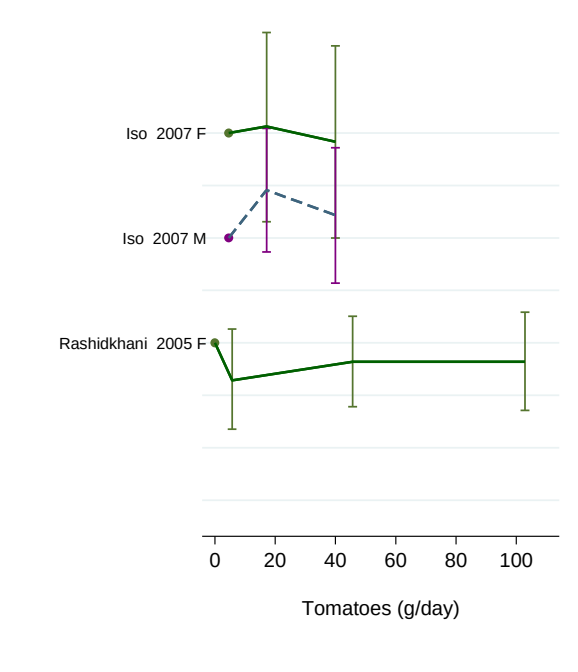
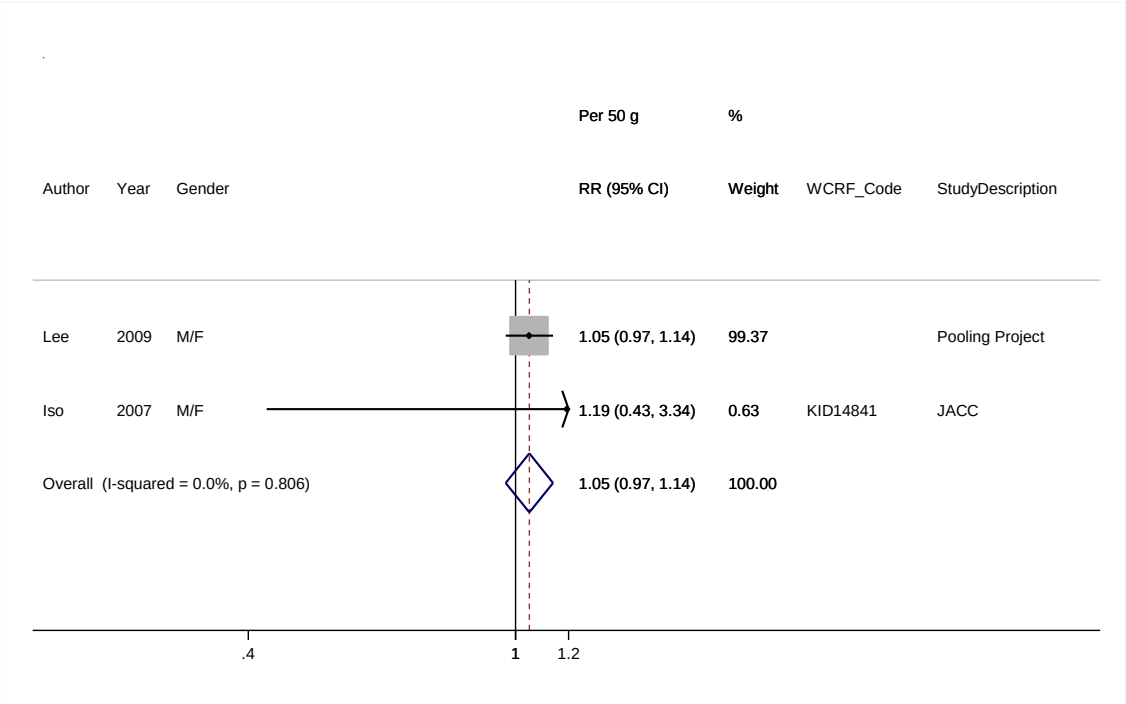


Figure 21 Dose-response meta-analysis per 50 g/d of tomato intake and kidney cancer. Pooling Project of Cohort Studies and CUP



2.2.2 Fruits

Methods

A total of 10 articles (9 cohort studies) have been published on fruits and kidney cancer risk up to 31 March 2013. Five new articles (5 new cohorts) were identified in the CUP and 5 were identified in the 2005 SLR. A meta-analysis including 8 cohorts was performed. Fruit intake was rescaled from servings to grams using a standard serving size of 80g (Lee et al, 2006, Prineas et al, 1997 and Rashidkhani et al, 2005a). In the NIH-AARP study (Daniel et al, 2013) fruit consumption was reported as servings/1000 kcal that was approximated to grams/day using the average energy intake per quintile of dietary fibre intake. The serving sizes in this study were based on MyPyramid Equivalents Database cup equivalents and one serving of raw fruits was equivalent to 225 grams. Dose-response analyses were conducted per 100 g/d.

Main results

The summary RR per 100 g/d was 0.99 (95% CI: 0.96-1.02, I^2=5.9%, $p_{heterogeneity}$=0.39). Only one study (VanDijk et al, 2005) stratified the analysis by smoking status. No associations were observed in never, former, and current smokers. All studies except one (Prineas et al, 1997) controlled for smoking status.

Egger's test showed no evidence of publication bias (p= 0.31). Results were similar in men (3 studies, RR: 0.93 (95% CI: 0.78-1.11, I^2=61.5%, p=0.07) and women (4 studies, RR: 0.97 (95% CI: 0.85-1.11, I^2=0%, p=0.78). In influence analysis, the RR did not vary significantly excluding any one study.

Two studies identified in the CUP were not included in the Pooling Project of Cohort Studies (NIH-AARP (Daniel et al, 2013) and EPIC (Weikert et al, 2006)). When these two studies were added to the results of the Pooling Project, which found significant inverse association, the summary RR for 100 grams increase of fruits was 0.98 (95% CI=0.93-1.03; I^2=74.6%, $p_{heterogeneity=}$0.02).

Heterogeneity

There was low heterogeneity, I^2=5.9%, $p_{heterogeneity}$=0.39.

Comparison with the Second Expert Report

No meta-analysis of cohort studies was conducted in the Second Expert Report. A meta-analysis of 2 case-control studies reported a RR for one serving increase of 0.94 (95% CI: 0.88-1.00). The CUP found no association between fruit intake and kidney cancer risk.

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (13 cohorts, 1478 cases) reported a pooled RRs of 0.79 (95% CI: 0.63-0.99), P_{trend} = 0.03 for total fruit intake of >=400 g/d versus <100 g/d (Lee et al, 2009) that was attenuated to 0.81 (95% CI: 0.64-1.02) after further adjustment for vegetable intake. The RR was 0.89 (95%=0.82-0.95) for a 200 g/d increment of total fruit.

Table 18 Studies on total fruit intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2013	United States	NIH-AARP Diet and Health Study	1816	9	M/F	0.98	0.84	1.15	2.26 vs. 0.3 servings/1000 kcal
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.79	0.55	1.14	257g/d vs. 29 g/d
George, 2009	United States	NIH-AARP Diet and Health Study	973	8	M	0.94	0.76	1.16	Q5 vs. Q1
			363		F	0.74	0.52	1.05	
Lee, 2006	United States	Both cohorts combined	248		All	0.62	0.38	1.02	>=6 vs. <3 servings/d
		Health Professionals Follow-Up Study	116	14	M	0.47	0.24	0.91	
		The Nurses' Health Study	132	20	F	0.78	0.43	1.40	
Weikert, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	306	6.2	All	1.03	0.97	1.08	Per 40 g/d increase
			169		M	1.03	0.96	1.10	
			137		F	1.02	0.93	1.12	

Table 19 Overall evidence on total fruit intake and kidney cancer

	Summary of evidence
2005 SLR	Five cohort studies were identified on fruit intake and kidney cancer risk. All of these reported no association.
Continuous Update Project	New results of five cohort studies were included in the meta-analysis. Overall, 8 cohorts (seven articles) were included in the CUP meta-analysis.

Table 20 Summary of results of the dose response meta-analysis of total fruits and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	8
Cases (n)	-	3041
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.99 (0.96-1.02)
Heterogeneity (I^2,p-value)	-	5.9%, p=0.39
Pooling Project, EPIC and NIH_AARP		
Studies (n)	-	15
Cases (n)	-	3600
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	0.98 (0.93-1.03)
Heterogeneity (I^2,p-value)	-	I^2=74.6%, p=0.02

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 21 Inclusion/exclusion table for meta-analysis of total fruits and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14858	Daniel	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Converted servings per 1000 kcal to grams per day Person/ years per category	-
KID14842	George	2009	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	No	No	-	Superseded by Daniel et al., 2013
KID14812	Bertoia	2010	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person/ years per category	-
KID14793	Lee	2006	Prospective Cohort Study	The Nurses' Health Study; Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Converted servings per day to grams per day Person/ years per category Mid-exposure values	-
KID14792	Weikert	2006	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	No	Rescale of reported RR for continuous increase	-
KID14407	Rashidkhani	2005a	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Converted servings per month to grams per day Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale of reported RR for continuous increase	-
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	No RR available
KID01081	Prineas*	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Converted servings per week to grams per day Mid-exposure values	-
KID01674	Frazer*	1990	Prospective Cohort Study	Californian Seventh Day Adventists' Study	Incidence	Yes	No	Yes	-	Only two categories

* Minimally adjusted results

Figure 22 Highest versus lowest forest plot of total fruits and kidney cancer

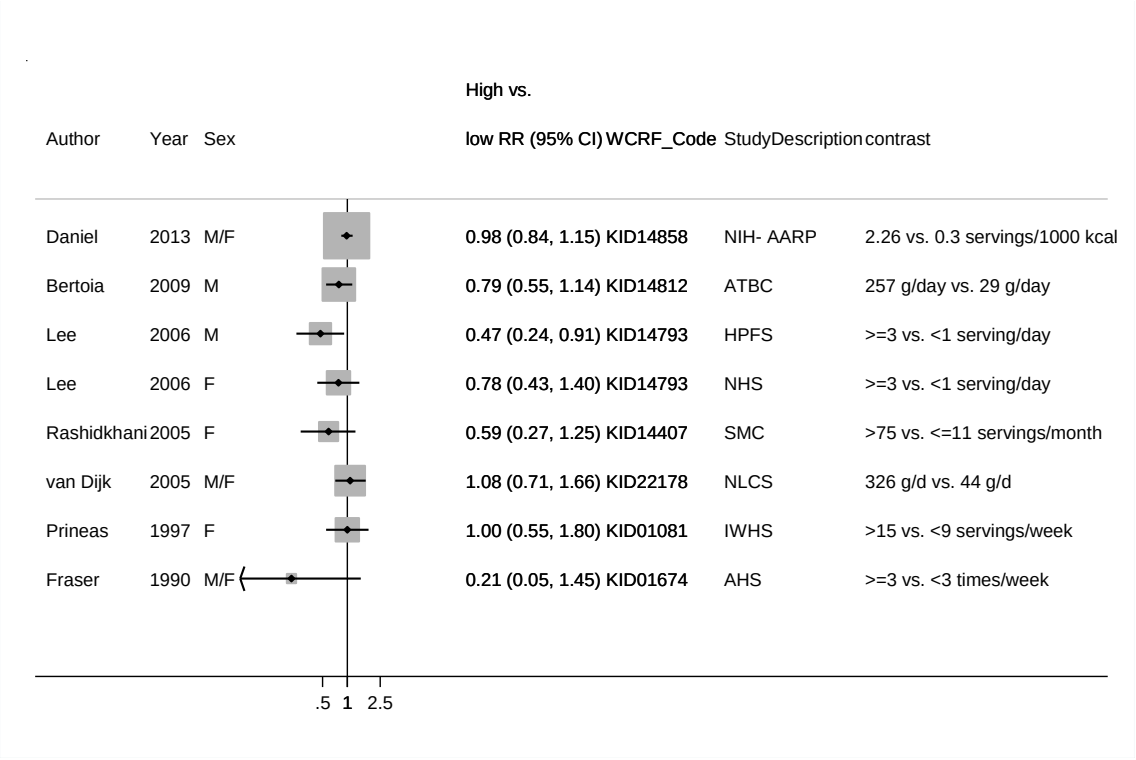


Figure 23 Dose-response meta-analysis per 100 g/d increase of total fruit intake and kidney cancer

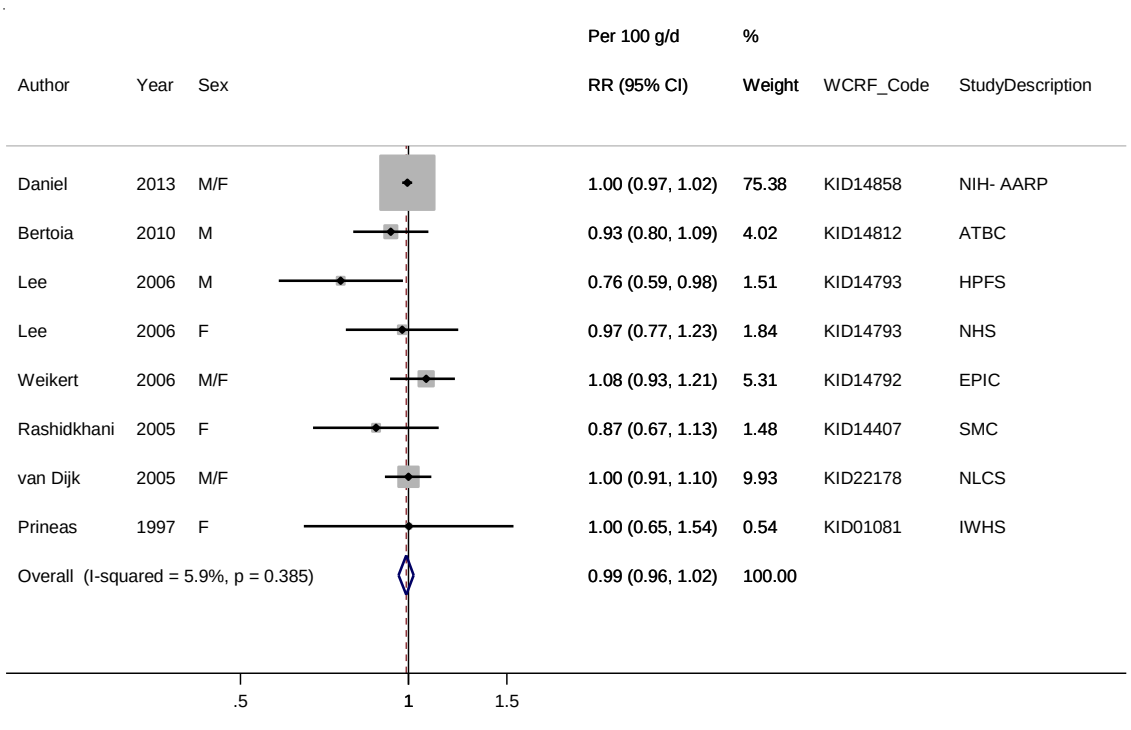


Figure 24 Funnel plot of total fruits and kidney cancer

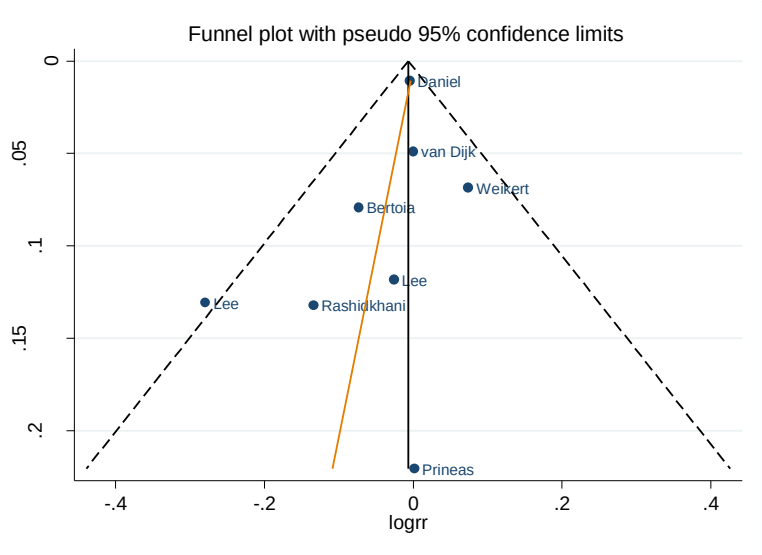


Figure 25 Dose-response graph of total fruits and kidney cancer

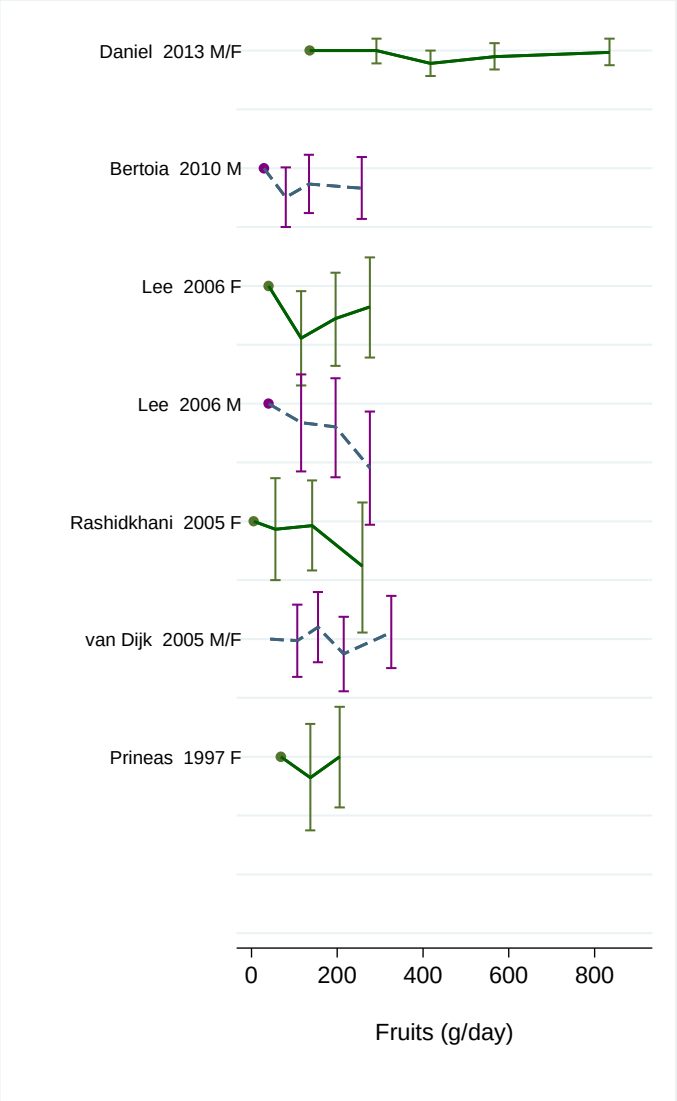


Figure 26 Dose-response meta-analysis per 100 g/d of fruit intake and kidney cancer, stratified by sex

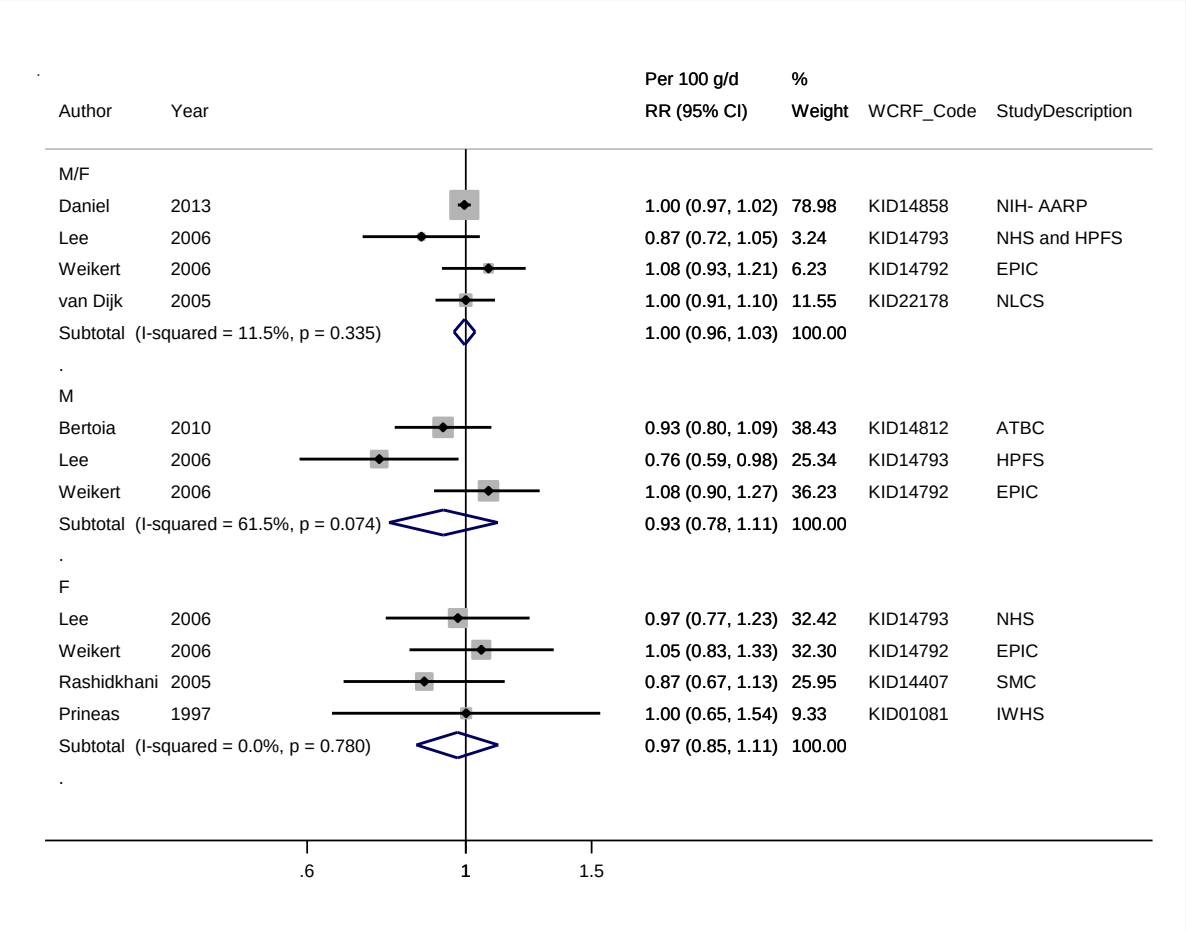
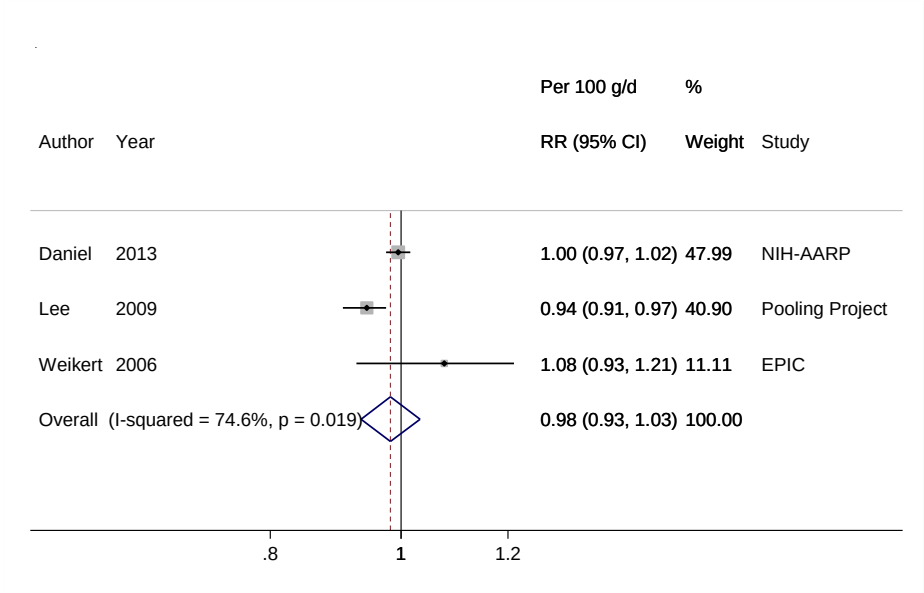


Figure 27 Dose-response meta-analysis per 100 g/d of fruit intake and kidney cancer. Pooling Project of Cohort Studies and CUP



2.2.2 Citrus fruit

Methods

Up to March 2013, a total of 6 articles were identified, from which four articles (5 cohorts) were identified in the CUP. A meta-analysis including 7 cohorts (2 identified during the 2005 SLR and 5 identified during the CUP) was performed. In two studies (Bertoia et al, 2010 and Iso et al, 2007) intake was expressed as times/day and times/week, respectively and they were converted to g/d using a conversion unit of 80 g as one serving of citrus fruit. The results for men and women in Iso et al, 2007 were pooled before inclusion in the meta-analysis. In the NIH-AARP (Daniel et al, 2013) citrus fruit consumption was expressed as grams/1000 kcal that was approximated to g/d using as approximation the average energy intake in the middle quintile of dietary fibre intake provided in the article. Dose-response analyses were conducted per 50 g/d increase.

Main results

The summary RR for an increase of 50 grams/day was 0.97 (95% CI: 0.93-1.00, I^2=0.0%, $p_{heterogeneity}$=0.75).

Egger's test showed no evidence of publication bias (p= 0.93). After stratification by sex, the RR per 50g/d was 0.89 (95% CI: 0.75 – 1.06, I^2=0%, $p_{heterogeneity}$=0.91, n=3) among men and 1.02 (95% CI: 0.88 – 1.20, I^2=0%, $p_{heterogeneity}$=0.91, n=3) among women.

In influence analysis, the RR ranged from 0.96 (95% CI: 0.92 – 0.99) when excluding the Netherlands Cohort Study to 1.00 (95% CI: 0.93-1.07) when excluding the NIH-AARP Diet and Health Study.

When the results of the two studies not included in the Pooling project (Daniel et al, 2013 and Iso et al, 2007) were summarized together with the results of the Pooling project, the overall RR for 50 g/d increase of citrus fruit intake was 0.98 (95% CI=0.96-1.00, I^2=0.0%, $p_{heterogeneity}$=0.37).

Heterogeneity

There was no evidence of heterogeneity, I^2=0.0%, $p_{heterogeneity}$=0.75

Comparison with the Second Expert Report

No meta-analysis of cohort studies was conducted in the Second Expert Report. The pooled relative risk estimate for one serving increase from two case-control studies was 0.97 (95% CI: 0.88-1.07). The CUP found a borderline inverse association between citrus fruit consumption and kidney cancer risk.

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (13 cohorts) found a pooled RRs of 0.97 (95% CI: 0.92-1.03), for 120 grams/day increase of intake of Rutaceae fruits (e.g., oranges, grapefruits) (Lee et al, 2009).

Table 22 Studies on citrus fruit identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2013	United States	NIH-AARP Diet and Health Study	1816	9	M/F	0.85	0.74	0.98	Per 100g per 1000 kcal, p = 0.03
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.85	0.60	1.22	0.56 vs. 0.01 times/d
Iso, 2007	Japan	Japan Collaborative Cohort Study	44	12	M	0.88	0.40	1.92	>=5 vs. <3 times/week
			18		F	0.84	0.27	2.66	
Lee, 2006	United States	Both cohorts combined	248		All	0.78	0.44	1.37	>=2 servings/d vs. <4 servings/week
		Health Professionals Follow-Up Study	116	14	M	0.59	0.26	1.34	
		The Nurses' Health Study	132	20	F	1.00	0.46	2.18	

Table 23 Overall evidence on citrus fruit and kidney cancer

	Summary of evidence
2005 SLR	Two cohort studies were identified on citrus fruit consumption and kidney cancer risk; both reported no association.
Continuous Update Project	Five cohorts were identified. Overall, 7 cohorts (6 articles) were included in the CUP meta-analysis.

Table 24 Summary of results of the dose response meta-analysis of citrus fruit and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	7
Cases (n)	-	2735
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	0.97 (0.93-1.00)
Heterogeneity (I^2,p-value)	-	0.0%, p=0.75
Pooling Project, NIH-AARP and JACC		
Studies (n)	-	15
Cases (n)	-	3356
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	0.98 (0.96-1.00)
Heterogeneity (I^2,p-value)	-	0.0%, p=0.37

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 25 Inclusion/exclusion table for meta-analysis of citrus fruit and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14858	Daniel	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	No	Converted increment of 100g/1000 kcal to grams per day Person/ years per category	-
KID14812	Bertoia	2010	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Converted times per day to grams per day Person/ years per category	-
KID14841	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Converted times per week to grams per day Mid-exposure values	-
KID14793	Lee	2006	Prospective Cohort Study	The Nurses' Health Study; Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Converted servings to grams per day Person/ years per category Mid-exposure values	-
KID14407	Rashidkhani	2005a	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	Converted servings to grams per day Person/ years per category Mid-exposure values	-
KID22178	Van Dijk	2005	Case Cohort Study	The Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Rescale of reported RR for continuous increase	-

Figure 28 Highest versus lowest forest plot of citrus fruit and kidney cancer

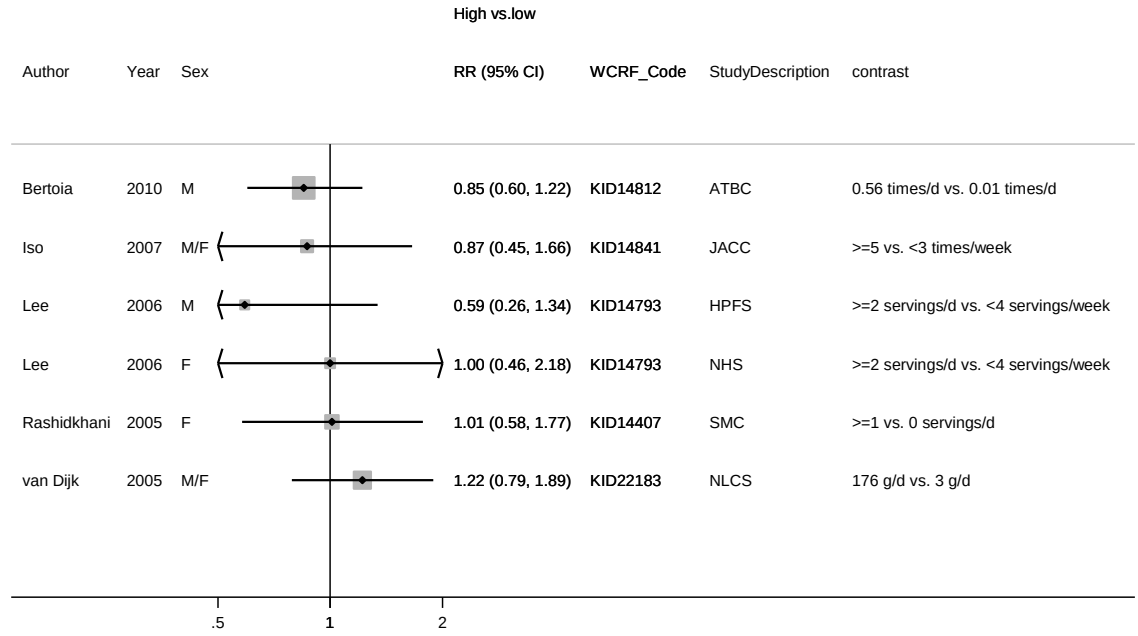


Figure 29 Dose-response meta-analysis per 50 g/d increase of citrus fruit intake and kidney cancer

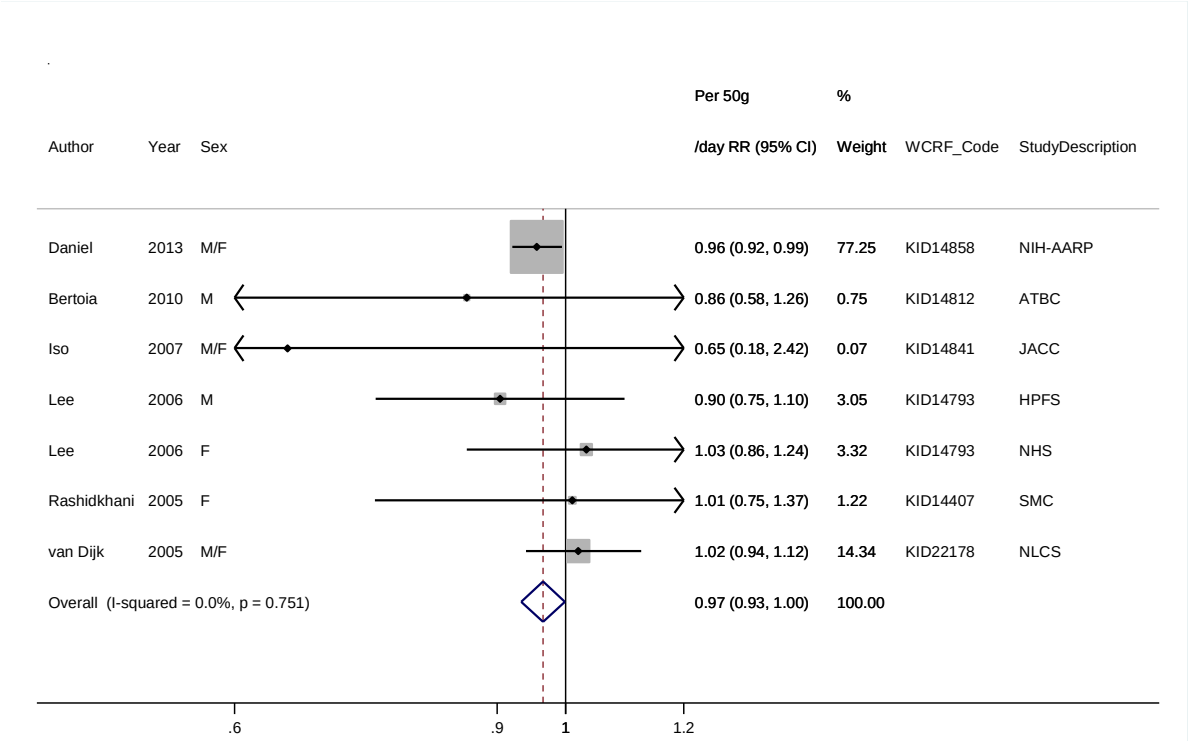


Figure 30 Funnel plot of citrus fruit and kidney cancer

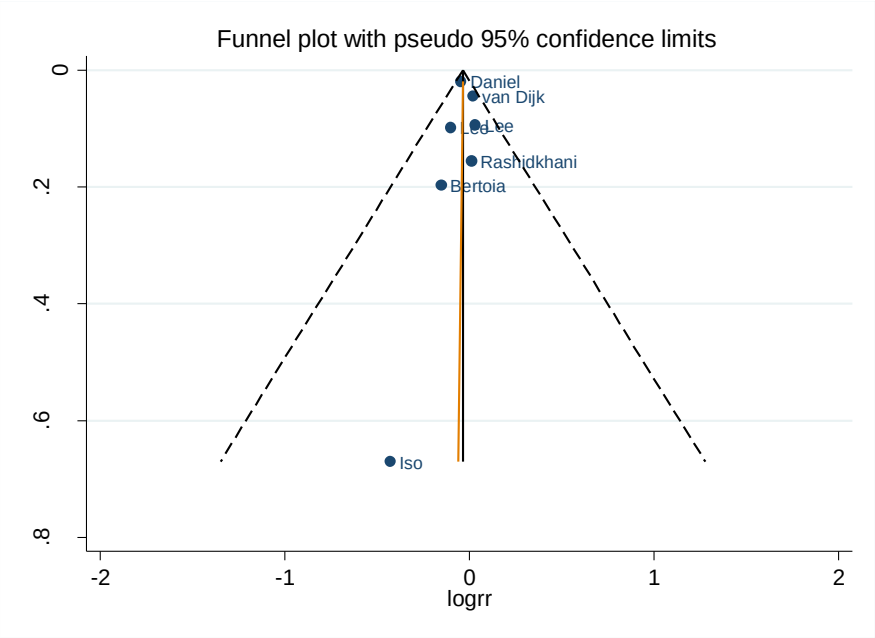


Figure 31 Dose-response graph of citrus fruit and kidney cancer

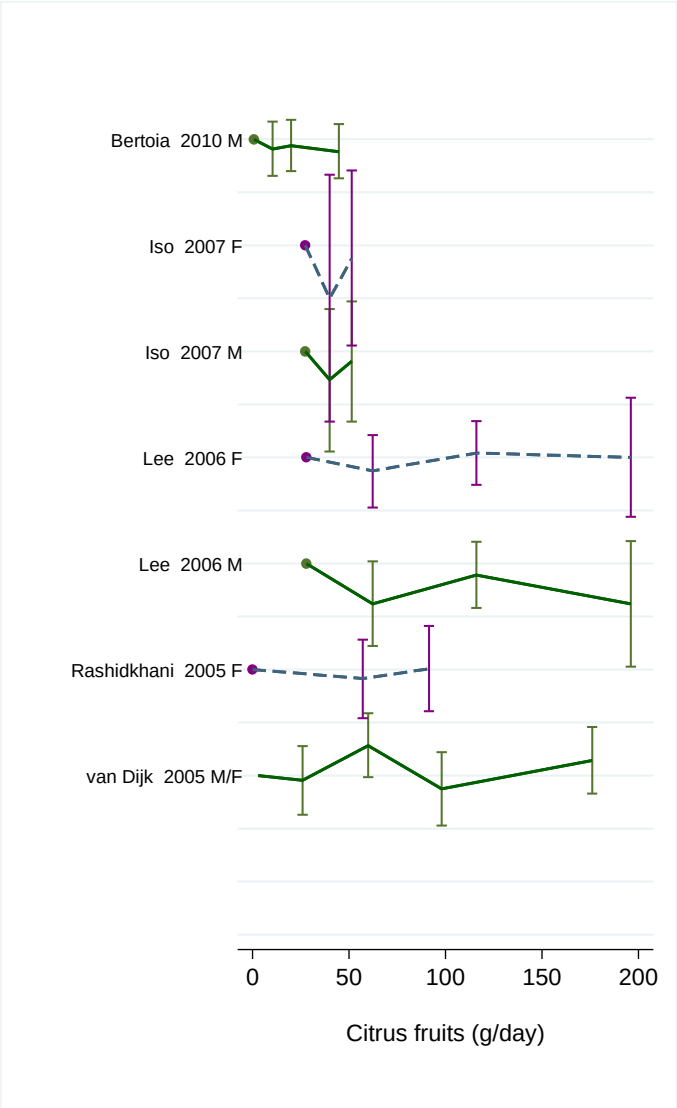


Figure 32 Dose-response meta-analysis per 50 g/d increase of citrus fruit intake and kidney cancer, stratified by sex

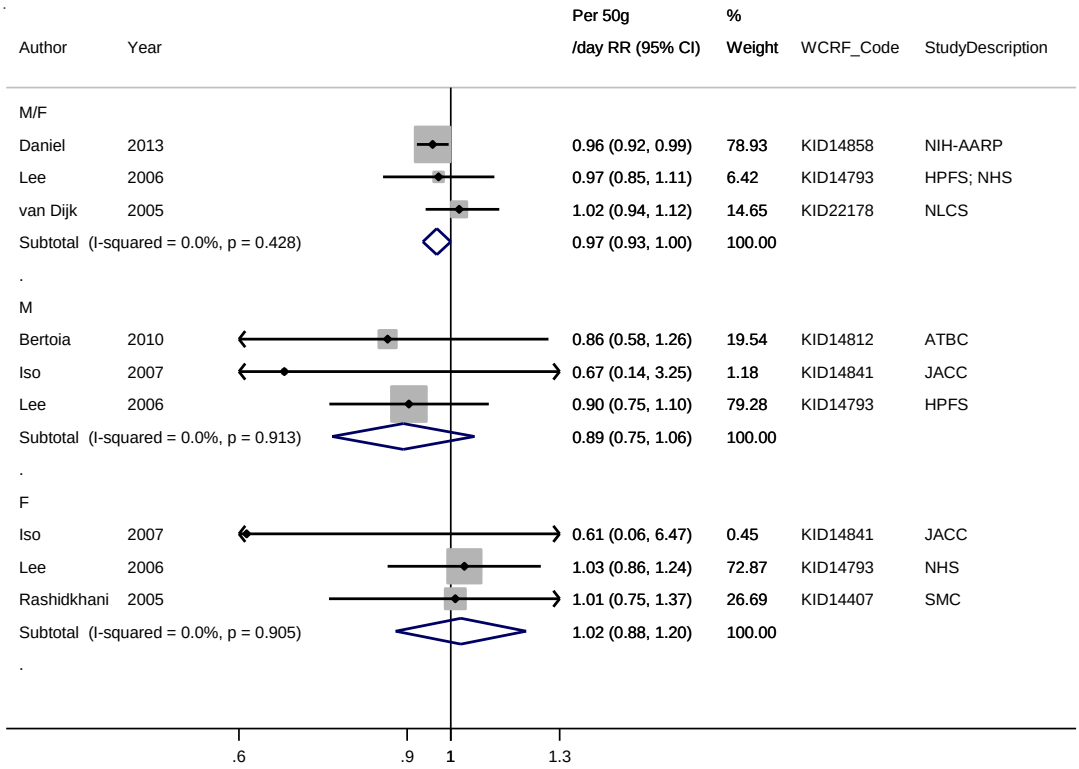
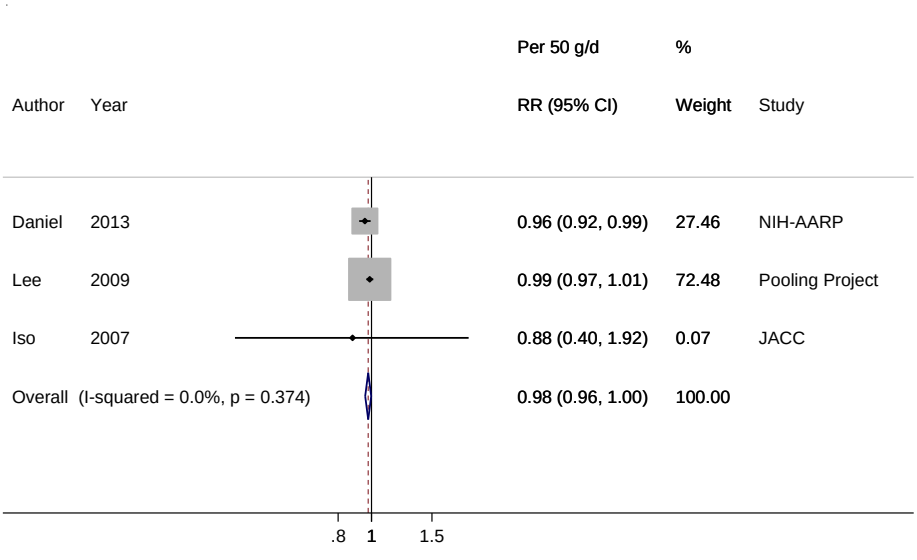


Figure 33 Dose-response meta-analysis per 50 g/d increase of citrus fruit and kidney cancer. Pooling Project of Cohort Studies and CUP



2.5.1 Meat

The Pooling Project of Cohort Studies (Lee et al, 2008) combined the results of 13 cohort studies that investigated red meat, processed meat and poultry, and renal cell carcinoma. The next sections describe the results of the Pooling Project and the studies identified in the CUP that were not included in the Pooling Project.

2.5.1.2 Processed meat

Methods

Four articles from two cohort studies were identified (three articles in the CUP and 1 in the 2005 SLR). None of the studies reported significant associations. Dose-response meta-analysis was not possible for lack of sufficient data.

The Pooling Project of Cohort Studies (13 cohorts) (Lee et al, 2008) reported no association of processed meat intake with renal cell cancer.

A meta-analysis of the Pooling Project, the NIH-AARP (Daniel et al, 2002) and the JCCS (Iso et al, 2007) was conducted. For the NIH- AARP, the RR per 10g/1000kcal/day was rescaled to g/d using the mean energy value of the 3rd quintile of meat intake reported in the publication as approximation (1825 kcal/day, Daniel et al,). For the Pooling Project, one serving was approximated to 50 grams. Only the results for men and kidney cancer mortality could be included for the JCCS.

Main results

The RR for an increase of 50 g/d of processed meat was 1.04 (95% CI: 0.99- 1.09, I^2=0%; p= 0.59).

Heterogeneity

Heterogeneity tests were not done as only three risk sets were included and one of them was the Pooling Project. There was no evidence of heterogeneity across studies in the Pooling Project. The results of the Pooling Project (Lee et al, 2008) were similar to those of the NIH-AARP. The small study on kidney cancer mortality in Japanese men reported a positive but not significant association.

Published meta-analyses or pooled analyses

The Pooling Project of Cohort Studies (13 cohorts) (Lee et al, 2008) reported no association of processed meat intake with renal cell cancer ($HR_{>=27 \text{ vs. } <4 \text{ g/d}}$ =1.21, 95% CI=0.97-1.51).

Comparison with the Second Expert Report

No cohort study was identified.

Table 26 Results of the Pooling Project of Cohort Studies on processed meat and kidney cancer risk and additional studies identified in the CUP and 2005 SLR

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lee, 2008	North America, Europe, Australia	Pooling Project of Cohort Studies	13 cohorts	7-20 years	M/F	1.21	0.97	1.51	>=27 vs. <4 g/d
					M/F	1.01	0.99	1.02	For 2 servings/week increase
Daniel, 2012	United States	NIH-AARP Diet and Health Study	1814	9	M/F	1.12	0.95	1.32	19.9 vs. 1.4 g/1000 kcal
Cross, 2007	United States	NIH-AARP Diet and Health Study	1363	6.8	M/F	1.18	0.98	1.43	22.6 vs. 1.6 g/1000 kcal
Iso, 2007	Japan	Japan Collaborative Cohort Study	Deaths: 33	12	M	1.49	0.52	4.25	Ham and sausages >=3-4/week vs. <1/week
			11		F	1.52	0.42	5.55	
Washio, 2005	Japan	Japan Collaborative Cohort Study	Deaths: 33	~9.6	M/F	1.16	0.42	3.24	Ham and sausages >1-2/week vs. seldom

Table 27 Overall evidence on processed meat intake and kidney cancer

	Summary of evidence
2005 SLR	Three case-control studies were identified. The overall RR estimate was 1.01 (95% CI: 1.00, 1.03). One cohort study showing no association was identified.
Continuous Update Project	Three articles from two cohort studies and the Pooling Project of cohort studies were identified. None of them showed significant association. No association was found in the dose-response meta-analysis.

Table 28 Summary of results of the dose response meta-analysis of processed meat and kidney cancer

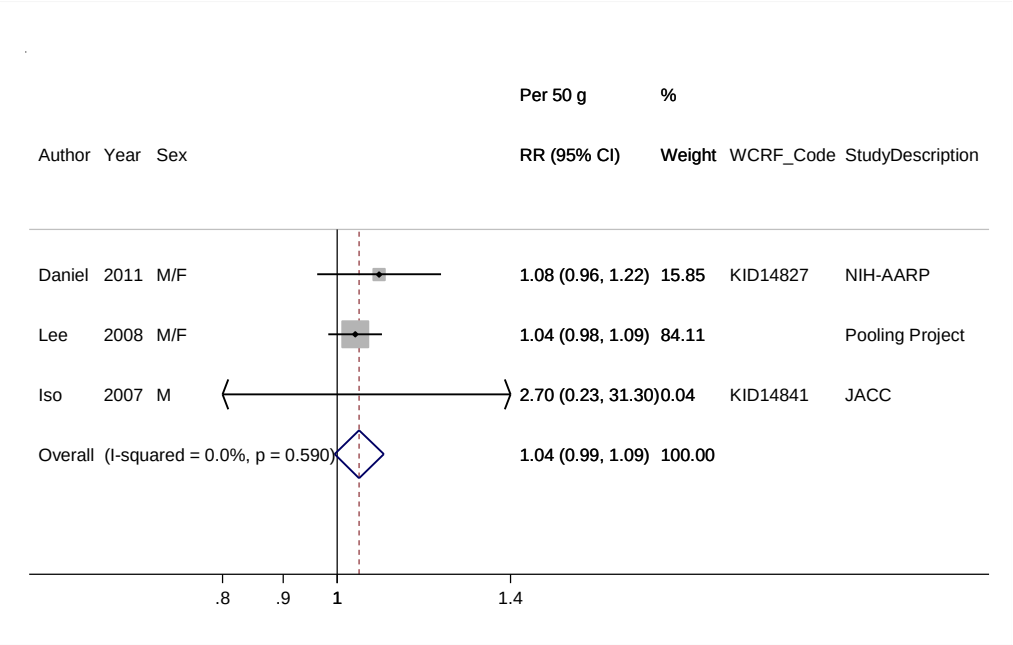
Kidney cancer		
Pooling Project, NIH-AARP and JACC		
Studies (n)	-	15
Cases (n)	-	3325
Increment	-	Per 50 g/d
Overall RR (95%CI)	-	1.04 (0.99-1.09)
Heterogeneity (I^2,p-value)	-	0.0%, p=0.59

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 29 Inclusion/exclusion table for meta-analysis of processed meat and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CU dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14827	Daniel	2012	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	No	No	Yes	Converted grams per 1000 kcal to grams/day Person/ years per category	-
KID14841	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort study for evaluation of Cancer Risk	Mortality	No	Yes	Yes	Times/week rescaled to g/day. Mid-exposure values.	-
KID14800	Cross	2007	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	Yes	No	No		Superseded by Daniel et al, 2012
KID14789	Washio	2005	Prospective Cohort Study	Japan Collaborative Cohort Study	Mortality	Yes	No	No		Superseded by Iso et al, 2007

Figure 34 Dose-response meta-analysis per 50 g/d increase of processed meat intake and kidney cancer. Pooling Project and CUP.



2.5.1.3 Red meat

Methods

Two articles from the NIH-AARP study were identified during the CUP. The most recent publication (Daniel et al, 2012) reported a positive association that was restricted to papillary renal cell carcinoma. The Pooling Project of Cohort Studies (13 cohorts, 1478 cases) (Lee et al, 2008) reported no association of red meat intake with renal cell cancer.

The results of the Pooling Project and the NIH-AARP were included in a meta-analysis. The RR was expressed for an intake increment of 100 g/d. For the NIH-AARP result, g/1000 kcal/d was approximated to g/d assigning 1825 kcal (mean energy intake in the 3rd quintile of red meat consumption) as average energy intake (Daniel et al, 2012). For the Pooling Project, a standard serving size of 120 g was assumed.

Two articles of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (Washio et al, 2005; Iso et al, 2007) reported on the association of intakes of beef and pork and kidney cancer mortality. No association was observed except a significant positive association for intake of beef 1-2 times/week compared to less than once in men but not in women (Iso et al, 2007). In the Adventists Health Study (Fraser et al, 1990), beef intake was not related to kidney cancer. Because there was no estimate for all red meat intake, these articles are not included in this section.

Main results

The overall dose-response estimate for the NIH-AARP and the Pooling Project) was 1.07 (95% CI: 0.97-1.19) for an increase of 100 g/d of red meat.

Heterogeneity

Only two risk sets were included. There was no evidence of heterogeneity across studies in the Pooling Project. There was no significant evidence of heterogeneity between the results of the Pooling Project and the NIH-AARP (I^2= 18.0%; p=0. 26). However, the NIH-AACR reported a significant positive association restricted to papillary carcinomas. The Pooling Project did not report results by cancer subtype.

Published meta-analyses or pooled analyses

The Pooling Project of Cohort Studies (13 cohorts) (Lee et al, 2008) reported no association of red meat intake with renal cell cancer ($HR_{>=80 \text{ vs. } <20 \text{ g/d}}$ =0.99, 95% CI=0.85-1.16).

Comparison with the Second Expert Report

One cohort study on red meat and kidney cancer was identified but no estimate of association was reported and therefore, the study is not included in the CUP review. An overall unadjusted OR of 1.02 (95% CI 1.00-1.04) per increase in serving per week was derived from two case-control studies.

Table 30 Results of the Pooling Project of Cohort Studies on red meat and kidney cancer and additional studies identified in the CUP and the 2005 SLR

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2012	United States	NIH-AARP Diet and Health Study	1814	9	M/F	1.19	1.01	1.40	62.7 vs. 9.8 g/1000 kcal/d
						1.15	1.04	1.26	For an increase of 10 g/1000 kcal
Lee, 2008	North America, Europe, Australia	Pooling Project of Cohort Studies	13 cohorts, 1478 cases	7-20 years	M/F	0.99	0.85	1.16	>=80 vs. <20 g/d
						1.00	0.95	1.06	For an increase of 2 servings/week
Cross, 2007	United States	NIH-AARP Diet and Health Study	1363	6.8	M/F	1.04	0.86	1.25	62.7 vs. 9.8 g/1000 kcal/d

Table 31 Overall evidence on red meat intake and kidney cancer

	Summary of evidence
2005 SLR	The overall RR estimate from 2 case-control studies was 1.02 (95% CI: 1.00-1.04) per serving/week. One cohort study was identified but no measure of association was reported.
Continuous Update Project	Two articles from one cohort study and the Pooling Project of cohort studies were identified. The NIH-AARP showed a significant positive association. No association was found in the dose-response meta-analysis.

Table 32 Summary of results of the dose response meta-analysis of red meat and kidney cancer

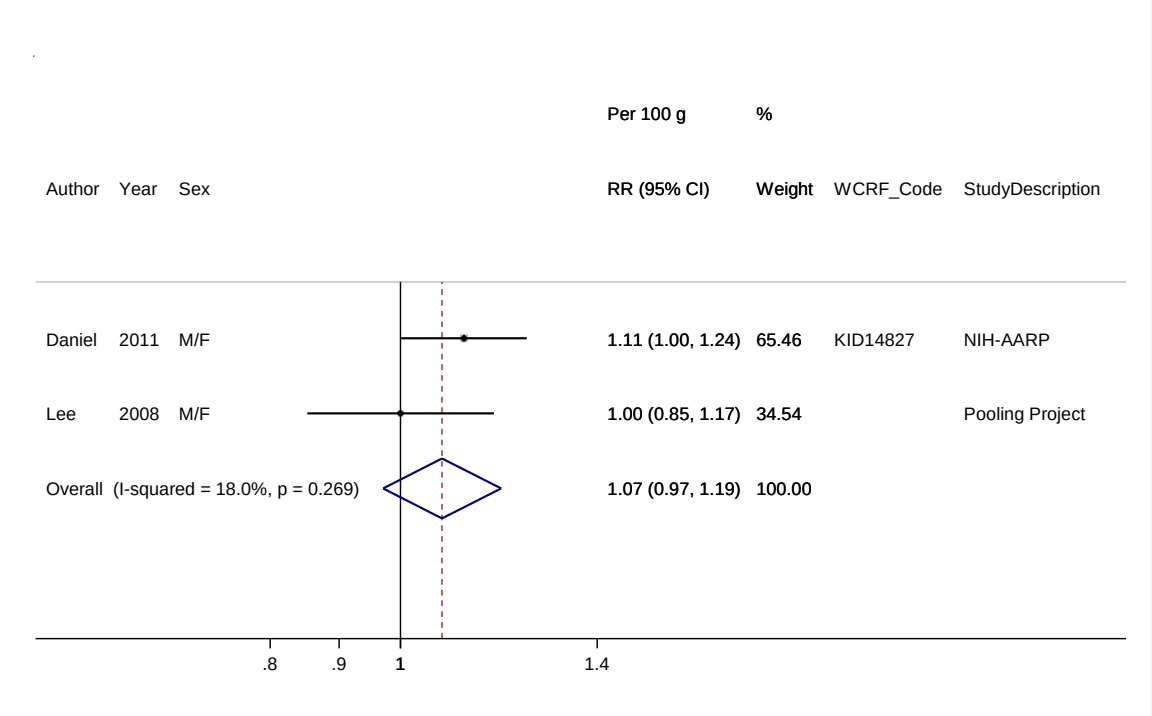
Kidney cancer		
Pooling Project, NIH-AARP		
Studies (n)	-	14
Cases (n)	-	3292
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	1.07 (0.97-1.19)
Heterogeneity (I^2,p-value)	-	18.0%, p=0.26

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 33 Inclusion/exclusion table for meta-analysis of red meat and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14827	Daniel	2012	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	No	No	Yes	Converted grams per 1000 kcal to grams/day Person/ years per category	-
KID14800	Cross	2007	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	Yes	No	No		Superseded by Daniel 2012 (KID14827)

Figure 35 Dose-response meta-analysis for 100 g/d intake increase of red meat intake and kidney cancer. Pooling project and CUP.



2.5.1.4 Poultry

Methods

Four articles from three cohort studies were identified (two in the CUP and two in the 2005 SLR). None of the studies reported significant associations.

The Pooling Project of Cohort Studies (13 cohorts) (Lee et al, 2008) reported no association of poultry intake with renal cell cancer.

The results of the Pooling Project were included in a meta-analysis with those of the NIH-AARP and the JCCS (Iso et al, 2007). The study by Fraser et al, 1990 did not provide enough data to be included in the meta-analysis.

Main results

The overall dose-response estimate for an increase of 100 g/d of poultry intake for the NIH-AARP and the Pooling Project was 1.03 (95% CI: 0.90-1.18; I^2= 0%; p=0. 70).

Heterogeneity

Only three risk sets were included. There was no evidence of heterogeneity across studies in the Pooling Project. There was no evidence of heterogeneity in the CUP meta-analysis (I^2= 0%; p=0. 70).

Published meta-analyses or pooled analyses

The Pooling Project of Cohort Studies (13 cohorts) (Lee et al, 2008) reported no association of poultry intake with renal cell cancer ($HR_{>=60 \text{ vs. } <14 \text{ g/d}}$ =1.25, 95% CI=0.83-1.88).

Comparison with the Second Expert Report

None of the two identified cohort studies reported association of poultry intake and kidney cancer risk.

Table 34 Results of the Pooling Project of Cohort Studies and additional studies identified in the CUP and the 2005 SLR on poultry intake and kidney cancer

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lee, 2008	North America, Europe, Australia	Pooling Project of Cohort Studies	13 cohorts	7-20 years	M/F	1.25	0.83	1.88	>=60 vs. <14 g/d
						1.01	0.93	1.10	For an increase of 2 servings/week
Daniel, 2011	United States	NIH-AARP Diet and Health Study	1814	9	M/F	1.01	0.87	1.18	47.1 vs. 4.4 g/1000 kcal
Iso, 2007	Japan	Japan Collaborative Cohort Study	Deaths: 30	12	M	1.58	0.58	4.28	>=3-4/week vs. <1/month
			15		F	1.48	0.42	5.16	
Washio, 2005	Japan	Japan Collaborative Cohort Study	Deaths: 30	~9.6	M/F	0.62	0.69	3.81	>3-4/week vs. 1-2/month
Fraser, 1990	United States	Adventist Health Study	14	6	M/F	0.47	0.02	2.69	>= 1/week vs <1/week <

Table 35 Overall evidence on poultry intake and kidney cancer

	Summary of evidence
2005 SLR	None of the two identified cohort studies reported association of poultry intake and kidney cancer risk. A case-control study on poultry intake and kidney cancer risk reported no association.
Continuous Update Project	Two articles from two cohort studies were identified. None of the studies reported significant associations. The Pooling Project of Cohort Studies reported no association of poultry intake with renal cell cancer. The CUP meta-analysis showed no association.

Table 36 Summary of results of the dose response meta-analysis of poultry intake and kidney cancer

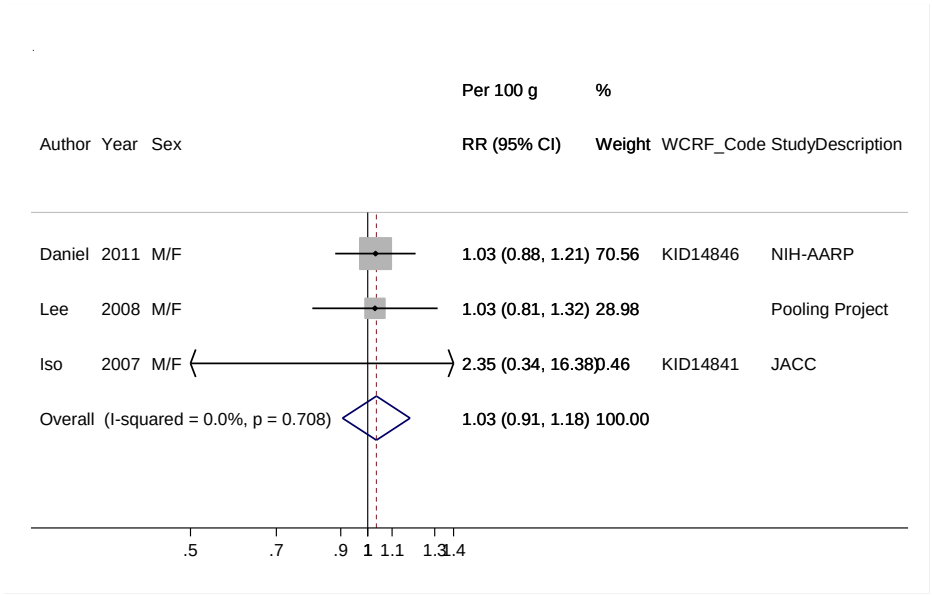
Kidney cancer		
Pooling Project, NIH-AARP		
Studies (n)	-	15
Cases (n)	-	3336
Increment	-	Per 100 g/d
Overall RR (95%CI)	-	1.03 (0.91-1.18)
Heterogeneity (I^2,p-value)	-	0%, p=0.70

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 37 Inclusion/exclusion table for meta-analysis of poultry and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14846	Daniel	2011	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Person years per quintiles g/1000 kcal/day rescaled to g/d Mid exposure values	-
KID14841	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort study for evaluation of Cancer Risk	Mortality	No	Yes	Yes	Times/week rescaled to g/d Mid-exposure values.	-
KID14789	Washio	2005	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	Yes	No	No	-	Superseded by Iso et al, 2007 (KID14841)
KID01674	Fraser	1990	Prospective Cohort Study	US California 1976-1982	Incidence	Yes	No	No	-	Only two categories were presented

Figure 36 Dose-response meta-analysis for 100 g/d increase of poultry intake and kidney cancer



2.5.2 Fish

Methods

Seven articles from 5 cohort studies have investigated on fish and kidney cancer risk up to 31 March 2013. Five articles (4 cohorts) were identified in the CUP. In one article (Iso et al, 2007) fish consumption was reported in times/week that was converted to g/d using 120 grams as one time. For the NIH-AARP study (Daniel et al, 2011) g/1000 kcal/day was rescaled to g/d using the average energy intake for each quintile of fish intake provided in the article. In the Japan Collaborative Cohort Study (Iso et al, 2007), only results for fresh fish consumption were included in the dose-response meta-analysis. A Swedish study (Walk et al, 2006) reported separately on lean and fatty fish and could not be included in this review. Three cohort studies were included in dose-response analysis. Dose-response analyses were conducted for an increase of 25 g/per day.

Main results

The summary RR per 25 g of fish per day was 1.08 (95% CI: 1.01-1.17, I^2=0% $p_{heterogeneity}$=0.80).

Heterogeneity

There was no evidence of heterogeneity (I^2=0% $p_{heterogeneity}$=0.80).

Comparison with the Second Expert Report

In the systematic review of the Second Expert Report the summary estimate of two case-control studies was 0.94 (95% CI: 0.79-1.12) for one serving increase of intake. The CUP analysis showed significant increased risk for fish consumption and kidney cancer.

Published Meta-analysis or Pooled studies

In a meta-analysis of 12 case-control and 3 cohort studies, the relative risk estimate of renal cell carcinoma and fish consumption was 0.99 (95% CI: 0.92-1.07) for the highest vs. the lowest intake (Bai et al., 2013). The estimate for the 3 cohort studies was 1.03 (95% CI=0.80-1.33; I^2=79.8%, $p_{heterogeneity}$=0.03).

Table 38 Studies on fish intake and kidney cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2012	USA	NIH- AARP Diet and Health Study	1814	9	All	1.14	0.95	1.29	23.1 g/100 kcal/day vs. 2.1 g/100 kcal/day
						1.01	0.97	1.05	Per 10g/1000 kcal/day
Daniel, 2011	USA	NIH- AARP Diet and Health Study	2065	9.1	All	1.10	0.93	1.28	21.4 g/1000 kcal/day vs. 3.6 g/1000 kcal/day
Wilson, 2009	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	228	15.2	All	1.4	0.9	1.9	> 50.7 g/d vs. <=21 g/d
Iso, 2007	Japan	Japan Collaborative Cohort study for Evaluation of Cancer Risk	43	15	M	1.15	0.55	2.42	>= 5 vs. <3 times/week
			16		F	0.65	0.16	2.67	
Walk, 2006	Sweden	Swedish Mammography Cohort Study	150	15.3	F	0.56	0.35	0.91	Fatty fish >=1 per week vs. none
						1.16	0.69	1.95	Lean fish >2-3/week vs. 0-3/month

Table 39 Overall evidence on fish and kidney cancer

	Summary of evidence
SLR 2005	Two cohort studies were identified and no association was reported.
Continuous Update Project	Five studies were identified. One study was on fatty fish and lean fish. Overall, three studied were included in meta-analysis.

Table 40 Summary of results of the dose-response meta-analysis of fish and kidney cancer

Kidney cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2352
RR (95% CI)	-	1.08 (1.01-1.17)
Increment	-	Per 25 g/d
Heterogeneity (I^2, p-value)	-	I^2=0% $p_{heterogeneity}$=0.80

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 41 Inclusion/exclusion table for meta-analysis of fish and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14827	Daniel	2012	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	No	No	No	-	Duplicate of Daniel et al., 2011 study (KID14846) with fewer number of cases
KID14846	Daniel	2011	Prospective Cohort Study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Person years per quintiles g/1000 kcal/day rescaled to g/d Mid exposure values	-
KID14815	Wilson	2009	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person years per quartiles	-
KID14841	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort study for evaluation of Cancer Risk	Mortality	No	Yes	Yes	Times/week rescaled to g/d Mid-exposure values.	-
KID14790	Wolk	2006	Prospective Cohort Study	Swedish Mammography Cohort Study	Incidence	No	No	No	-	Results are separated for fatty fish and lean fish
KID14789	Washio	2005	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	Yes	No	No	-	Superseded by Iso et al, 2007 study
KID01674	Fraser	1990	Prospective Cohort Study	US California 1976-1982	Incidence	Yes	No	No	-	Only two categories were presented

Figure 37 Highest versus lowest forest plot of fish and kidney cancer

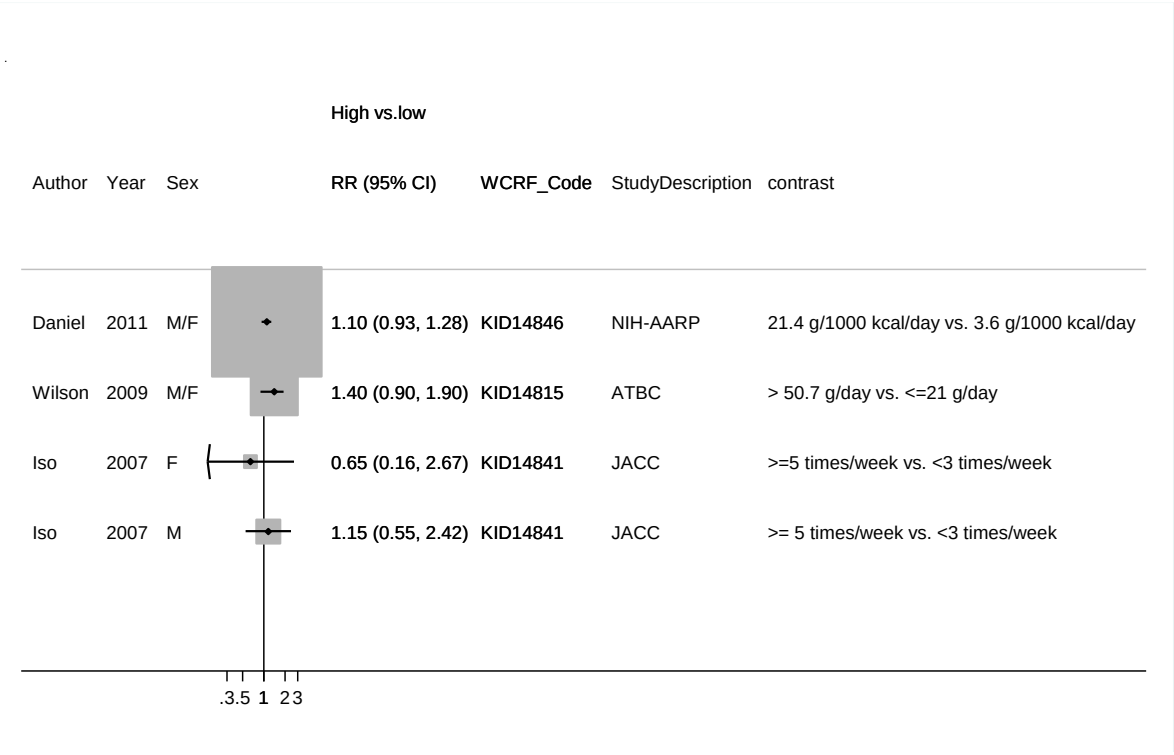


Figure 38 Dose-response meta-analysis per 25 g/d increase of fish intake and kidney cancer

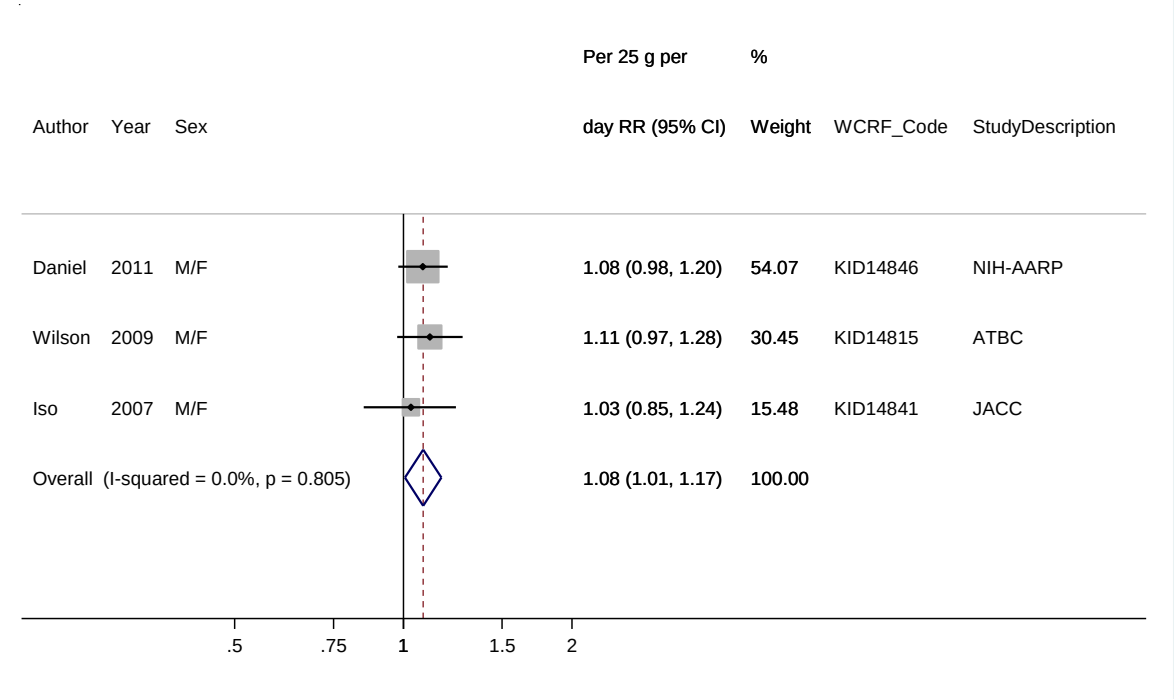


Figure 39 Funnel plot of fish intake and kidney cancer

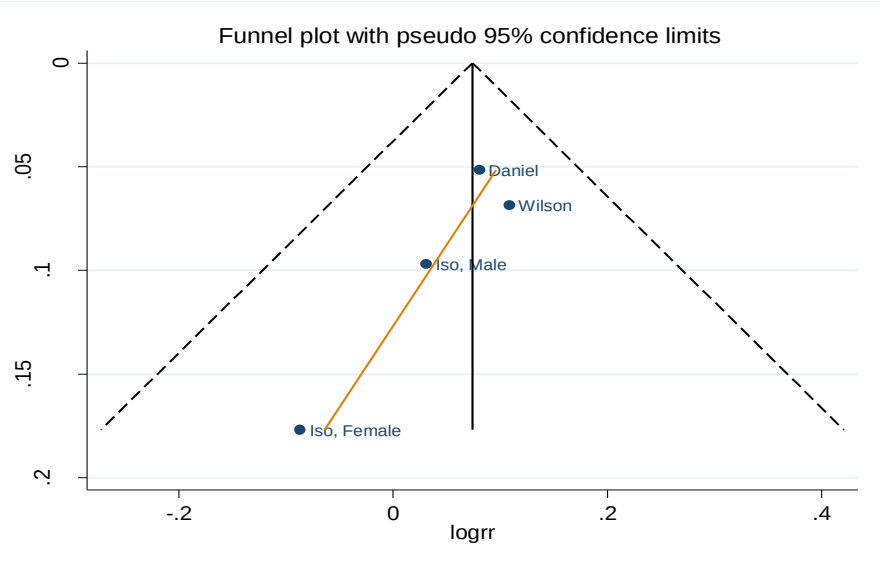
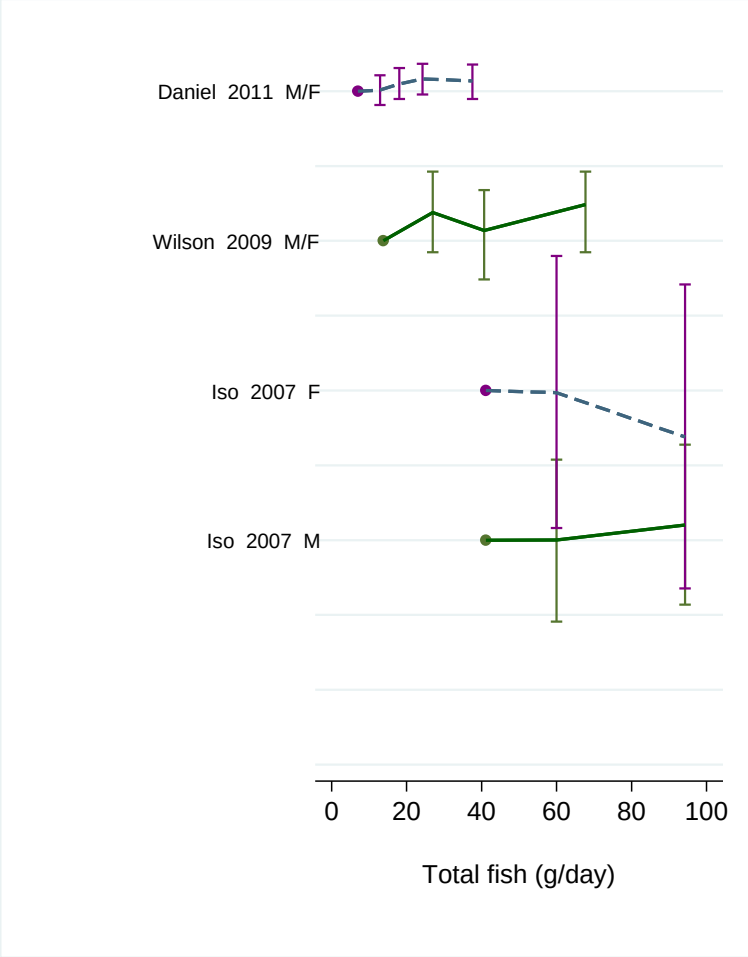


Figure 40 Dose-response graph of fish intake and kidney cancer



3 Beverages

3.6.1 Coffee

Methods

A total of 9 articles (7 cohort studies) have been published on coffee and kidney cancer risk up to 31 March 2013, three of which were identified in the CUP. Dose-response analyses were conducted for an increase of 1 cup per day. Drinks/day, occasions/day and times/day were approximated to cup/day in 3 studies (Allen et al., 2011; Nilsson et al., 2010; Iso et al., 2007). Overall, five cohort studies were included in dose-response analysis.

Main results

The summary RR per 1 cup of coffee per day was 0.94 (95% CI: 0.86-1.03, I^2=35.9% $p_{heterogeneity}$=0.18) for all studies combined. In influence analysis the RR ranged from 0.90 (95% CI: 0.78-1.04) when excluding the Million Women Study (Allen et al, 2011) to 0.98(95% CI: 0.94-1.02) when excluding the Västerbotten Intervention Project (Nilsson et al, 2010).
The summary RR was 0.93 (95% CI: 0.84-1.02, I^2=44.6% $p_{heterogeneity}$=0.14) when the study with mortality as outcome (Iso et al., 2007) was excluded from the analysis.

The Pooling Project of Cohort Studies was meta-analysed with the nonoverlapping studies (Allen et al., 2011; Nilsson et al., 2010; Iso et al., 2007; Stensvold et al., 1994), identified in the 2005 SLR and the CUP. The summary RR for an increase of one cup of coffee per day was 0.97 (95% CI: 0.92-1.03, I^2=47.6% $p_{heterogeneity}$=0.09) for all studies combined. The summary RR was 0.97 (95% CI: 0.94–1.0, I^2=0% $p_{heterogeneity}$=0.39) for women and 1.00 (95% CI: 0.94–1.05, I^2=0% $p_{heterogeneity}$=0.61) for men.

Heterogeneity

There was evidence of moderate heterogeneity (I^2=35.9% $p_{heterogeneity}$=0.18). Egger's test did not show evidence of publication bias (p=0.46).

Comparison with the Second Expert Report

In the systematic review of the Second Expert Report it was concluded that it is unlikely that coffee has a substantial effect on the risk of kidney cancer.

Meta-analysis and Pooled studies

In the Pooling Project of Cohort Studies (13 prospective cohort studies, 1,478 incident renal cell cancer cases), the relative risk estimates for 3 or more cups/day versus less than one cup/day of coffee was 0.84 (95% CI: 0.67–1.05; p trend =0.22) (Lee et al., 2007).The summary RR for an increment of one cup per day was 0.97 (95% CI: 0.93–1.01; $p_{heterogeneity}$ = 0.29) for men and women combined, 0.95 (95% CI: 0.90–1.01) for women and 1.00 (95% CI: 0.94–1.06) for men in the pooling project.

The association was not modified by BMI, history of hypertension, smoking habits, alcohol intake or age at diagnosis. There was a marginally significant difference by oral contraceptive use (p value, test for interaction =0.09) in women, but no clear differences in risk of renal cell cancer by parity and hormone replacement therapy use.

Table 42 Studies on coffee identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Allen, 2011	UK	The Million Women Study	588	5.2	F	0.98 1.05	0.94 0.78	1.02 1.42	Per 1 drink/day increase >=12 vs. 1 drink/day
Nilsson, 2010	Sweden	Västerbotten Intervention Project	56	15	All	0.30	0.11	0.79	>=4 vs. <1 occasion/day
Iso, 2007	Japan	Japan Collaborative Cohort Study	41	15	M	1.76	0.69	4.49	>=2 times/day vs. <=2 times/month
			19		F	0.90	0.27	3.06	
Lee, 2008	International	Pooling Project of Cohort Studies	1478 (13 cohorts)	7-20 years	M/F	0.84	0.67	1.05	>=3 vs. <1 servings/day
						0.97	0.93	1.01	Per 1 serving/day increase

Table 43 Overall evidence on coffee and kidney cancer

	Summary of evidence
SLR 2005	Five cohort studies reported on coffee and kidney cancer. None of them found significant association. The judgement was that an effect of coffee on kidney cancer risk was unlikely.
Continuous Update Project	Three prospective studies were identified. Only one study reported a significant inverse association. In the meta-analysis with the Pooling project, no association was observed.

Table 44 Summary of results of the dose-response meta-analysis of coffee and kidney cancer

Kidney cancer			
	CUP		
	Incidence and mortality	Incidence	
Studies (n)	5	4	
Cases (n)	805	749	
RR (95% CI) for 1 cup/day	0.94 (0.86-1.03)	0.93 (0.84-1.02)	
Heterogeneity (I^2, p-value)	I^2=35.9%, p=0.18	I^2=44.6%, p=0. 14	
Incidence and mortality (CUP results pooled with Pooling Project)			
	All	Women	Men
Studies (n)	16	10	8
Cases (n)	2180	1297	840
RR (95% CI) for 1 cup/day	0.97 (0.93-1.01)	0.97 (0.94-1.00)	1.0 (0.94-1.05)
Heterogeneity (I^2, p-value)	I^2=29.1%, p=0.22	I^2=0%, p=0.39	I^2=0%, p=0.61

No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 45 Inclusion/exclusion table for meta-analysis of coffee and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14826	Allen	2011	Prospective cohort study	The Million Women Study	Incidence	No	Yes	Yes	Midpoints Person-years	-
KID14821	Nilsson	2010	Prospective cohort study	Västerbotten Intervention Project	Incidence	No	Yes	Yes	Midpoints Person/years Times/day rescaled to cup/day	-
KID14841	Iso	2007	Prospective cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	Mortality	No	Yes (men) No (women)	Yes	Midpoints Times/month and times/week rescaled to cup/day	Women excluded from dose-response analysis for missing results. Men included
KID14789	Washio	2005	Prospective cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	Mortality	Yes	No	No	-	Superseded by Iso, 2007
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No results available
KID01081	Prineas	1997	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints Cup/week rescaled to cup/day	-
KID01376	Hiatt	1994	Nested case-control study	California USA 1964-1989	Incidence	Yes	No	No	-	No intake levels available
KID14205	Stensvold	1994	Prospective cohort study	Norwegian Health Screening Service	Incidence	Yes	Yes (men) No (women)	Yes	Midpoints Confidence Interval	Women excluded from dose-response analysis for missing results
KID01972	Jacobsen	1986	Prospective cohort study	Norwegian Cohorts (men)	Incidence	Yes	No	Yes	Confidence Interval	Only high vs. low comparison

Figure 41 Highest versus lowest forest plot of coffee and kidney cancer

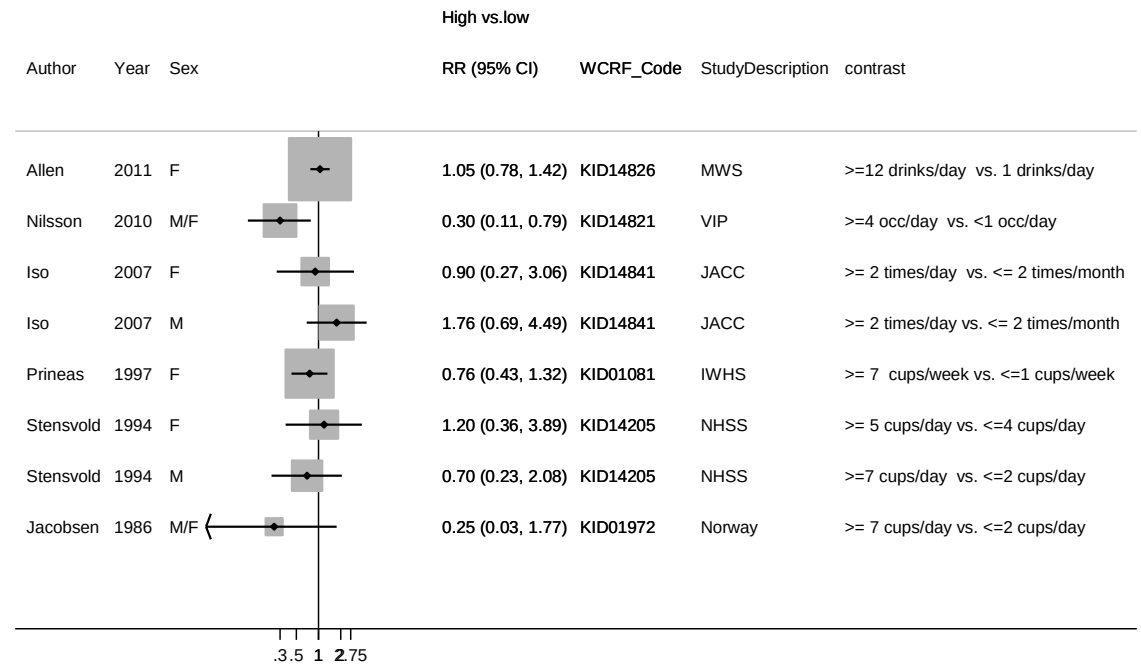


Figure 42 Dose-response meta-analysis of coffee and kidney cancer, per 1 cup/day

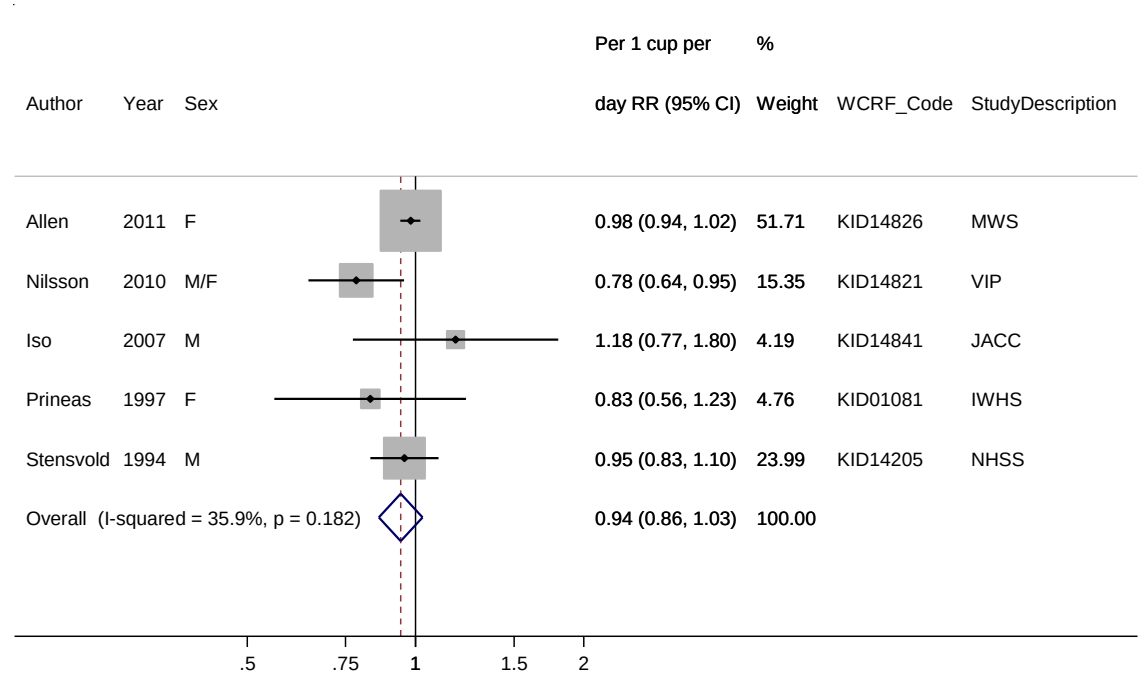


Figure 43 Funnel plot of coffee and kidney cancer

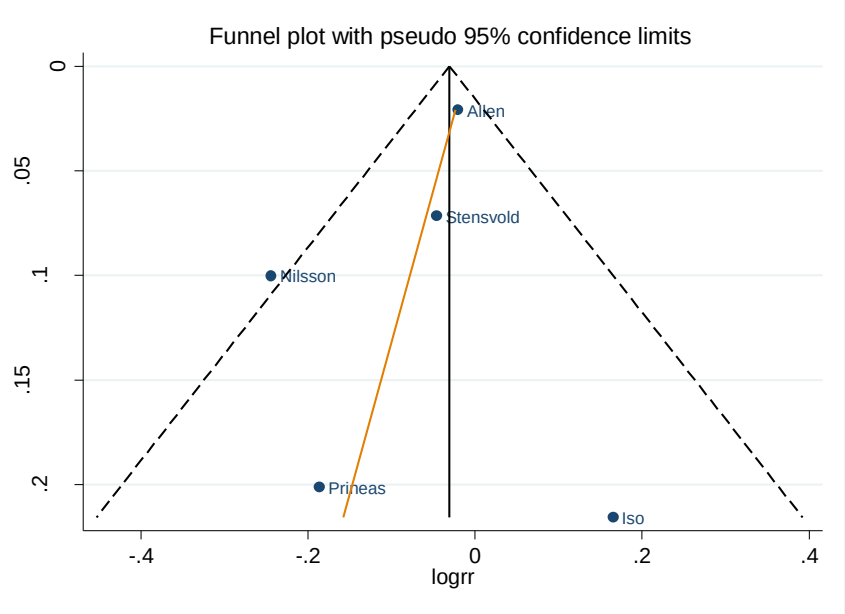


Figure 44 Dose-response graph of coffee and kidney cancer

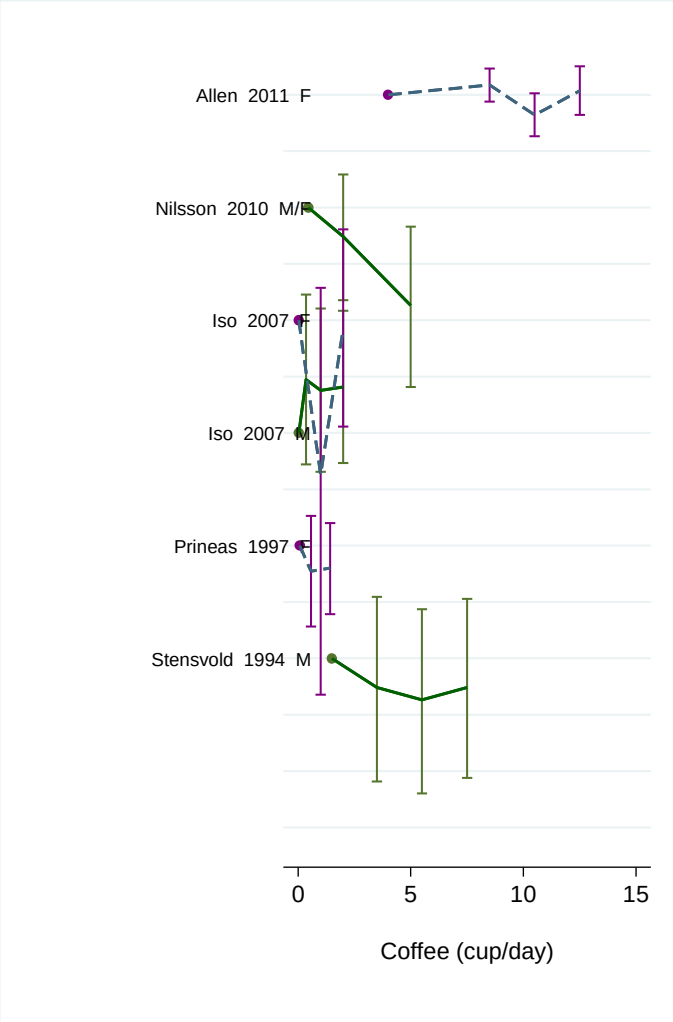
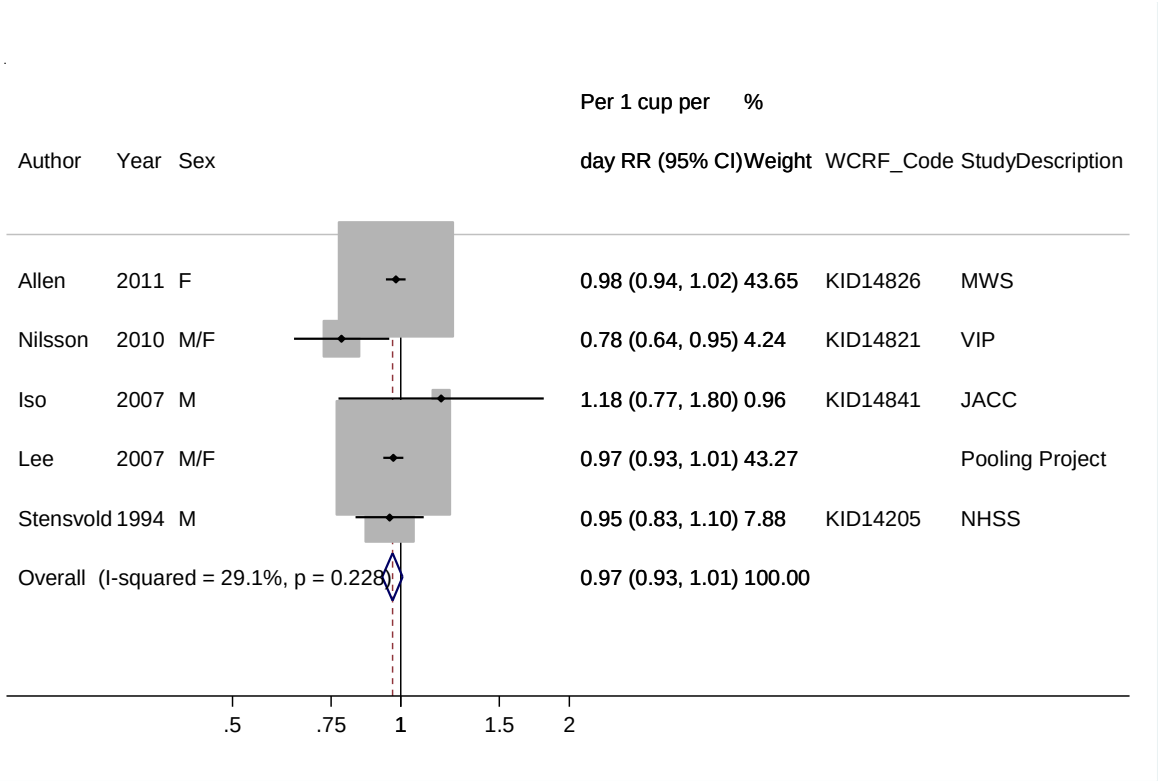


Figure 45 Dose-response meta-analysis per 1 cup/day increase of coffee intake. Pooling Project and CUP



3.6.2 Tea

Methods

A total of 6 articles from 4 cohort studies have been published on tea and kidney cancer risk up to 31 March 2013, two of which were identified in the CUP. Dose-response analyses were conducted for an increase of 1 cup per day (8 ounces, 237 ml). The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study reported tea consumption in g/d (Wilson et al., 2009) which was converted to cups/day, using a conversion unit of 200 ml equivalent to 1 cup of tea Overall, three studies were included in dose-response meta-analysis.

Main results

The summary RR per one cup increase was 0.88 (95% CI: 0.69-1.13, I^2=57.4% $p_{heterogeneity}$=0.096) for all studies combined. The RR in women was 0.85 (95% CI: 0.55-1.34, I^2=69.7% $p_{heterogeneity}$=0.07) after excluding the Alpha-Tocopherol Beta Carotene Cancer Prevention Study, a study in men smokers (Wilson et al., 2009).

All the studies identified in the CUP were included in the Pooling Project (Lee et al., 2007), except the Million Women Study (Allen et al., 2011). The pooling project result for women was pooled with the result of the Million Women Study identified in the CUP, the summary RR for an increase of one cup of tea per day was 1.01 (95% CI: 0.98-1.04, I^2=0% $p_{heterogeneity}$=0.672).

Heterogeneity

Moderate heterogeneity was observed (I^2=57.4%, $p_{heterogeneity}$=0.1). Egger's test did not show evidence of publication bias (p=0.11) but only three studies were included.

Comparison with the Second Expert Report

Four cohort studies were identified during the Second Expert Report but no meta-analysis could be conducted. The summary RR from 3 case-control studies was 1.04 (95% CI: 0.99-1.09) for one cup increase of intake. The evidence was limited and no conclusion was possible

Meta-analysis and Pooled studies

In the Pooling Project of Cohort Studies (13 prospective cohort studies), (Lee et al., 2007). the relative risk estimate for one or more cups/day of tea versus none was 0.85 (95% CI: 0.71–1.02; p trend =0.04). The RR for an increment of one cup per day was 0.96 (95% CI: 0.89–1.03) for men and women combined, 0.99 (95% CI: 0.91–1.08) for women and 0.89 (95% CI: 0.77–1.04) for men in the Pooling Project.

The association was not modified by BMI, history of hypertension, smoking habits, alcohol intake or age at diagnosis. There was a marginally significant difference by oral contraceptive use (p value, test for interaction =0.09) in women, but no clear differences in risk of renal cell cancer by parity and hormone replacement therapy use.

Table 46 Studies on tea identified and kidney cancer in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Allen, 2011	UK	The Million Women Study	588	5.2	F	0.98 1.01	0.76 0.97	1.25 1.04	>= 12 vs. 1-7 drinks/day Per one drink/ day increase
Wilson, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	228	15.2	M	0.8	0.5	1.2	> 219.6 vs. 0 g/d
Lee, 2008	International	Pooling Project of Cohort Studies	1478 (13 cohorts)	7-20 years	M/F	0.85 0.96	0.71 0.89	1.02 1.03	2-3 vs <1 serving/day

Table 47 Overall evidence on tea and kidney cancer

	Summary of evidence
2005 SLR	Four cohort studies were identified. No meta-analysis was conducted.
Continuous Update Project	Two additional articles and the Pooling Project were identified. Nohne of the studies reported significant association

Table 48 Summary of results of the dose-response meta-analysis of tea and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	877
RR (95% CI)	-	0.88 (0.69-1.13)
Increment	-	Per 1 cup/day
Heterogeneity (I^2, p-value)	-	I^2=57.4%, p=0.1
Pooling Project and CUP		
Studies (n)		14
Cases (n)		1297
RR (95% CI)		1.01 (0.98-1.04)
Increment		Per 1 cup/day
Heterogeneity (I^2, p-value)		0%, p=0.67

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 49 Inclusion/exclusion table for meta-analysis of tea and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14826	Allen	2011	Prospective cohort study	The Million Women Study	Incidence	No	Yes	Yes	Midpoints Person-years	-
KID14815	Wilson	2009	Prospective cohort study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No results available
KID00506	Hirvonen	2001	Prospective cohort study	Alpha-Tocopherol Beta- Carotene Cancer Prevention	Incidence	Yes	No	No	-	No results available
KID13151	Zheng	1996	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints Person-years	-
KID01843	Kinlen	1988	Prospective cohort study	London, UK 1969-1986	Mortality	Yes	No	No	-	No RR available

Figure 46 Highest versus lowest forest plot of tea and kidney cancer

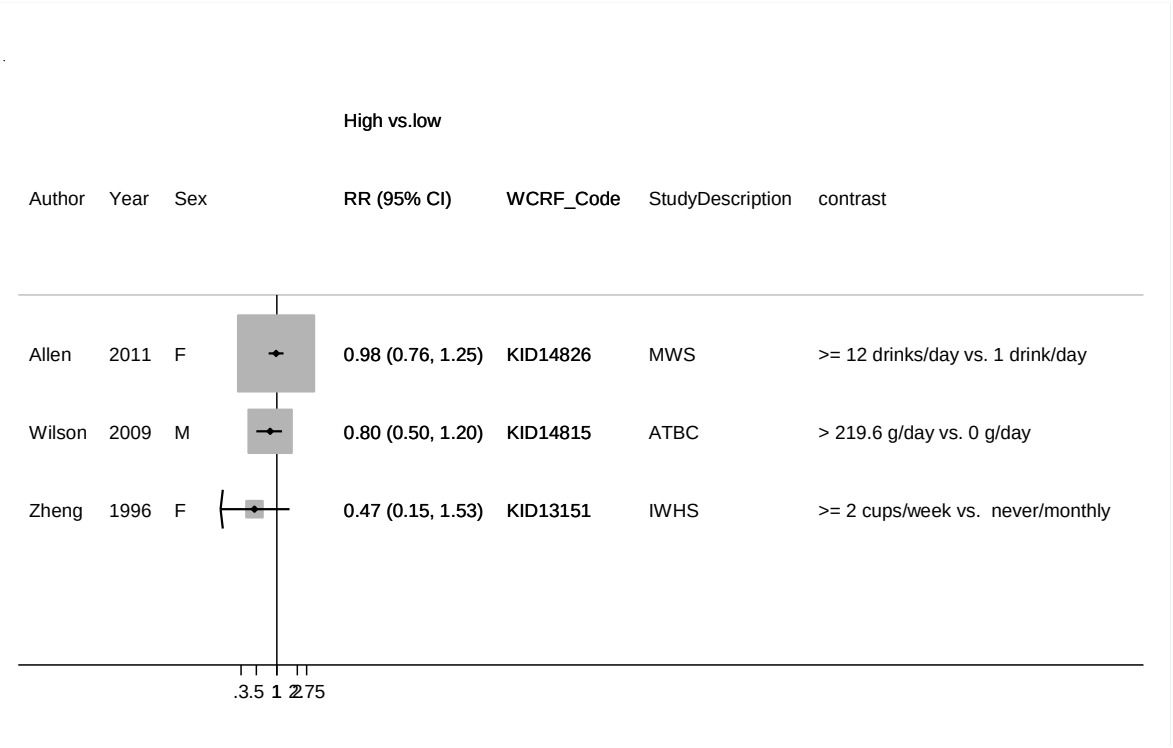


Figure 47 Dose-response meta-analysis of tea and kidney cancer, per 1 cup/day

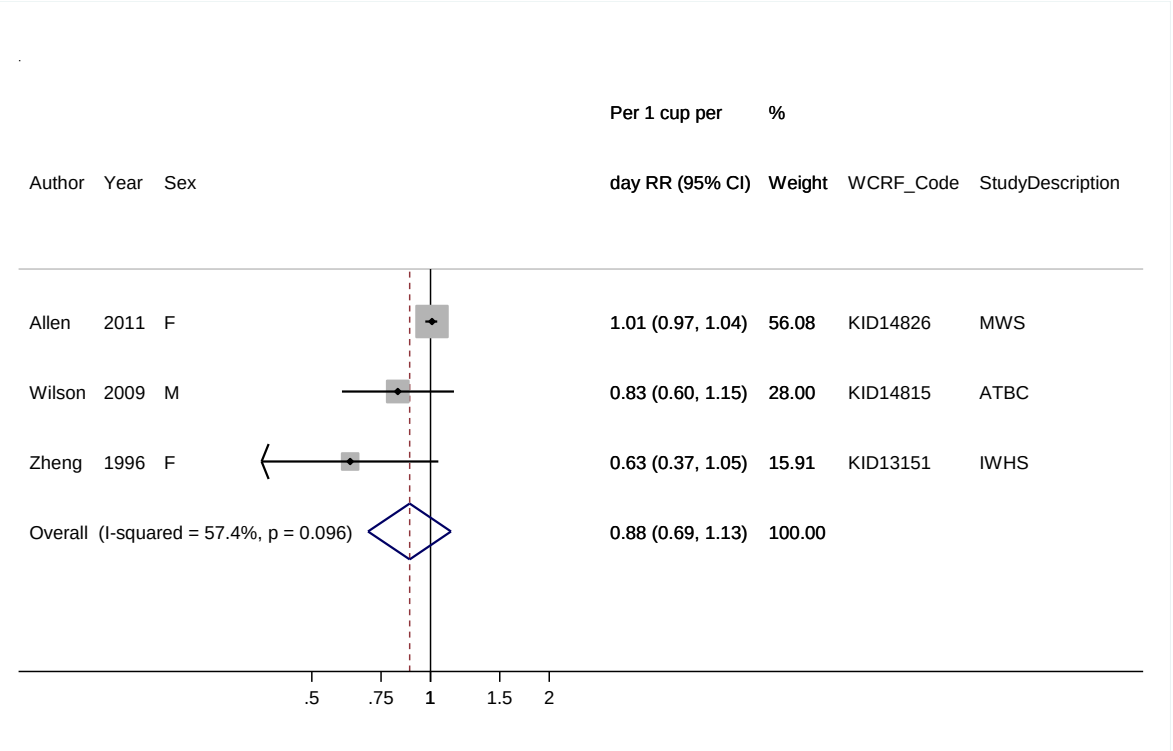


Figure 48 Dose-response graph of tea and kidney cancer

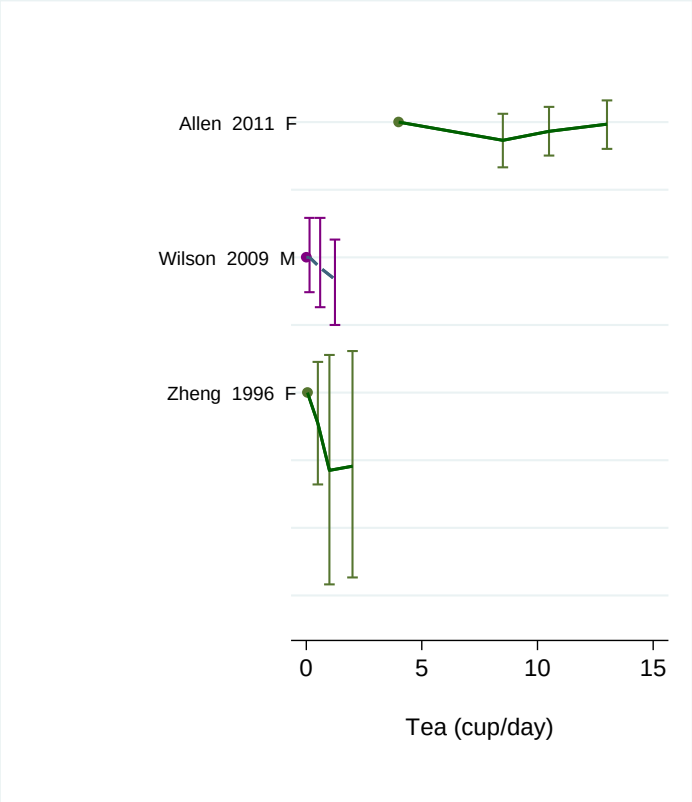
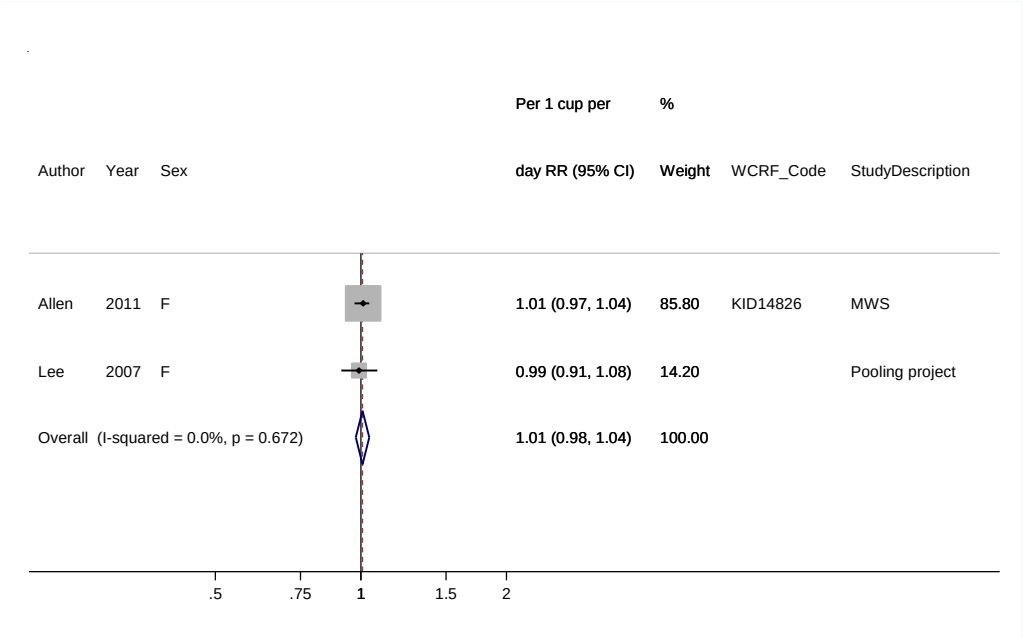


Figure 49 Dose-response meta-analysis per 1 cup/day increase of tea intake and kidney cancer in women. Pooling Project and CUP.



4 Food production, preservation, processing and preparation

4.1.2.7.2 Arsenic

Methods

Four publications from different cohort studies were identified up to March 2013; one was published after the 2005 SLR. Exposure assessment to arsenic, outcomes and measures of association varied across studies and no meta-analysis was conducted. The results are summarized in a table.

Main results

Studies were relatively of small size. Exposure to arsenic was measured in drinking water or well water in the residence areas of the participants and exposure values individually estimated according to time lived in the area. In a small study with 9 kidney cancer cases in an arseniasis-endemic area in north eastern Taiwan (Chiou et al, 2001), the measure of association was the standardised incidence ratio with the general population of Taiwan as comparison. This was the only study showing a significant positive association. dn None of the three other studies reported significant associations of kidney cancer incidence (Baastrup et al, 2008) (Kurttio et al, 1999) or mortality (Lewis et al, 1999) with arsenic in drinking water.

Comparison with the Second Expert Report

In the Second Expert Report the evidence was judged as limited suggestive an increased risk of kidney cancer in relation to arsenic in water.

Table 50 Overall evidence on arsenic and kidney cancer

SLR	Summary of evidence
2005 SLR	Three cohorts were identified. One small study showed increased risk. No significant associations were reported in the other studies. The evidence was judged limited suggestive of an increased risk of kidney cancer in relation to arsenic in drinking water
Continuous update	One cohort was identified. No association was observed. No meta-analysis was conducted.

Table 51 Studies on arsenic and kidney cancer identified in the CUP and 2005 SLR

Author, year	Country	Study	Cases	Follow up	Sex	RR	LCI	UCI	Exposure and contrast
Baastrup, 2008	Denmark	Diet, Cancer and Health	53 incident cases	~ 10 years	M/F	0.88	0.58	1.35	For 1 µg/L increase in time-weighted average exposure (drinking water)
						0.94	0.81	1.09	For 5-mg increase in cumulated exposure (drinking water)
Chiou, 2001	Taiwan	Residents in arseniasis-endemic area	9 incident cases	~5 years	M/F	2.82	1.29	5.36	Standardised incidence ratio compared with general population Taiwan
Kurttio, 1999	Finland	Finns living outside municipal drinking-water system during 1967-1980	49 incident cases	~ 14 years	M/F	Concentration of arsenic in well water 3-9 years before cancer diagnosis			
						1.49	0.67	3.31	>=0.5 vs <0.1 µg/L
						1.16	0.80	1.69	(log) continuous
						Concentration of arsenic in well water 10 years before cancer diagnosis			
						1.07	0.46	2.52	>=0.5 vs <0.1 µg/L
						0.72	0.38	1.36	(log) continuous
						Daily dose of arsenic in well water 3-9 years before cancer diagnosis			
						1.21	0.52	2.82	>=1 vs <0.2 µg/d
						1.10	0.77	1.58	(log) continuous
						Daily dose of arsenic in well water 10 years before cancer diagnosis			
						0.94	0.39	2.27	>=1 vs <0.2 µg/d
						0.59	0.28	1.23	(log) continuous
						Cumulative dose of arsenic in well water 3-9 years before cancer diagnosis			
						0.80	0.42	1.86	>=2 vs <0.5 g/d
						0.59	0.28	1.23	(log) continuous
						Cumulative dose of arsenic in well water 10 years before cancer diagnosis			
						0.47	0.21	1.04	>=2 vs <0.5 g/d
						0.76	0.44	1.30	(log) continuous
Lewis, 1999	United States	Historic records of Mormons in Utah		9 years	M	1.75	0.80	3.32	Standardised mortality ratio compared with white male population in Utah
						1.43	-	-	>=5000 ppb-years arsenic in well water
				4years	F	0.44	0.44	4.11	Standardised mortality ratio compared with white female population in Utah
						1.13	-	-	>=5000 ppb-years arsenic in well water

5 Dietary constituents

5.1.2 Non-starch polysaccharides/dietary fibre

Methods

Up to March 2013, 3 articles were identified; 2 new articles were identified in the CUP. A meta-analysis was conducted including the two cohort studies published after the CUP (Allen et al, 2009; Daniel et al, 2013). In The NIH-AARP study (Daniel et al, 2013) dietary fibre intake was reported as grams/1000 kcal and it was rescaled to grams/day using as approximation the average energy intake per quintile of dietary fibre reported in the article. Dose-response analyses were conducted for an intake increase of 10 grams/day.

Main results

The summary RR per 10 grams/day was 0.87 (95% CI: 0.79 -0.95, I^2=0%, $p_{heterogeneity}$=0.32). Egger's test was not conducted and funnel plot is not showed as only two studies were available.

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.32.

Comparison with the Second Expert Report

No meta-analysis of prospective studies was conducted in the Second Expert Report. The only prospective study (the ATBC study, Hirvoneen et al, 2001) reported baseline median intake of fibre of 23.9 grams/day in renal cell cancer patients and 24.3 grams/day in no cancer participants.

Meta-analysis and Pooled studies

No pooled analysis or meta-analysis was identified.

Table 52 Studies on dietary fibre intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2013	United States	NIH-AARP Diet and Health Study	1816	9	M/F	0.81	0.69	0.95	15.9 vs 6.6 g/1000 kcal/d
Allen, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	507	8.8	M/F	1.06	0.73	1.53	27.7 vs 16.4 g/d
						0.93	0.79	1.09	For 10 g/d increase (uncalibrated)
						0.87	0.67	1.11	For 10 g/d increase (calibrated)
Hirvonen, 2001	Finland	ATBC	92	6.1	Male smokers	Median intake at baseline was 23.9 grams/day in renal cell cancer patients and 24.3 grams/day in no cancer participants			

Table 53 Overall evidence on dietary fibre and kidney cancer

	Summary of evidence
2005 SLR	One cohort studies was identified. No measure of association was reported.
Continuous Update Project	Two cohorts were identified and included in a meta-analysis. No association was observed in EPIC. The NIH-AARP reported a significant inverse association of renal cancer with fibre intake.

Table 54 Summary of results of the dose response meta-analysis of dietary fibre and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	2323
Increment	-	Per 10 g/d
Overall RR (95%CI)	-	0.87 (0.79-0.95)
Heterogeneity (I^2,p-value)	-	I^2=0%, p=0.320

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 55 Inclusion/exclusion table for meta-analysis of dietary fibre and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14858	Daniel	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Converted grams per 1000 kcal to grams/day Person/ years per category	-
KID14811	Allen	2009	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	-	-
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	No RR available

Figure 50 Highest versus lowest forest plot of dietary fibre and kidney cancer

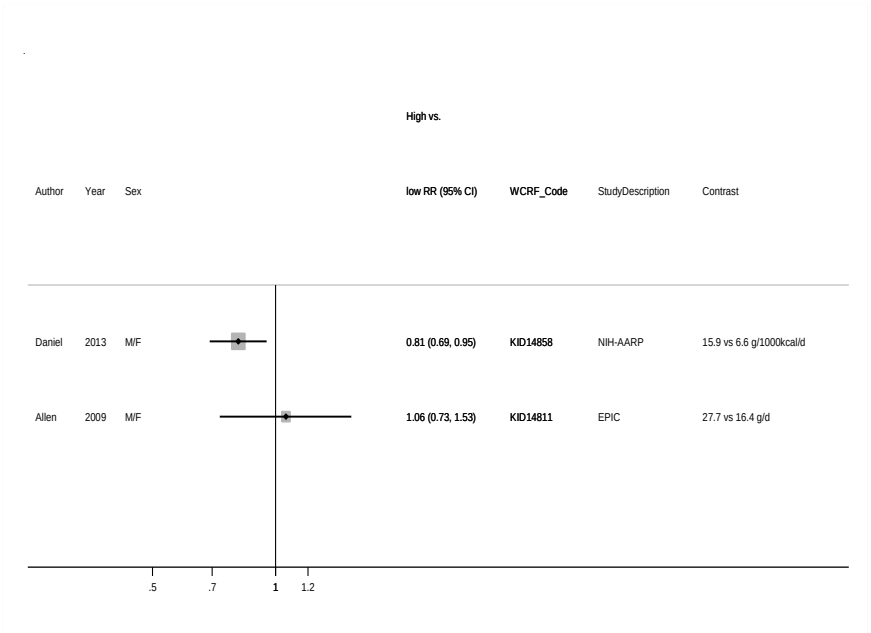


Figure 51 Dose-response meta-analysis per 10 g/d increase of dietary fibre intake and kidney cancer

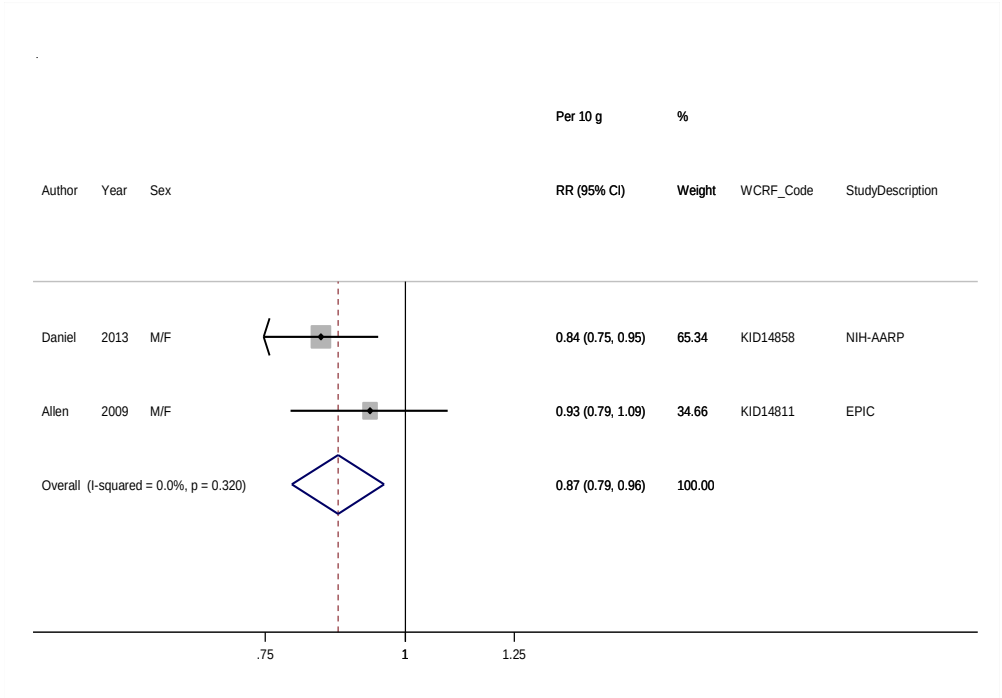
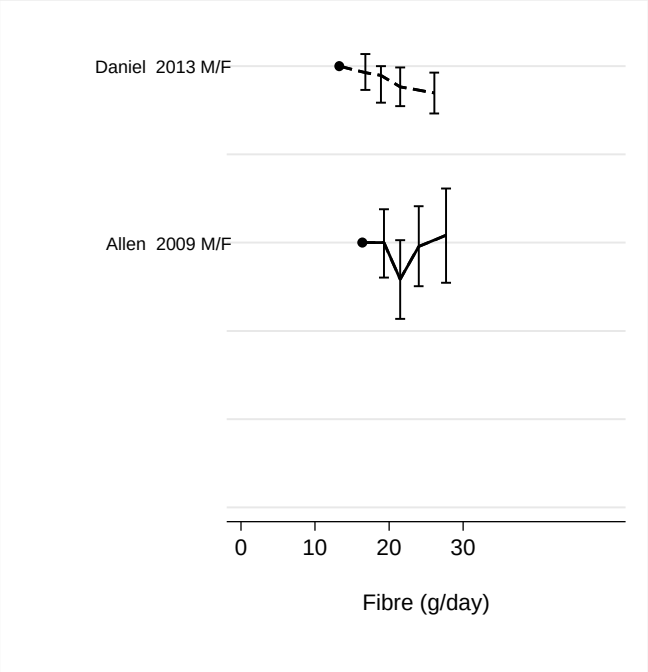


Figure 52 Dose-response graph of dietary fibre and kidney cancer



5.2 Lipids

One study was identified during the CUP (EPIC, Allen et al, 2009; 507 cases of renal cell carcinoma). The study found no association between the risk of renal cell carcinoma and the intakes of total, saturated, monounsaturated and polyunsaturated fatty acids, and cholesterol.

The Pooling Project of Cohort Studies investigated a link between total, saturated, monounsaturated and polyunsaturated fatty acids, animal, plant fat and cholesterol and the risk of kidney cancer (Lee et al, 2008). No associations were observed with any of these exposures.

EPIC and the Pooling project were included in a meta-analysis. The results are summarized in a table below.

Table 56 Studies on fat intake and kidney cancer

Author, year	Study name	Cases, years of follow-up	Fat type	RR	LCI	UCI	Increase
Lee, 2008	Pooling Project of Cohort Studies	1478 cases (13 cohorts) (M/F) 7-20 years of follow-up	Total fat	1.02	0.98	1.07	5% energy intake
			Saturated fat	0.98	0.86	1.13	
			Monounsaturated fat	1.17	0.98	1.38	
			Polyunsaturated fat	0.95	0.81	1.10	
			Animal fat	1.01	0.93	1.10	
			Plant fat	1.01	0.92	1.10	
			Cholesterol	1.03	0.94	1.14	100mg/ 1000kcal
Allen, 2009	EPIC	507 cases 8.8 years of follow-up (M/F)	Total fat	1.05	0.76	1.39	10% energy intake
			Saturated fat	1.17	0.95	1.50	5% energy intake
			Monounsaturated fat	1.10	0.73	1.53	5% energy intake
			Polyunsaturated fat	0.80	0.61	1.03	3% energy intake
			Cholesterol	1.00	0.61	1.41	200 grams

Table 57 Meta-analysis of the Pooling Project of Cohort Studies and the additional study identified in the CUP on intake of lipids and kidney cancer

Studies, number of cases	Fat type	RR (95% CI)	Increment	I^2, p heterogeneity
Pooling Project and EPIC 14 cohorts, 1985 cases (M/F)	Total fat	1.02 (0.98-1.06)	5% energy	$I^{2=}$0%, p=1
	Saturated fat	1.04 (0.88-1.23)	5% energy	$I^{2=}$41.3%, p=0.19
	Monounsaturated fat	1.16 (1.01-1.33)	5% energy	$I^{2=}$0%, p=0.76
	Polyunsaturated fat	0.76 (0.40-1.44)	5% energy	$I^{2=}$58.2%, p=0.12

5.3 Protein

Two cohort studies were identified in the CUP but the data was not enough to do meta-analysis. One study was identified in the 2005 SLR. None of the studies reported significant association.

The Pooling Project of Cohort Studies (13 cohorts, 1478 cases) investigated the association between total, animal, and plant protein and the risk of kidney cancer (Lee et al, 2008). No associations were reported between any protein type and renal cell cancer risk.

The EPIC and the Pooling Project were meta-analysed together in this review. The WHI study (Prentice et al, 2009) did not provide enough information fort dose-response meta-analysis and one study by Prineas et al, 1997 (IWHS) that was identified during the 2005 SLR was already included in the Pooling Project of Cohort Studies of total protein and kidney cancer.

Table 58 Results of prospective studies on protein intake by type and kidney cancer identified in the CUP.

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lee, 2008	North America, Europe, Australia	Pooling Project of Cohort Studies	1478 (13 cohorts)	7-20	M/F	Total protein			
						1.06	0.89	1.26	Q5 vs. <Q1
						1.07	0.97	1.17	For 5% increase of caloric intake from protein
						Animal protein			
						1.04	0.84	1.29	Q5 vs. <Q1
						1.09	0.98	1.21	For 5% increase of caloric intake from protein
						Plant protein			
						0.99	0.78	1.26	Q5 vs. <Q1
						0.99	0.73	1.34	For 5% increase of caloric intake from protein
Allen, 2009a	Europe	European Prospective Investigation into Cancer and Nutrition	507	8.8	M/F	Total protein			
						1.30	0.95	1.79	19.4% vs. 14.9% of energy
						1.15	0.88	1.43	For 3% increase of caloric intake from protein
						Animal protein			
						1.19	0.85	1.66	13.1% vs 7.9 % of energy
						1.12	0.93	1.36	For 3% increase of caloric intake from protein
						Plant protein			

						0.93	0.65	1.32	7.4 % vs 5.5% of energy
						0.98	0.71	1.28	For 3% increase of caloric intake from protein
Prentice, 2009	North America	Women's Health Initiative DM trial and observational study	123	Max 13 years	F	0.86	0.48	1.53	Q4 vs. Q1

Table 59 Meta-analysis of the Pooling Project of Cohort Studies and the additional study identified in the CUP on intake of proteins and kidney cancer

Studies, number of cases	**Protein type**	**RR (95% CI)**	**Increment**	**I^2, p heterogeneity**
Pooling Project and EPIC 14 cohorts, 1985 cases (M/F)	Total protein	1.07 (0.98-1.18)	5% energy	I^2=0%, p=0.43
	Animal protein	1.10 (0.99-1.21)	5% energy	I^2=0%, p=0.57
	Plant protein	0.97 (0.75-1.25)	5% energy	I^2=0%, p=0.94

5.4.1 Alcohol (as ethanol)

Methods

Up to March 2013, 12 articles were identified, six of which during the CUP. Overall, results from eight different cohort studies were identified. A meta-analysis including 7 studies (5 identified during the CUP and 2 identified during the 2005 SLR) was performed.

In the Million Women Study (Allen et al, 2011) alcohol intake was reported as drinks/day and these were converted to g/d of ethanol using data reported in another publication of the same study (1 drink equivalent to 10 g) (Allen et al, 2009). In the NIH-AARP Diet and Health study (Lew et al, 2011) the reference category was ">0-<5" grams of alcohol per day for men and women separately. The RRs were recalculated using 0 g/d as reference category and the results for men and women were pooled before inclusion in the meta-analysis of both sexes combined. The outcome was renal cell cancer incidence in all studies. The dose-response results are presented for an increment of 10 g/d.

Two studies that investigated alcohol intake and mortality were not included in the CUP meta-analysis. In the Japan Collaborative Cohort Study (Osaza et al, 2007), the relative risk of mortality for kidney cancer in drinkers compared to non-drinkers was 2.26 (95% CI: 0.79-6.43; 46 deaths) in men and 0.37 (95% CI: 0.04- 2.92; 19 deaths) in women. In the Korea National Health Insurance Corporation's Health Examinee Cohort (Kim et al, 2010), the relative risks of kidney cancer mortality were 0.46 (0.23–0.93) and 0.37 (0.15–0.89) for 15-29.9 g/d and 30 g/d or more respectively compared with non-drinkers.

Non-linear dose-response meta-analysis was conducted using restricted cubic splines models. To be included in the analysis, studies should report relative risk estimates for four or more categories of alcohol intake. Only three studies could be included in the analysis (Schouten et al, 2008; Wilson et al, 2009; Lew et al, 2011).

The Pooling Project (Lee et al, 2007b) and the additional studies identified in the CUP (MWS, Allen et al, 2011; NIH-AARP, Lew et al, 2011; MEC Setiawan et al, 2007) were included in a dose-response meta-analysis. In this linear meta-analysis, the participants of the Pooling Project with alcohol intake >30 g/day were excluded.

Main results

The summary RR per 10 g/d was 0.92 (95% CI: 0.86-0.97; I^2= 55.1%, $P_{heterogeneity}$=0.04) for all studies combined. After stratification by sex, the RR per 10g/d was 0.92 (95% CI: 0.84 – 1.00, I^2=70.7%, $p_{heterogeneity}$=0.03, n=3) among men and 0.81 (95% CI: 0.68 – 0.96, I^2=43.9%, $p_{heterogeneity}$=0.13, n=5) among women.

In influence analysis, the RR ranged from 0.89 (95% CI: 0.83-0.96) when the NIH-AARP Diet and Health study (Lew et al, 2011) was excluded to 0.93 (95% CI: 0.88-0.98) when the Multiethnic Cohort study was excluded (Setiawan et al, 2007).

The test for nonlinearity was not significant (p=0.78).

The meta-analysis of the Pooling Project and the additional published studies showed a RR: 0.88 (95% CI: 0.79-0.97). There was evidence of high heterogeneity (I^2:79.9%, pheterogeneity=0.002, ~4179 cases, 15 cohort studies). It was not possible to combine in nonlinear dose response meta-analysis the Pooling Project and the remaining studies identified in the CUP. Three studies identified in the CUP are not included in the nonlinear analysis of the Pooling Project. In the Multi-ethnic Cohort Study ,(Setiawan et al, 2007) and the Million Women Study (Allen et al, 2011) inverse associations were observed. The highest intake categories were ~11 g of ethanol per day and 2 glasses of more per day respectively. The only study that looked are heavy drinking was the NIH-AARP Diet and Cancer Study (Lew et al, 2011). In this study, the association of alcohol intake and renal cell carcinoma was linear, with no threshold effect among heavy drinkers (30 or more g/d).

Heterogeneity

Egger's test showed evidence of small study bias (p= 0.001). The two smaller studies (the SMC, Rashidkhani et al, 2005b, and the IWHS Nicodemus et al, 2004) found stronger inverse associations than the other studies.

Significant heterogeneity was observed (I^2= 55.1%, p=0.04). The overall heterogeneity appeared to be explained by the weaker inverse association (compared to other studies) reported by the NIH-AARP study, mainly for men (Lew et al, 2011). The heterogeneity decreased after exclusion of this study (I^2 = 25.1%, p=0.263).

Comparison with the Second Expert Report

The summary RR per one serving per day increase of three studies out of four studies (six articles) identified in the 2005 SLR was 0.48 (95% CI: 0.25- 0.90). The Panel judged that it was unlikely that alcohol increases the risk of kidney cancer and that a protective effect could not be ruled out. The CUP also found an inverse association of ethanol intake with kidney cancer.

Meta-analysis and Pooled studies

The Pooling Project of Cohort Studies (Lee et al, 2007b) and two meta-analyses (Bellocco et al, 2012; Song et al, 2012) were identified during the CUP.

In the Pooling Project of Cohort Studies (12 cohort studies, 711 female and 719 male renal cell cancer cases; Lee et al, 2007b) The RR of renal cell cancer was 0.72 (95% CI: 0.60 - 0.86; *P* trend <.001) comparing >=15 g/d of alcohol intake vs nondrinking alcohol. Associations were similar by sex (P heterogeneity = 0.89) and across alcoholic beverage type. The association was not modified by age, BMI, history of hypertension, and smoking status. There was evidence of nonlinearity (p=0.03). A linear inverse association was observed for alcohol intake up to approximately 30 g/d, and the association appeared flat above this intake value. After exclusion of participants with intake >30 g/d, the relative risk estimate for an increase of 10 g/d of alcohol intake was 0.81 (95% CI: 0.74-0.90).

In a meta-analysis by Bellocco et al, 2012 including the results of the Pooling Project (Lee et al, 2007b), the MEC study (Setiawan et al, 2007), the MWS (Allen et al, 2011) and two Asian cohort studies on kidney cancer mortality, the RR's compared with non-drinking, were 0.89 (95% CI: 0.82–0.97) for light alcohol intake (less than 12.49 g/d), and 0.74 (95% CI: 0.61–

0.88) for moderate intake (12.5–49.9 g/d). The estimates were similar for case-control studies and in analyses stratified by geographic area, sex, study quality index, smoking, BMI and hypertension. The RR estimates obtained from the best-fitting two-term fractional polynomial models were 0.84 (95% CI: 0.79–0.90) for 12 g/d, 0.68 (95% CI: 0.59–0.78) for 32 g/d, 0.60 (95% CI: 0.50–0.73) for 50 g/d. The curve appeared to flatten above ~60 g/d.

Another meta-analysis (Song et al, 2012) included the results of the pooling project and all the remaining studies identified in the CUP. The overall relative risk for the highest compared to the lowest alcohol intake was 0.71 (95% CI: 0.63–0.78) (for cohort studies). The inverse association was significant for all types of alcoholic beverages. The RR for highest versus lowest category of alcoholic beverage intake among females was 0.70 (95% CI: 0.56-0.84) and 0.71 (95% CI: 0.61-0.80) among males.

Table 60 Studies on alcohol (as ethanol) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Allen, 2011*	United Kingdom	The Million Women Study	588	5.2	F	0.73 0.90	0.58 0.81	0.92 0.99	>=2 vs. 0 to < 1 drink/day Per drink/d increase
Lew, 2011	United States	NIH-AARP Diet and Health Study	1348	9	M	0.96	0.94	0.99	Per drink/d increase
						0.71	0.59	0.85	>=30 g/d vs. >0-<5 g/d
			466		F	0.73	0.60	0.88	Per drink/d increase
						0.43	0.22	0.84	>=30 g/d vs. >0-<5 g/d
Wilson, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Cohort	229	15.2	M	0.6	0.4	0.9	>26.8 g/d vs. <=3.5 g/d
Lee, 2007	International	Pooling Project of Cohort Studies	1430	7-20	M/F	0.72	0.60	0.86	>=15 g/d vs nondrinker
					M	0.71	0.56	0.89	
					F	0.73	0.54	0.98	
					M/F	0.79	0.70	0.89	Per 10 g/d ethanol intake
Schouten, 2008	The Netherlands	The Netherlands Cohort Study	291	11.3	M/F	0.61	0.38	0.98	>=30 g/d vs. no alcohol
						0.94	0.86	1.02	Per 10g/d ethanol increase
Setiawan, 2007	United States	Multiethnic Cohort	347	8.3	M	0.69	0.49	0.96	>=10.9 g/d vs. none
					F	0.80	0.48	1.35	>=3.3 g/d vs. none

*The Million Women study published two articles (Allen et al, 2009; Allen et al, 2011)

Table 61 Overall evidence on alcohol (as ethanol) and kidney cancer

	Summary of evidence
2005 SLR	Six articles from four cohort studies were identified. Three studies were included in a meta-analysis. The summary estimate showed a significant inverse association. The judgement was that it is unlikely that alcohol intake increases the risk of kidney cancer; a protective effect could not be ruled out.
Continuous Update Project	Six articles from five cohort studies were identified and the five cohorts were included in the meta-analysis. Overall, seven studies were included in the CUP meta-analysis. A significant inverse association was observed.

Table 62 Summary of results of the dose response meta-analysis of alcohol (as ethanol) and kidney cancer

Renal cell cancer risk		
	SLR*	Continuous Update Project
Studies (n)	3	7
Cases (n)	-	3525
Increment	Serving/day	Per 10g/d
Overall RR (95%CI)	0.48 (0.25-0.90)	0.92 (0.86-0.97)
Heterogeneity (I^2,p-value)	-	55.1%, p=0.04
Pooling Project of Cohort Studies		
Studies (n)		12
Cases (n)		1430
Increment**		Per 10g/d
Overall RR (95%CI)		0.81 (0.74-0.90)
Heterogeneity (I^2,p-value)		p=0.99***
CUP and Pooling Project		
Studies (n)		15
Cases (n)		~4179***
Increment**		Per 10g/d
Overall RR (95%CI)		0.88 (0.79-0.97)
Heterogeneity (I^2,p-value)		I^2= 79.9% p=0.002

*One study reported non-adjusted results.

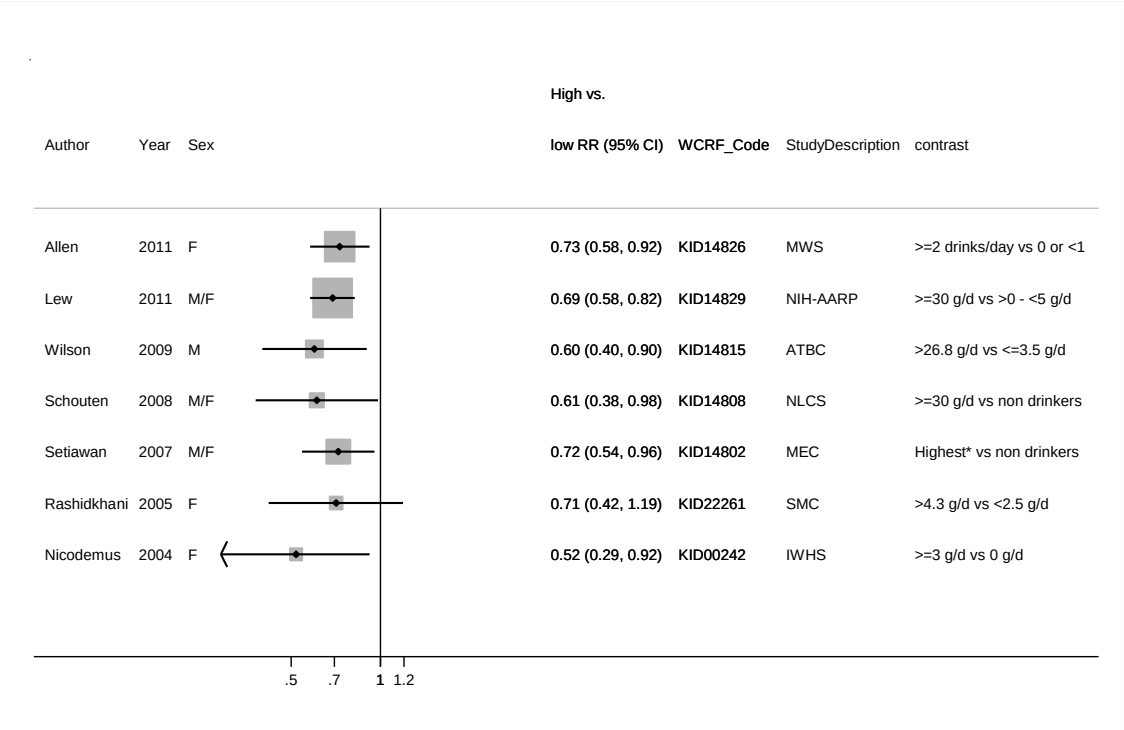
** Participants in the Pooling Project with intake >30 g/d were excluded

*** For the category ≥15 g/d

Table 63 Inclusion/exclusion table for meta-analysis of alcohol (as ethanol) and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14826	Allen	2011	Prospective Cohort Study	The Million Women Study	Incidence	No	Yes	Yes	Mid-exposure values	-
KID14829	Lew	2011	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Drinks/day converted to grams/day; rescale of reference category to none alcohol intake Mid-exposure values, Person/years per category	-
KID14816	Allen	2009b	Prospective Cohort Study	The Million Women Study	Incidence	No	No	No	-	Superseded by Allen et al, 2011
KID14815	Wilson	2009	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person/ years per quartile Mid-exposure values	-
KID14808	Schouten	2008	Case Cohort Study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	-
KID14802	Setiawan	2007	Prospective Cohort Study	Multiethnic Cohort	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
KID14374	Mahabir	2005	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Superseded by Wilson et al, 2009
KID22261	Rashidkhani	2005b	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	Yes	Yes	-	-
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	-
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Results expressed as difference in means. Wilson et al, 2009 was used
KID01081	Prineas	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Nicodemus et al, 2004
KID14184	Kato	1992	Prospective Cohort Study	USA Hawaii 1965-1968	Incidence	Yes	No	No	-	Mean exposure only

Figure 53 Highest versus lowest forest plot of alcohol (as ethanol) and kidney cancer



*In Setiawan et al., 2007 study the highest category of total intake of alcohol (grams of ethanol/day) was >=10.9 g/d among men and >=3.3 g/d among women.

Figure 54 Dose-response meta-analysis of alcohol intake and kidney cancer - per 10 g/d (as ethanol)

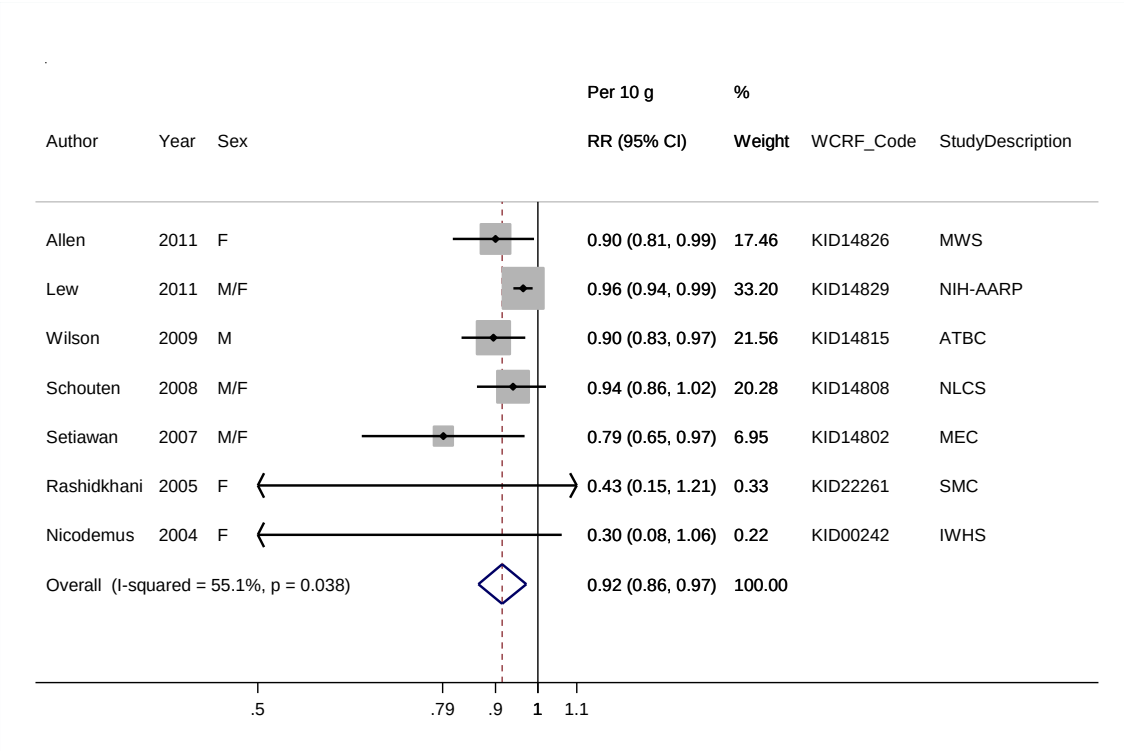


Figure 55 Funnel plot of alcohol (as ethanol) and kidney cancer

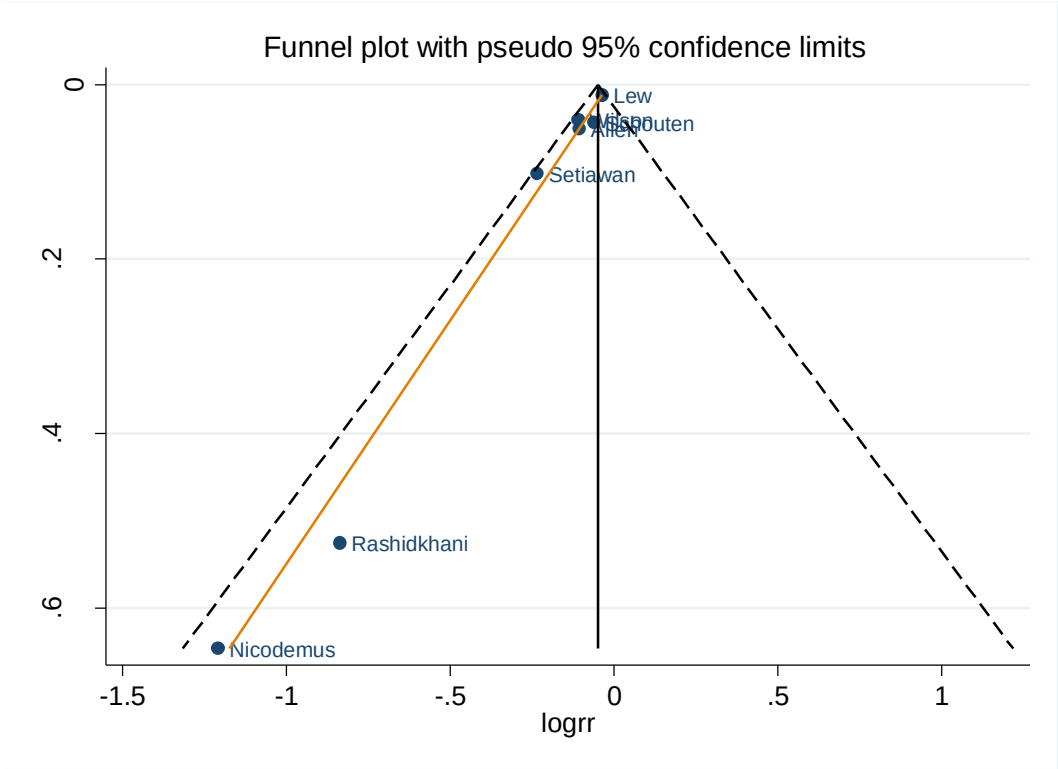


Figure 56 Dose-response graph of alcohol (as ethanol) and kidney cancer

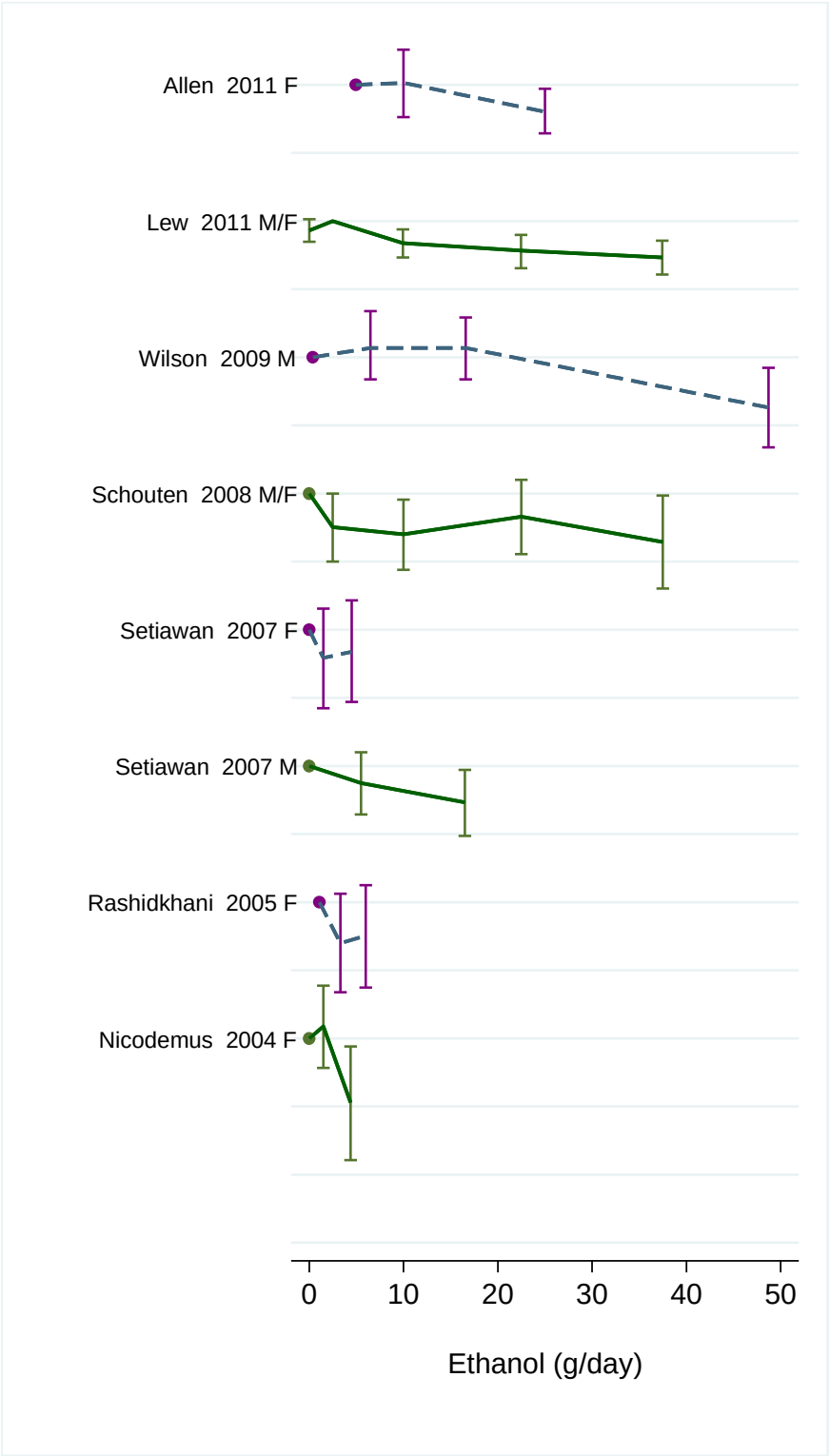


Figure 57 Dose-response meta-analysis of alcohol (as ethanol) and kidney cancer, stratified by sex – per 10g /day

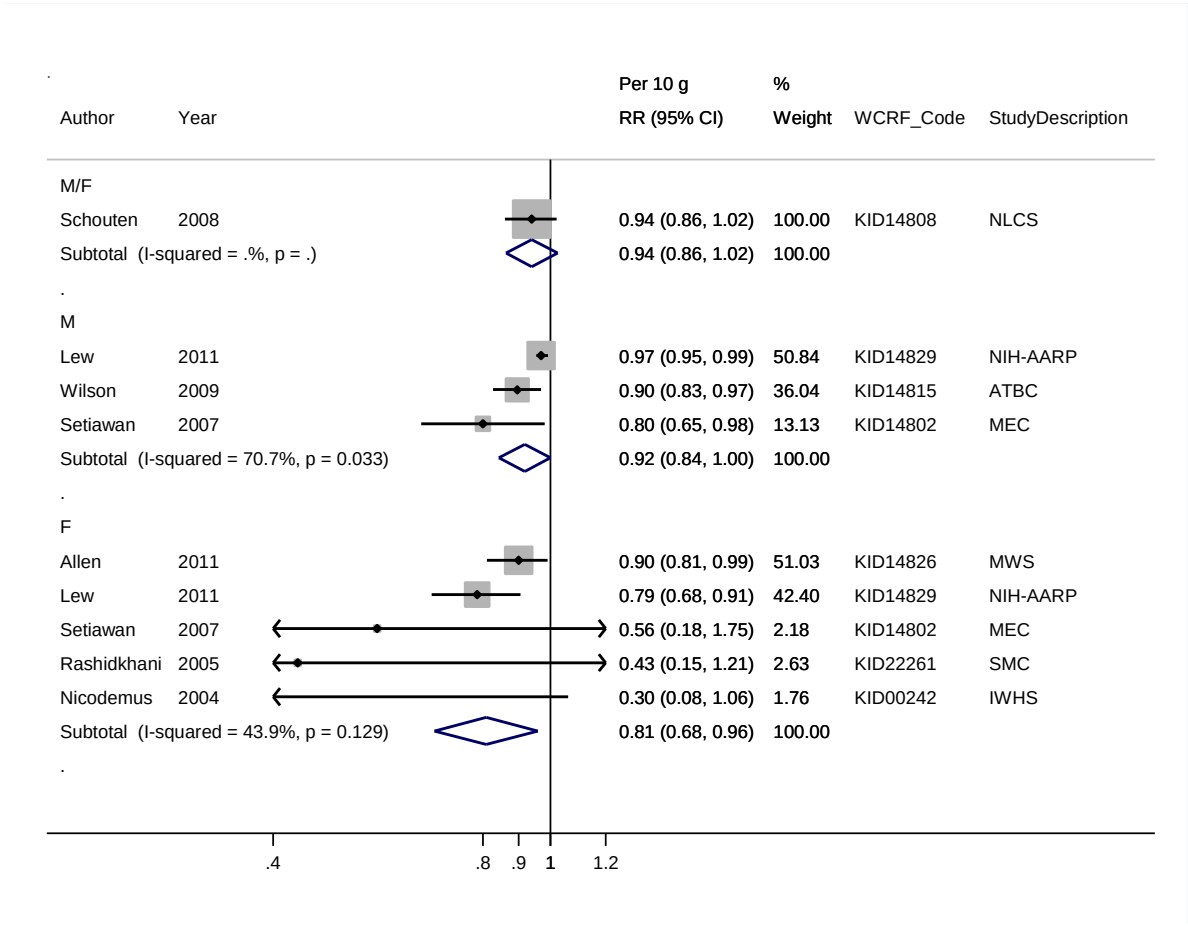
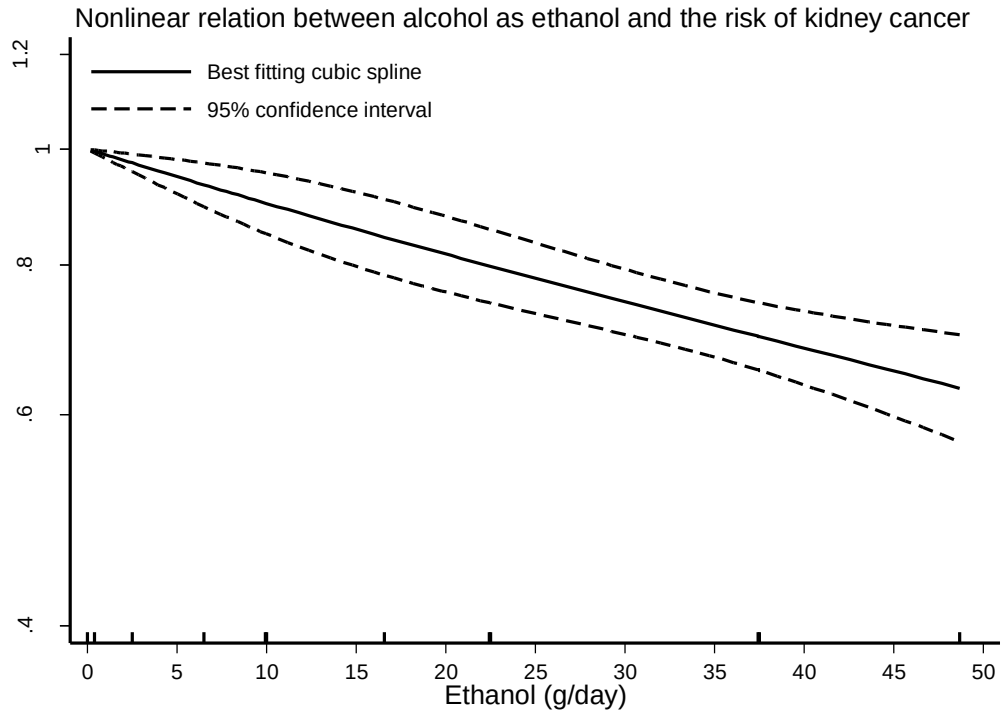


Figure 58 Nonlinear dose-response analysis of ethanol and kidney cancer



$P_{nonlinearity}$=0.78

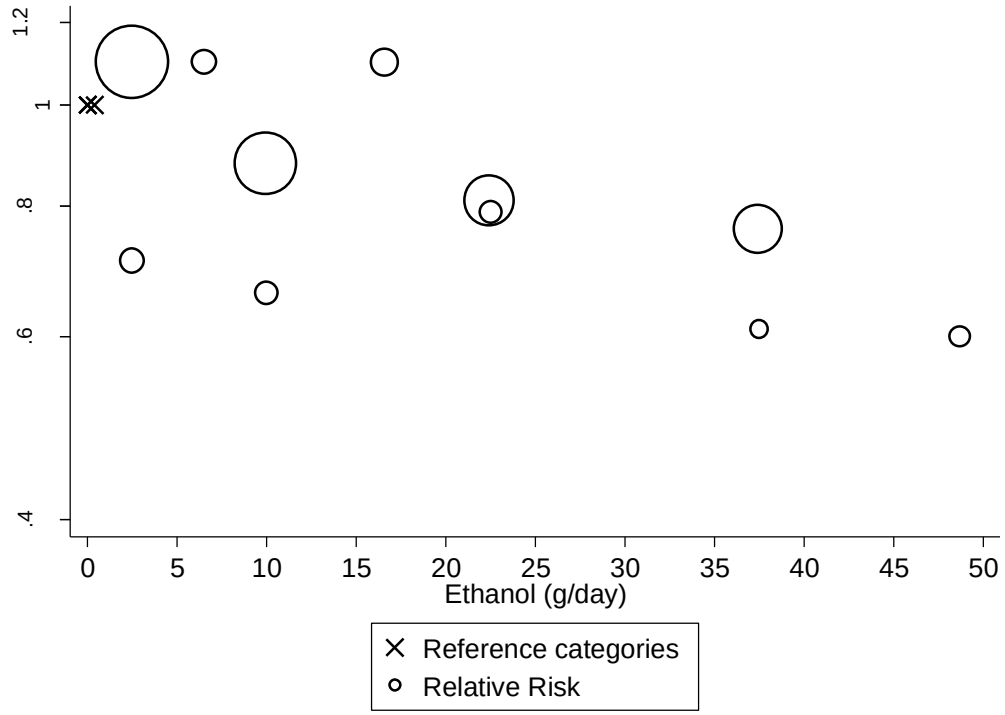


Table 64 RRs for nonlinear dose-response analysis

Ethanol (g/d)	RR (95%CI)
0	1
2.5	0.97 (0.96-0.99)
6.5	0.93 (0.90-0.97)
10	0.90 (0.85-0.96)
22.5	0.80 (0.74-0.86)
37.5	0.70 (0.65-0.74)

Figure 59 Dose-response meta-analysis of alcohol (as ethanol) and kidney cancer - per 10 g/d . Pooling Project of Cohort Studies and CUP

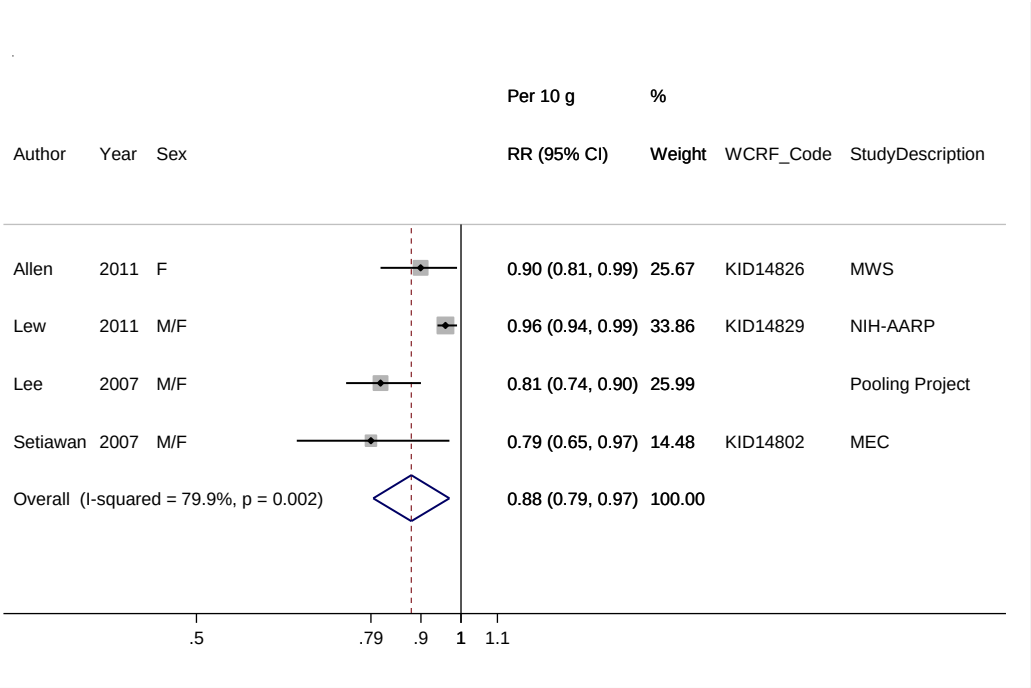
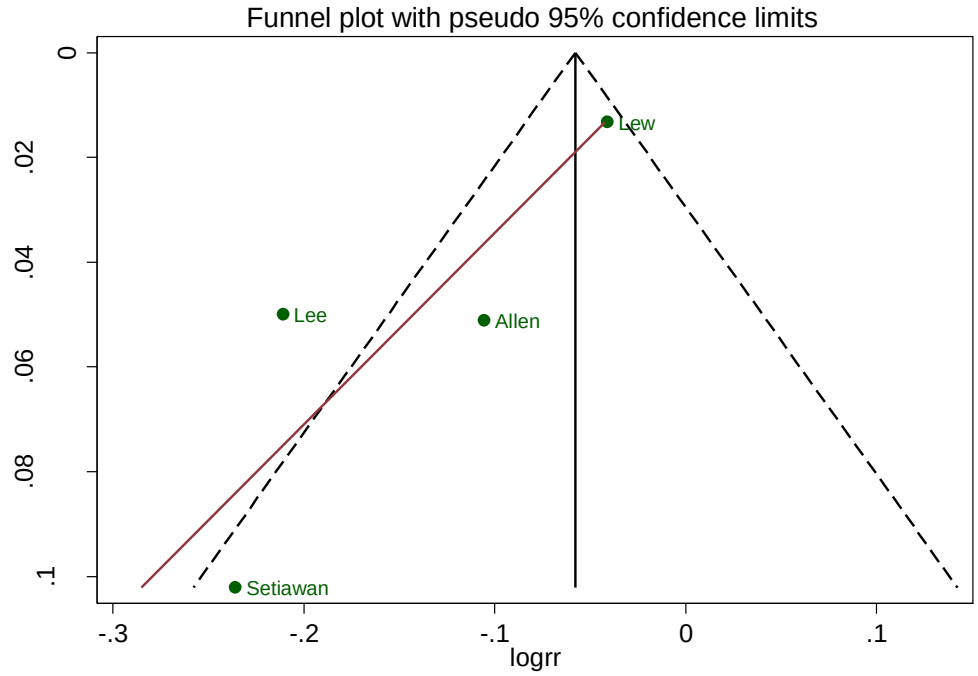


Figure 60 Pooling Project of Cohort Studies and CUP: Funnel plot of alcohol (as ethanol) and kidney cancer



5.4.1.1 Beer (as ethanol)

Methods

Up to March 2013, 7 articles from 7 cohort studies were identified; 2 were identified during the CUP. In this report, a meta-analysis including 3 studies was performed. In Lew et al., 2011 study RR was presented for men and women separately with a reference category of >0-<5 grams of ethanol from liquor per day. The RRs were recalculated with a new reference category of 0 g/d intake and pooled. The dose-response results are presented for an increment of 10 g/d.

Main results

The summary RR per 10 g/d was 0.77 (95% CI: 0.65- 0.92; I^2= 58.6%, $P_{heterogeneity}$=0.089) for all studies combined.

Heterogeneity

High heterogeneity was observed (I^2= 58.6%, p=0.09). Egger's test showed no evidence of publication bias (p= 0.89) but only three studies were included.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP results found no association between beer intake and kidney cancer risk.

Meta-analysis and Pooled studies

In the Pooling Project of Cohort Studies (12 cohort studies), the RR when comparing 5.0–14.9 g/d of ethanol from beer with nondrinking was 0.87 (95% CI: 0.68 - 1.11) (Lee et al, 2007b).

In a meta-analysis by Song et al, 2012 including the results of the Pooling Project (Lee et al, 2007b) and a cohort study (Lew et al, 2011), the RR for the highest versus lowest category of beer intake was 0.81 (95% CI: 0.70-0.91). Lew et al, 2011 study is the same study that was identified in the CUP.

Table 65 Studies on beer (as ethanol) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lew, 2011	United States	NIH-AARP Diet and Health Study	1348	9	M	0.63	0.49	0.80	>=15 g/d vs. >0 - <5 g/d
			466		F	0.95	0.50	1.82	>=5 g/d vs. >0 - <5 g/d
Schouten, 2008	The Netherlands	The Netherlands Cohort Study	291	11.3	M/F	0.69	0.32	1.45	>=15 g/d vs. no alcohol
						0.92	0.73	1.16	Per 10g/d increase

Table 66 Overall evidence on beer (as ethanol) and kidney cancer

	Summary of evidence
2005 SLR	Five cohort studies were identified. Two studies reported an inverse but non-significant relationship between intake of ethanol from beer and kidney cancer.
Continuous Update Project	Two cohort studies were identified and included in the final meta-analysis. Overall, three studies were included in the CUP meta-analysis.

Table 67 Summary of results of the dose response meta-analysis of beer (as ethanol) and kidney cancer

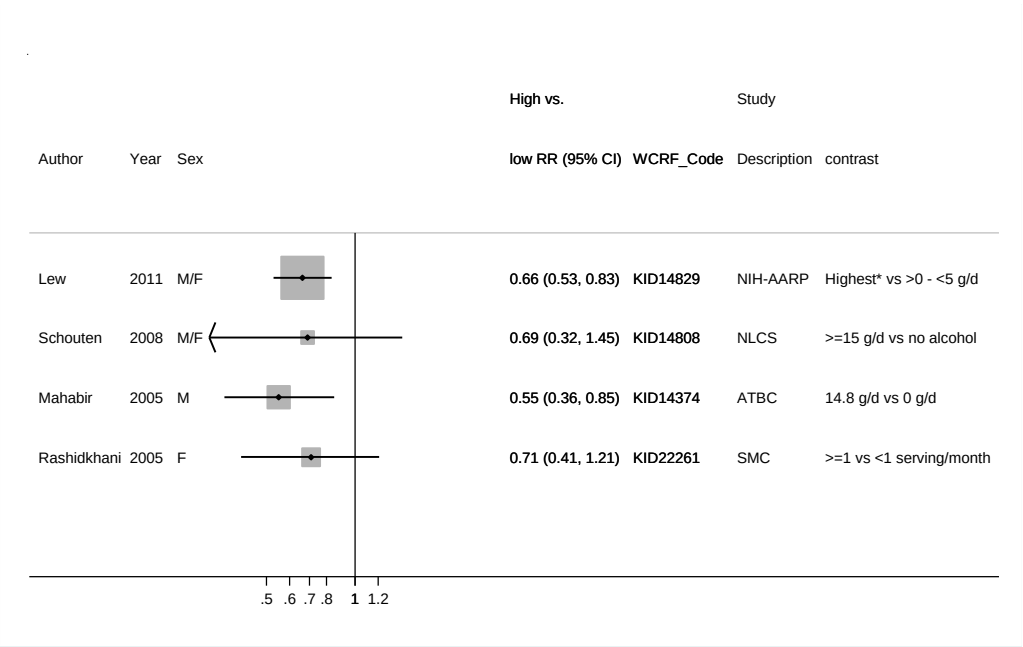
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2432
Increment	-	Per 10g/d
Overall RR (95%CI)	-	0.77 (0.65-0.92)
Heterogeneity (I^2,p-value)	-	58.6%, p=0.09

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 68 Inclusion/exclusion table for meta-analysis of beer (as ethanol) and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14829	Lew	2011	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values Person/years per category RR recalculated using 0 g/d as a new reference category	-
KID14808	Schouten	2008	Case Cohort Study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	-
KID14374	Mahabir	2005	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	-	-
KID22261	Rashidkhani	2005b	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	No	Yes	-	High vs. low intake only
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Users vs. non users
KID14184	Kato	1992	Prospective Cohort Study	USA Hawaii 1965-1968	Incidence	Yes	No	No	-	Mean exposure only
KID14238	Jensen	1979	Prospective Cohort Study	Denmark 1939-1963	Incidence	Yes	No	No	-	SIR only

Figure 61 Highest versus lowest forest plot of beer (as ethanol) and kidney cancer



*In Lew et al., 2011 study the highest vs. lowest intake was >=5 g/d vs. >0 - <5 g/d among women and >=15 g/d vs. >0 - <5 g/d among men.

Figure 62 Dose-response meta-analysis of beer (as ethanol) and kidney cancer - per 10 g/d

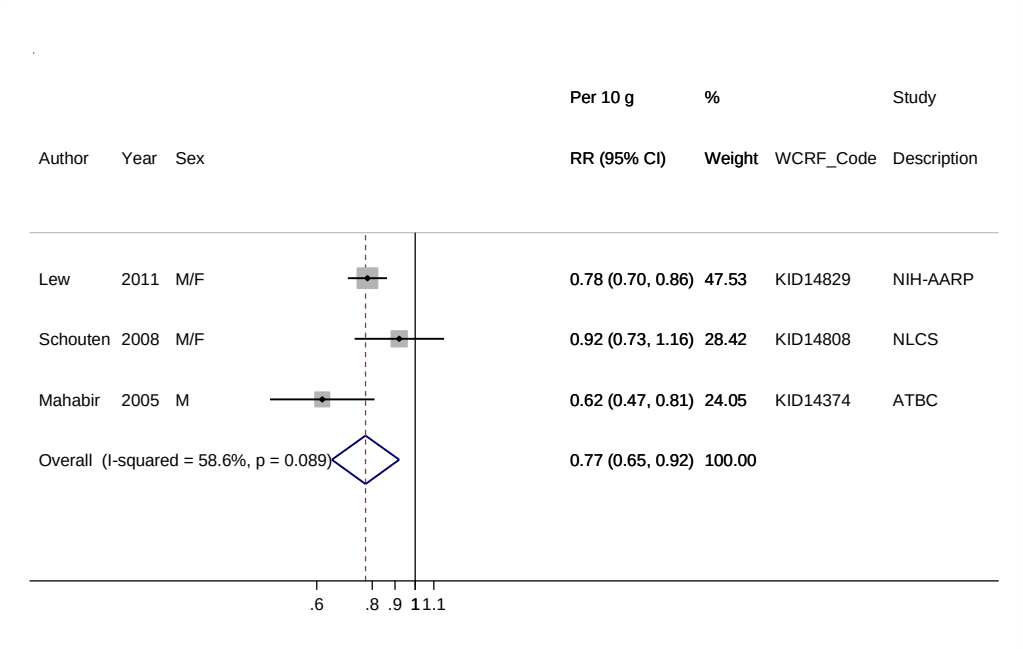
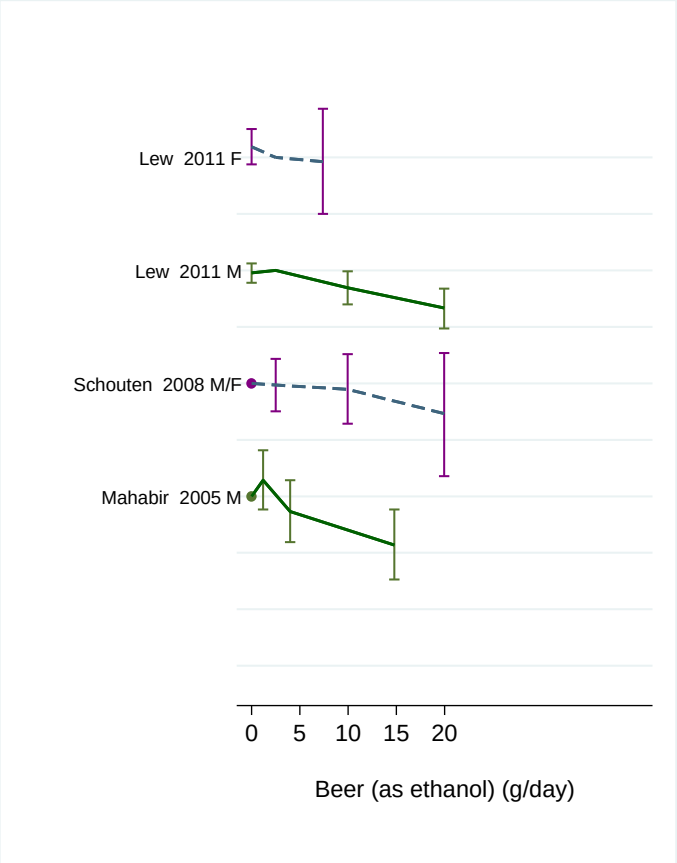


Figure 63 Dose-response graph of beer (as ethanol) and kidney cancer



5.4.1.2 Wine (as ethanol)

Methods

Up to March 2013, 8 articles from 7 cohort studies were identified; 4 were identified during the CUP. In this report, a meta-analysis including 4 studies (all identified during the CUP) was performed.
In Lew et al, 2011 the RR was presented for men and women separately with a reference category of >0-<5 grams of ethanol from wine per day. The RRs were recalculated with a new reference category of 0 g/d intake using the method by Hamling et al, 2008 and pooled. The dose-response results are presented for an increment of 10 g/d.

Main results

The summary RR per 10 g/d was 0.96 (95% CI: 0.91-1.02; I^2= 18.3%, $P_{heterogeneity}$=0.3) for all studies combined.

Heterogeneity

Low heterogeneity was observed (I^2= 18.3%, p=0.3). Egger's test showed significant evidence of publication bias (p= 0.01) but only four studies were included.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP results found no evidence of an association between wine intake and kidney cancer risk.

Meta-analysis and Pooled studies

In the Pooling project of 12 cohort studies, the RR when comparing 5.0– 14.9 g/d of ethanol from wine with nondrinking was 0.72 (95% CI: 0.59 – 0.87) (Lee et al, 2007b).

In a meta-analysis by Song et al, 2012 including the results of the pooling project published by Lee et al, 2007b and a cohort study (Lew et al, 2011), the RR for the highest versus lowest category of wine intake was 0.81 (95% CI: 0.65-0.97). Lew et al, 2011 study is the same study that was identified in the CUP and no more studies could be included in the meta-analysis.

Table 69 Studies on wine (as ethanol) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lew, 2011	United States	NIH-AARP Diet and Health Study	1348	9	M	0.97	0.77	1.10	>=15 g/d vs. >0 - <5 g/d
			466		F	0.78	0.55	1.12	>=5 g/d vs. >0 - <5 g/d
Allen, 2009b	United Kingdom	The Million Women Study	318	7.2	F	0.87	0.71	1.05	Per 10g/d increase
Wilson, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Cohort	245	15.2	M	0.9	0.5	1.6	>37 g/d vs. 0 g/d
Schouten, 2008	The Netherlands	The Netherlands Cohort Study	291	11.3	M/F	0.64	0.38	1.08	>=15 g/d vs. no alcohol
						0.87	0.73	1.03	Per 10g/d increase

Table 70 Overall evidence on wine (as ethanol) and kidney cancer

	Summary of evidence
2005 SLR	Four cohort studies evaluated the association between wine intake and kidney cancer risk. The dose response estimate of 0.87 (95% CI: 0.32 to 2.34) per glass per day increase was only derived for one study. No study investigated ethanol from wine.
Continuous Update Project	Four cohort studies were identified and included in the final meta-analysis. Overall, four studies were included in the CUP meta-analysis.

Table 71 Summary of results of the dose response meta-analysis of wine (as ethanol) and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	2668
Increment	-	Per 10g/d
Overall RR (95%CI)	-	0.96 (0.91-1.02)
Heterogeneity (I^2,p-value)	-	18.3%, p=0.3

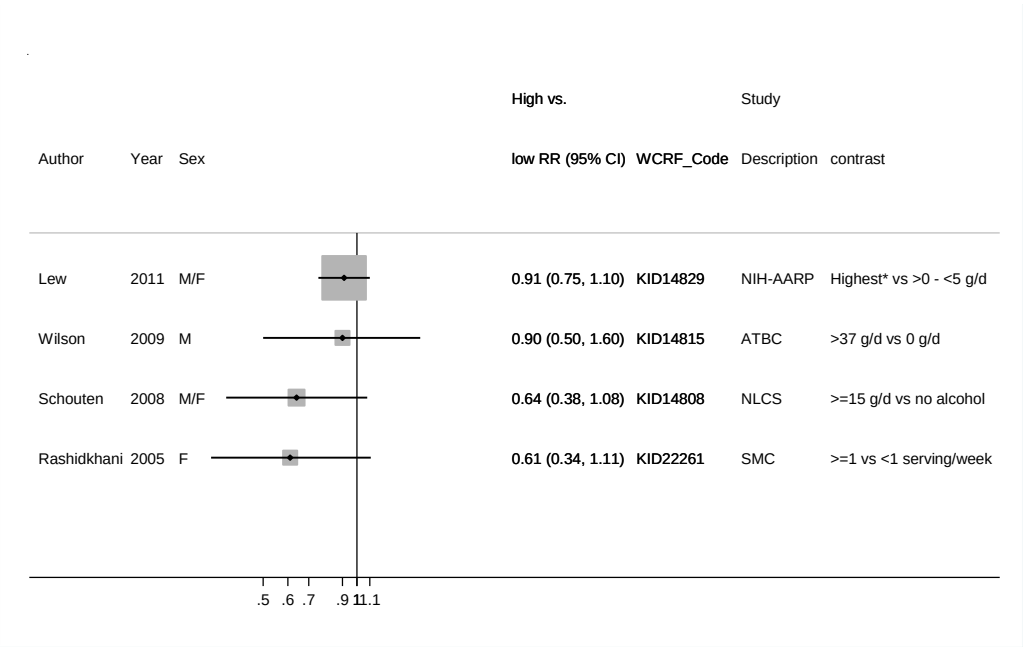
*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 72 Inclusion/exclusion table for meta-analysis of wine (as ethanol) and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14829	Lew	2011	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values Person/years per category RR recalculated using 0 g/d as a new reference category	-
KID14816	Allen*	2009b	Prospective Cohort Study	The Million Women Study	Incidence	No	Yes	No	-	-
KID14815	Wilson	2009	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person/ years per quartile Mid-exposure values	-
KID14808	Schouten	2008	Case Cohort Study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	-
KID22261	Rashidkhani	2005b	Prospective Cohort Study	Swedish Mammography Cohort	Incidence	Yes	No	Yes	-	High vs. low intake
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Red and white wine results reported separately; Users vs. non users
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Results expressed as difference in means, superseded by Wilson et al., 2009
KID14184	Kato	1992	Prospective Cohort Study	USA Hawaii 1965-1968	Incidence	Yes	No	No	-	Mean exposure only

*Women who drank wine exclusively.

Figure 64 Highest versus lowest forest plot of wine (as ethanol) and kidney cancer



*In Lew et al., 2011 study the highest vs. lowest intake was >=5 g/d vs. >0 - <5 g/d among women and >=15 g/d vs. >0 - <5 g/d among men.

Figure 65 Dose-response meta-analysis of wine (as ethanol) and kidney cancer - per 10 g/d

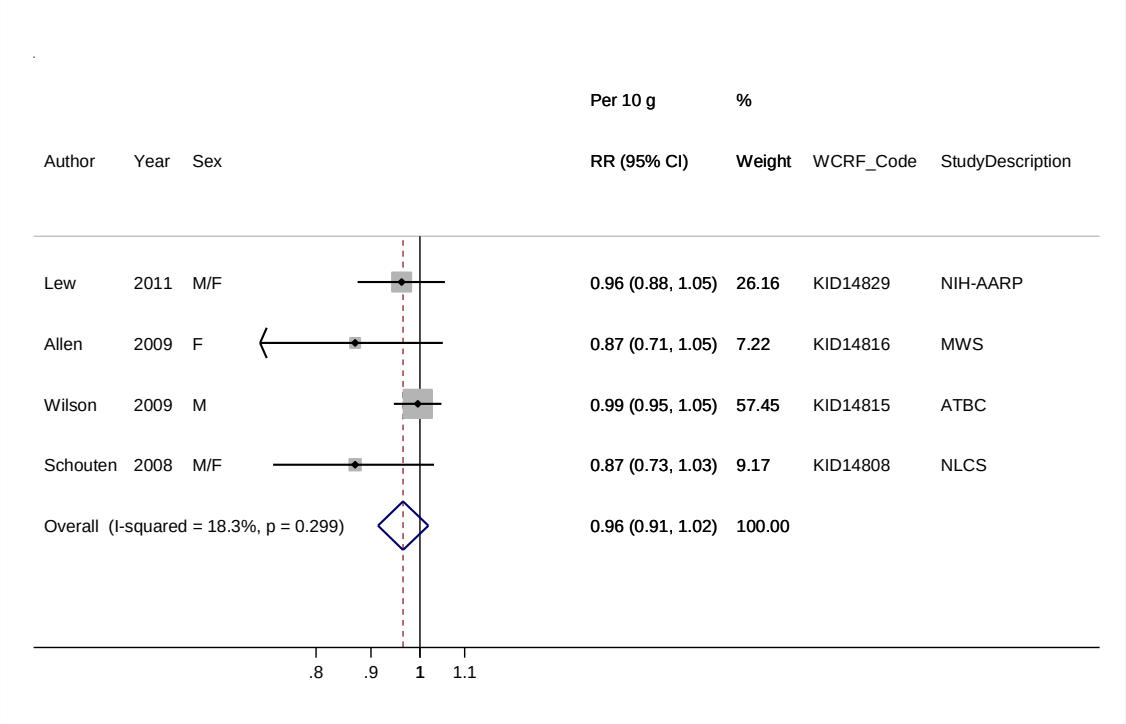
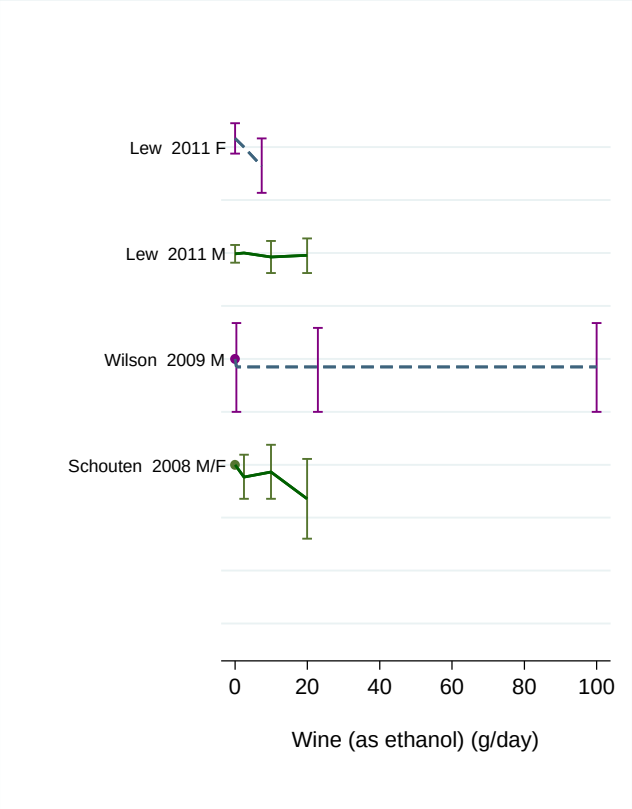


Figure 66 Dose-response graph of wine (as ethanol) and kidney cancer



5.4.1.3 Spirits (as ethanol)

Methods

Up to March 2013, 6 articles from 6 cohort studies were identified; 2 were identified during the CUP. A meta-analysis including 3 studies (2 studies identified during the CUP and 1 study identified during the 2005 SLR) was performed. In Lew et al., 2011 study RR was presented for men and women separately with a reference category of >0-<5 grams of ethanol from liquor per day. The RRs were recalculated with a new reference category of 0 g/d intake and pooled. The dose-response results are presented for an increment of 10 g/d.

Main results

The summary RR per 10 g/d was 0.91 (95% CI: 0.82-1.01; I^2= 58.9%, $P_{heterogeneity}$=0.09) for all studies combined.

Heterogeneity

High heterogeneity was observed (I^2= 58.9%, p=0.09). Egger's test showed no evidence of publication bias (p= 0.45) but only three studies were included.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP results found no evidence of an association between intake of spirits and kidney cancer risk.

Meta-analysis and Pooled studies

In the Pooling project of 12 cohort studies, the RR when comparing 5.0– 14.9 g/d of ethanol from spirits with nondrinking was 0.88 (95% CI: 0.75 - 1.03) (Lee et al, 2007b).

In a meta-analysis by Song et al, 2012 including the results of the pooling project published by Lee et al, 2007b and another cohort study (Lew et al, 2011), the RR for the highest versus lowest category of spirits intake was 0.87 (95% CI: 0.77-0.97). Lew et al, 2011 study is the same study that was identified in the CUP and no more studies could be included in the meta-analysis.

Table 73 Studies on spirits (as ethanol) identified in the CUP Studies on spirits (as ethanol) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Lew, 2011	United States	NIH-AARP Diet and Health Study	1348	9	M	0.87	0.73	1.04	>=15 g/d vs. >0 - <5 g/d
			466		F	0.85	0.56	1.29	>=5 g/d vs. >0 - <5 g/d
Schouten, 2008	The Netherlands	The Netherlands Cohort Study	291	11.3	M/F	0.98	0.68	1.43	>=15 g/d vs. no alcohol
						0.98	0.87	1.11	Per 10 g/d increase

Table 74 Overall evidence on spirits (as ethanol) and kidney cancer

	Summary of evidence
2005 SLR	Four cohort studies evaluated the association between spirits intake and kidney cancer risk. One study reported a significant RR of 0.775 (95% CI: 0.645 to 0.932) per unit serving per day increase.
Continuous Update Project	Two cohort studies were identified and included in the final meta-analysis. Overall, three studies were included in the CUP meta-analysis.

Table 75 Summary of results of the dose response meta-analysis of spirits (as ethanol) and kidney cancer

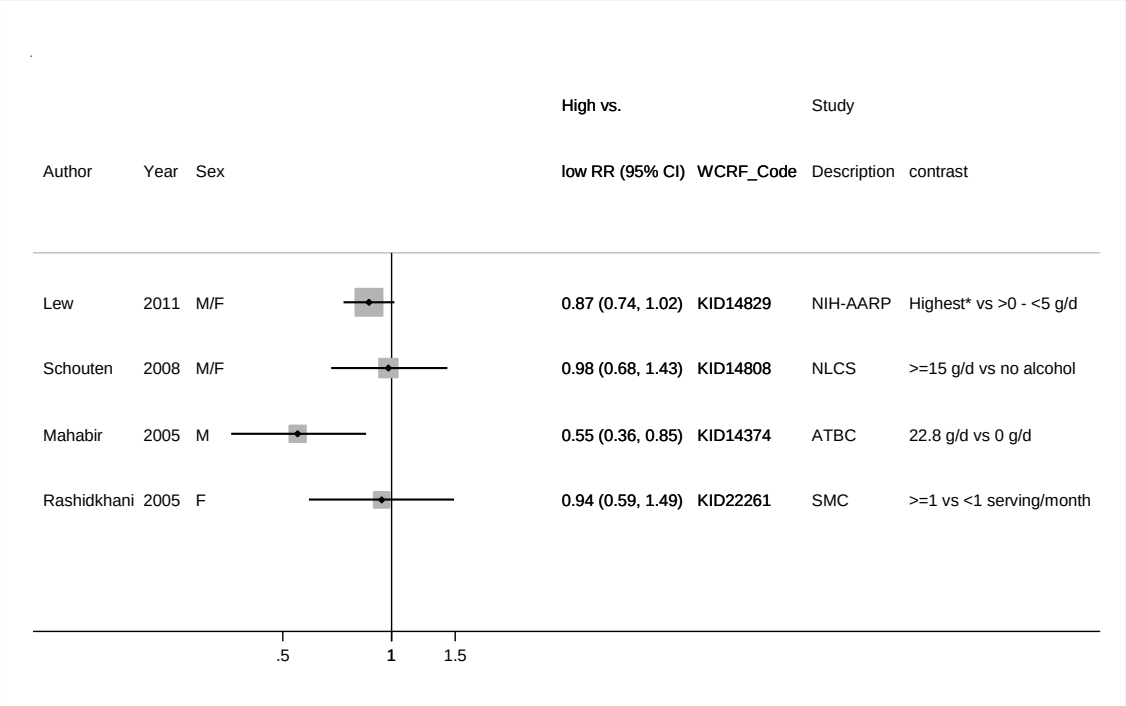
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2300
Increment	-	Per 10g/d
Overall RR (95%CI)	-	0.91 (0.82-1.01)
Heterogeneity (I^2,p-value)	-	58.9%, p=0.09

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 76 Inclusion/exclusion table for meta-analysis spirits (as ethanol) and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14829	Lew	2011	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values Person/years per category RR recalculated using 0 g/d as a new reference category	-
KID14808	Schouten	2008	Case Cohort Study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	-
KID14374	Mahabir	2005	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	-	-
KID22261	Rashidkhani	2005b	Prospective Cohort Study	Swedish Mammography Study	Incidence	Yes	No	Yes	-	High vs. low intake only
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Users vs. non users
KID14184	Kato	1992	Prospective Cohort Study	USA Hawaii 1965-1968	Incidence	Yes	No	No	-	Mean exposure only

Figure 67 Highest versus lowest forest plot of spirits (as ethanol) and kidney cancer



*In Lew et al., 2011 study the highest vs. lowest intake was >=5 g/d vs. >0 - <5 g/d among women and >=15 g/d vs. >0 - <5 g/d among men.

Figure 68 Dose-response meta-analysis of spirits (as ethanol) and kidney cancer - per 10 g/d

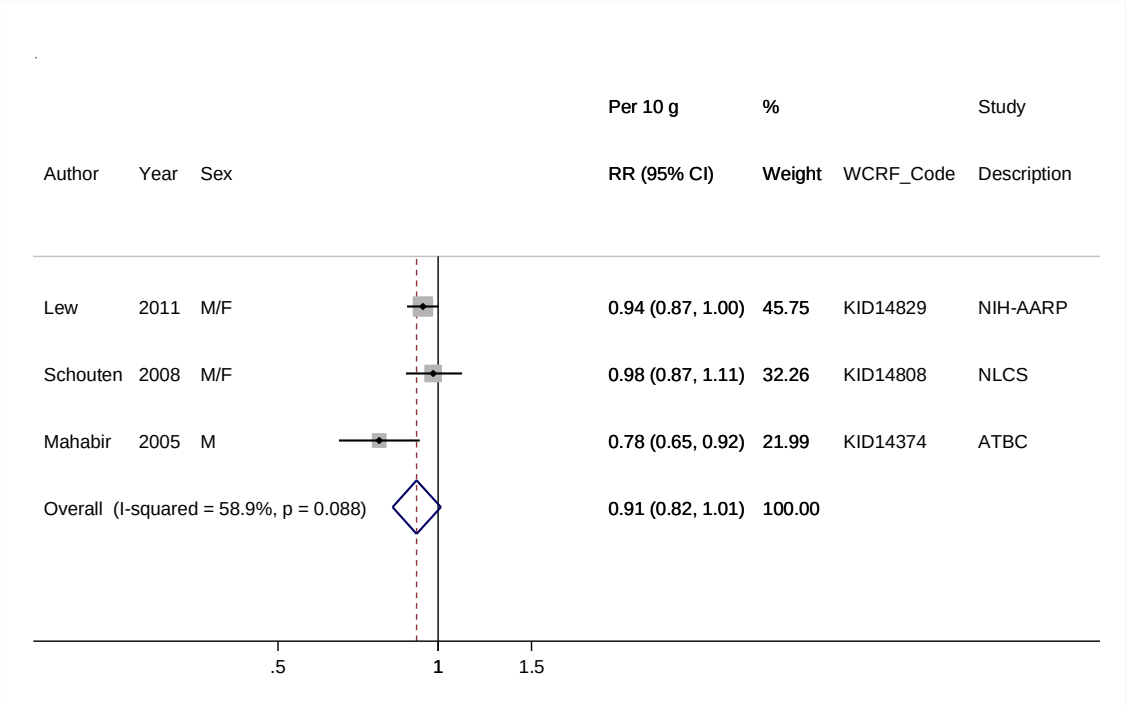
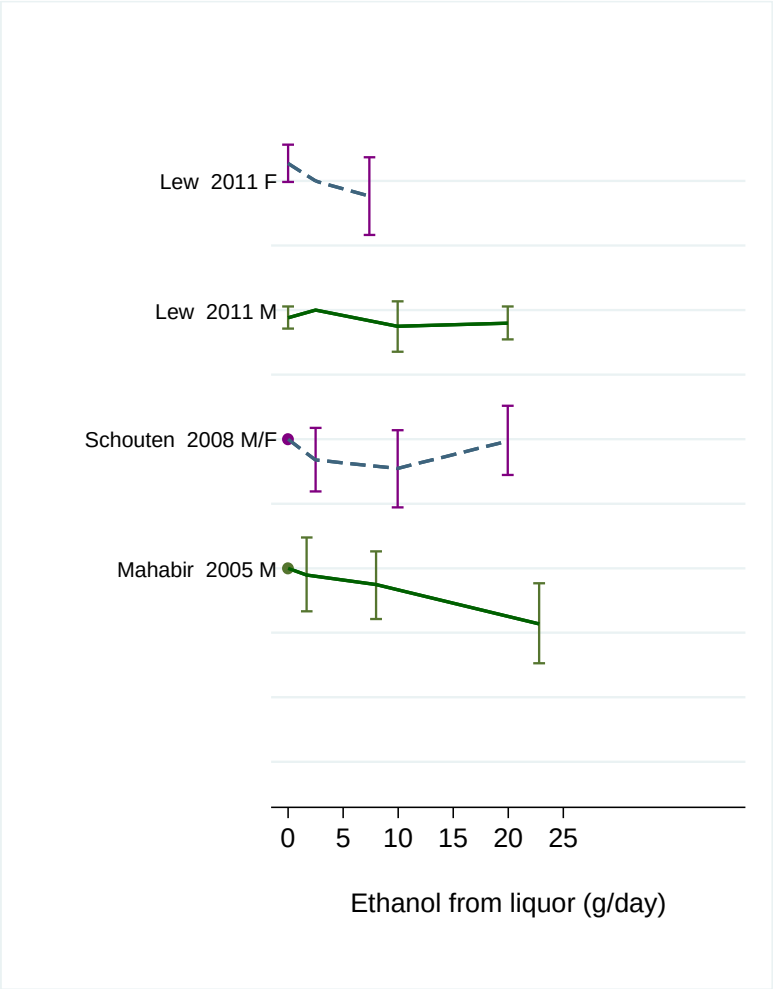


Figure 69 Dose-response graph of spirits/liquor (as ethanol) and kidney cancer



5.5.1.2.1 Dietary alpha-carotene

Methods

A total of 3 articles (4 cohort studies) have been published on dietary alpha-carotene and kidney cancer risk up to 31 March 2013, all of them were identified in the CUP. The dose-response results are presented for an increment of 600 μg per day. Overall, four studies from 3 articles were included in dose-response meta-analysis.

The Pooling project was published in the period. All studies included in the CUP were included in the Pooling Project.

Main results

The summary RR for 600 μg/d increase was 0.95 (95% CI: 0.86-1.06, I^2=35.7%, $P_{heterogeneity}$=0.2) for all studies combined. In influence analysis the results were similar when the studies were excluded in turn.

Heterogeneity

Low heterogeneity was observed (I^2=35.7%, $p_{heterogeneity}$=0.2). Egger's test suggested no evidence of publication bias (P=0.84).

Comparison with the Second Expert Report

No prospective cohort study on dietary alpha-carotene intake and kidney cancer was identified during the SLR.

Meta-analysis and Pooled studies

In the Pooling Project of Cohort Studies (13 studies, 1,478 incident renal cell cancer cases), the relative risk estimates of renal cell carcinoma for comparing the highest vs. lowest quintiles of dietary alpha-carotene was 0.87 (95% CI: 0.73-1.03, p trend =0.30) (Lee et al, 2009). The summary RR for an increment of 660 μg/d was 0.93 (95% CI: 0.88-0.99) for all studies combined.

The RR for 660 μg /day increment of alpha-carotene were 0.89 (0.79- 1.00) for never smokers, 0.94 (0.81-1.10) for past smokers, and 1.06 (0.94-1.21) for current smokers (P for interaction = 0.02). The association was not modified by BMI, history of hypertension, alcohol intake, age at diagnosis and multivitamin use.

Table 77 Studies on dietary alpha-carotene identified in the CUP

Author,year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	1.20	0.83	1.75	1435 vs. 124 µg/d
Lee, 2009	International	Pooling Project of Cohort Studies	1478	7-20	0.87	0.73	1.03	Q5 vs Q1
					0.93	0.88	0.99	Per 660 µg/d increase
VanDijk, 2008	Netherlands	Netherlands Cohort Study on Diet and Cancer	284	11.3	0.90 0.99	0.62 0.97	1.31 1.01	1.31 vs. 0.19 mg/d (men) 1.32 vs. 0.18 mg/d (women) Per 0.1 mg/d increase
Lee, 2006	USA	Both cohorts combined	248		0.71	0.42	1.19	1668 vs. 351 µg/d (men) 1327 vs. 254 µg/d (women)
		The Nurses' Health Study	132	19.2	0.90	0.54	1.49	1327 vs. 254 µg/d
		Health Professionals Follow-Up Study	116	12.7	0.53	0.29	0.98	1668 vs. 351 µg/d

Table 78 Overall evidence on dietary alpha-carotene and kidney cancer

	Summary of evidence
2005 SLR	No prospective cohort study was identified.
Continuous Update Project	Four prospective cohort studies were identified during the CUP. The Health Professionals Follow-Up Study reported a significant inverse association in men only. Four cohort studies were included in the meta-analysis. No association was observed.

Table 79 Summary of results of the dose-response meta-analysis of dietary alpha-carotene and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
Increment	-	Per 600 µg/d
RR (95% CI)	-	0.95 (0.86-1.06)

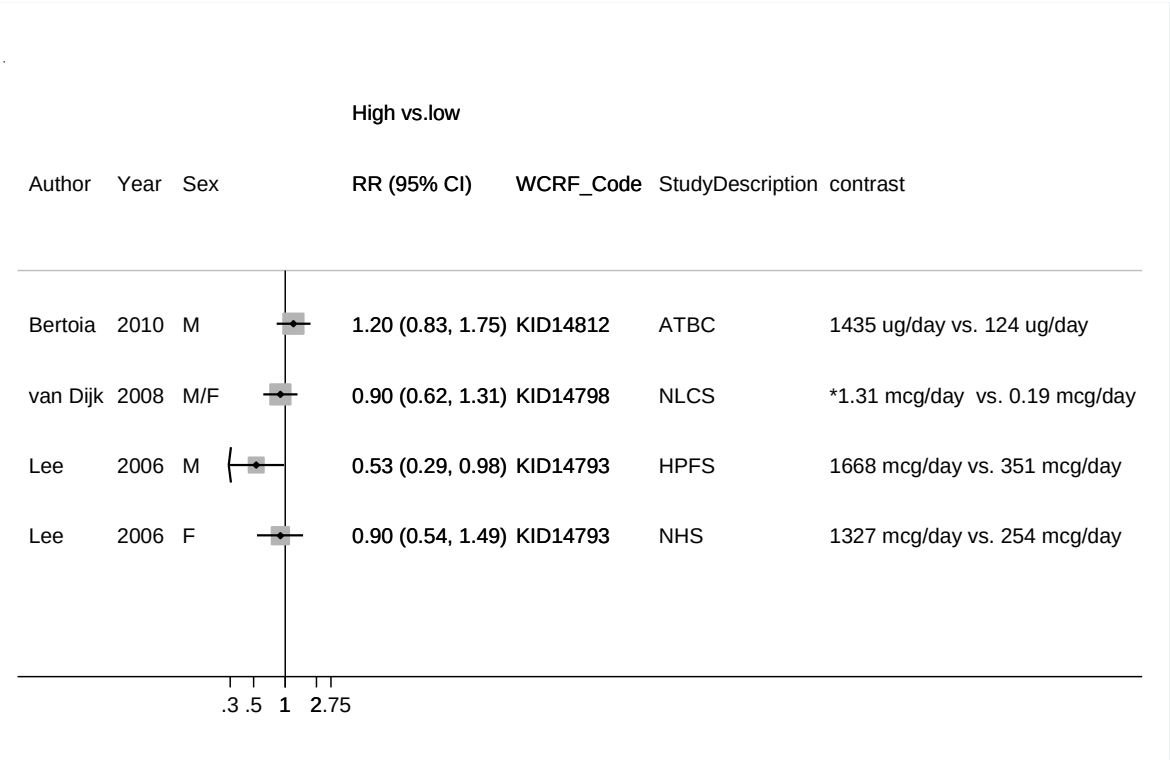
Heterogeneity (I^2, p-value)	-	I^2=35.7%, $p_{heterogeneity}$=0.2
		Pooling Project
Studies (n)	-	13
Cases (n)	-	1478
Increment	-	Per 660 μg/d
RR (95% CI)	-	0.93 (0.88-0.99)
Heterogeneity (I2, p-value)	-	Pheterogeneity=0.2

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 80 Inclusion/exclusion table for meta-analysis of dietary alpha-carotene and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile mg/d rescaled to µg/ day	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-

Figure 70 Highest versus lowest forest plot of dietary alpha-carotene and kidney cancer



*Highest vs. lowest quintiles were 1.31 mg/d vs. 0.19 mcg/d in men and 1.32 mg/d vs. 0.18 mg/d in women (van Dijk et al, 2008).

Figure 71 Dose-response meta-analysis of dietary alpha-carotene and kidney cancer, per 600 µg/d

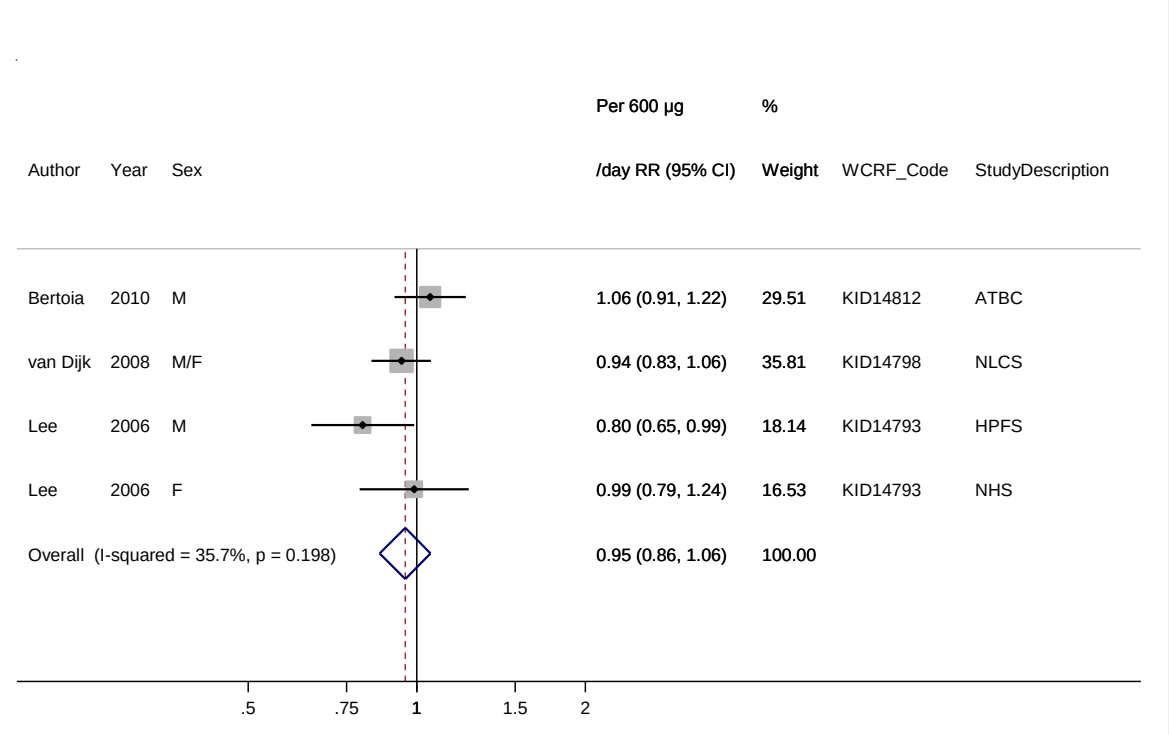
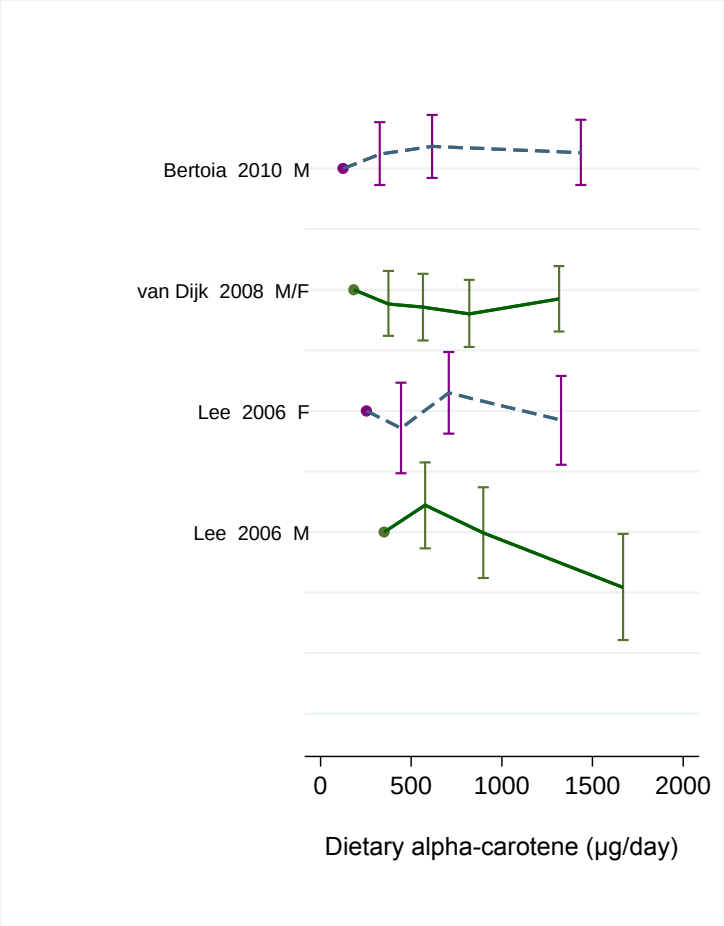


Figure 72 Dose-response graph of dietary alpha-carotene and kidney cancer



5.5.1.2.2 Dietary beta-carotene

Only one study was identified in the CUP (Van Dijk et al, 2008).
The Pooling Project of Cohort Studies investigated the link between dietary beta-carotene and the risk of kidney cancer (Lee et al, 2009). The RR comparing Q5 vs. Q1 was 0.82 (95% CI: 0.69-0.98, P_{trend} = 0.01, $P_{heterogeneity}$ = 0.73). The association remained significant when intake was modelled as a continuous value. The RR per 100 µg/d increment of intake was 0.91 (95% CI: 0.85-0.97). The Pooling Project of Cohort Studies included the only study identified in the CUP (van Dijk et al, 2008).

5.5.1.2.3 Dietary beta-cryptoxanthin

Methods

A total of three articles (four cohort studies) have been published on dietary beta-cryptoxanthin and renal cell cancer risk up to 31 March 2013, all of which were identified in the CUP. The dose-response results are presented for an increment of 100 μg per day. Overall, four studies from 3 articles were included in dose-response meta-analysis.

All the studies identified in the CUP were included in the Pooling project (Lee et al, 2009).

Main results

The summary RR per 100 μg/d was 0.93 (95% CI: 0.74-1.15, I^2=66.8%, $p_{heterogeneity}$=0.03) for all studies combined.

In influence analysis the results were similar after excluding one study in turn.

Heterogeneity

There was evidence of significant heterogeneity (I^2=66.8%, $p_{heterogeneity}$=0.03). There was no evidence of publication bias with Egger's test (p=0.27).

Comparison with the Second Expert Report

No prospective cohort study on dietary beta-cryptoxanthin intake and kidney cancer was identified during the SLR.

Meta-analysis and Pooled studies

In a pooled analysis of 13 prospective cohort studies (1,478 incident renal cell cancer cases), the relative risk estimates of renal cell carcinoma for comparing the highest vs. lowest quintile of dietary beta-cryptoxanthin was 0.86 (95% CI:0.73-1.01; p trend =0.18) (Lee et al., 2009). The summary RR for an increment of 100 μg/d was 0.99 (95% CI: 0.96-1.02).

The association was not modified by BMI, history of hypertension, smoking habits, alcohol intake, age at diagnosis and multivitamin use.

All the studies identified in the CUP were included in the Pooling project (Lee et al, 2009).

Table 81 Studies on dietary beta-cryptoxanthin identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.90	0.63	1.28	83 vs. 2.8 µg/d
Lee, 2009	International	Pooling Project of Cohort Studies	1478	7-20	M/F	0.86	0.73	1.01	Q5 vs Q1
						0.99	0.96	1.02	Per 100 µg/d increase
VanDijk, 2008	Netherlands	The Netherlands Cohort Study	284	11.3	All	1.17 1.03	0.78 1.00	1.74 1.06	0.36 vs. 0.01 mg/d in men, 0.50 vs. 0.03 mg/d in women Per 0.05 mg/d increase
Lee, 2006	USA	Both cohorts combined	248	17	All	0.70	0.34	1.47	179 vs. 21 µg/d
		The Nurses' Health Study	132	19.2	F	1.2	0.61	1.69	152 vs. 24 µg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.48	0.27	0.84	179 vs. 21 µg/d

Table 82 Overall evidence on dietary beta-cryptoxanthin and kidney cancer

	Summary of evidence
2005 SLR	No prospective cohort study was identified.
Continuous Update Project	Four prospective cohort studies were identified during the CUP. Only the Health Professionals Follow-Up Study reported a significant inverse association (men). Overall, four cohort studies included in the meta-analysis.

Table 83 Summary of results of the dose-response meta-analysis of dietary beta-cryptoxanthin and kidney cancer

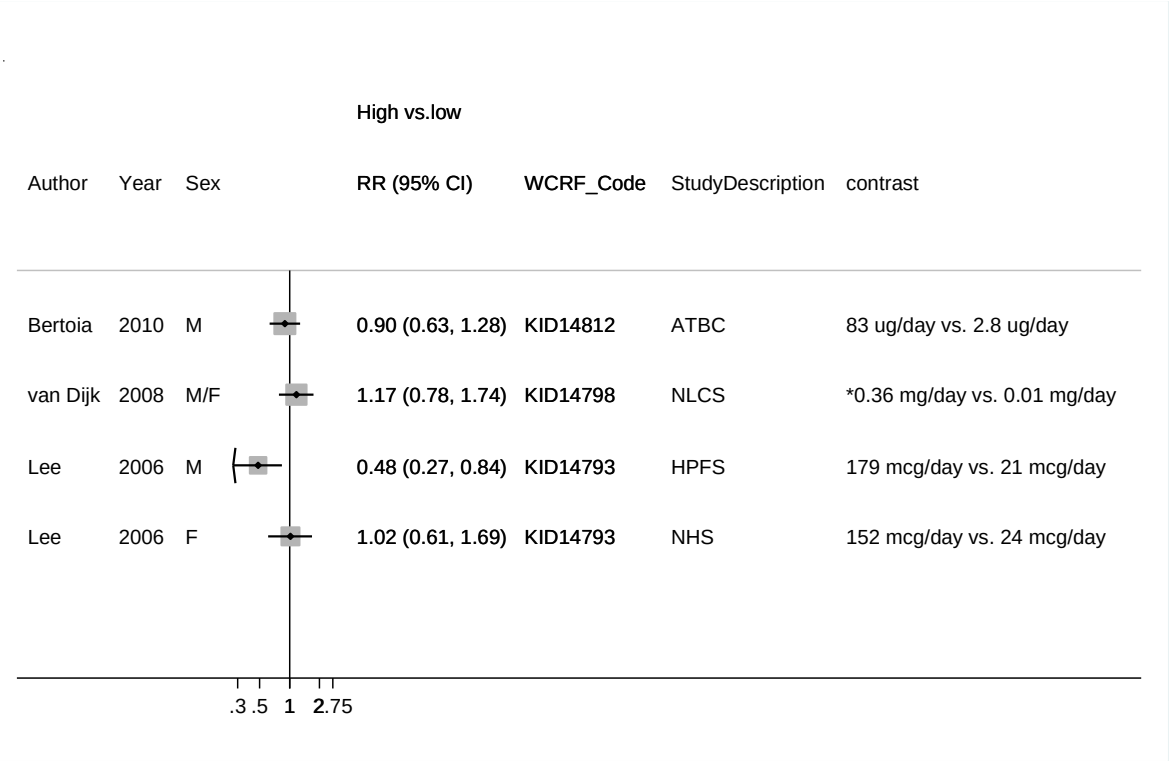
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
RR (95% CI)	-	0.93 (0.74-1.15)
Increment	-	Per 100 μg/d
Heterogeneity (I^2, p-value)	-	I^2=66.8%, p=0.03
		Pooling Project
Studies (n)	-	13
Cases (n)	-	1478
RR (95% CI)	-	0.99 (0.96-1.02)
Increment	-	Per 100 μg/d

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 84 Inclusion/exclusion table for meta-analysis of dietary beta-cryptoxanthin and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile Mg/d rescaled to µg/ day	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-

Figure 73 Highest versus lowest forest plot of dietary beta-cryptoxanthin and kidney cancer



*Dietary beta-cryptoxanthinin intake in the highest vs. lowest quintiles was 0.36 mg/d vs. 0.01 mg/d in men and 0.50 mg/d vs. 0.03 mg/d in women (van Dijk et al., 2008).

Figure 74 Dose-response meta-analysis of dietary beta-cryptoxanthin and kidney cancer, per 100 µg/d

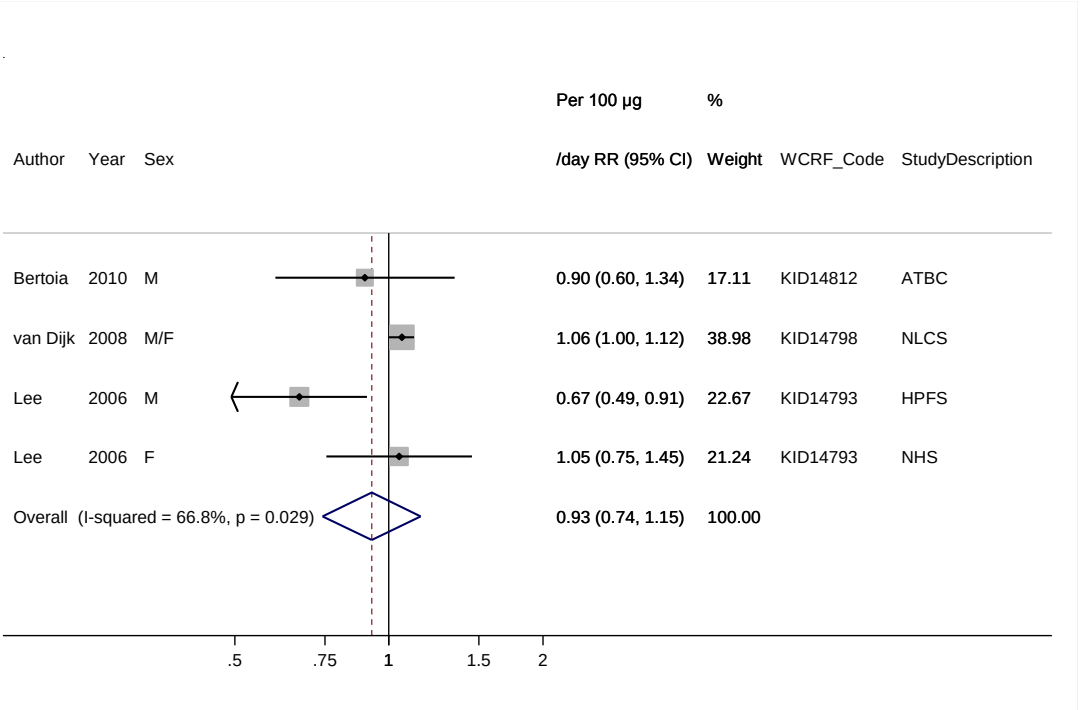
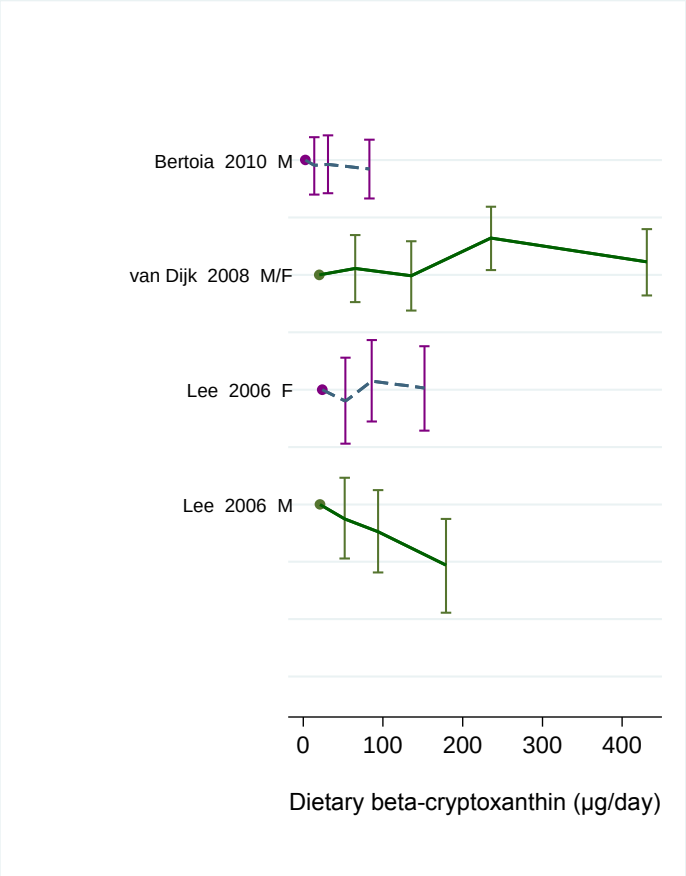


Figure 75 Dose-response graph of dietary beta-cryptoxanthin and kidney cancer



5.5.2.1 Dietary lutein and zeaxanthin

Methods

A total of 3 articles (4 cohort studies) have been published on dietary lutein and zeaxanthin and kidney cancer risk up to 31 March 2013, all of them were identified in the CUP. The dose-response results are presented for an increment of 1000 μg per day. Overall, four studies from 3 articles were included in dose-response meta-analysis.

All the studies identified in the CUP are included in the Pooling Project.

Main results

The summary RR per 1000 μg/d was 0.99 (95% CI: 0.92-1.07, I^2=52.7%, $p_{heterogeneity}$=0.1) for all studies combined. In influence analysis the RR ranged from 0.96 (95% CI: 0.85-1.05) excluding the Nurses' Health Study (Lee et al., 2006) to 0.98 (95% CI: 0.88-1.09) when excluding the Netherlands Cohort Study (Van Dijk et al., 2008).

Heterogeneity

Moderate heterogeneity was observed (I^2=52.7%, $p_{heterogeneity}$=0.1). Egger's test suggested no evidence of publication bias (P=0.59).

Comparison with the Second Expert Report

No prospective cohort study on dietary lutein and zeaxanthin intake and kidney cancer was identified during the SLR.

Meta-analysis and Pooled studies

In a pooled analysis of 13 prospective cohort studies (1,478 incident renal cell cancer cases), the relative risk estimates of renal cell carcinoma for comparing the highest vs. lowest quintiles of dietary lutein and zeaxanthin was 0.82 (95% CI: 0.64-1.06; p trend =0.04) (Lee et al., 2009). The summary RR for an increment of 2700 μg/d was 0.91(95% CI: 0.85-0.97) for all studies combined.

The association was not modified by BMI, history of hypertension, smoking habits, alcohol intake, age at diagnosis and multivitamin use.

All the studies identified in the CUP are included in the Pooling Project.

Table 85 Studies on dietary lutein and zeaxanthin identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.97	0.62	1.53	2133 vs. 867 µg/d
Lee, 2009	International	Pooling Project of Cohort Studies	1478	7-20	M/F	0.82	0.64	1.06	Q5 vs Q1
						0.91	0.85	0.97	Per 2,700 µg/d increase
VanDijk, 2008	Netherlands	The Netherlands Cohort Study	284	11.3	M/F	0.90 1.01	0.62 0.91	1.29 1.12	3.89 vs. 1.42 mg/d in men & 3.77 vs. 1.30 mg/d in women Per 1mg/d increase
Lee, 2006	USA	Both cohorts combined	248	17	M/F	0.80	0.28	2.30	6044 vs. 1523 µg/d in men & 7248 vs. 1552 µg/d in women
		The Nurses' Health Study	132	19.2	F	1.36	0.81	2.29	7248 vs. 1552 µg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.46	0.26	0.82	6044 vs. 1523 µg/d

Table 86 Overall evidence on dietary lutein and zeaxanthin and kidney cancer

	Summary of evidence
2005 SLR	No prospective cohort study was identified.
Continuous Update Project	Four prospective cohort studies were identified during the CUP. The Health Professionals Follow-Up Study reported a significant inverse association (men). Overall, four cohort studies included in the meta-analysis and showed no association.

Table 87 Summary of results of the dose-response meta-analysis of dietary lutein and zeaxanthin and kidney cancer

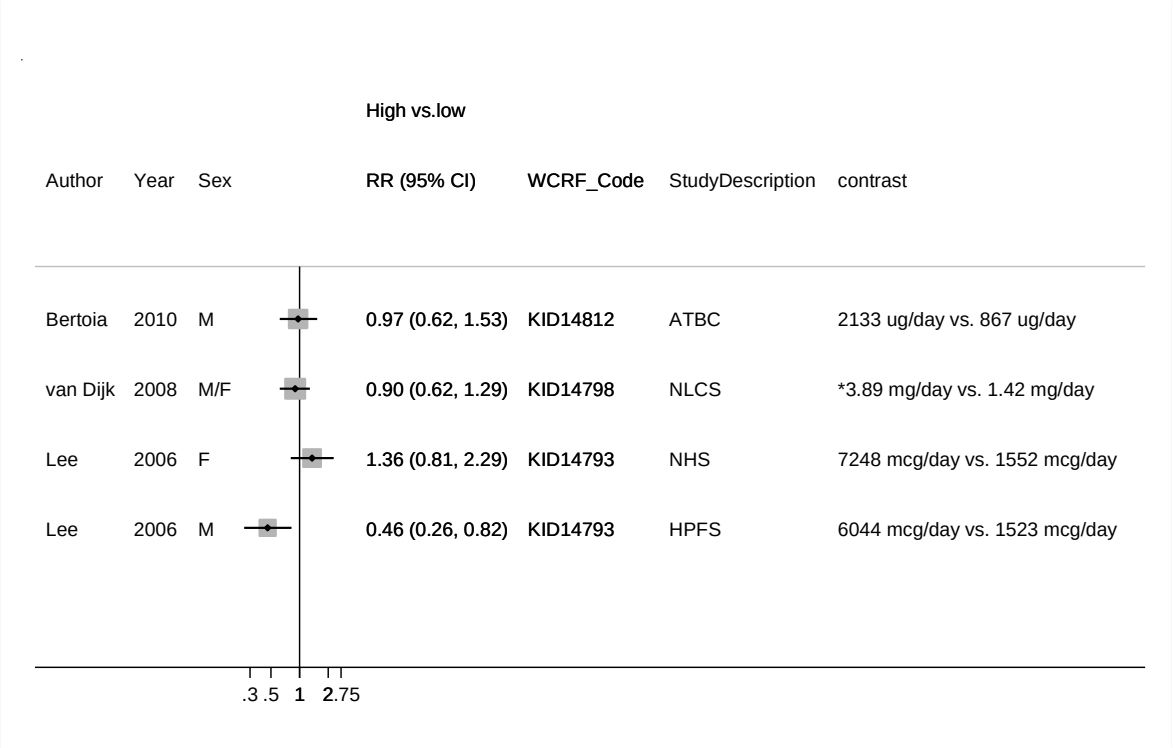
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
RR (95% CI)	-	0.99 (0.92-1.07)
Increment	-	Per 1000 μg/d
Heterogeneity (I^2, p-value)	-	I^2=52.7%, $p_{heterogeneity}$=0.1
		Pooling Project
Studies (n)	-	13
Cases (n)	-	1478
RR (95% CI)	-	0.91 (0.85-0.97)
Increment	-	Per 2700 μg/d

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 88 Inclusion/exclusion table for meta-analysis of dietary lutein and zeaxanthin and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile Mg/d rescaled to µg/ day	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-

Figure 76 Highest versus lowest forest plot of dietary lutein and zeaxanthin and kidney cancer



*Dietary lutein and zeaxanthin intake in the highest vs. lowest quintiles was 3.89 mg/d vs. 1.42 mg/d in men and 3.77 mg/d vs. 1.30 mg/d in women (van Dijk et al., 2008).

Figure 77 Dose-response meta-analysis of dietary lutein and zeaxanthin and kidney cancer, per 1000 µg/d

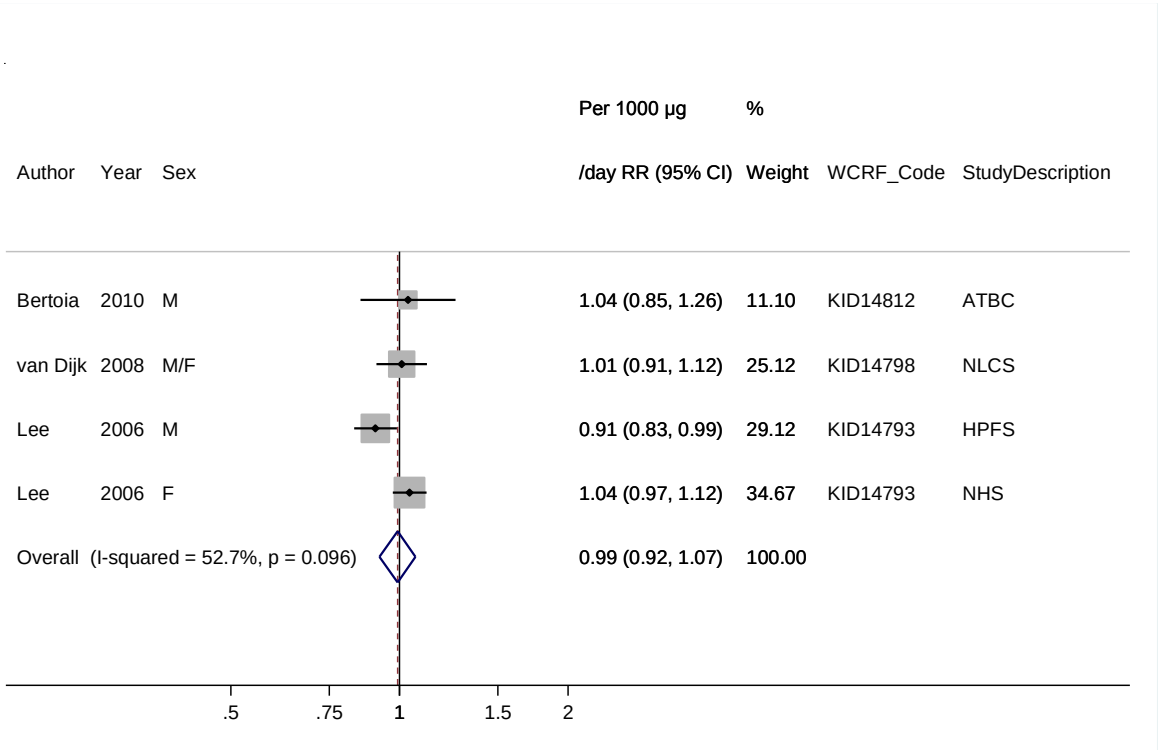
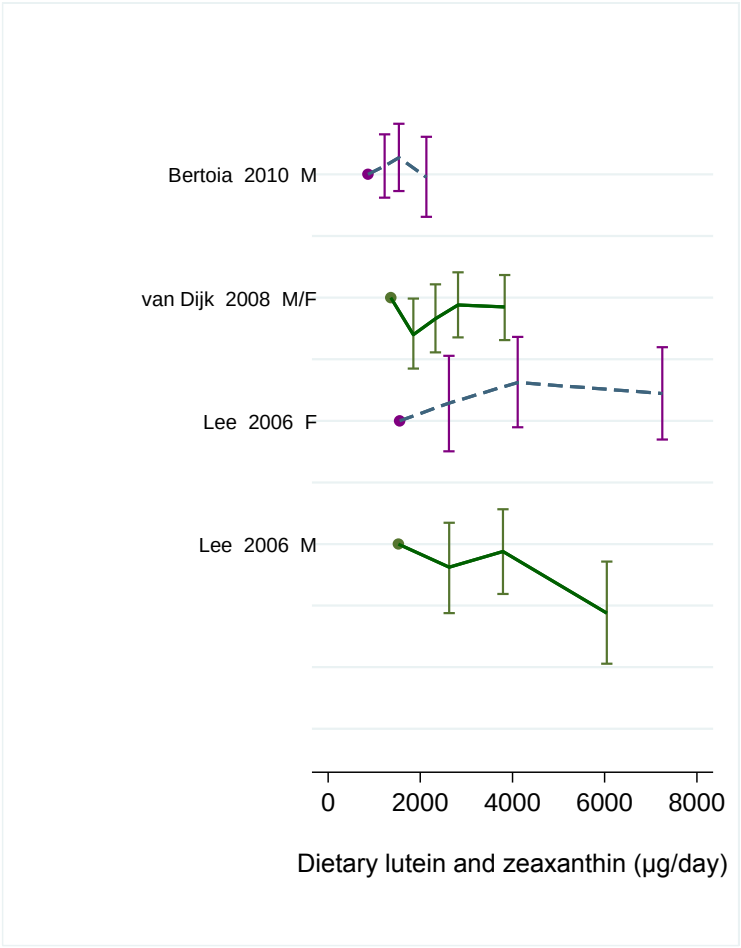


Figure 78 Dose-response graph of dietary lutein and zeaxanthin and kidney cancer



5.5.2.2 Dietary lycopene

Methods

A total of 3 articles (4 cohort studies) have been published on dietary lycopene and kidney cancer risk up to 31 March 2013, all of them were identified in the CUP. The dose-response results are presented for an increment of 4000 μg per day. Overall, four studies from 3 articles were included in dose-response meta-analysis.

All the cohort studies identified in the CUP were included in the Pooling project.

Main results

The summary RR per 4000 μg/d was 0.94 (95% CI: 0.85-1.04, I^2=0%, $p_{heterogeneity}$=0.50) for all studies combined. In influence analysis the RR ranged from 0.94 (95% CI: 0.83-1.06) when excluding the Netherlands Cohort Study (Van Dijk et al., 2008) to 0.97 (95% CI: 0.75-1.25) when excluding the Nurses' Health Study (Lee et al., 2006).

Heterogeneity

No heterogeneity was observed (I^2=0%, $p_{heterogeneity}$=0.50). Egger's test suggested no evidence of publication bias (P=0.06).

Comparison with the Second Expert Report

No prospective cohort study on dietary lycopene intake and kidney cancer was identified during the SLR.

Meta-analysis and Pooled studies

In a pooled analysis of 13 prospective cohort studies (1478 incident renal cell cancer cases), the relative risk estimates of renal cell carcinoma for comparing the highest vs. lowest quintiles of dietary lycopene was 1.13 (95% CI: 0.95–1.34; p trend =0.40) (Lee et al., 2009). The summary RR for an increment of 5400 μg/d was 1.03 (95% CI: 0.98–1.09) for all studies combined.

The association was not modified by BMI, history of hypertension, smoking habits, alcohol intake, age at diagnosis and multivitamin use.

All the cohort studies identified in the CUP were included in the Pooling project.

Table 89 Studies on dietary lycopene identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	1.30	0.89	1.88	1743 vs. 147 µg/d
Lee, 2009	International	Pooling Project of Cohort Studies	1478	7-20	M/F	1.13	0.95	1.34	Q5 vs Q1
						1.03	0.98	1.09	Per 5400 µg/d increase
VanDijk, 2008	Netherlands	Netherlands Cohort Study on Diet and Cancer	284	11.3	M/F	1.17 1.01	0.79 0.88	1.72 1.17	1.98 vs. 0.14 mg/d in men & 2.33 vs. 0.17 mg/d in women Per 0.5 mg/d
Lee, 2006	USA	Both cohorts combined	248	17	M/F	0.79	0.54	1.16	16180 vs. 4192 µg/d in men & 12296 vs. 3668 µg/d in women
		The Nurses' Health Study	132	19.2	F	0.90	0.51	1.57	12296 vs. 3668 µg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.71	0.42	1.20	16180 vs. 4192 µg/d

Table 90 Overall evidence on dietary lycopene and kidney cancer

	Summary of evidence
2005 SLR	No prospective cohort study was identified.
Continuous Update Project	Four prospective cohort studies were identified during the CUP. All studies were included in the meta-analysis that showed no association.

Table 91 Summary of results of the dose-response meta-analysis of dietary lycopene and kidney cancer

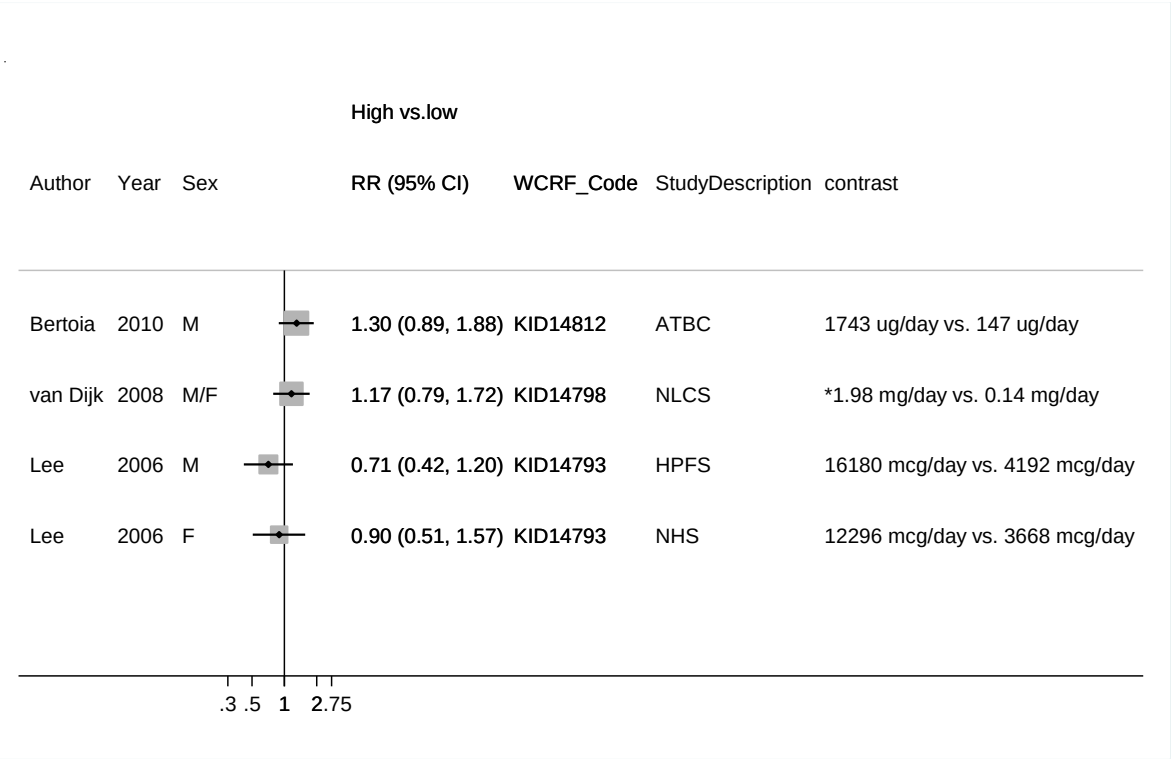
Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
RR (95% CI)	-	0.94 (0.85-1.04)
Increment	-	Per 4000 µg/d
Heterogeneity (I^2, p-value)	-	I^2=0%, $p_{heterogeneity}$=0.50
		Pooling Project
Studies (n)	-	13
Cases (n)	-	1478
RR (95% CI)	-	1.03 (0.98-1.09)
Increment	-	Per 5400 µg/d

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 92 Inclusion/exclusion table for meta-analysis of dietary lycopene and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile Mg/d rescaled to µg/ day	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-

Figure 79 Highest versus lowest forest plot of dietary lycopene and kidney cancer



*Dietary lycopene intake in the highest vs. lowest quintiles was 1.98 mg/d vs. 0.14 mg/d in men and 2.33 mg/d vs. 0.17 mg/d in women (van Dijk et al., 2008).

Figure 80 Dose-response meta-analysis of dietary lycopene and kidney cancer, per 4000µg/d

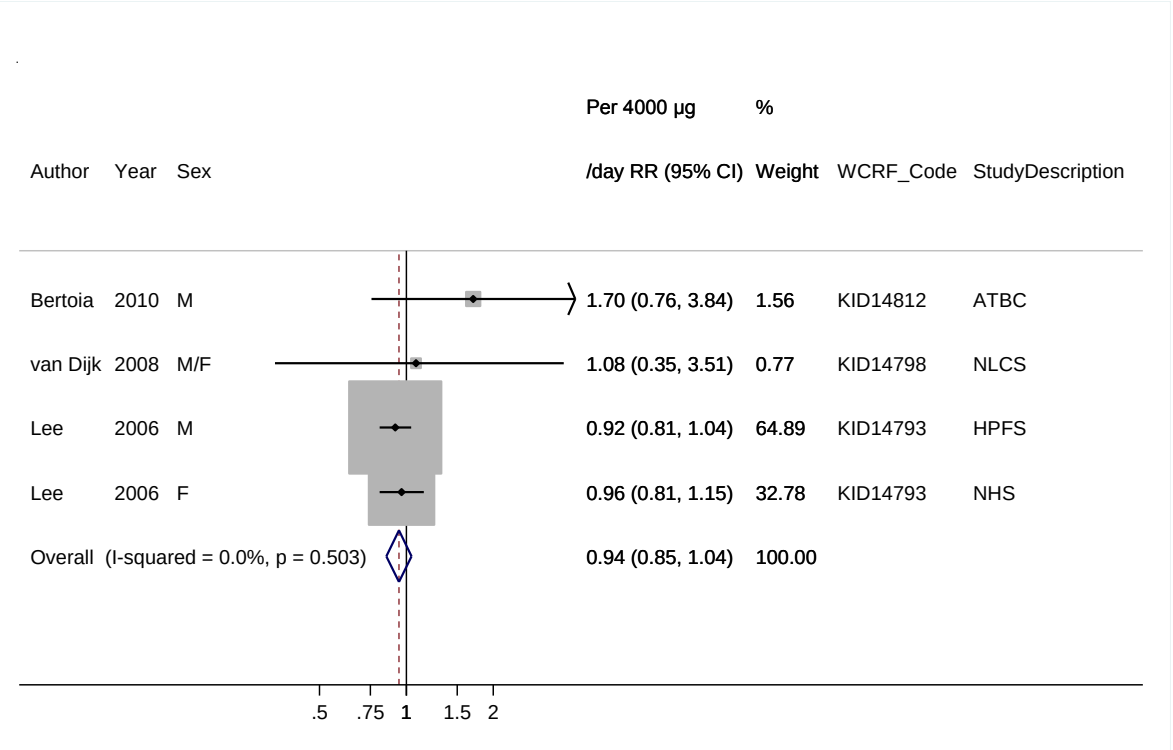
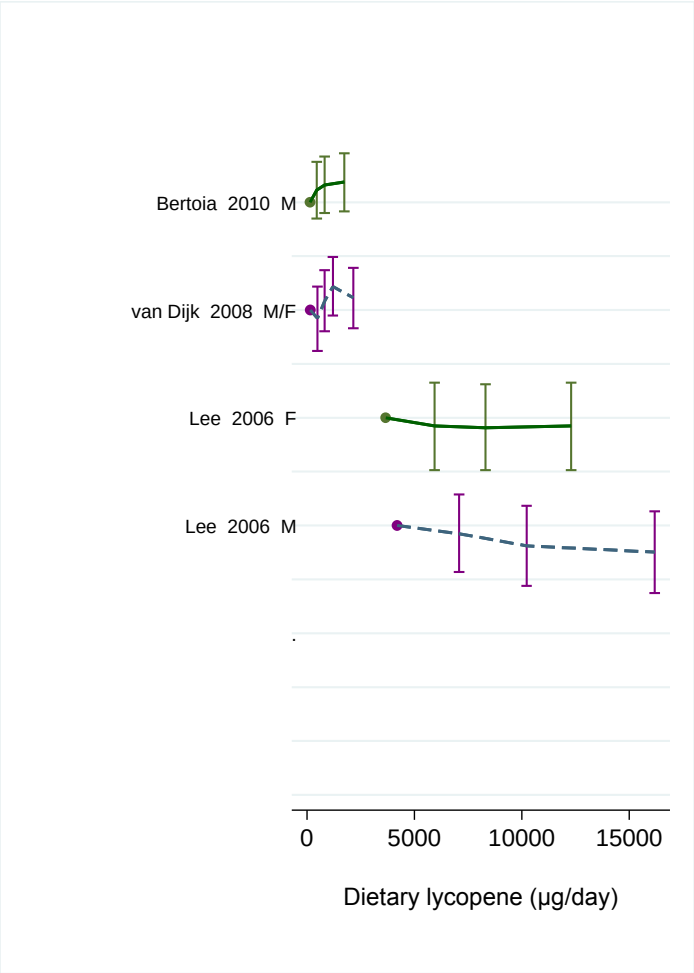


Figure 81 Dose-response graph of dietary lycopene and kidney cancer



5.5.3.2 Dietary folate

Methods

Up to March 2013, 4 articles from 3 cohort studies were identified; 2 new articles (3 cohorts) were identified in the CUP. A meta-analysis including 3 cohorts (all identified during the CUP) was performed. The dose-response results are presented for an increment of 100 µg/d.

Main results

The summary RR per 100 µg/d was 1.02 (95% CI: 0.91-1.15, I^2=0.0%, $p_{heterogeneity}$=0.49). Egger's test showed no evidence of publication bias (p= 0.64) but only three cohorts were included.

Heterogeneity

No heterogeneity was observed, I^2=0.0%, $p_{heterogeneity}$=0.49.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP found no association between dietary folate intake and kidney cancer risk.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 93 Studies on dietary folate and kidney cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Cho, 2013	United States	Health Professionals Follow-Up Study	211	22	M	1.27	0.75	2.15	506.5 µg/d vs. 254.7 µg/d
		The Nurses' Health Study	225	24	F	1.01	0.57	1.77	389.8 µg/d vs. 201.6 µg/d
Van Dijk, 2008	The Netherlands	The Netherlands Cohort study	284	11.3	All	0.99	0.83	1.19	Per 0.1 mg/d increase
						0.95	0.65	1.40	Q5 vs. Q1*

***** The highest vs. lowest median intake of dietary folate in subcohort was 0.31 mg/d vs. 0.15 mg/d among men and 0.27 mg/d vs. 0.13 mg/d among women.

Table 94 Overall evidence on dietary folate and kidney cancer

	Summary of evidence
2005 SLR	One cohort study was identified that only reported a difference in means of 1g per day.
Continuous Update Project	Three cohorts (two articles) were identified. Overall, 3 cohorts were included in the CUP meta-analysis. No association was observed.

Table 95 Summary of results of the dose response meta-analysis of dietary folate and kidney cancer

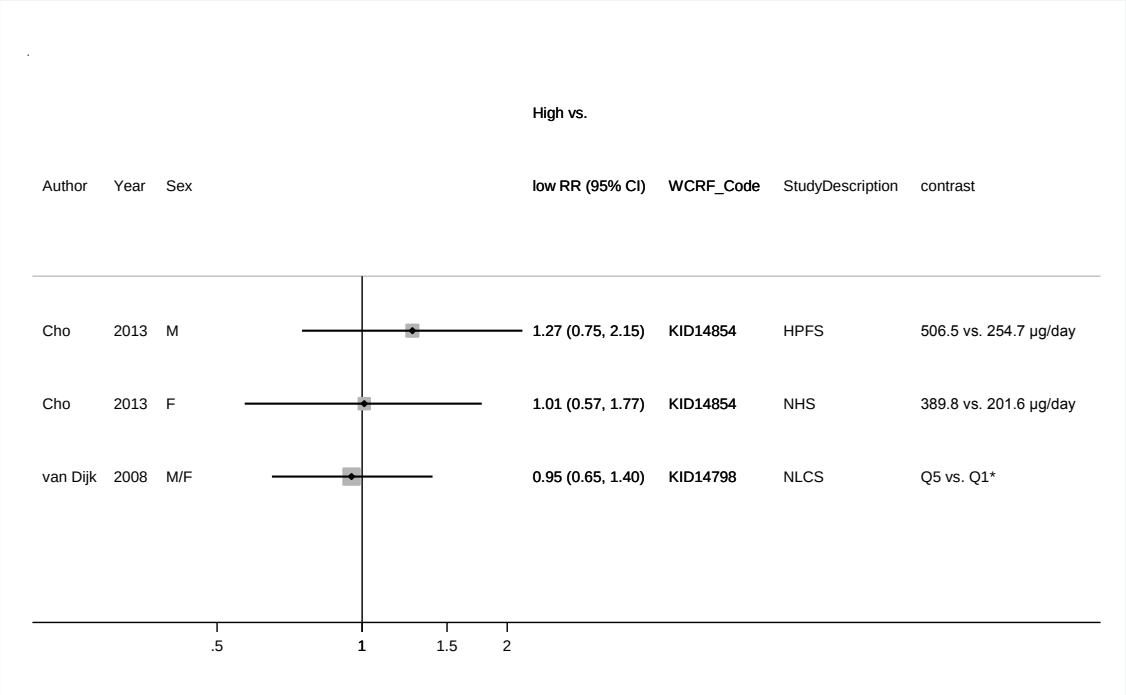
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	720
Increment	-	Per 100 µg/d
Overall RR (95%CI)	-	1.02 (0.91-1.15)
Heterogeneity (I^2,p-value)	-	0%, p=0.49

*No meta-analysis for cohort studies was conducted in the Second Export Report

Table 96 Inclusion/exclusion table for meta-analysis of dietary folate and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14854	Cho	2013	Prospective Cohort Study	The Nurses' Health Study; Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/ years per category	-
KID14798	Van Dijk	2008	Case Cohort Study	The Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Converted mg/d to µg/d Calculated weighted average of intake for individual dose response analysis	-
KID00506	Hirvonen	2001	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Mean values only

Figure 82 Highest versus lowest forest plot of dietary folate and kidney cancer



*In van Dijk et al., 2008 study the highest vs. lowest median intake of dietary folate in subcohort was 0.31 mg/d vs. 0.15 mg/d among men and 0.27 mg/d vs. 0.13 mg/d among women.

Figure 83 Dose-response meta-analysis of dietary folate and kidney cancer - per 100 µg/d

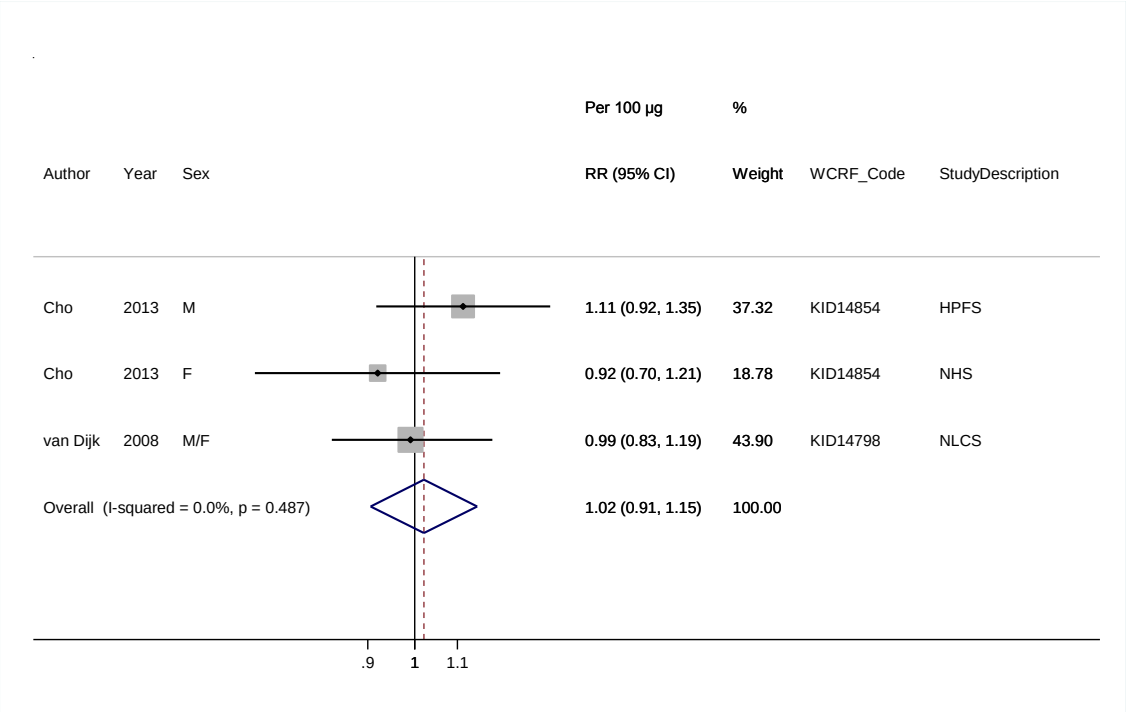
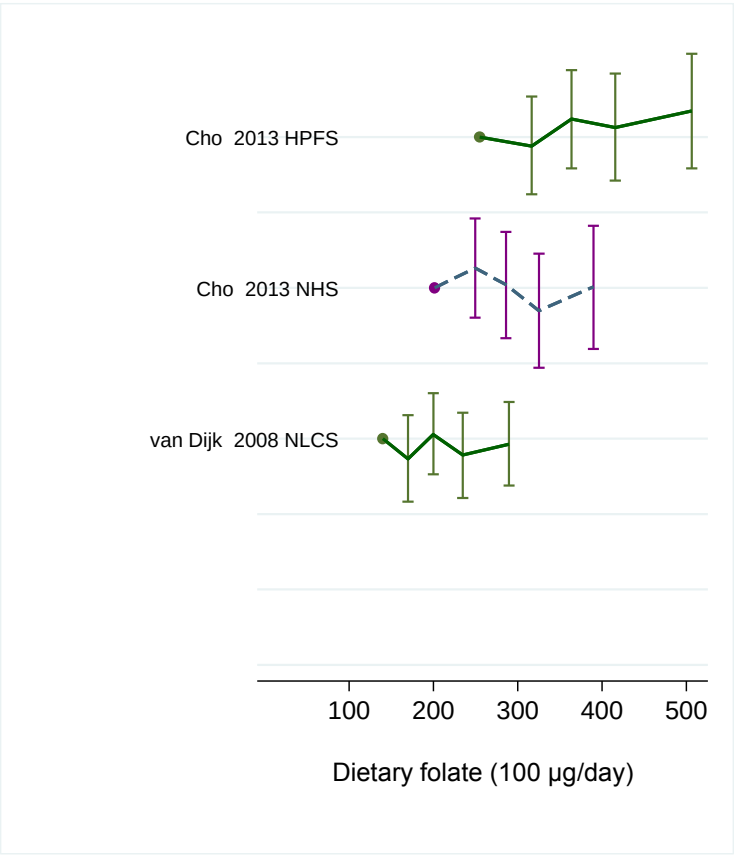


Figure 84 Dose-response graph of dietary folate and kidney cancer



5.5.7 Total Pyridoxine - vitamin B6 (food and supplements)

Methods

A total of 3 articles from 4 cohort studies have been published on total vitamin B6 and kidney cancer risk up to 31 March 2013; one publication (two studies) was identified in the CUP. Dose-response analyses were conducted for an increase of 1 mg per day. Overall, three studies from 2 articles were included in dose-response meta-analysis.

Main results

The summary RR per one mg per day was 1.0 (95% CI: 0.99-1.01, I^2=0% $p_{heterogeneity}$=0.73) for all studies combined.

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, $p_{heterogeneity}$=0.73). Egger test showed no evidence of publication bias (p=0.80).

Comparison with the Second Expert Report

In the systematic review of the Second Expert Report the evidence relating total vitamin B6 (diet and supplement) to cancer risk was limited and no conclusion was possible.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 97 Studies on total vitamin B6 identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Cho, 2013	USA	The Nurses' Health Study	225	24 years	F	0.9	0.59	1.37	19.9 mg/d vs. 1.5 mg/d
		Health Professionals Follow-up Study	211	22 years	M	0.86	0.56	1.33	19.1 mg/d vs. 1.8 mg/d

Table 98 Overall evidence on total vitamin B6 and kidney cancer

	Summary of evidence
2005 SLR	Two articles (one cohort) were identified during the SLR.
Continuous Update Project	One publication (two cohort studies) on total vitamin B6 intake and kidney cancer was identified. Overall, three cohort studies from 2 articles were included in the meta-analysis. No association was observed.

Table 99 Summary of results of the dose-response meta-analysis of total vitamin B6 and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	498
RR (95% CI)	-	1.0 (0.99-1.01)
Increment	-	Per 1 mg/d
Heterogeneity (I^2, p-value)	-	I^2=0%, p=0.73

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 100 Inclusion/exclusion table for meta-analysis of total vitamin B6 and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14854	Cho	2013	Prospective cohort study	The Nurses' Health Study & Health Professionals Follow-up Study	Incidence	No	Yes	Yes	Person years per quintiles	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Only highest vs. lowest age-adjusted RR was available
KID01081	Prineas	1997	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	-

Figure 85 Highest versus lowest forest plot of total vitamin B6 and kidney cancer

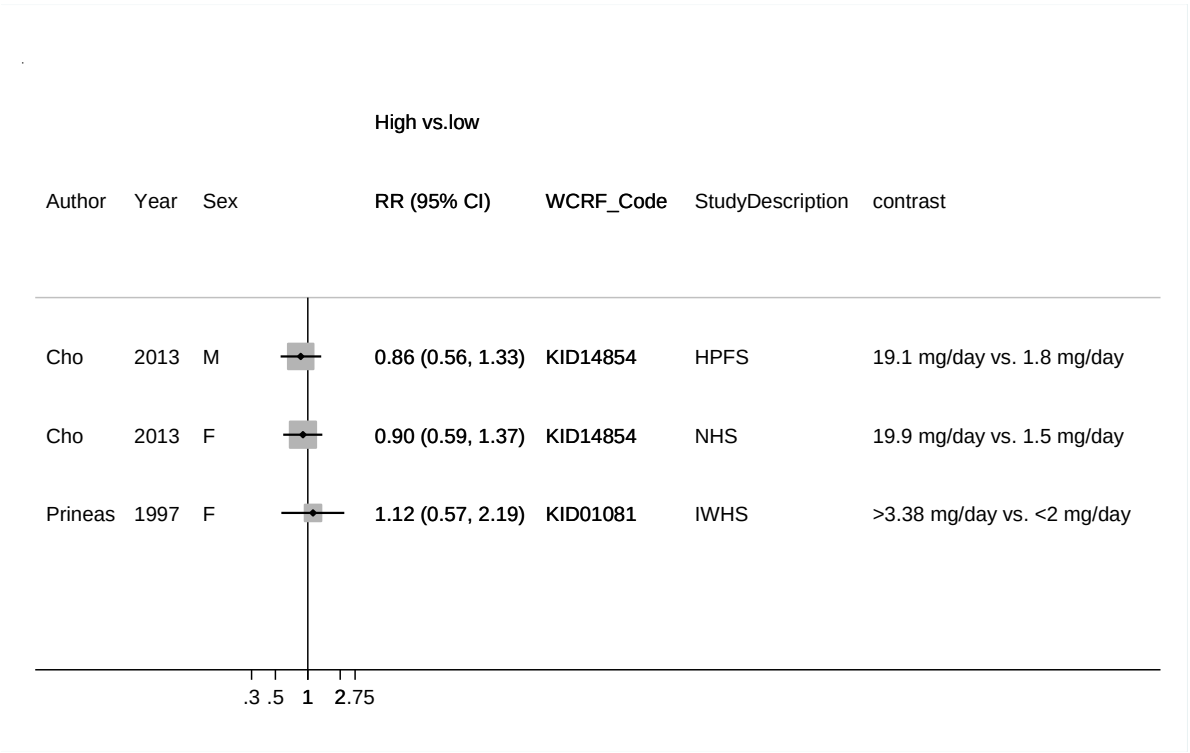


Figure 86 Dose-response meta-analyses of total vitamin B6 and kidney cancer, per 1 mg/d

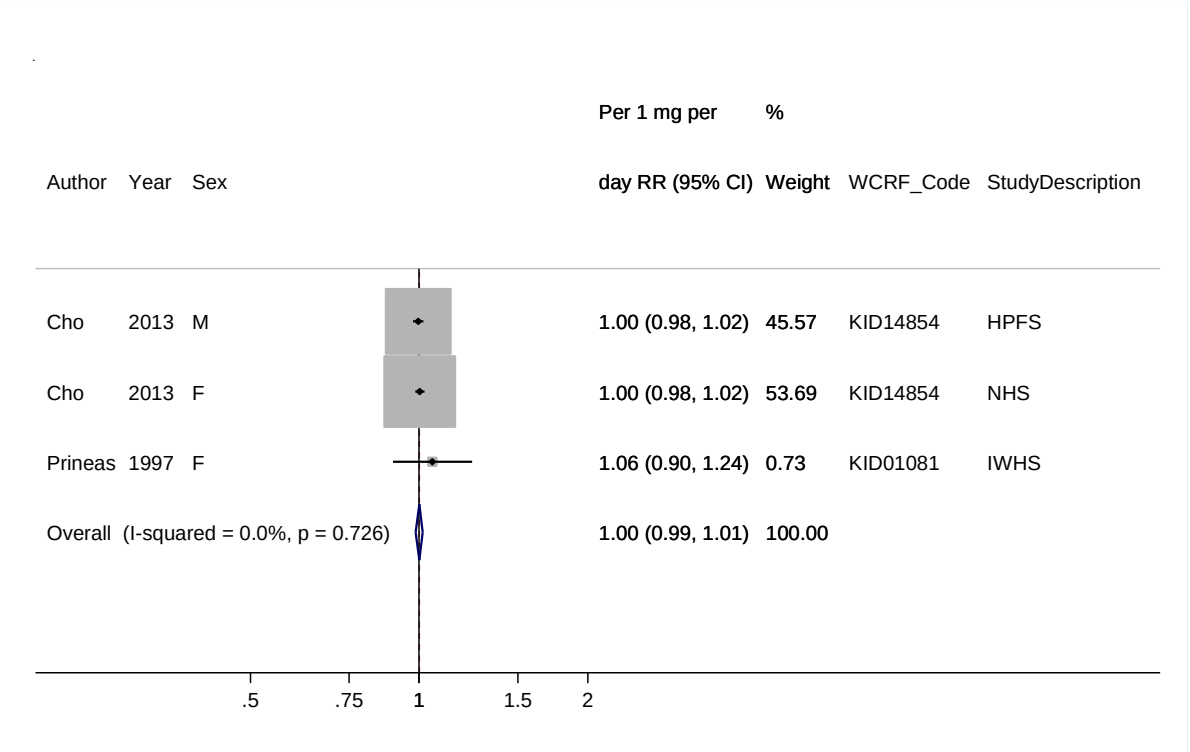
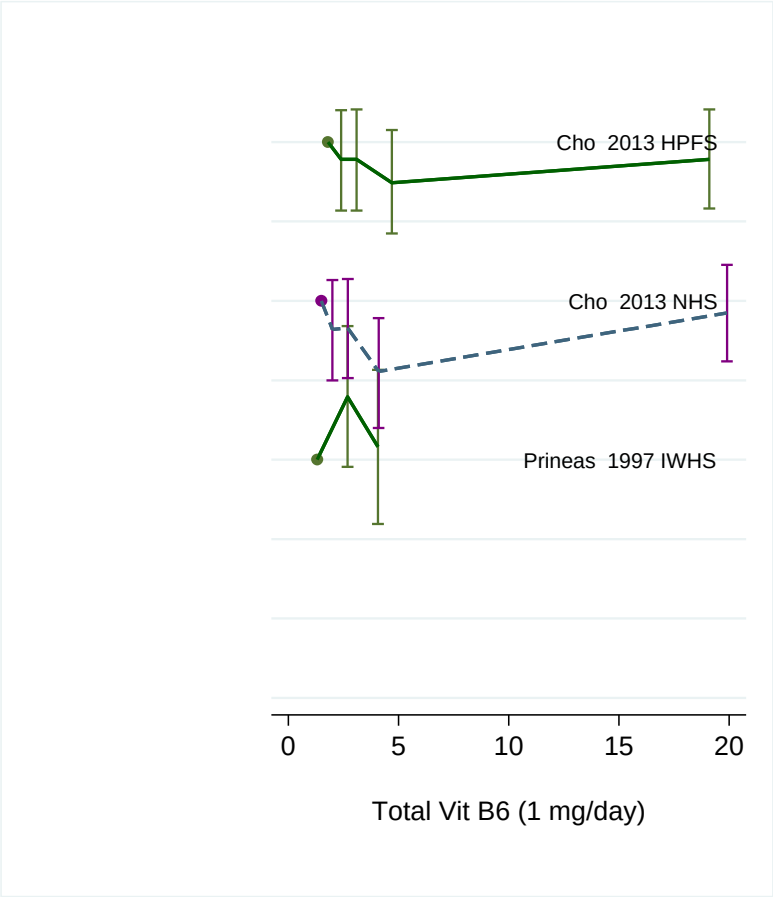


Figure 87 Dose-response meta-analysis of total vitamin B6 and kidney cancer



5.5.9 Total vitamin C (food and supplements)

Methods

A total of 3 articles (3 cohort studies) have been published on total vitamin C and kidney cancer risk up to 31 March 2013; one publication (two studies) was identified in the CUP. The dose-response results are presented for an increment of 200 mg per day. Overall, three studies from 2 articles were included in dose-response meta-analysis.

Main results

The summary RR per 200 mg/d was 1.05 (95% CI: 0.91-1.21, I^2=50.3%, $p_{heterogeneity}$=0.13) for all studies combined.

Heterogeneity

Moderate heterogeneity was observed (I^2=50.3%, $p_{heterogeneity}$=0.13). Egger's test showed no evidence of publication bias (p=0.70).

Comparison with the Second Expert Report

Two articles (one study) were identified during the SLR but no meta-analysis could be conducted. The evidence was limited.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 101 Studies on total vitamin C identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Lee, 2006	USA	Both cohorts combined	248	17	All	0.93	0.62	1.38	907 vs. 114 mg/d in men 633 vs. 96 mg/d in women
		The Nurses' Health Study	132	19.2	F	0.89	0.51	1.56	633 mg/d vs. 96 mg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.97	0.55	1.71	907 mg/d vs. 114 mg/d

Table 102 Overall evidence on total vitamin C and kidney cancer

	Summary of evidence
2005 SLR	One of the two articles from the Iowa Women's Health Study identified in the SLR showed significant increased risk (Nicodemus et al., 2004).
Continuous Update Project	One article including two prospective cohorts identified during the CUP. Overall, three studies were included in the meta-analysis. No association was observed overall.

Table 103 Summary of results of the dose-response meta-analysis of total vitamin C and kidney cancer

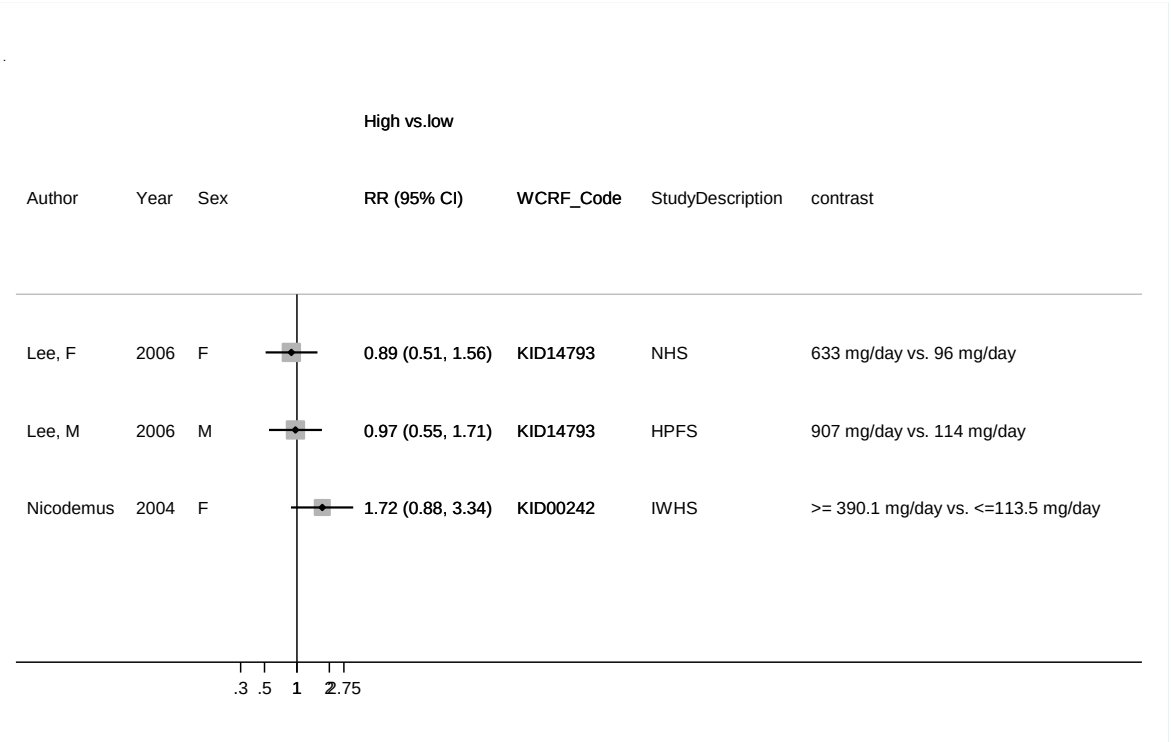
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	372
RR (95% CI)	-	1.05 (0.91-1.21)
Increment	-	Per 200 mg/d
Heterogeneity (I^2, p-value)	-	I^2=50.3%, $p_{heterogeneity}$=0.13

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 104 Inclusion/exclusion table for meta-analysis of total vitamin C and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/years per quintiles Midpoints per quintiles	-
KID01081	Prineas	1997	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Nicodemus et al., 2004

Figure 88 Highest versus lowest forest plot of total vitamin C and kidney cancer



(Total vitamin C intake mistyped in Nicodemus et al., 2004 as IU/day)

Figure 89 Dose-response meta-analysis of total vitamin C and kidney cancer, per 200 mg/d

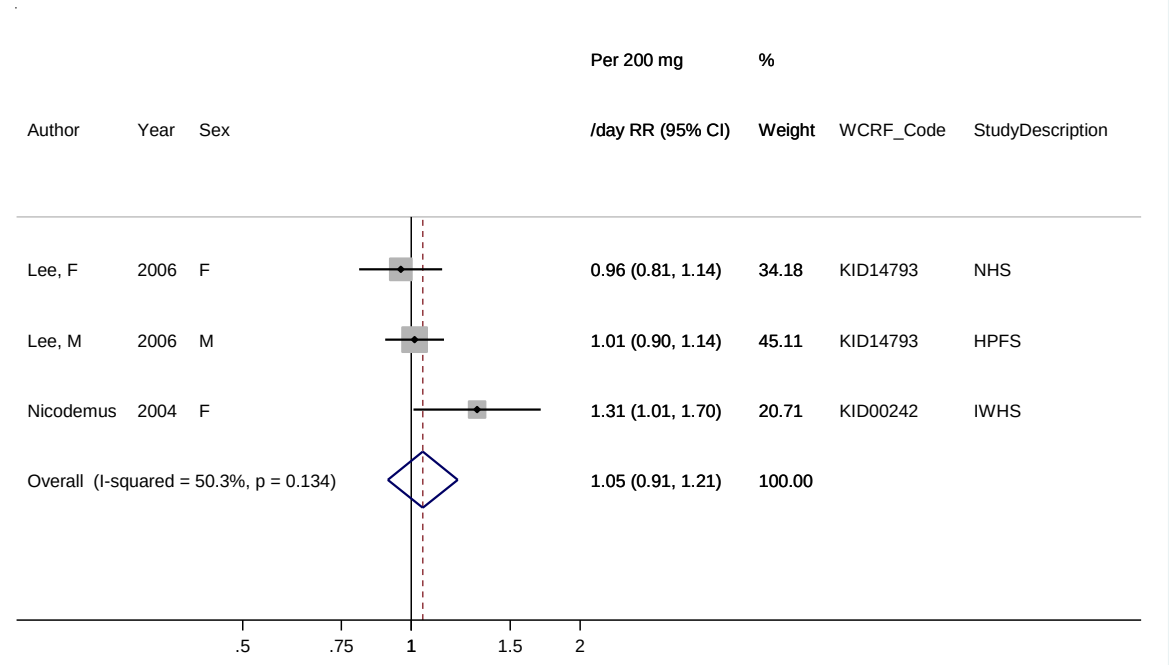
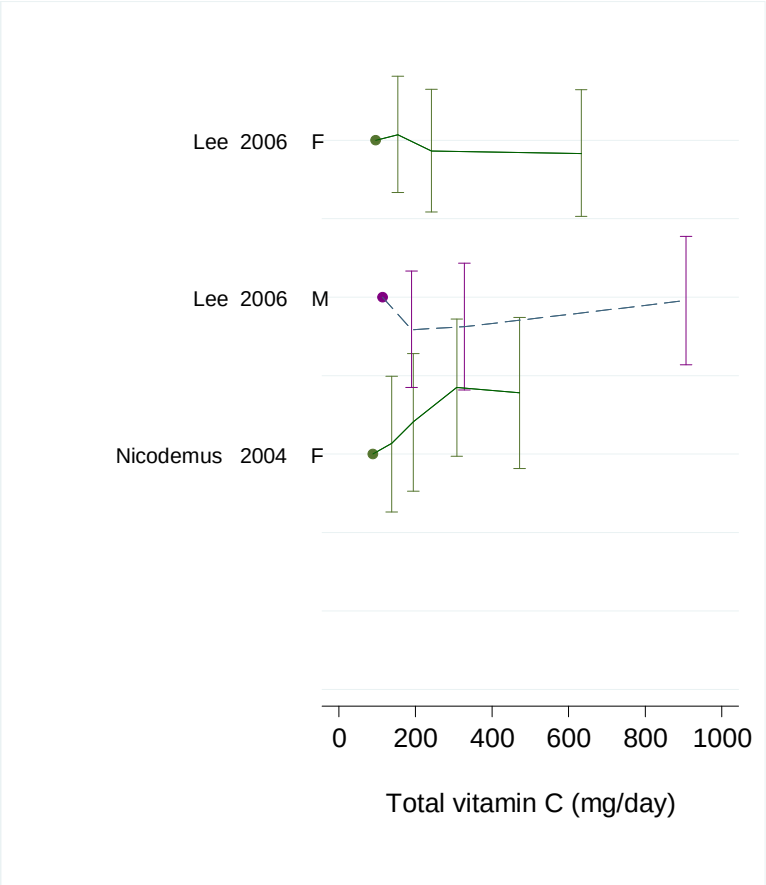


Figure 90 Dose-response graph of total vitamin C and kidney cancer



5.5.9.1 Dietary vitamin C

Methods

A total of 5 articles (5 cohort studies) have been published on dietary vitamin C and kidney cancer risk up to 31 March 2013; three articles (four studies) were identified in the CUP. There are two articles from ATBC study. One of these studies included updated results from the ATBC prevention study. The dose-response results are presented for an increment of 10 mg per day. Overall, four studies from 3 articles were included in dose-response meta-analysis.

Main results

The summary RR per 10 mg/d was 1.00 (95% CI: 0.98-1.01, I^2=54.6%, $p_{heterogeneity}$=0.09) for all studies combined. In influence analysis the RR was 0.99 (95% CI: 0.97-1.01) when excluding either the Nurses' Health Study (Lee et al., 2006) or the Netherlands Cohort Study (Van Dijk et al., 2008).

Heterogeneity

Moderate heterogeneity was observed (I^2=54.6%, $p_{heterogeneity}$=0.09). Egger's test did not show evidence of publication bias (p=0.14).

Comparison with the Second Expert Report

Two studies were identified during the SLR but no meta-analysis could be conducted. The evidence was limited.

Meta-analysis and Pooled studies

No published met-analysis was identified.

Table 105 Studies on dietary vitamin C identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	0.99	0.67	1.46	161 mg/d vs. 50 mg/d
VanDijk, 2008	Netherlands	The Netherlands Cohort Study	284	11.3	All	1.01 1.01	0.72 0.98	1.43 1.04	129.76 vs. 52.23mg/d (men), 140.84 vs. 58.93 mg/d (women) Per 10 mg/d increase
Lee, 2006	USA	Both cohorts	248	17	All	0.79	0.35	1.82	243 vs. 91 mg/d (men) 196 vs. 79 mg/d (women)
		The Nurses' Health Study	132	19.2	F	1.20	0.74	1.95	196 vs. 79 mg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.51	0.30	0.88	243 vs. 91 mg/d

Table 106 Overall evidence on dietary vitamin C and kidney cancer

	Summary of evidence
2005 SLR	Two studies identified during the SLR, one of which reported significant increased risk with kidney cancer (Nicodemus et al., 2004).
Continuous Update Project	Three articles including four cohort studies were identified during the CUP. The Health Professionals Follow-Up Study reported a significant inverse association in men only. Overall, four cohort studies were included in the meta-analysis. No association was observed.

Table 107 Summary of results of the dose-response meta-analysis of dietary vitamin C and kidney cancer

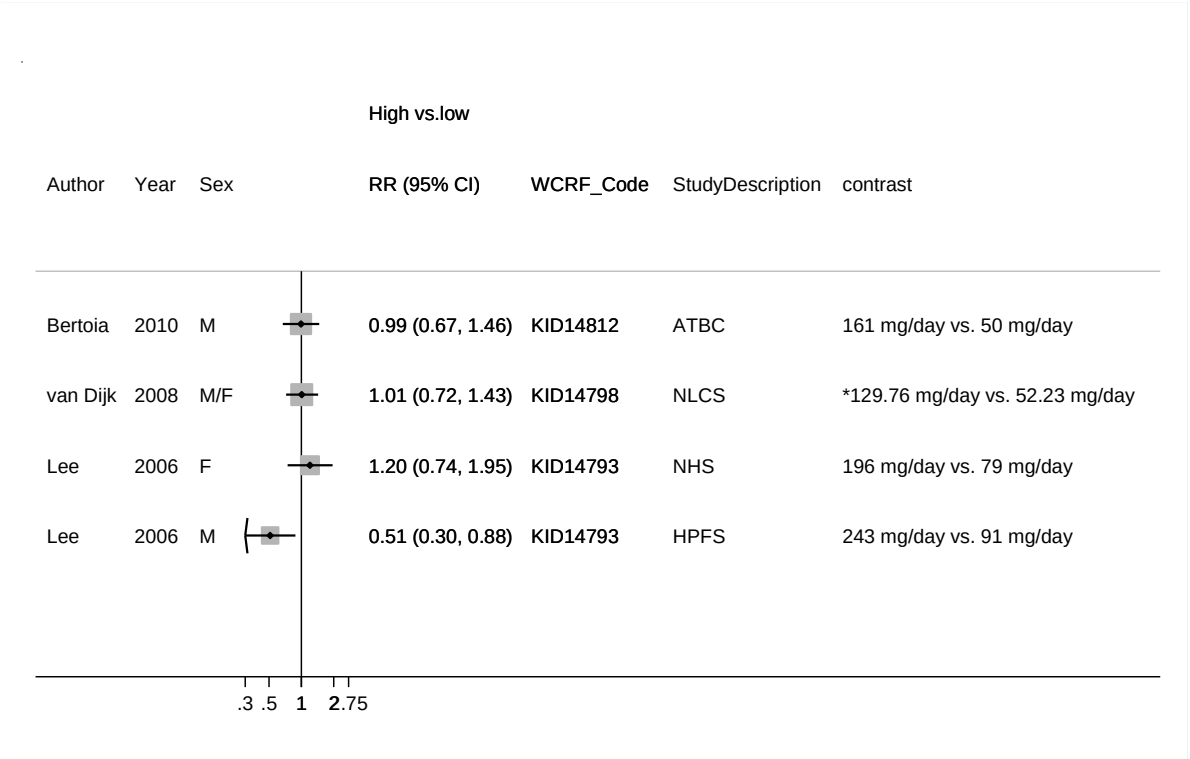
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
RR (95% CI)	-	Per 10 mg/d
Increment	-	1.00 (0.98-1.01)
Heterogeneity (I^2, p-value)	-	I^2=54.6%, $p_{heterogeneity}$=0.09

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 108 Inclusion/exclusion table for meta-analysis of dietary vitamin C and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile. Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No dietary intake data available
KID00506	Hirvonen	2001	Prospective cohort study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Mean values only

Figure 91 Highest versus lowest forest plot of dietary vitamin C and kidney cancer



*Dietary vitamin C intake in the highest vs. lowest quintiles was 129.76 mg/d vs. 52.23 mg/d in men and 140.84 mg/d vs. 58.93 mg/d in women (Van Dijk et al., 2008).

Figure 92 Dose-response meta-analysis of dietary vitamin C and kidney cancer, per 10 mg/d

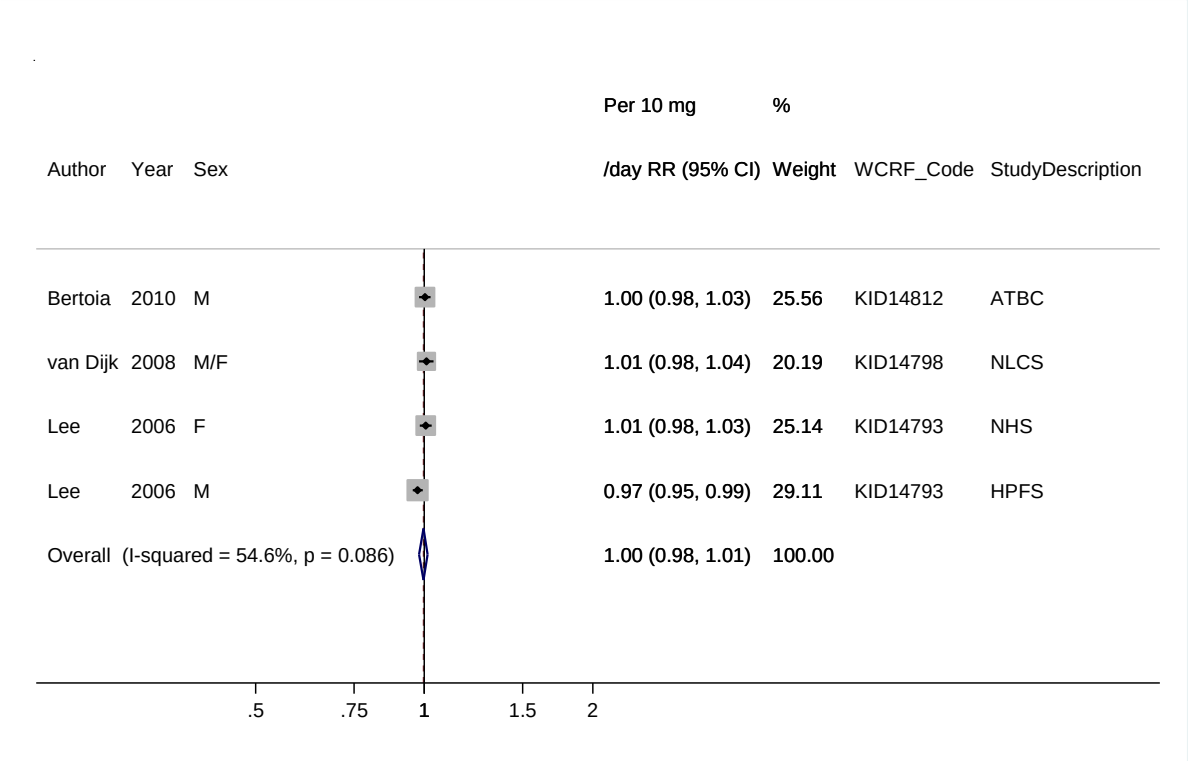
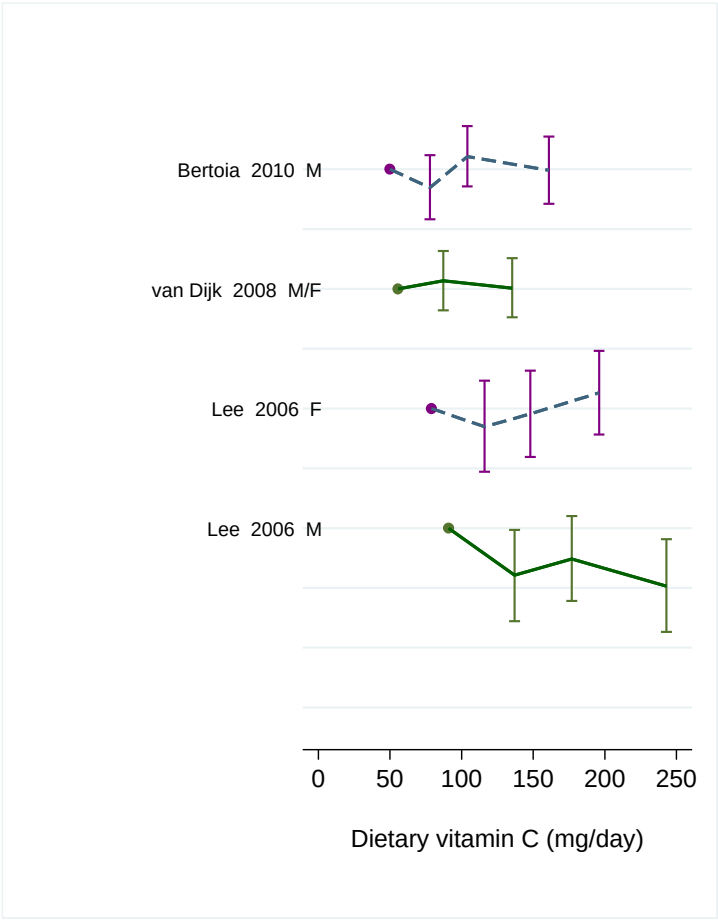


Figure 93 Dose-response graph of dietary vitamin C and kidney cancer



5.5.11 Total vitamin E (food and supplements)

Methods

A total of 3 articles 3 cohort studies) have been published on total vitamin E and kidney cancer risk up to 31 March 2013; one publication (two studies) was identified in the CUP. In one study (Nicodemus et al., 2004) IU/day of vitamin E was rescaled to mg/d using as approximation 1 mg alpha-tocopherol equals to 1.49 IU *d*-alpha-tocopherol (natural, *RRR* form). The conversion of synthetic Vitamin E from IU to mg was not possible. The dose-response results are presented for an increment of 5 mg per day. Overall, three studies from 2 articles were included in dose-response meta-analysis.

Main results

The summary RR per 5 mg/d was 0.98 (95% CI: 0.94-1.02, I^2=80.7%, $p_{heterogeneity}$=0.006) for all studies combined. The RR in women was 0.94 (95% CI: 0.80-1.10, I^2=90.0%, $p_{heterogeneity}$=0.002) -excluding the Health Professionals Follow-Up Study.

Heterogeneity

There was evidence of heterogeneity across the limited number of published studies (I^2=80.7%, $p_{heterogeneity}$=0.006).). Egger's test did not show evidence of publication bias (p=0.74).

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 109 Studies on total vitamin E identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Lee, 2006	USA	Both cohorts	248	17	All	0.90	0.51	1.60	162 vs. 8 mg/d in men 103 vs. 6 mg/d in women
		The Nurses' Health Study	132	19.2	F	1.20	0.66	2.16	103 vs. 6 mg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.67	0.36	1.24	162 vs. 8 mg/d

Table 110 Overall evidence on total vitamin E and kidney cancer

	Summary of evidence
2005 SLR	Two articles from the Iowa Women's Health Study' were identified during the SLR, one of them reported significant inverse association with kidney cancer among postmenopausal women (Nicodemus et al., 2004).
Continuous Update Project	One publication including two cohorts identified during the CUP. Three studies were included in the meta-analysis. No association was observed overall.

Table 111 Summary of results of the dose-response meta-analysis of total vitamin E and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	372
RR (95% CI)	-	0.98 (0.94-1.02)
Increment	-	Per 5 mg/d
Heterogeneity (I^2, p-value)	-	I^2=80.7%, $p_{heterogeneity}$=0.006

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 112 Inclusion/exclusion table for meta-analysis of total vitamin E and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/years per quintiles IU/day rescaled to mg/d	-
KID01081	Prineas	1997		Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Nicodemus et al., 2004

Figure 94 Highest versus lowest forest plot of total vitamin E and kidney cancer

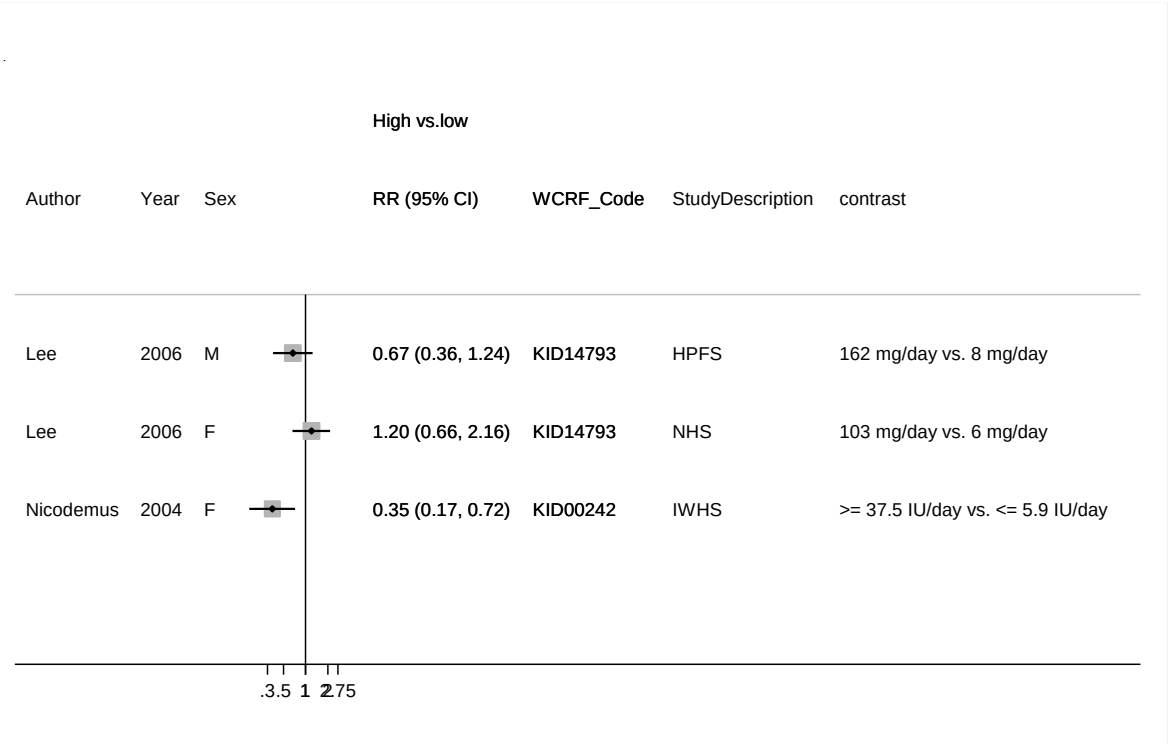


Figure 95 Dose-response meta-analysis of total vitamin E and kidney cancer, per 5 mg/d

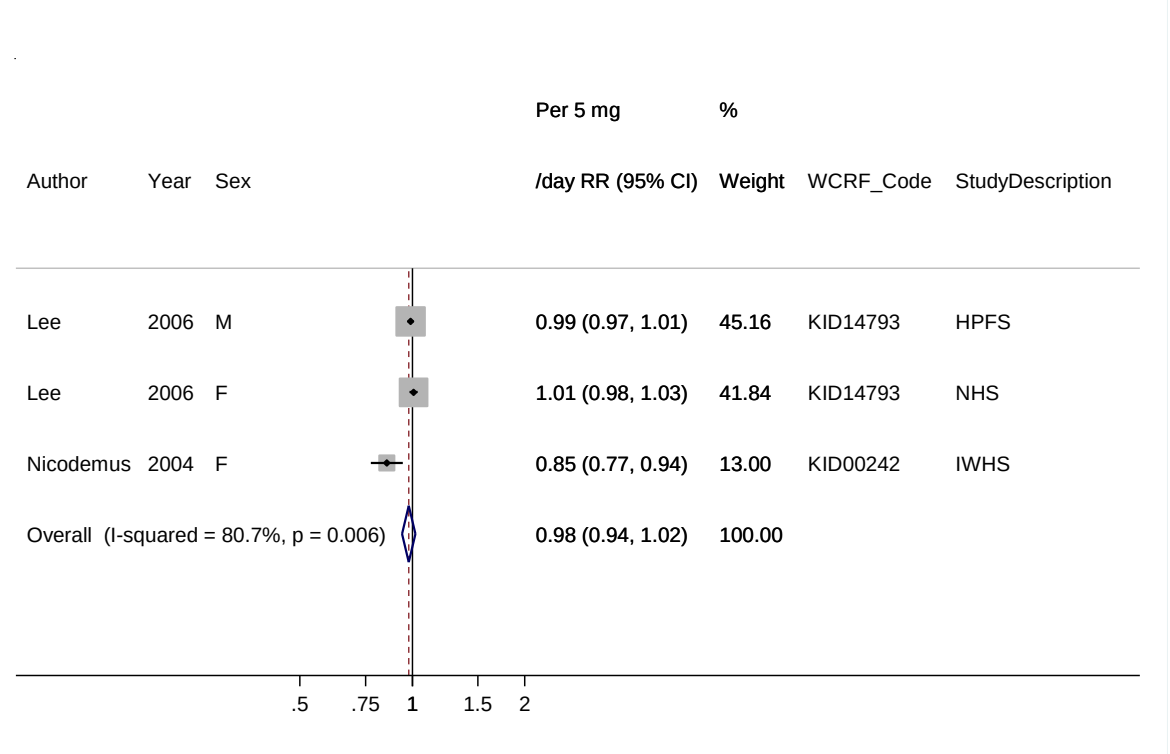
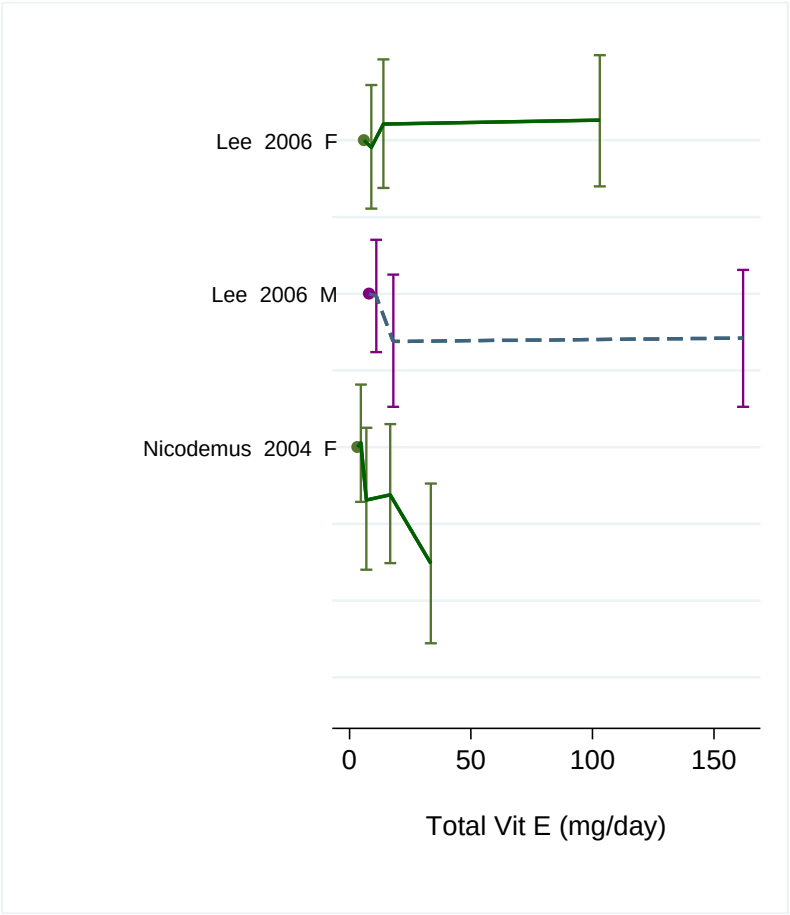


Figure 96 Dose-response graph of total vitamin E and kidney cancer



5.5.11.1 Dietary vitamin E

Methods

A total of 5 articles (5 cohort studies) have been published on dietary vitamin E and kidney cancer risk up to 31 March 2013, three articles (four studies) of the articles were identified in the CUP. Bertoia et al., 2010 provided updated results from ATBC study. The dose-response results are presented for an increment of 5 mg per day. Overall, three studies from 2 articles were included in dose-response meta-analysis.

Main results

The summary RR per 5 mg/d was 1.04 (95% CI: 0.98-1.11, I^2=0%, $p_{heterogeneity}$=0.64) for all studies combined. In influence analysis the RR was 1.03 (95% CI: 0.96-1.10) when excluding the Nurses' Health Study (Lee et al., 2006) and remained almost the same, 1.03 (95% CI: 0.95-1.12), after excluding the Netherlands Cohort Study on Diet and Cancer (van Dijk, 2008).

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, $p_{heterogeneity}$=0.64). Egger's test showed no evidence of publication bias (p=0.87).

Comparison with the Second Expert Report

Two articles from one study (ATBC prevention study) were identified during the SLR; one of them reported significant inverse association with kidney cancer among postmenopausal women (Nicodemus et al., 2004). No meta-analysis was conducted in the systematic review of the 2007 expert report.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 113 Studies on dietary vitamin E and kidney cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Bertoia, 2010	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	255	19	M	1.09	0.73	1.64	20 vs. 6.5 mg/d
VanDijk, 2008	Netherlands	The Netherlands Cohort Study	284	11.3	All	1.0 1.05	0.68 0.95	1.47 1.15	23.76 vs. 7.18 mg/d in men 19.55 vs. 6.13 mg/d in women Per 5 mg/d increase
Lee, 2006	USA	The Nurses' Health Study and Health Professionals Follow-Up Study	248	17	All	1.13	0.76	1.67	13 vs. 8 mg/d in men 10 vs. 6 mg/d in women
		The Nurses' Health Study	132	19.2	F	1.31	0.75	2.28	10 vs. 6 mg/d
		Health Professionals Follow-Up Study	116	12.7	M	0.97	0.56	1.70	13 vs. 8 mg/d

Table 114 Overall evidence on dietary vitamin E and kidney cancer

	Summary of evidence
2005 SLR	Of two studies identified during the SLR, one study reported a significant inverse association with kidney cancer among postmenopausal women (Nicodemus et al., 2004).
Continuous Update Project	Four studies (from 3 articles) identified during the CUP. All were included in the meta-analysis. No association was observed.

Table 115 Summary of results of the dose-response meta-analysis of dietary vitamin E and kidney cancer

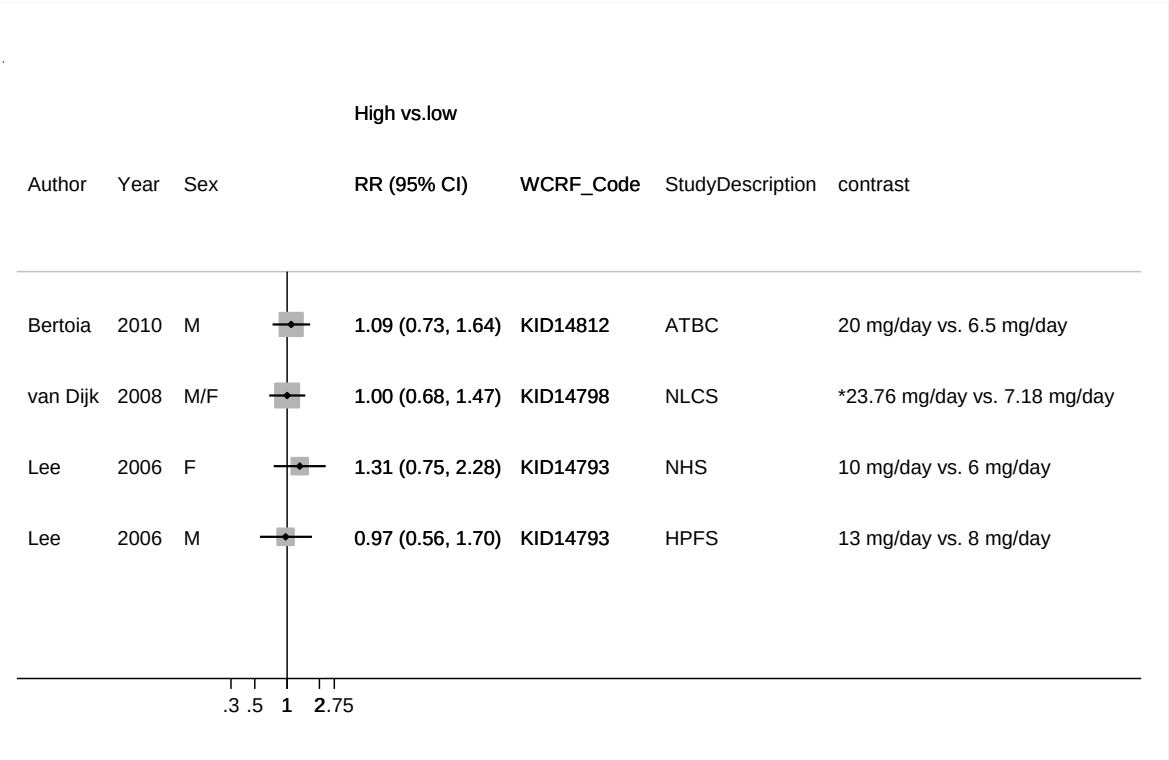
Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	787
RR (95% CI)	-	1.04 (0.98-1.11)
Increment	-	Per 5 mg/d
Heterogeneity (I^2, p-value)	-	I^2=0%, $p_{heterogeneity}$=0.64

*No meta-analysis for cohort studies was conducted in the Second Expert Report

Table 116 Inclusion/exclusion table for meta-analysis of dietary vitamin E and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14812	Bertoia	2010	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Person-years per quartile	-
KID14798	Van Dijk	2008	Case-cohort study	The Netherlands Cohort Study	Incidence	No	Yes	Yes	Cases per quintile Weighted average intake range calculated for men and women	-
KID14793	Lee	2006	Prospective cohort study	The Nurses' Health Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
			Prospective cohort study	Health Professionals Follow-Up Study	Incidence	No	Yes	Yes	Person/years per quartile Cases per quartile	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No dietary intake data available
KID00506	Hirvonen	2001	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	superseded by Bertoia et al., 2010 Mean values only

Figure 97 Highest versus lowest forest plot of dietary vitamin E and kidney cancer



* Dietary vitamin E intake in the highest vs. lowest quintiles was 23.76 mg/d vs. 7.18 mg/d in men and 19.55 mg/d vs. 6.13 mg/d in women (van Dijk et al., 2008).

Figure 98 Dose-response meta-analysis of dietary vitamin E and kidney cancer, per 5 mg/d

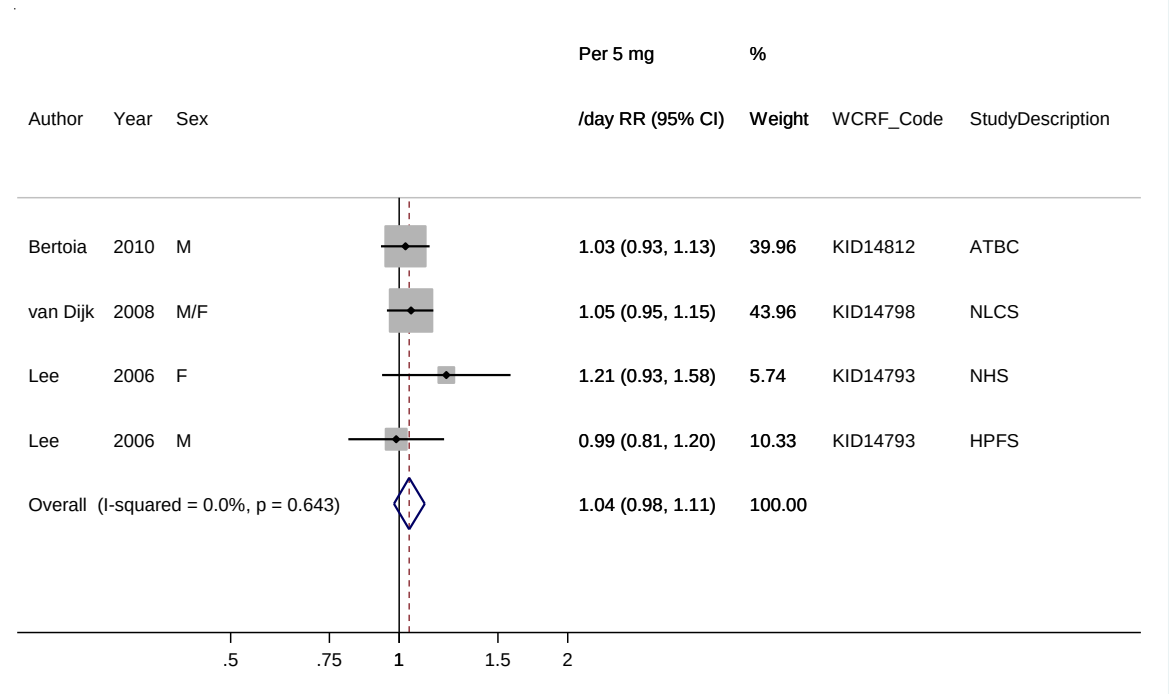
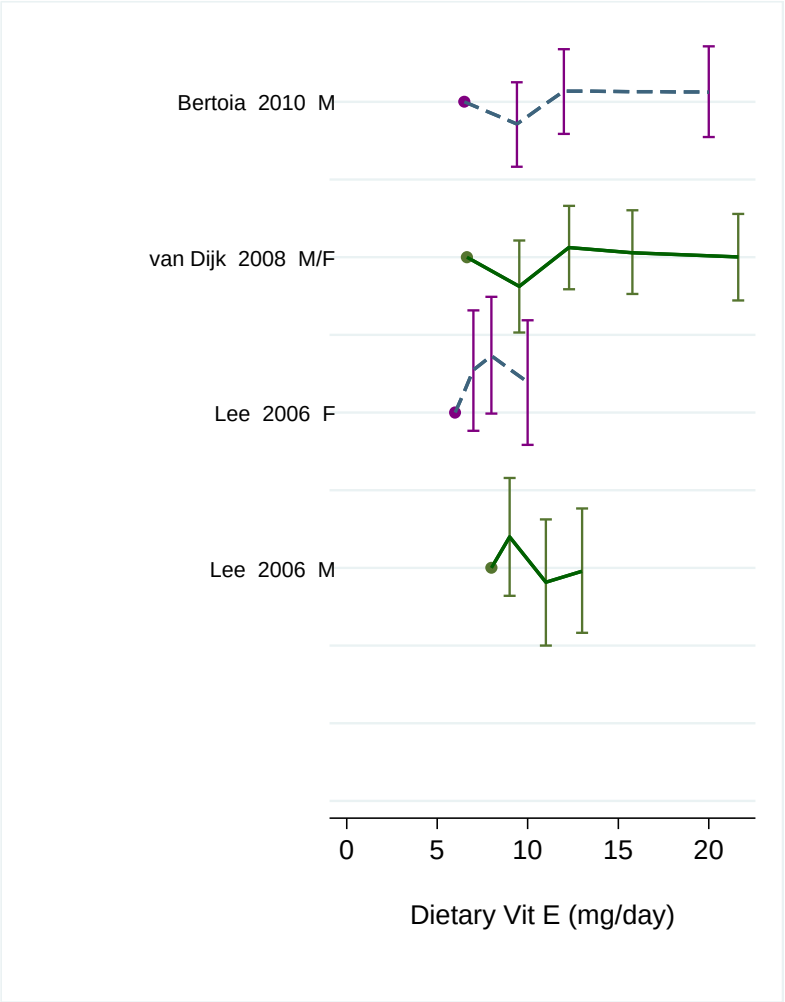


Figure 99 Dose-response graph of dietary vitamin E and kidney cancer



5.6.3 Total calcium (food and supplements)

Methods

A total of four articles from three cohort studies were identified up to 31 March 2013; two articles were identified in the CUP. A meta-analysis including three cohorts was conducted. In the NIH-AARP study (Park et al., 2009) the RRs estimates for men and women were pooled before inclusion in the meta-analysis. The dose-response results are presented for an increment of 200 mg/d.

Main results

The summary RR per 200 mg/d was 0.97 (95% CI: 0.94-0.99, I^2=0.0%, $p_{heterogeneity}$=0.7). Egger's test showed no evidence of publication bias (p= 0.44) but only three cohorts were included.

Heterogeneity

No heterogeneity was observed, I^2=0.0%, $P_{heterogeneity}$=0.7.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP found a significant inverse association between total calcium intake and kidney cancer risk.

Meta-analysis and Pooled studies

No published meta-analysis was identified.

Table 117 Studies on total calcium and kidney cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Park, 2009	United States	NIH-AARP Diet and Health Study	991	7	M	0.8	0.64	1.01	1530 mg/d vs. 498 mg/d
			367		F	0.79	0.55	1.13	1881 mg/d vs. 494 mg/d
Wilson, 2009	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	229	15.2	M	0.8	0.3	2.2	>1636.1 mg/d vs. <=1136.4 mg/d

Table 118 Overall evidence on total calcium and kidney cancer

	Summary of evidence
2005 SLR	One cohort was identified. No association was found between total calcium intake and the risk of kidney cancer.
Continuous Update Project	Two cohorts were identified. Overall, 3 cohorts were included in the CUP meta-analysis.

Table 119 Summary of results of the dose response meta-analysis of total calcium and kidney cancer

Kidney cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1711
Increment	-	Per 200 mg/d
Overall RR (95%CI)	-	0.97 (0.94-0.99)
Heterogeneity (I^2,p-value)	-	0.0%, p=0.7

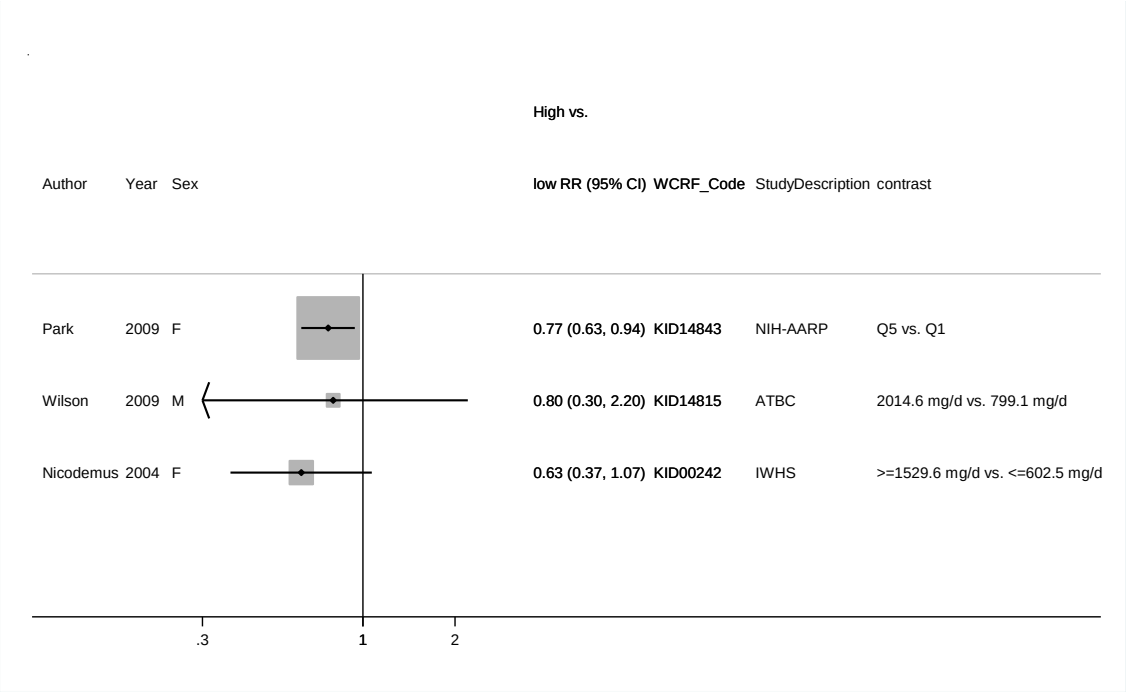
*No meta-analysis for cohort studies was conducted in the Second Expert Report.

Table 120 Inclusion/exclusion table for meta-analysis of total calcium intake and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14843	Park	2009	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Person/ years per category Calculated weighted average intake	-
KID14815	Wilson	2009	Prospective Cohort Study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Cohort	Incidence	No	Yes	Yes	Person/ years per category Mid-exposure values	-
KID00242	Nicodemus*	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person/ years per category Mid-exposure values	-
KID01081	Prineas*	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Nicodemus et al., 2004

* Minimally adjusted results.

Figure 100 Highest versus lowest forest plot of total calcium intake and kidney cancer



**In Park et al., 2009 study the highest vs. lowest median intake of total calcium was 1530 mg/d vs. 498 mg/d among men and 1881 mg/d vs. 494 mg/d among women.*

Figure 101 Dose-response meta-analysis of total calcium intake and kidney cancer - per 200 mg/d

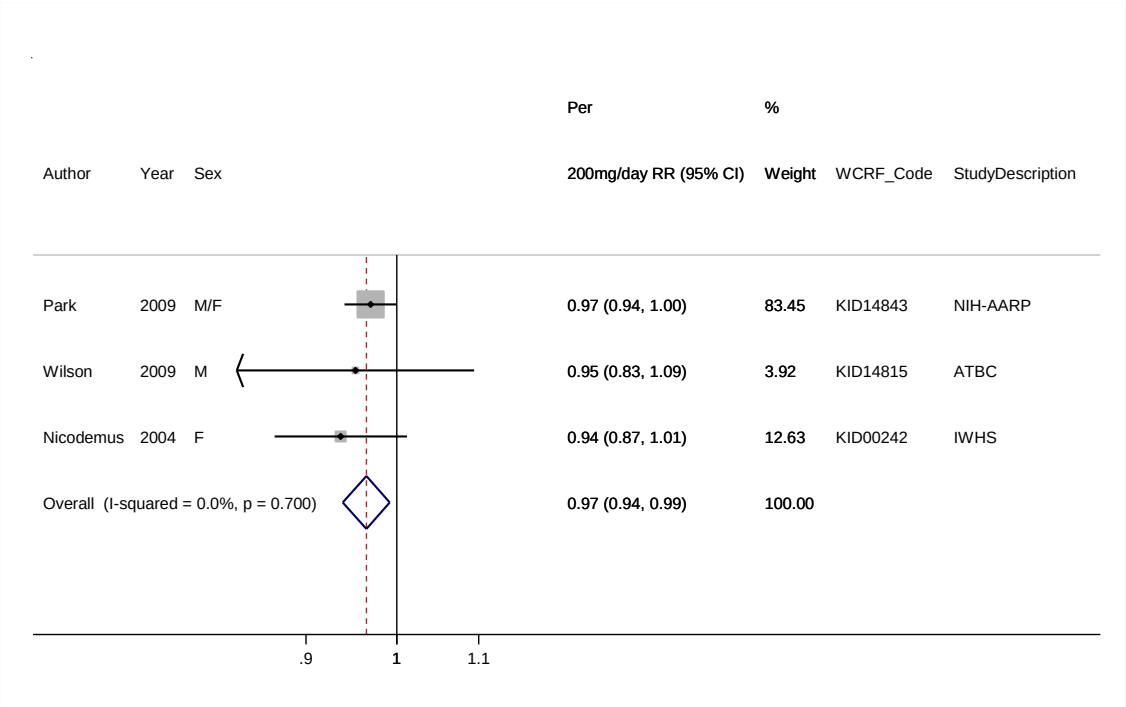
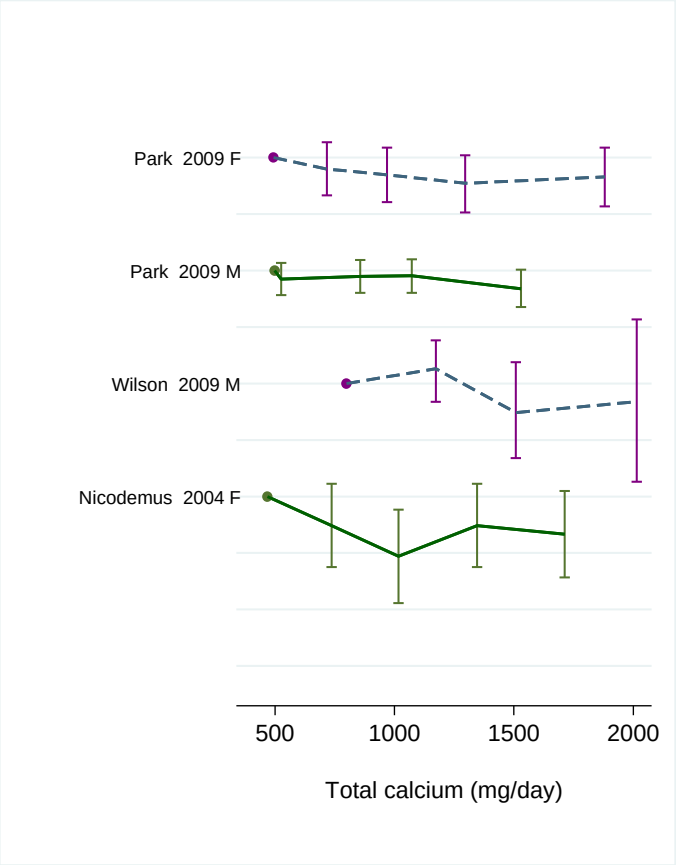


Figure 102 Dose-response graph of total calcium and kidney cancer



5.6.3.1 Dietary calcium

Methods

Three cohort studies were identified up to March 2013; two of them during the CUP, from which one is a nested case control study in male smokers (ATBC study). A meta-analysis including the three studies was conducted. In the NIH-AARP study (Park et al., 2009) the dose-response estimates for men and women were pooled before inclusion in the meta-analysis. The dose-response results are presented for an increment of 200 mg/day.

Main results

The summary RR per 200 mg/day was 0.99 (95% CI: 0.93-1.05, I^2=0.0%, $p_{heterogeneity}$=0.41). Egger's tests showed no evidence of publication bias (p= 0. 128) but only three cohorts were included.

Heterogeneity

No heterogeneity was observed, I^2=0.0%, $p_{heterogeneity}$=0.41

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Table 121 Studies on dietary calcium and kidney cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Southard, 2012*	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	154	8	M	0.9	0.5	1.5	>1932.9 vs <773.2 mg/d
Park, 2009	United States	National Health Institute-American Association of Retired Persons	991	7	M	0.98	0.78	1.24	1247 vs 478 mg/d
			367		F	1.02	0.70	1.48	1101 vs 409 mg/d

**Southard et al, 2012: Unadjusted relative risk estimates. Cases and control matched by age, pack-years, ATBC treatment group and follow-up time*

Table 122 Overall evidence on dietary calcium and kidney cancer

SLR	Summary of evidence
2005 SLR	One cohort in women was identified. No association was found between dietary calcium intake and the risk of kidney cancer
Continuous update	One study in women and one study in male smokers were identified.

Table 123 Summary of results of the dose response meta-analysis of dietary calcium and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1574
Increment unit used	-	Per 200 mg/day
Overall RR (95%CI)	-	0.99 (0.93-1.05)
Heterogeneity (I^2,p-value)	-	0%, p=0.417

*No meta-analysis for cohort studies was conducted in the second report

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Table 124 Inclusion/exclusion table for meta-analysis of dietary calcium intake and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14843	Park	2009	Prospective Cohort Study	National Health Institute- American Association of Retired Persons	Incidence	No	Yes	Yes	Person/ years per quintile Cases per quintile	-
KID14830	Southard	2012	Nested case-control study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Incidence	No	Yes	Yes	Mid-exposure values	-
KID01081	Prineas*	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	

*Minimally adjusted results.

Figure 103 Highest versus lowest forest plot of dietary calcium intake and kidney cancer

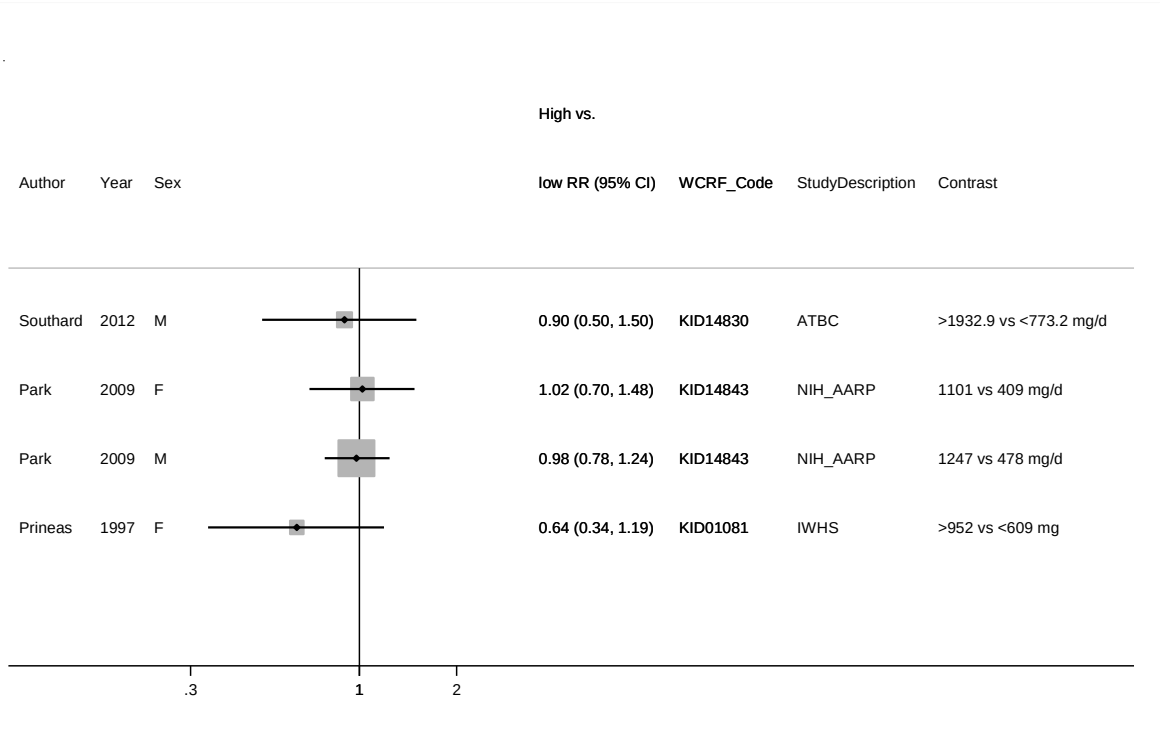


Figure 104 Dose-response meta-analysis of dietary calcium intake and kidney cancer - per 200 mg/d

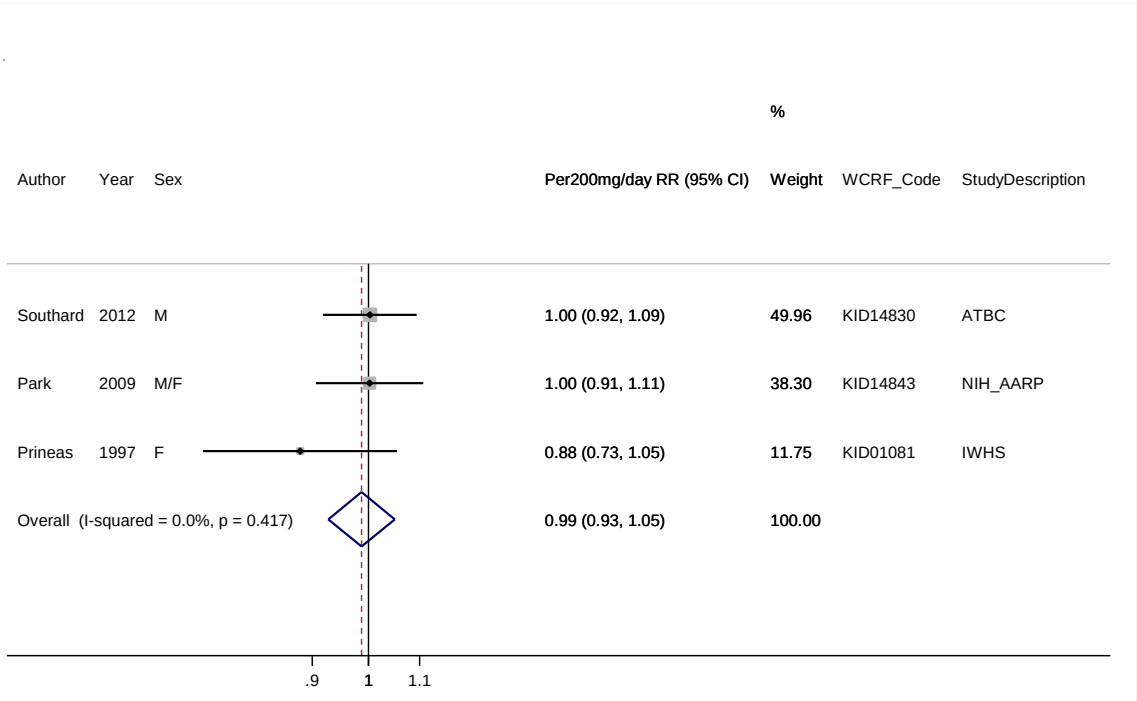


Figure 105 Funnel plot of dietary calcium intake and kidney cancer

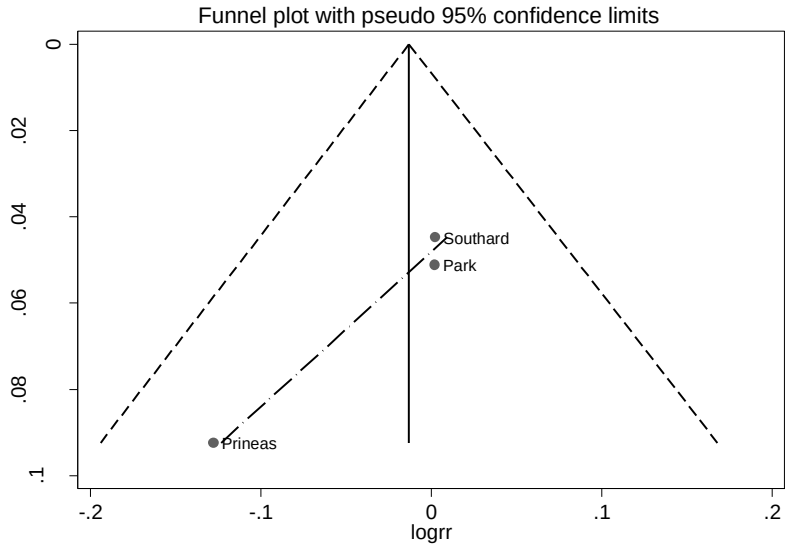
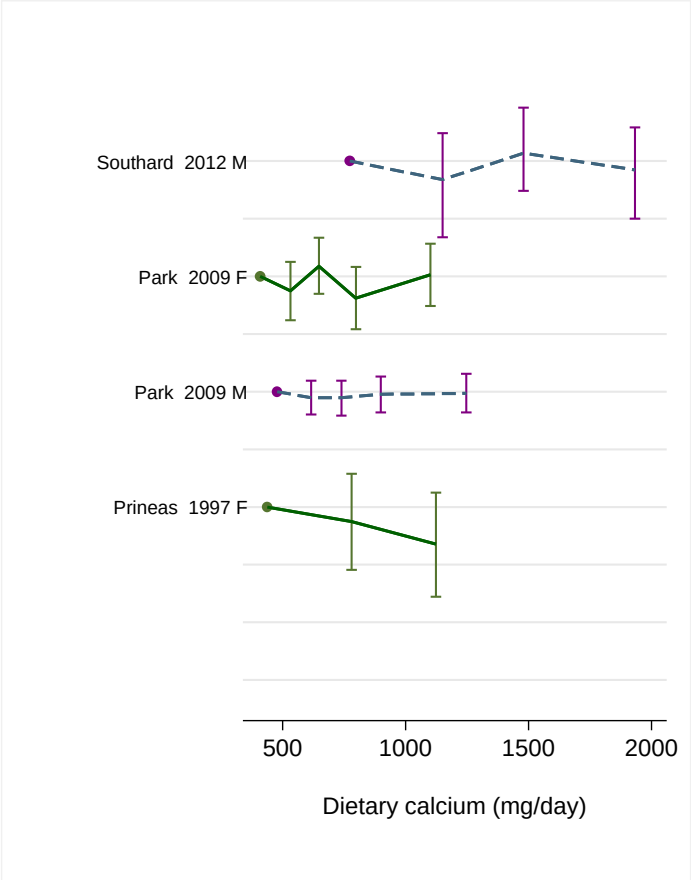


Figure 106 Dose-response graph of dietary calcium and kidney cancer



5.6.3.2 Calcium from supplements

Methods

Three articles from two cohort studies were identified up to March 2013; one of them during the CUP. A meta-analysis of the two studies, comparing use vs no use of supplement calcium was conducted. In the NIH-AARP study (Park et al., 2009) the RRs estimated for the different supplement levels were rescaled to " use" using the Hamling method.

Main results

The summary RR for use vs. no use of supplements of calcium was 0.99 (95% CI: 0.87 ; 0.77-0.97), I^2=0%, $p_{heterogeneity}$=0.60).

Heterogeneity

No heterogeneity was observed, I^2=0%, $p_{heterogeneity}$=0.60

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Table 125 Studies on supplemental calcium and kidney cancer identified in the CUP and the 2005 SLR

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Park, 2009	United States	National Health Institute-American Association of Retired Persons	991	7	M	0.90	0.61	1.34	>1000 mg vs. 0 mg
			367		F	0.79	0.57	1.12	

Table 126 Overall evidence on supplemental calcium and kidney cancer

SLR	Summary of evidence
2005 SLR	Two articles from a cohort in women were identified. A significant inverse association was observed in the first report but not in the most recent.
Continuous update	One study identified showing no association. Overall, no association was observed.

Table 127 Summary of results of the dose response meta-analysis of supplemental calcium and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	1482
Contrast	-	Use vs. non use
Overall RR (95%CI)	-	0.87 (0.77-0.97)
Heterogeneity (I^2,p-value)	-	0%, p=0.60

*No meta-analysis for cohort studies was conducted in the second report.

Table 128 Inclusion/exclusion table for meta-analysis of supplemental calcium intake and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14843	Park	2009	Prospective Cohort Study	National Health Institute- American Association of Retired Persons	Incidence	No	Yes	Yes	Person/ years per quintile Cases per quintile RR rescaled to Use vs. no use	-
KID00242	Nicodemus	2004	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	-	-
KID01081	Prineas	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	No	-	Superseded by Nicodemus, 2004

Figure 107 Highest versus lowest forest plot of supplemental calcium intake and kidney cancer

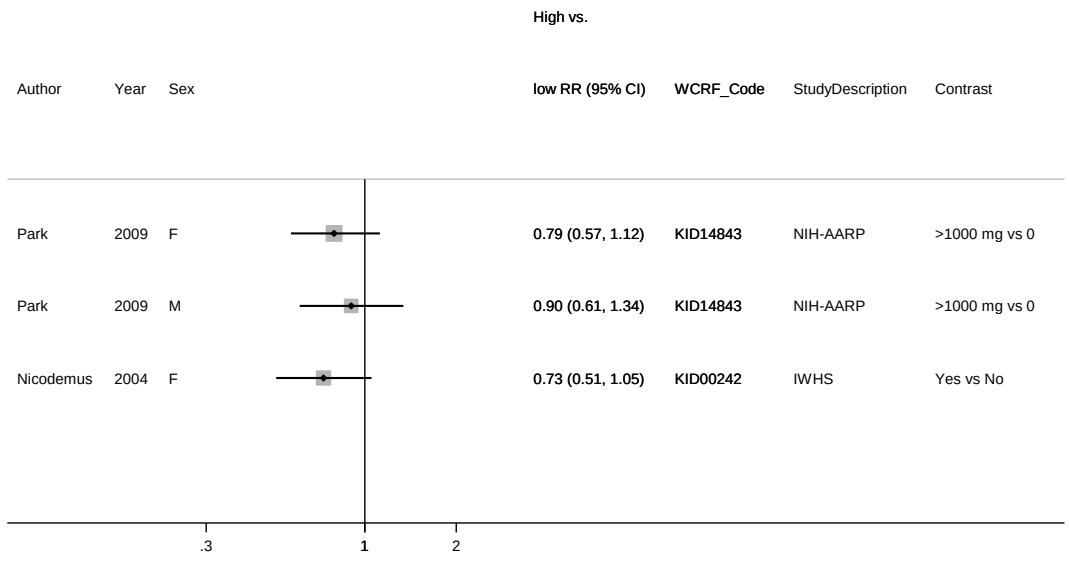
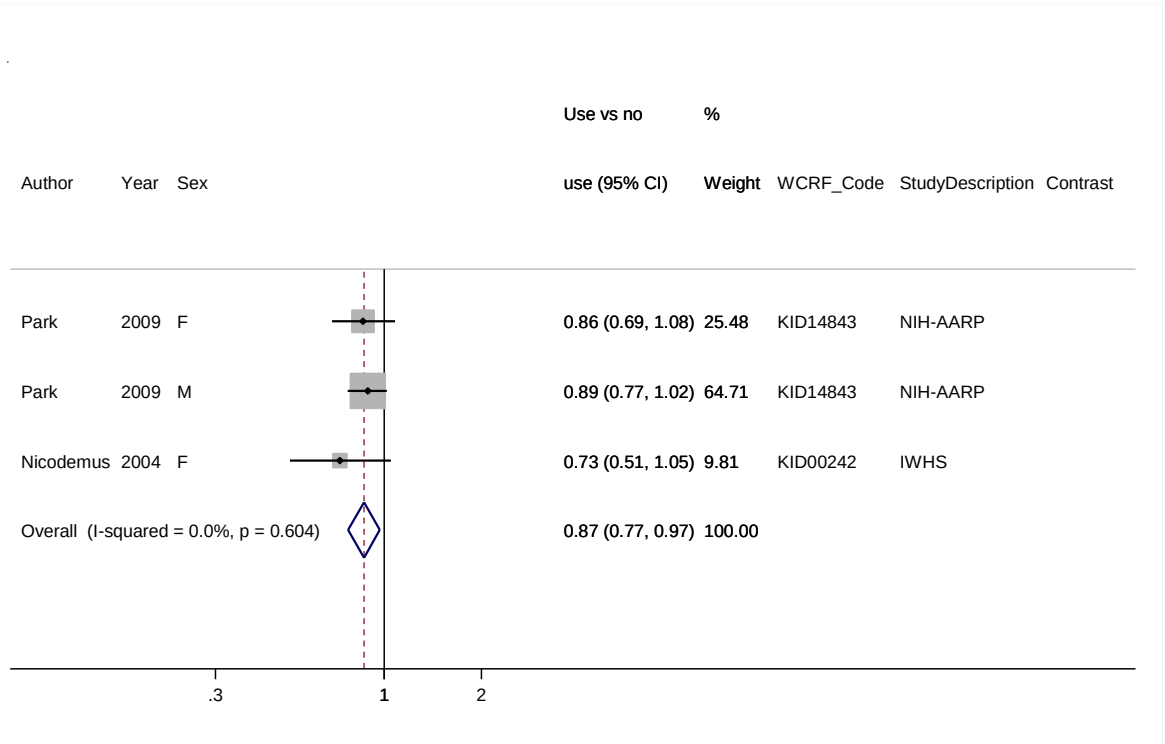


Figure 108 Meta-analysis of supplemental calcium and kidney cancer – (Use vs. no use)



6 Physical activity

6.1 Total physical activity

Methods

Up to 31 March 2013, 4 articles (4 cohort studies) have been identified; one was identified during the CUP. One (Prineas et al, 1997) reported relative risks adjusted only for age. Overall, four studies were included in high versus low meta-analysis.

Main results

Only a meta-analysis of highest versus lowest level of physical activity could be conducted. No association was observed (RR=0.89; 95% CI: 0.72-1.10).

Heterogeneity

There was no evidence of heterogeneity (I^2= 0%, p=0.47). Egger's test showed no evidence of publication bias (p= 0.15) but only five estimates were included.

Comparison with the Second Expert Report

In the SLR the evidence relating physical activity to kidney cancer was considered limited and no conclusion was possible.

Meta-analysis and Pooled studies

In a published meta-analysis the relative risk of renal cell cancer for the highest compared to the lowest level of physical activity in 11 cohort studies was 0.87 (95% CI: 0.76–0.99, I^2=33%) (Behrens and Leitzmann, 2013). In influence analysis, the relative risk estimate was similar after excluding two studies with kidney cancer mortality as endpoint (RR=0.88; 95% CI: 0.80–0.98). There was no effect modification by hypertension, type 2 diabetes, adiposity, gender, smoking, or geographic region.

Table 129 Studies on total physical activity identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Setiawan, 2007	USA	Hawaii-Los Angeles Multiethnic Cohort Study	220	8.3	M	1.09	0.75	1.58	Q4 vs. Q1
			127		F	0.66	0.4	1.1	Q4 vs. Q1

Table 130 Overall evidence on total physical activity and kidney cancer

	Summary of evidence
2005 SLR	Three cohort studies reported on total physical activity and kidney cancer. None of the studies reported evidence of association between overall physical activity and risk of kidney cancer.
Continuous Update Project	One study was identified during the CUP, which showed an inverse trend of renal cell cancer risk .in women but not in men. Overall, no association was observed.

Table 131 Inclusion/exclusion table for meta-analysis of total physical activity and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14802	Setiawan	2007	Prospective Cohort Study	Hawaii Los Angeles Multiethnic Cohort Study	Incidence	No	No	Yes	-	-
KID00217	Mahabir	2004	Prospective Cohort Study	Alpha-Tocopherol Beta-Carotene Cancer Prevention	Incidence	Yes	No	Yes	-	-
KID00590	Bergström	2001	Prospective Cohort Study	Swedish Twin Cohort	Mortality and incidence	Yes	No	Yes	-	-
KID01081	Prineas	1997	Prospective Cohort Study	Iowa Women's Health Study	Incidence	Yes	No	Yes	-	-

Figure 109 Highest versus lowest forest plot of total physical activity and kidney

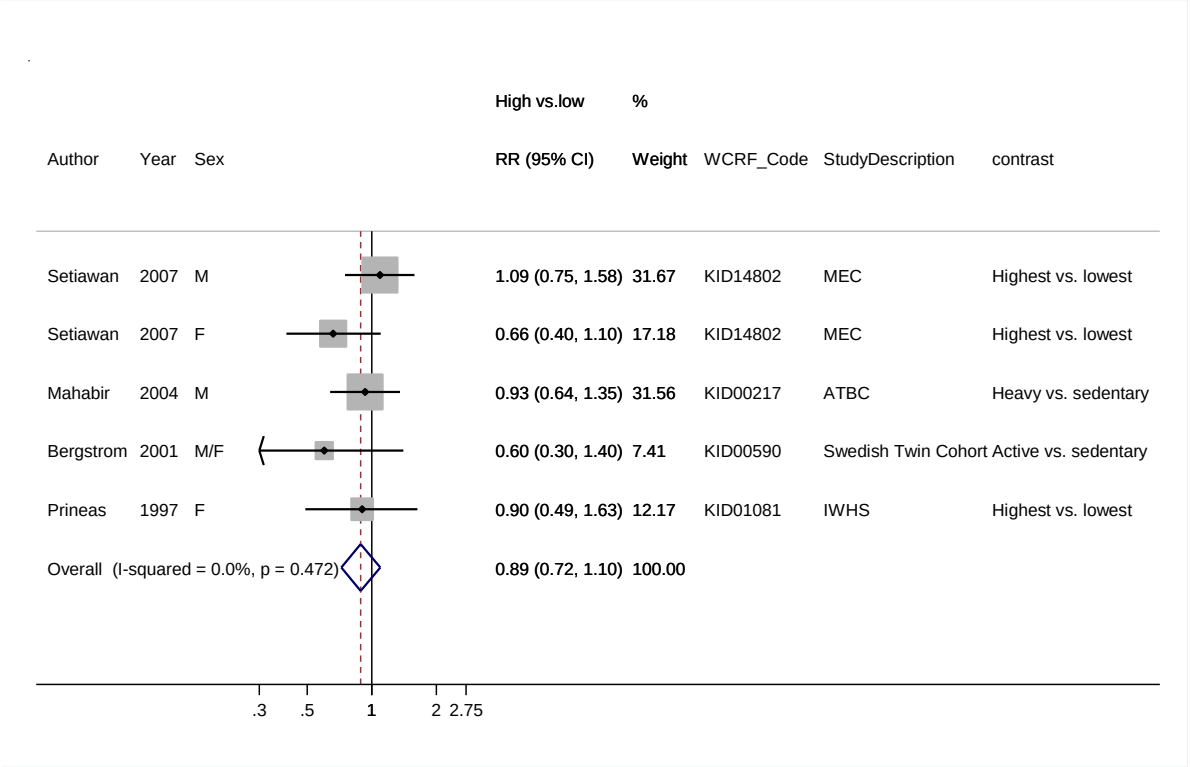
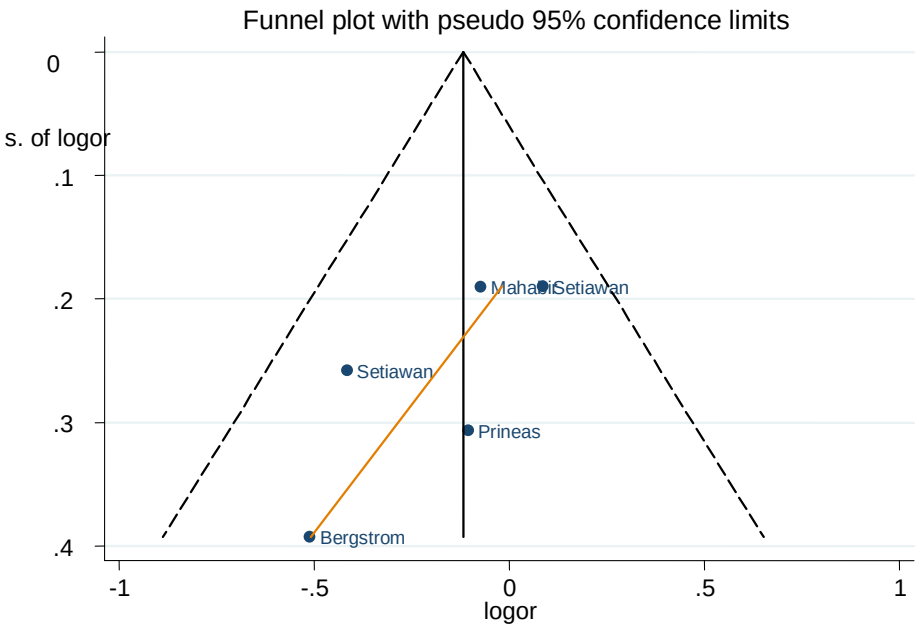


Figure 110 Funnel plot of total physical activity and kidney cancer



6.1.1.1 Occupational physical activity

Methods

A total of 5 articles (5 cohort studies) have been published Up to 31 March 2013, all identified during the 2005 SLR. No new study was identified during the CUP. Overall, five studies were included in a high versus low meta-analysis.
The NIH-AARP (Moore et al, 2008) reported a RR=0.89 (95% CI: 0.60-1.31) for the comparison of heavy work vs mainly sitting in daily routine activities. The study was not included here because the exposure was not only occupational activity.

Main results

A High versus Low meta-analysis was conducted because this was not done during the SLR.A weak significant association was observed when comparing the highest vs. the lowest level of occupational physical activity (RR=0.96; 95% CI: 0.76-1.23).

Heterogeneity

Significant heterogeneity was detected (I^2= 55.6%, $p_{heterogeneity}$=0.047). Egger's test showed no evidence of publication bias (p= 0.60) but only six estimates were included.

Comparison with the Second Expert Report
In the SLR the evidence relating physical activity to kidney cancer was considered limited and no conclusion was possible. No meta-analysis of cohort studies was conducted

Meta-analysis and Pooled studies

In a published meta-analysis including 19 case-control and cohort studies (10756 renal cancer cases), the relative risk estimates of renal cell cancer was 0.87 (95% CI: 0.69-1.08), when comparing high versus low levels of occupational physical activity (Behrens and Leitzmann, 2013).

Table 132 Overall evidence on occupational physical activity and kidney cancer

	Summary of evidence
2005 SLR	Five studies were identified, and one of them reported inverse association - in men only (Bergstrom, 1997). Overall no association with kidney cancer risk was observed when comparing the highest vs the lowest category of occupational physical activity.
Continuous Update Project	No study was identified during the CUP.

Table 133 Inclusion/exclusion table for meta-analysis of occupational physical activity and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14789	Washio	2005	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	Yes	No	Yes	-	-
KID00217	Mahabir	2004	Prospective Cohort Study	Alpha- Tocopherol Beta- Carotene Cancer Prevention Study	Incidence	Yes	No	Yes	-	-
KID14405	Van Dijk	2004	Nested case-control study	Netherland Cohort Study	Incidence	Yes	No	Yes	-	-
KID00590	Bergström	2001	Prospective Cohort	Swedish Twin Cohort 1959-1961	Mortality and incidence	Yes	No	Yes	-	-
KID00759	Bergström	1999	Nested Case Control	Sweden 1960-1970	Incidence	Yes	No	Yes	-	-

Figure 111 Highest versus lowest forest plot of occupational physical activity and kidney cancer

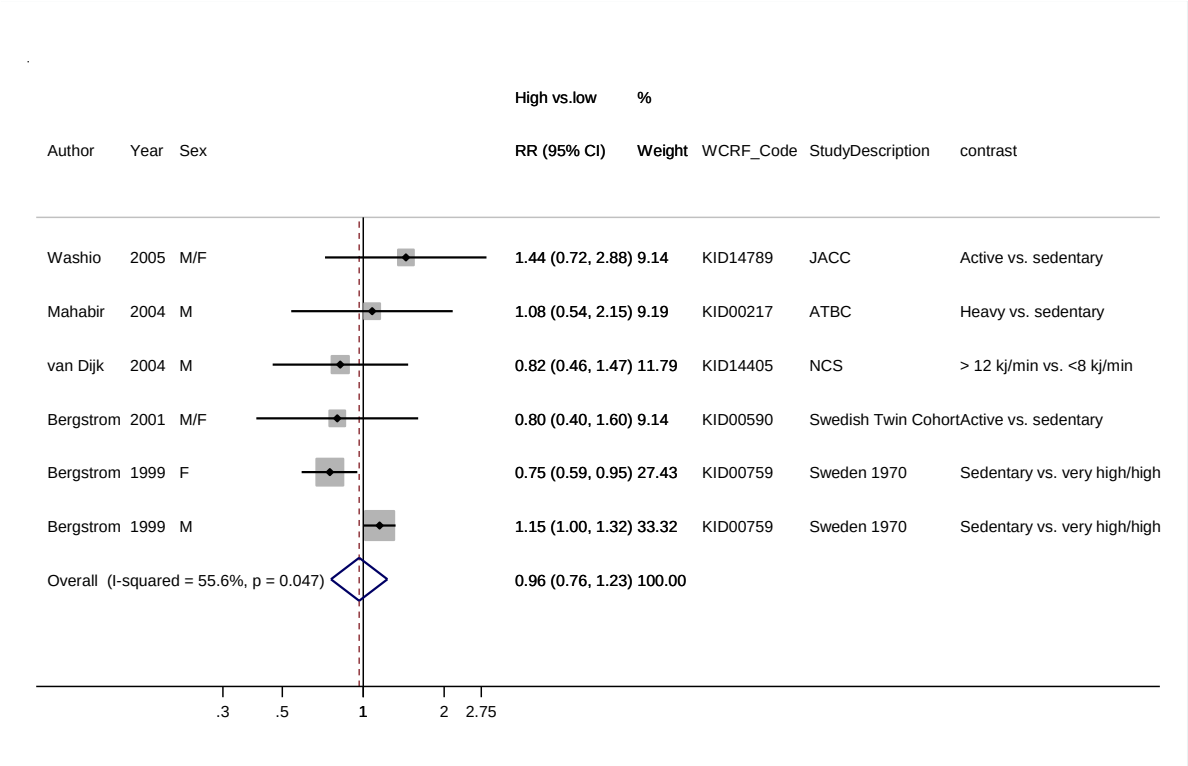
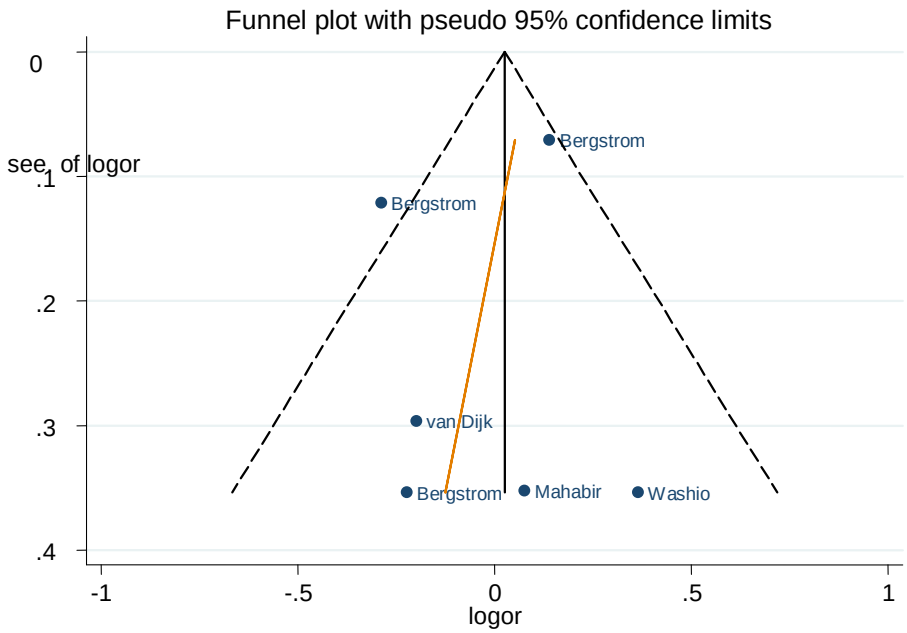


Figure 112 Funnel plot of occupational physical activity and kidney cancer



6.1.1.2 Recreational physical activity

Methods

Up to 31 March 2013, 9 articles (7 cohort studies) have been published; 4 of them were identified during the CUP. Included were studies that reported on "leisure time physical activity" and two studies (Moore et al, 2008; Suzuki et al, 2007) that reported on sports/exercise activities. Overall, seven studies were included in a high versus low meta-analysis.

Main results

The summary relative risk for the highest vs. the lowest level of recreational physical activity was 0.84 (95% CI= 0.70-1.01). In influence analysis, the estimates ranged from 0.88 (95% CI=0.77-0.99) when a study in male smokers was excluded (Wilson et al, 2009).

Heterogeneity

Moderate heterogeneity was observed (I^2= 27.4%, $p_{heterogeneity}$=0.20). Egger's test showed no evidence of publication bias (p= 0.66).

Comparison with the Second Expert Report

In the SLR the evidence relating physical activity to kidney cancer was considered limited and no conclusion was possible.

Meta-analysis and Pooled studies

In a published meta-analysis including 19 case-control and cohort studies (10756 renal cancer cases), the relative risk estimates of renal cell cancer was 0.88 (95% CI: 0.77-1.00), when comparing high versus low levels of recreational physical activity (Behrens and Leitzmann, 2013).

Table 134 Studies on recreational physical activity identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Wilson, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	228	15.2	M	0.3	0.1	0.8	Heavy vs. light leisure time physical activity
Yun, 2008	Korea	Korean National Health Insurance Corporation Study	395	6	M	1.01	0.83	1.23	Moderate- high vs. low leisure time physical activity
Moore, 2008	USA	NIH-AARP Diet and Health Study	1238	8.2	M/F	0.81	0.67	0.98	>=5 times/week vs. never/rarely current exercise/sports
Suzuki,	JAPAN	Japan	35	~15	M	1.22	0.49	3.04	<1 hour/week

2007		Collaborative Cohort study for Evaluation of Cancer Risk	16		F	1.27	0.28	5.70	vs. >3 hours/week of sport time <1 hour/week vs. >3 hours/week

Table 135 Overall evidence on recreational physical activity and kidney cancer

	Summary of evidence
2005 SLR	Five studies were identified; two of them reported inverse association.
Continuous Update Project	Four studies were identified during the CUP. The highest vs. lowest summary showed no association.

Table 136 Inclusion/exclusion table for meta-analysis of recreational physical activity and kidney cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14815	Wilson	2009	Prospective Cohort Study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Incidence	No	No	Yes	-	-
KID14849	Yun	2008	Prospective Cohort Study	Korean National Health Insurance Corporation Study	Incidence	No	No	Yes	-	-
KID14807	Moore	2008	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	No	Yes	-	-
KID14851	Suzuki	2007	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	No	Yes	-	-
KID14789	Washio	2005	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	Yes	No	No	-	Superseded by Suzuki et al, 2007
KID14405	Van Dijk	2004	Case Cohort Study	The Netherlands Cohort Study	Incidence	Yes	No	Yes	-	-
KID00217	Mahabir	2004	Prospective Cohort Study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No	-	Superseded by Wilson et al., 2009
KID00590	Bergström	2001	Prospective Cohort Study	Swedish Twin Cohort	Mortality and incidence	Yes	No	Yes	-	-
KID02053	Whittemore	1984	Case Cohort Study	Harvard and Pennsylvania Alumni Study 1916-1950	Mortality and incidence	Yes	No	No	-	Exposure is sport activities at College

Figure 113 Highest versus lowest forest plot of recreational physical activity and kidney cancer

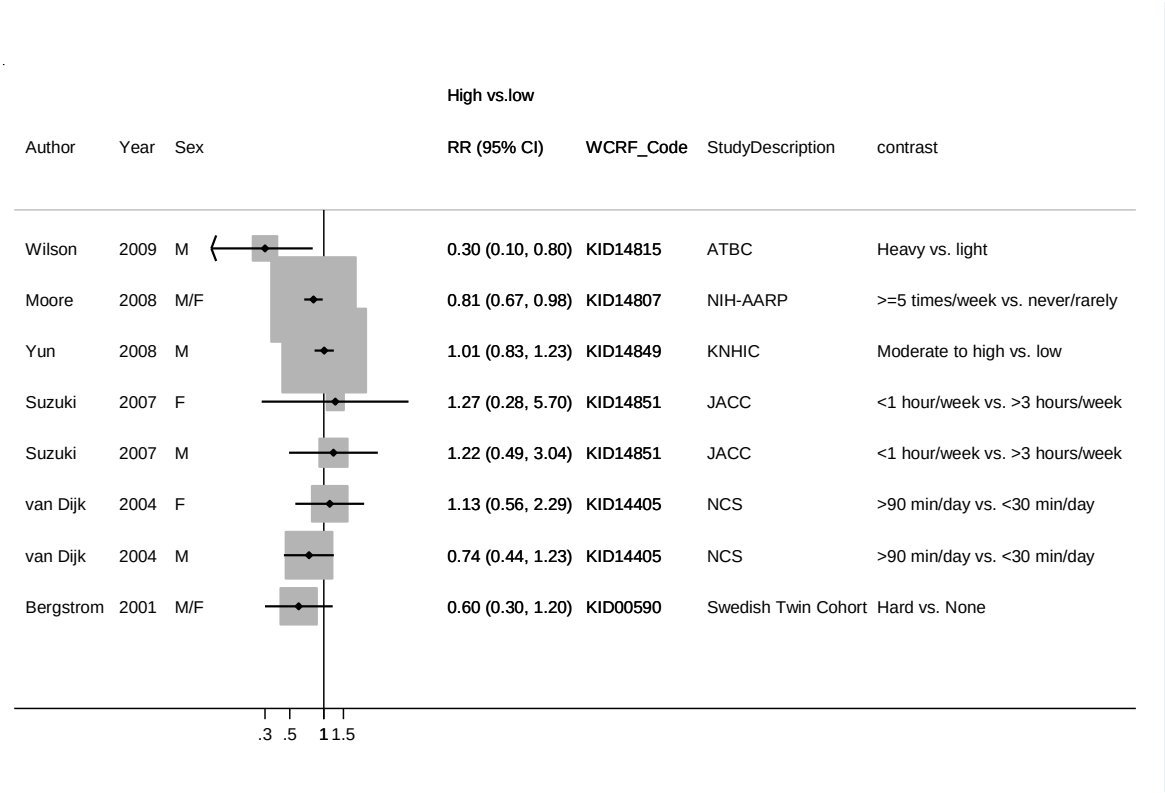
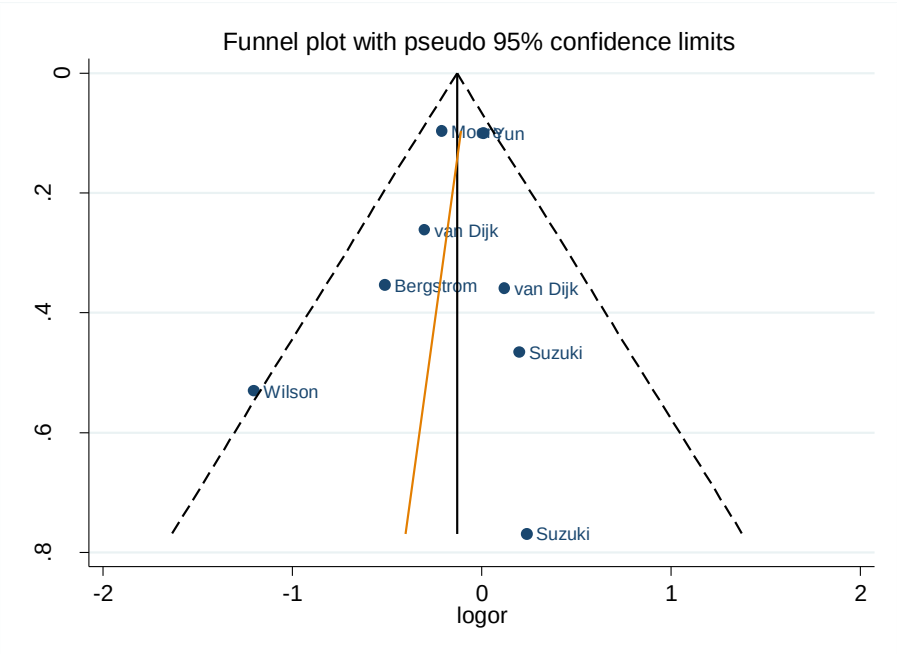


Figure 114 Funnel plot of recreational physical activity and kidney cancer



6.1.1.4.1 Walking

In the JACC study the relative risk for kidney cancer death was 0.69 (95% CI=0.36-1.34) in people who walk 30 min/day or more compared to those who walk less than 30 min/day (Washio et al, 2005). The relative risks for walking less than 30 min/day compared to more than one hour/day were 1.84 (95% CI= 0.82-4.15) in men and 2.49 (05% CI: 0.83-7.48) in women (Suzuki et al, 2007).

6.2 Physical inactivity

Two studies reported on time spent watching TV and sitting time.

In the JACC study (Suzuki et al, 2007), the relative risk for watching TV more than 4 hours/day compared to less than 2 hours/day was 1.32 (95% CI=0.50-3.48) in men and 0.53 (95% CI=0.18- 1.54) in women.
Sitting time was not related to renal cell cancer risk in the NIH-AARP study (George et al, 2011). The relative risk for sitting 9 hours or more compared to less than 3 hours per day was 0.96 (95% CI=0.66-1.38). In analysis on time sitting watching TV or videos, the relative risk was 0.96 (95% CI=0.66-1.38) when comparing watching TV for 7 hours or more vs less than one hour.

8 Anthropometry

8.1.1 BMI

Methods

A total of 36 articles including 28 studies of BMI and kidney cancer were identified. Seventeen articles (14 studies) of these were identified in the CUP.
Dose-response analyses and stratified analyses of BMI and kidney cancer risk were conducted per 5 BMI units. The method by Hamling et al, 2008 was used to convert risk estimates when the reference category was not the lowest category.

Main results

The summary RR per 5 BMI units was 1.30 (95% CI: 1.25-1.35, I^2=38.8%, $p_{heterogeneity}$=0.06, n=23). The association was similar among men and women, with summary RR = 1.29 (95% CI: 1.23-1.36, I^2=29.5%, $p_{heterogeneity}$=0.12) for men and summary RR = 1.28 (95% CI: 1.24-1.32, I^2=0%, $p_{heterogeneity}$=0.46) for women. When stratified by outcome type, the summary RR was 1.30 (95% CI: 1.25-1.36, I^2=38.9%, $p_{heterogeneity}$=0.04, n=21) for studies of incidence and 1.32 (95% CI: 1.01-1.71, I^2=37.4%, $p_{heterogeneity}$=0.21, n=2) for studies of mortality. When stratified by geographic location the summary RR was 1.29 (95% CI: 1.20-1.39, I^2=55.8%, $p_{heterogeneity}$=0.02, n=10) for American studies, 1.27 (95% CI: 1.24-1.31, I^2=0%, $p_{heterogeneity}$=0.77, n=9) for European studies and 1.47 (95% CI: 1.26-1.72, I^2=16.1%, $p_{heterogeneity}$=0.31, n=4) for Asian studies. The test for nonlinearity was not significant, p=0.07. Of the articles not included in the analyses 8 were duplicates, 3 did not report risk estimates, one was a case-control study and one reported results in <3 categories (see Table 118 for details).

Heterogeneity

Heterogeneity was moderate, but statistically significant (p=0.03) in the analyses for all studies combined, however when stratified by gender there was no significant heterogeneity in either men or women (p=0.12 and p=0.46, respectively). The funnel plot shows that the smaller studies reported estimates above the pooled value obtained for all studies combined. There was no indication of publication bias with Egger's test, p=0.14.

Comparison with the Second Expert Report

In the SLR the evidence that greater body fatness increases risk of kidney cancer was considered convincing.

Published meta-analyses and pooled analyses

A meta-analysis of cohort studies reported a summary RRs per 5 kg/m^2 increase of 1.24 (95% CI: 1.15-1.34, I^2=37%, n=11) and 1.34 (95% CI: 1.25-1.43, I^2=45%, n=12) among men and women, respectively (Renehan, 2008). Two other meta-analyses reported summary RRs for each unit increase in BMI of 1.05 (95% CI: 1.04-1.06) among men (Iladaphonse et al, 2009, 13 cohorts) and 1.06 (95% CI: 1.05-1.07) among women (Mathew et al, 2009, 15 cohorts). A pooled analysis of 39 Asian cohort studies reported a pooled HR for mortality of kidney cancer of 1.59 (95% CI: 0.78-3.24) for BMI ≥30 vs. 18.5-24.9 and 1.20 (95% CI: 0.86-1.66)

per 5 unit increase in BMI (Parr et al, 2011). The studies were from China, Japan, South Korea, Singapore, Thailand, Taiwan, Australia and New Zealand. None of the studies was included in the CUP.

A pooled analysis within the Me-Can project (7 cohorts) reported a RR of 1.51 (95% CI: 1.13-2.03) when comparing BMI 31.7 with 21.5 kg/m^2 for men and a RR of 2.21 (95% CI: 1.32-3.70) when comparing BMI 31.7 with 20 kg/m^2 for women (Haggstrom et al, 2013).Two of the cohorts were included in the CUP.

A pooled analysis of 57 prospective studies (422 kidney cancer deaths), reported a pooled HR of 1.23 (95% CI: 1.06-1.43) per 5 kg/m^2 increase (Prospective Studies Collaboration).

Table 137 Studies on BMI identified in the CUP

Author, year	**Country**	**Study name**	**Cases**	**Years of follow up**	**Sex**	**RR**	**LCI**	**UCI**	**Contrast (kg/m^2)**
Southard, 2012	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	154 cases	12.1 years	M	1.9	1.1	3.2	30.5 vs. 22.8
Smits, 2010	Netherlands	Netherlands Cohort Study	187	11.3 years	M/F	0.29 1.08 1.72 1.09	0.04 1.01 0.76 1.02	2.17 1.15 3.89 1.16	>30 vs. 18.5-<25.0 Per 1 unit (VHL mutation, wild-type) >30 vs. 18.5-<25.0 Per 1 unit (VHL mutation)
Sawada, 2010	Japan	Japan Public Health Center-based Prospective Study	139 cases	13.5 years	M F	1.99 1.18 1.55 1.16	1.04 0.83 0.76 0.71	3.81 1.68 3.18 1.90	≥27 vs. 23-24.9 Per 5 units ≥25 vs. 21-24.9 Per 5 units
Andreotti, 2010	USA	Agricultural Health Study	148	10 years	M F	0.72 1.00 2.30 1.02	0.31 0.93 0.96 0.95	1.70 1.08 5.49 1.10	30-34.9 vs. 18.5-24.9 Per 1 unit 30-34.9 vs. 18.5-24.9 Per 1 unit
Wilson, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	228	15 years	M	2.1	1.4	3.1	>28.5 vs. ≤23.7
Prentice, 2009	USA	Women's Health Initiative	99	12 years	F	1.14	0.59	2.20	Per 10 units
Song, 2008	Korea	National Health	102	8.75	F	2.61	1.06	6.41	≥30 vs. 21-22.9

		Insurance Corporation Study	cases	years		1.08	1.02	1.15	Per 1 unit
Jee, 2008	Korea	National Health Insurance Corporation Study	2439 cases	10.8 years	M/F	1.38 1.21	0.76 0.58	2.52 2.53	≥30 vs. 23-24.9 ≥30 vs. 23-24.9
Adams, 2008	USA	NIH-AARP Diet and Health Study	1366 cases	8.2 years	M F	2.47 2.59	1.72 1.70	3.53 3.96	≥35 vs. 18.5-<22.5 ≥35 vs. 18.5-<22.5
Setiawan, 2007	USA	Multiethnic Cohort Study	347 cases	8.3 years	M F	1.76 2.27	1.20 1.37	2.58 3.74	≥30 vs. <25 ≥30 vs. <25
Fujino, 2007	Japan	Japan Collaborative Cohort Study	117 cases	~14 years	M F	2.89 4.49	0.39 0.55	21.31 36.20	≥30 vs. 18.5-24 ≥30 vs. 18.5-24
Luo, 2007	USA	Women's Health Initiative	269 cases	7.7 years	F	1.6 1.03	1.1 1.01	2.4 1.05	≥35.0 vs. <25.0 Per 1 unit
Reeves, 2007	United Kingdom	Million Women's Study	615 cases 382 deaths	5.4 years 7.0 years	F	1.51 1.53 1.71 1.65	1.31 1.27 1.39 1.28	1.77 1.84 2.09 2.13	≥30 vs. 22.5-24.9 Per 10 units ≥30 vs. 22.5-24.9 Per 10 units
Samanic, 2006	Sweden	Swedish Construction Worker's Study	444 cases	19 years	M	1.61	1.27	2.04	≥30 vs. <25
Pischon, 2006	8 European countries	European Prospective Investigation into Cancer and Nutrition	287 cases	6.0 years	M F	1.22 2.25	0.74 1.14	2.03 4.44	≥29.4 vs. <23.6 ≥29.1 vs. <21.8
Lukanova, 2006	Sweden	Northern Sweden Health and Disease Cohort Study	45 cases	8.2 years	M F	3.63 1.79	1.23 0.55	10.66 5.27	≥30 vs. 18.5-24.9 ≥30 vs. 18.5-24.9
Rapp, 2005	Austria	The Vorarlberg Health Monitoring and Promotion Program	229	9.9 years	M F	1.46 1.14	0.87 0.58	2.46 2.24	≥30 vs. 18-24.9 ≥30 vs. 18-24.9

Table 138 Overall evidence on BMI and kidney cancer

	Summary of evidence
2005 SLR	Twenty studies were identified and four of these did not provide risk estimates. All studies reported risk estimates above 1, and the associations were significant in 5 studies. The evidence of association was judged as convincing
Continuous Update Project	Of the fourteen additional cohort studies identified in the CUP, nine reported significant positive associations that were restricted to men in two studies and women in one study, while the remaining studies reported

	no association, although most were in the direction of increased risk (not significant). Overall, a significant association was observed.

Table 139 Summary of results of the dose-response meta-analysis of BMI and kidney cancer

Kidney cancer		
	SLR	Continuous Update Project
Studies (n)	7	23
Cases (n)	8602	15575
RR (95% CI)	1.31 (1.24-1.39)	1.30 (1.25-1.35)
Quantity	5 units	5 units
Heterogeneity (I^2, p-value)	12.0%, p=0.34	38.8%, p=0.03
By gender		
Men	-	1.29 (1.23-1.36),
Heterogeneity (I^2, p-value)	-	29.5%, p=0.12
Women	-	1.28 (1.24-1.32)
Heterogeneity (I^2, p-value)	-	0%, p=0.46
By outcome type		
Incidence	-	1.30 (1.25-1.36)
Heterogeneity (I^2, p-value)	-	38.9%, p=0.04
Mortality	-	1.32 (1.01-1.71)
Heterogeneity (I^2, p-value)	-	37.4%, p=0.21

Table 140 Inclusion/exclusion table for meta-analysis of BMI and kidney cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14830	Southard	2012	Nested case-control study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	M	Incidence	No	No	No	-	Overlap with Wilson et al, 2009 KID14815, which had a larger number of cases
KID14823	Smits	2010	Case cohort study	Netherlands Cohort Study	M/F	Incidence	No	No	No	-	Overlap with van Dijk et al, 2004, KID14405, which had a larger number of cases and did not stratify by genetic factors in the main analysis
KID14822	Sawada	2010	Prospective cohort study	Japan Public Health Centre-based Prospective Study	M/F	Incidence	No	Yes	Yes	Midpoints, converted RRs	-
KID14836	Andreotti	2010	Prospective cohort study	Agricultural Health Study	M/F	Incidence	No	Yes	Yes	Person-years, midpoints	-
KID14815	Wilson	2009	Prospective cohort study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	M	Incidence	No	Yes	Yes	Person-years	-
KID14835	Prentice	2009	Prospective cohort study	Women's Health Initiative	F	Incidence	No	No	No	-	Overlap with Luo et al, 2007, KID14799
KID14804	Song	2008	Prospective cohort study	National Health Insurance Corporation Study	F	Incidence	No	No	No	-	Overlap with Jee et al, 2008, KID14832
KID14832	Jee	2008	Prospective cohort study	National Health Insurance Corporation Study	M/F	Incidence	No	Yes	Yes	Person-years, midpoints, converted RRs	-
KID14803	Adams	2008	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints, person-years, converted RRs	-
KID14802	Setiawan	2007	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-

KID14850	Fujino	2007	Prospective cohort study	Japan Collaborative Cohort Study	M/F	Mortality	No	Yes	Yes	Midpoints, converted RRs	-
KID14799	Luo	2007	Prospective cohort study	Women's Health Initiative	F	Incidence	No	Yes	Yes	Midpoints	-
KID14801	Reeves	2007	Prospective cohort study	Million Women's Study	F	Incidence/ Mortality	No	Yes	Yes	Converted RRs	-
KID14796	Samanic	2006	Prospective cohort study	Swedish Construction Workers' Cohort Study	M	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14795	Pischon	2006	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14797	Lukanova	2006	Prospective cohort study	Northern Sweden Health and Disease Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14860	Rapp	2005	Prospective cohort study	The Vorarlberg Health Monitoring and Promotion Program	M/F	Incidence	No	Yes	Yes	Midpoints	-
KID14789	Washio	2005	Prospective cohort study	Japan Collaborative Cohort Study	M/F	Mortality	Yes	No	No		Surpassed by Fujino et al, 2007, KID14850
KID14249	Kuriyama	2005	Prospective cohort study	Miyagi Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints, person-years	-
KID14316	Oh	2005	Prospective cohort study	National Health Insurance Corporation Study	M/F	Incidence	Yes	No	No	-	Surpassed by Jee et al, 2008, KID14832
KID14698	Flaherty	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes	Midpoints	-
KID14698	Flaherty	2005	Prospective cohort study	Health Professional's Follow-up Study	M	Incidence	Yes	Yes	Yes	Midpoints	-

KID14405	van Dijk	2004	Case cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Converted RRs	-
KID00242	Nicodemus	2004	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints, person-years	-
KID14404	Bjorge	2004	Prospective cohort	Norwegian Tuberculosis Screening Study	M/F	Incidence	Yes	Yes	Yes	Midpoints, converted RRs	-
KID02777	Calle	2003	Prospective cohort	Cancer Prevention Study 2	M/F	Mortality	Yes	Yes	Yes	Midpoints, person-years	-
KID00234	Ali	2003	Nested case-control study	New York University Women's Health Study	F	Incidence	Yes	No	No	-	No risk estimates (only mean)
KID00506	Hirvonen	2001	Prospective cohort	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	M	Incidence	Yes	No	No	-	Overlap with Wilson et al, 2009 KID14815
KID00590	Bergström	2001	Case-control study	NA	M/F	Incidence	Yes	No	No	-	Case-control study, no risk estimates
KID00648	Chow	2000	Prospective cohort	Swedish Construction Workers Cohort Study	M	Incidence	Yes	No	No	-	Overlap with Samanic et al, 2006, KID14796
KID00762	Kurttio	1999	Nested case-control	Finland 1967-1980	M/F	Incidence	Yes	No	Yes	-	Only two categories of exposure
KID14209	Tulinius	1997	Prospective cohort	Icelandic Cardiovascular Risk Factor Study	F	Incidence	Yes	Yes	No	-	Continuous estimate, no result for men
KID01081	Prineas	1997	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	No	No	-	Overlap with Nicodemus et al, 2004 KID14405
KID01140	Gamble	1996	Nested case-control	New Jersey Refineries	M	Incidence	Yes	Yes	Yes	Midpoints	-
KID01376	Hiatt	1994	Nested case-control	Kaiser Permanente Medical Care Program	M/F	Incidence	Yes	Yes	Yes	Midpoints	-
KID01674	Fraser	1990	Prospective cohort	Adventist Health Study	M/F	Incidence	Yes	No	No	-	No risk estimates

KID02053	Whittemore	1984	Case cohort	Harvard and Pennsylvania Alumni Study 1916-1950	M	Incidence	Yes	No	No	-	No risk estimates

Figure 115 Highest versus lowest forest plot of BMI and kidney cancer

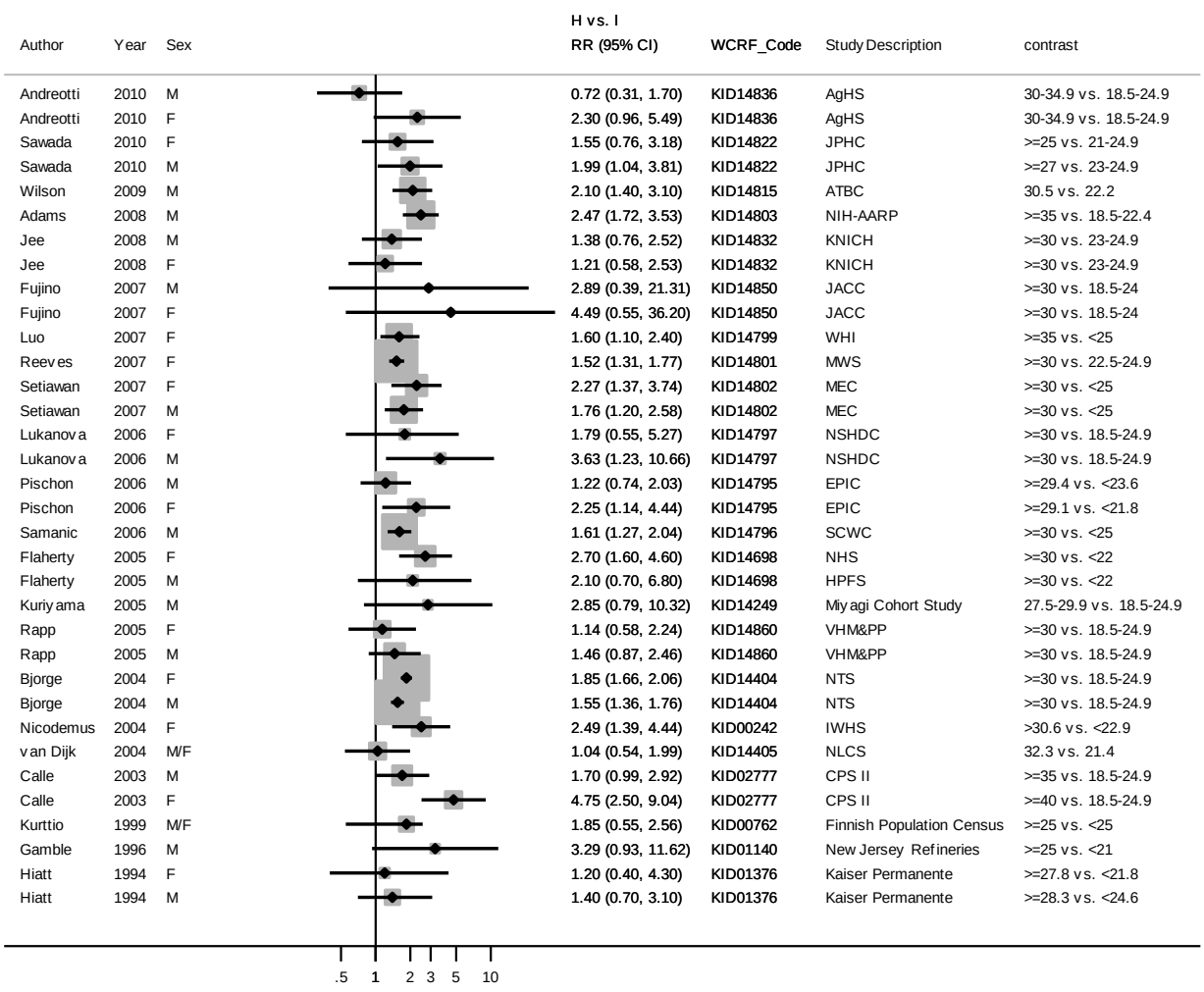


Figure 116 Dose-response meta-analysis of BMI and kidney cancer - per 5 units

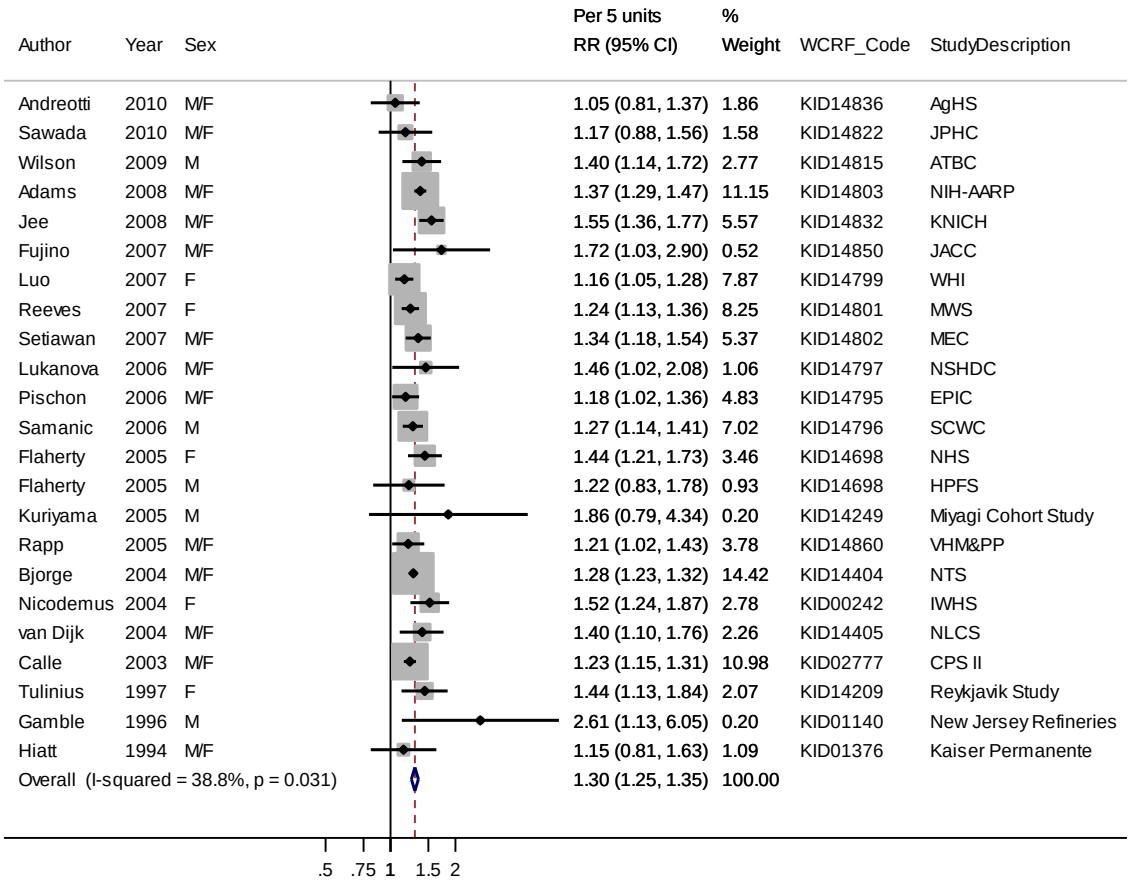


Figure 117 Funnel plot of BMI and kidney cancer

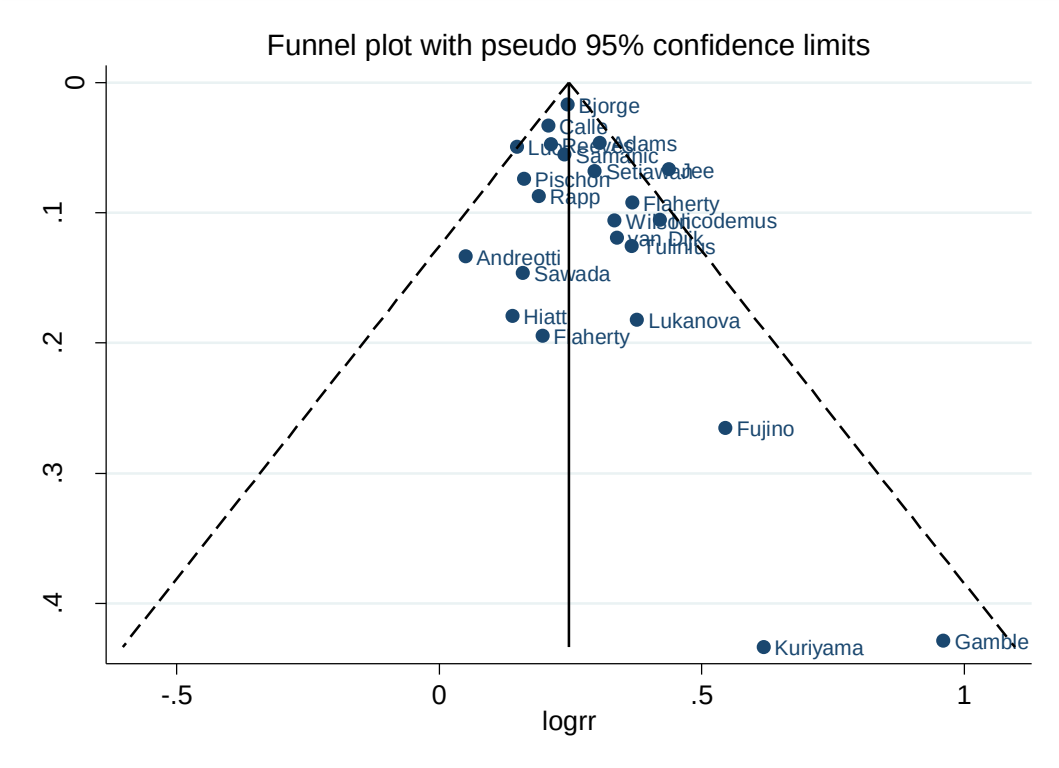


Figure 118 Dose-response graph of BMI and kidney cancer

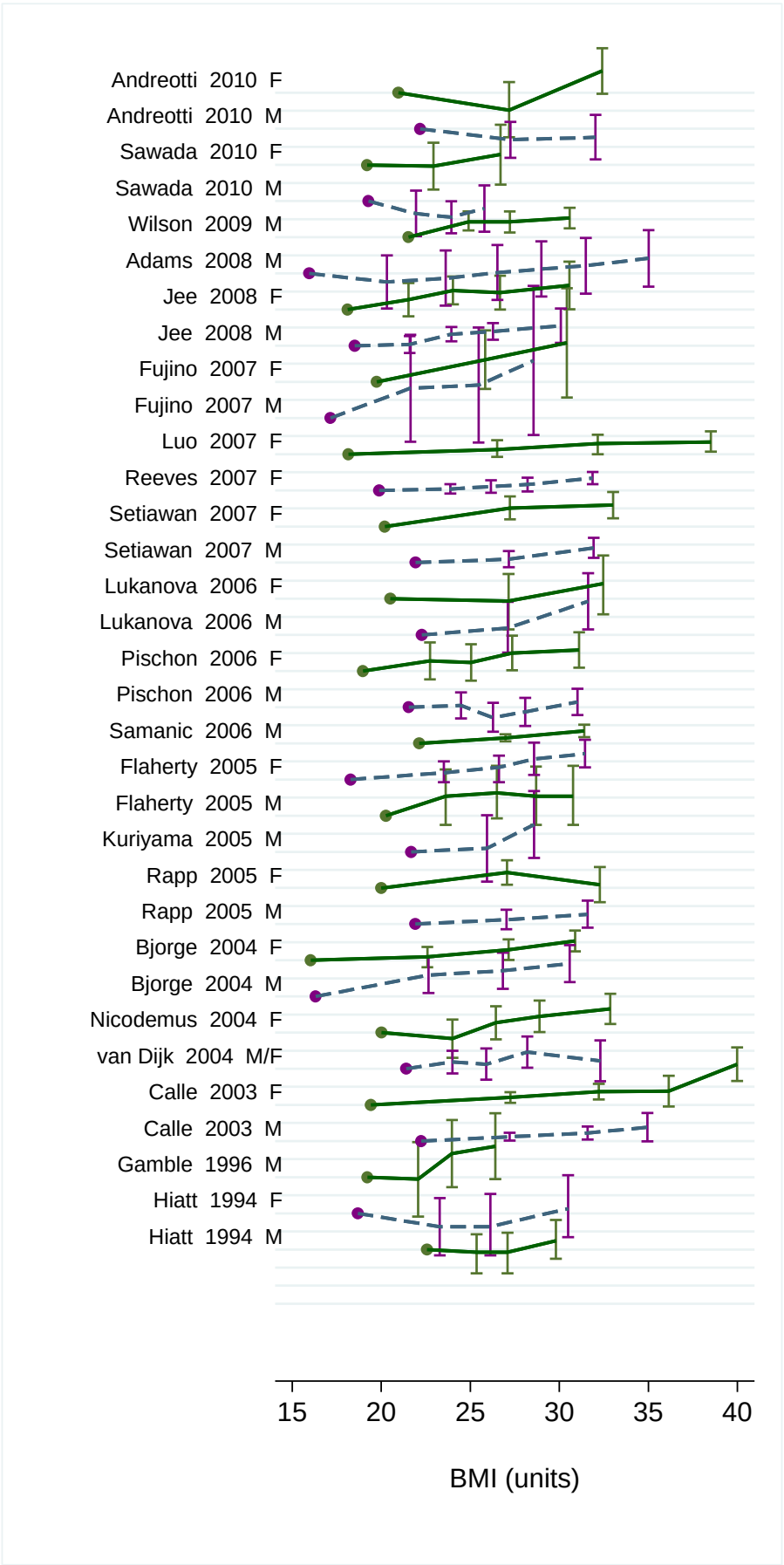


Figure 119 Dose-response meta-analysis of BMI and kidney cancer, stratified by sex – per 5 units

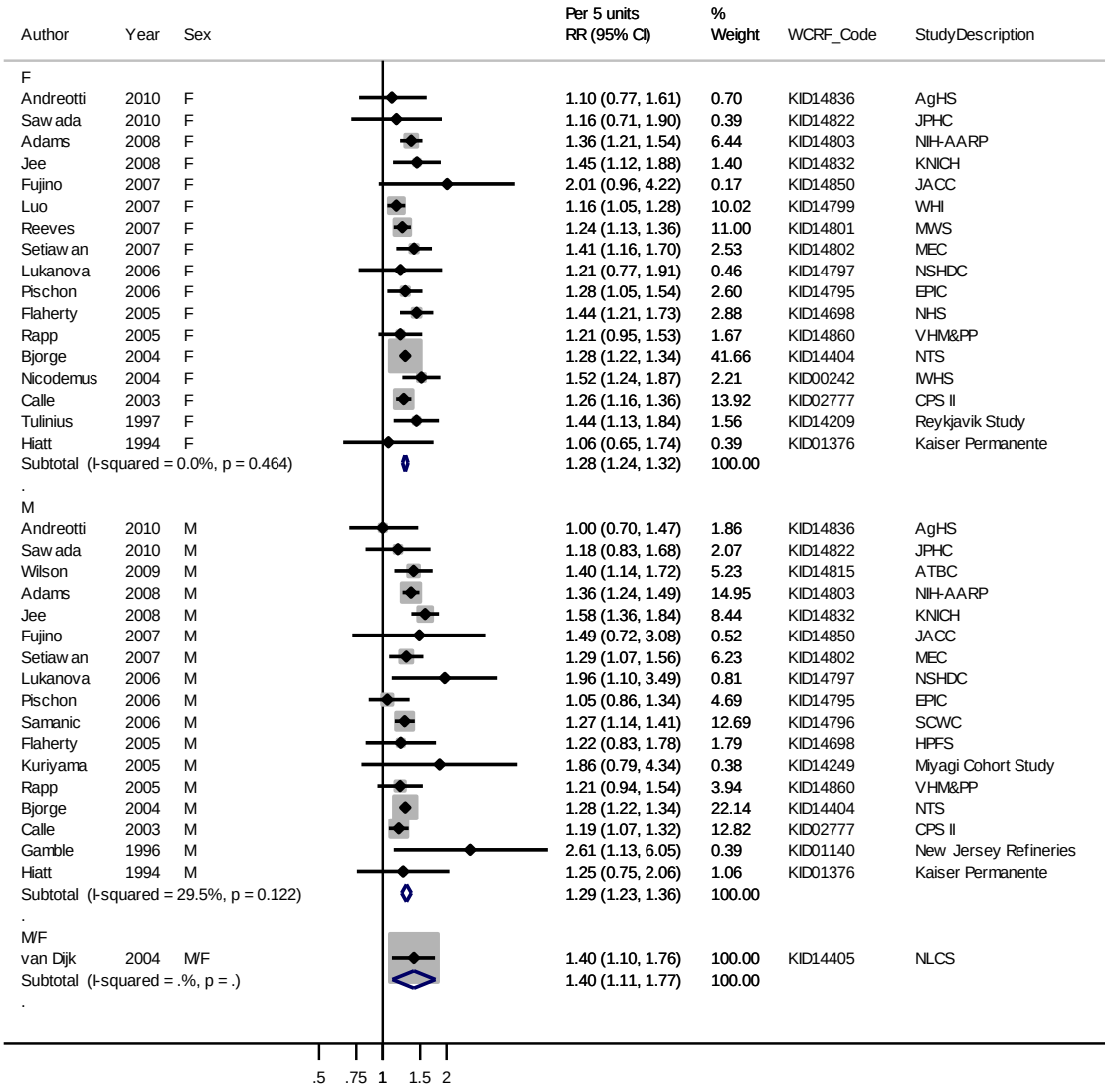


Figure 120 Dose-response meta-analysis of BMI and kidney cancer, stratified by outcome type – per 5 units

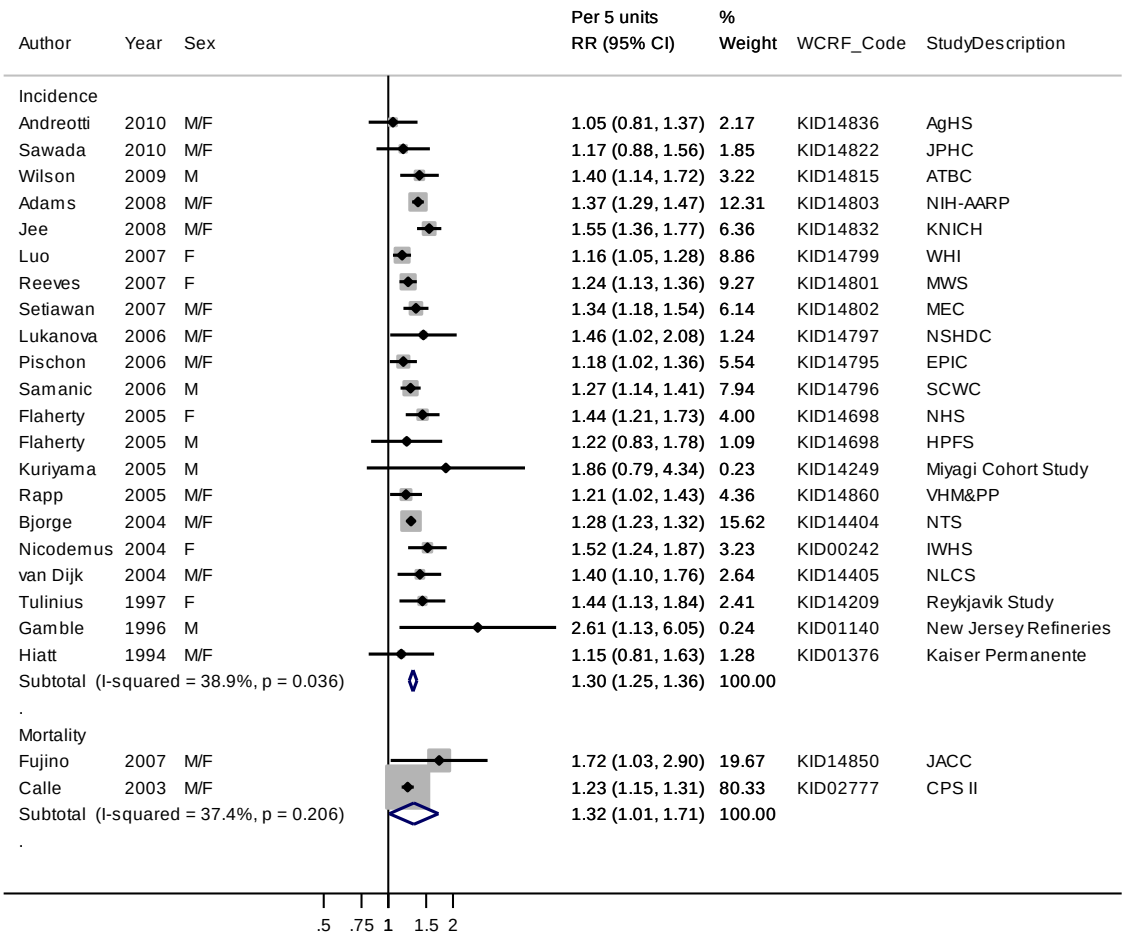


Figure 121 Dose-response meta-analysis of BMI and kidney cancer, stratified by geographic location – per 5 units

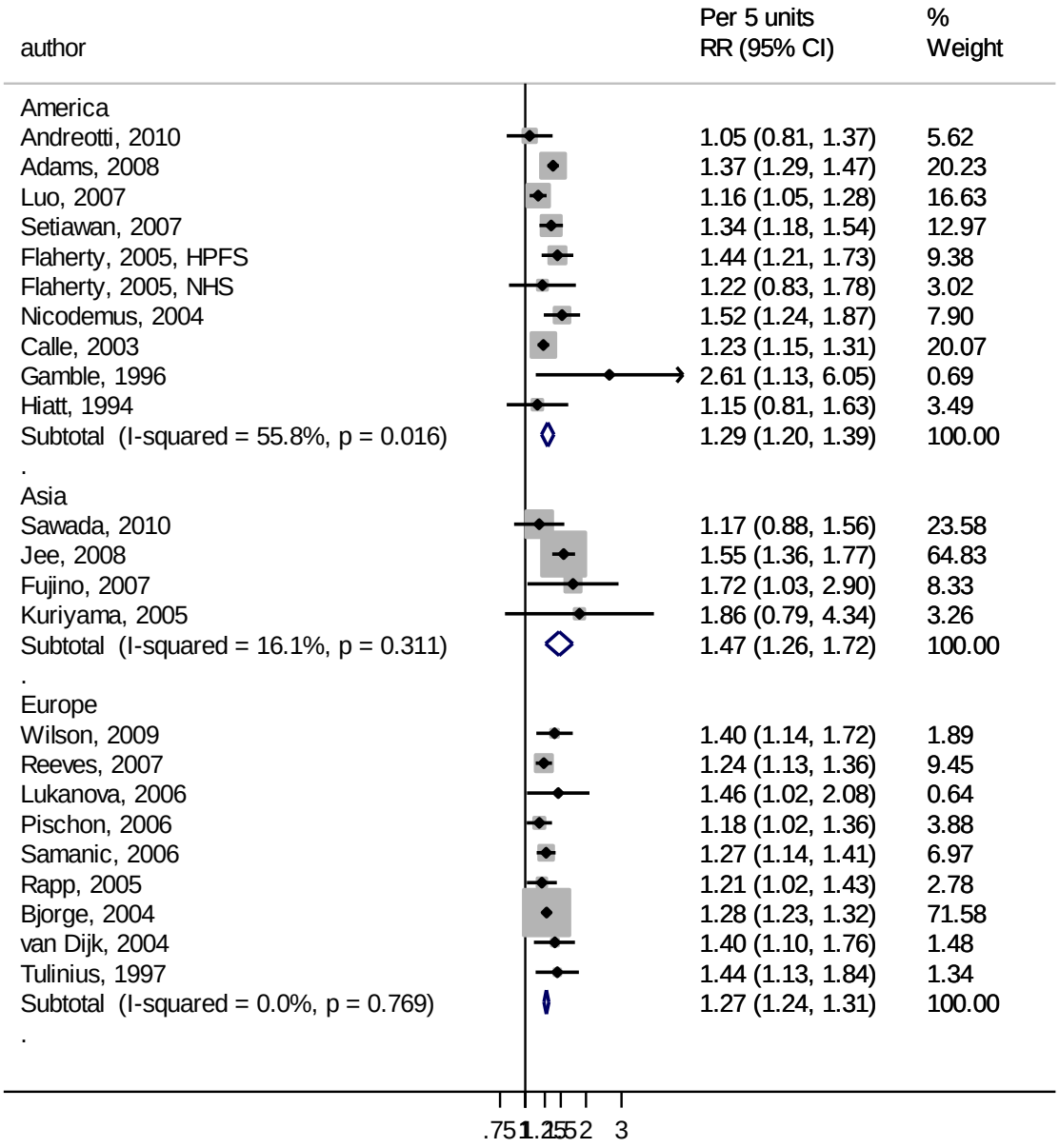
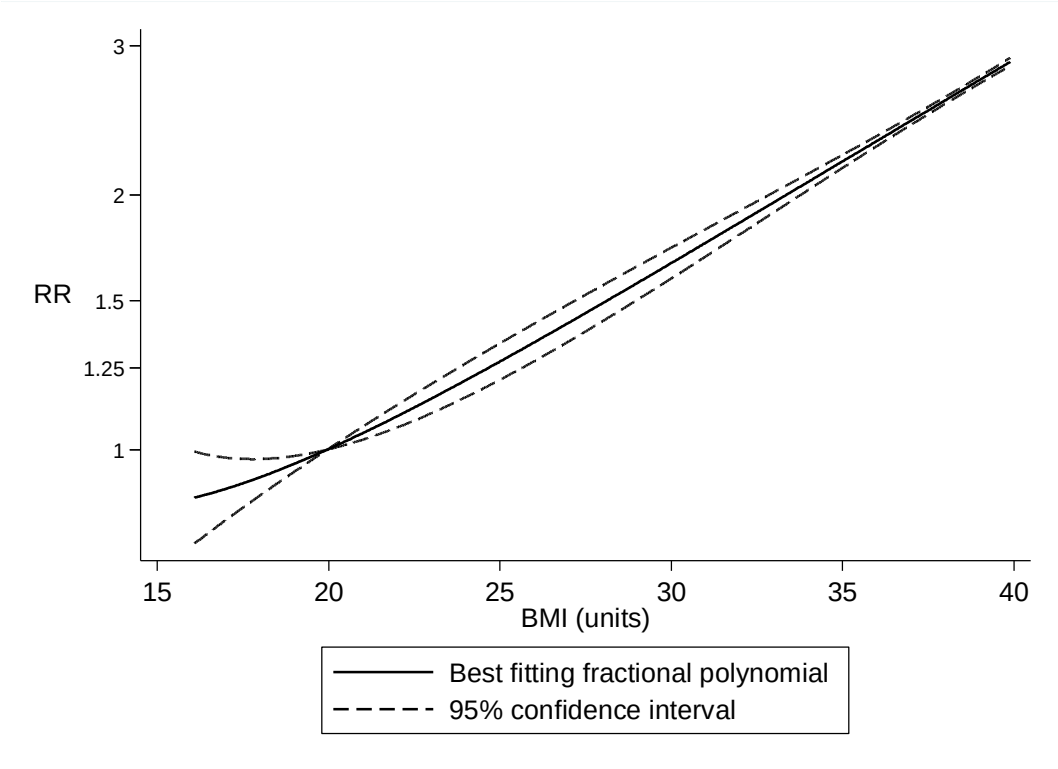


Figure 122 Nonlinear dose-response analysis of BMI and kidney cancer



p for nonlinearity=0.07

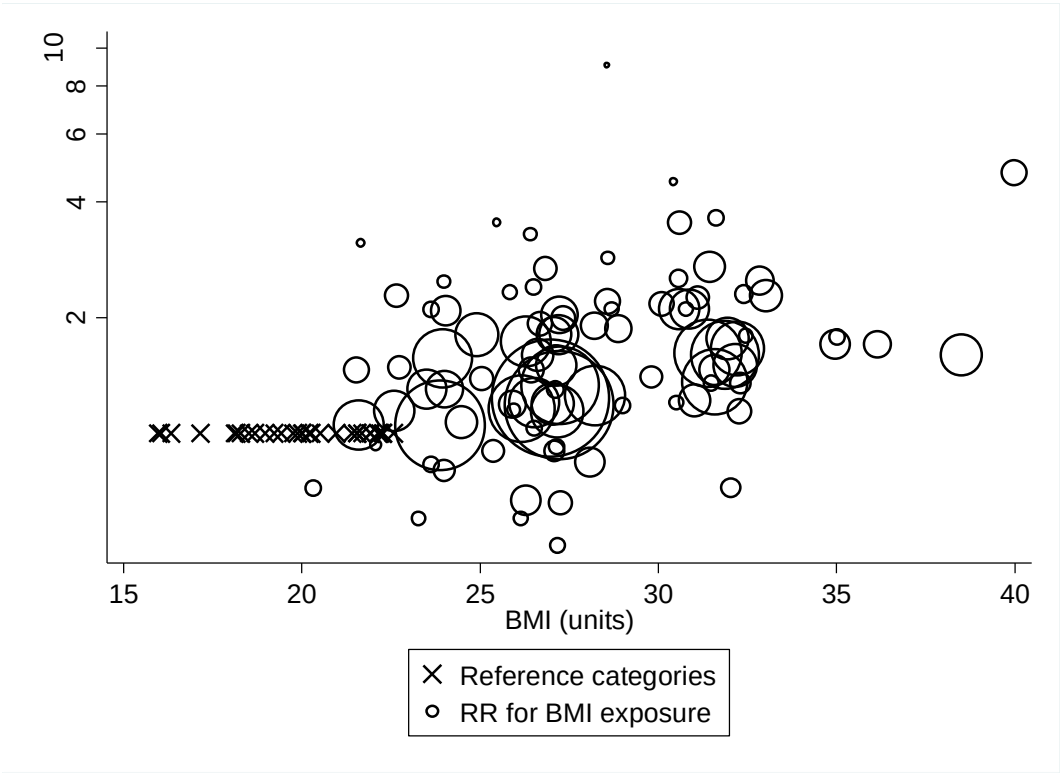


Table 141 RRs for nonlinear dose-response analysis

BMI	RR (95% CI)
17.5	0.91 (0.86-0.97)
20	1.00
22.5	1.12 (1.08-1.16)
25	1.27 (1.21-1.34)
27.5	1.45 (1.38-1.53)
30	1.66 (1.59-1.73)
32.5	1.91 (1.86-1.97)
35	2.19 (2.15-2.23)
37.5	2.51 (2.49-2.55)
40	2.90 (2.86-2.93)

8.1.3 Weight

Methods

A total of 9 studies (9 articles) of weight and kidney cancer were identified and three of these were identified in the CUP.
Dose-response analyses and stratified analyses of weight and kidney cancer risk were conducted per 5 kg weight.

Main results

The summary RR per 5 kg was 1.11 (95% CI: 1.07-1.14, I^2=18.2%, $p_{heterogeneity}$=0.29, n=7). The association was stronger in women than in men, with summary RR = 1.15 (95% CI: 1.11-1.19, I^2=0%, $p_{heterogeneity}$=0.58) for women and summary RR = 1.06 (95% CI: 1.02-1.10, I^2=0%, $p_{heterogeneity}$=0.77) for men. There was no evidence of a nonlinear association between weight and kidney cancer, $p_{nonlinearity}$=0.39.

Heterogeneity

There was little heterogeneity in the analyses, I^2=18.2%, $p_{heterogeneity}$=0.29). There was no indication of publication bias with Egger's test, p=0.31.

Comparison with the Second Expert Report

In the SLR the evidence relating body fatness to kidney cancer was considered convincing.

Table 142 Studies on weight identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Setiawan, 2007	USA	Multiethnic Cohort Study	347 cases	8.3 years	M F	1.52 3.39	0.84 1.71	2.75 6.72	Quartile 4 vs. 1 Quartile 4 vs. 1
Fujino, 2007	Japan	Japan Collaborative Cohort Study	117 cases	~14 years	M F	1.40 1.70	0.66 0.55	2.95 5.28	≥63 vs. <55 kg ≥55 vs. <49 kg
Pischon, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	287 cases	6.0 years	M F	1.28 1.02 2.13 1.10	0.73 0.95 1.16 1.02	2.25 1.10 3.90 1.18	≥90.0 vs. <71.0 kg Per 5 kg ≥75.6 vs. <57.4 kg Per 5 kg

Table 143 Overall evidence on weight and kidney cancer

	Summary of evidence
2005 SLR	Four studies reported risk estimates and all found increased risk, and this was significant in three of the studies.
Continuous Update Project	Three additional cohort studies were identified in the CUP, and all reported increased risk, although this was significant only in two of the studies and among women.

Table 144 Summary of results of the dose-response meta-analysis of weight and kidney cancer

Kidney cancer		
	SLR	Continuous Update Project
Studies (n)	4	7
Cases (n)	582	1333
RR (95% CI)	1.12 (1.07-1.16)[1]	1.11 (1.07-1.14)
Quantity	5 kg	5 kg
Heterogeneity (I^2, p-value)	0%, p=0.39	18.2%, p=0.29
By gender		
Men	-	1.06 (1.02-1.10)
Heterogeneity (I^2, p-value)	-	0%, p=0.77
Women	-	1.15 (1.11-1.19)
Heterogeneity (I^2, p-value)	-	0%, p=0.58

[1]Unadjusted risk estimate

Table 145 Inclusion/exclusion table for meta-analysis of weight and kidney cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14802	Setiawan	2007	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14850	Fujino	2007	Prospective cohort study	Japan Collaborative Cohort Study	M/F	Mortality	No	Yes	Yes	Midpoints	-
KID14795	Pischon	2006	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14698	Flaherty	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	No	No	Midpoints	No risk estimates
KID14698	Flaherty	2005	Prospective cohort study	Health Professional's Follow-up Study	M	Incidence	Yes	No	No	Midpoints	No risk estimates
KID14405	van Dijk	2004	Case cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	-	-
KID00242	Nicodemus	2004	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints, person-years	-
KID14209	Tulinius	1997	Prospective cohort	Reykjavik Study	F	Incidence	Yes	Yes	No	-	Continuous estimate
KID01081	Prineas	1997	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	No	No	-	Overlap with Nicodemus et al, 2004 KID14405
KID02053	Whittemore	1984	Case cohort	Harvard and Pennsylvania Alumni Study 1916-1950	M	Incidence	Yes	Yes	Yes	-	-

Figure 123 Highest versus lowest forest plot of weight and kidney cancer

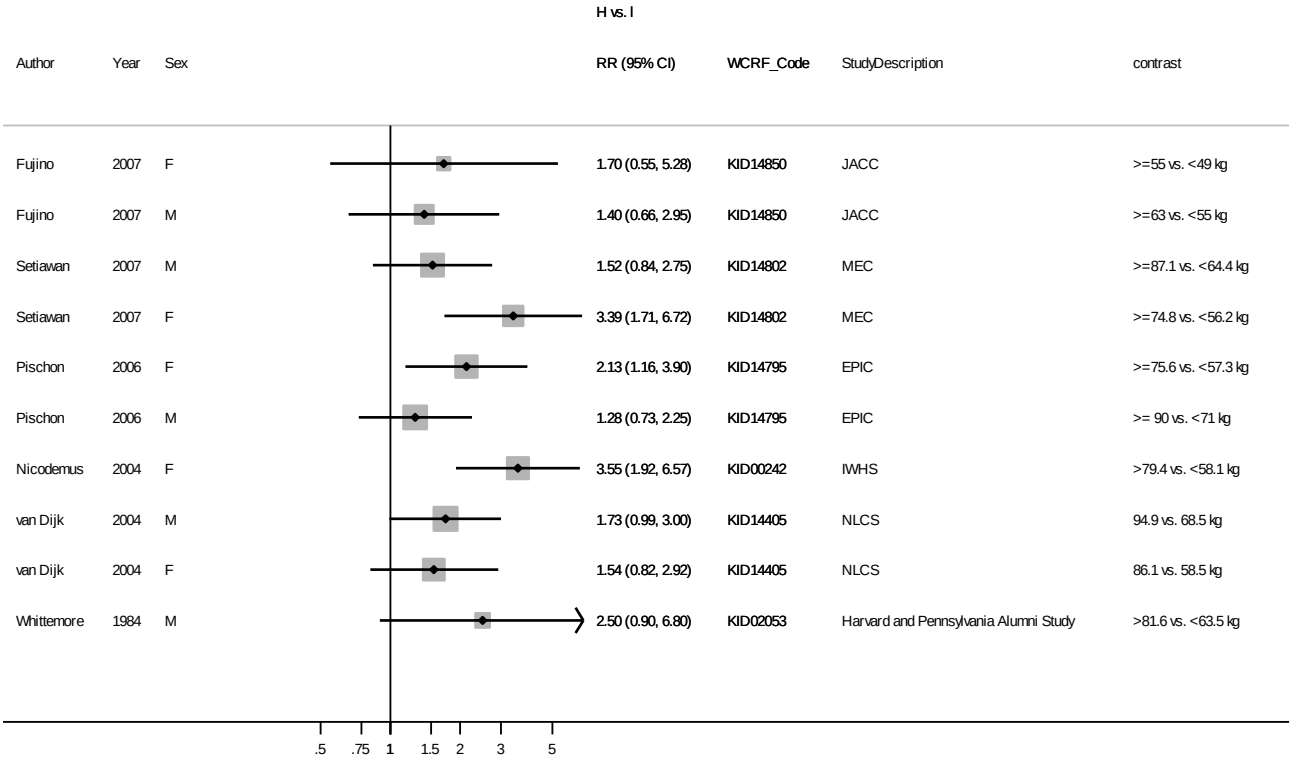


Figure 124 Dose-response meta-analysis of weight and kidney cancer - per 5 kg

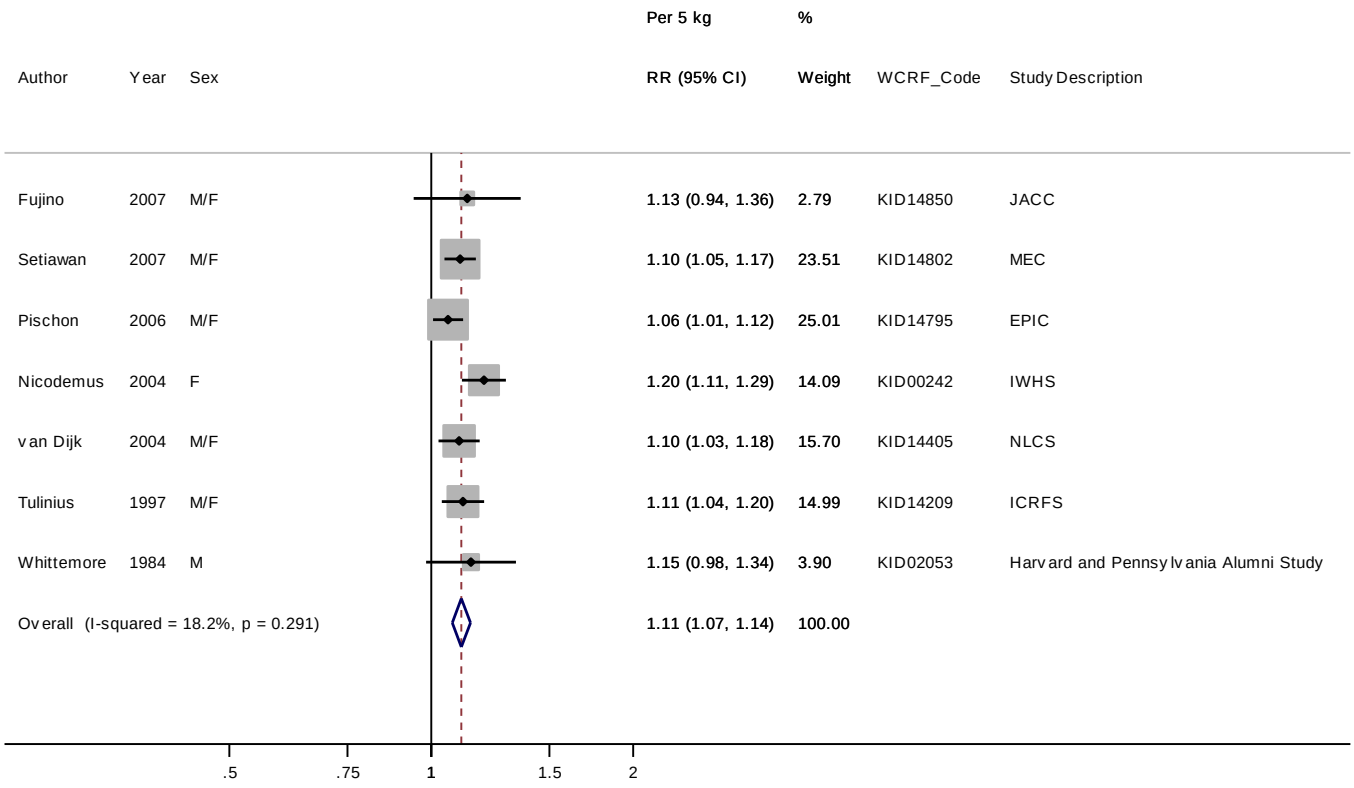


Figure 125 Funnel plot of weight and kidney cancer

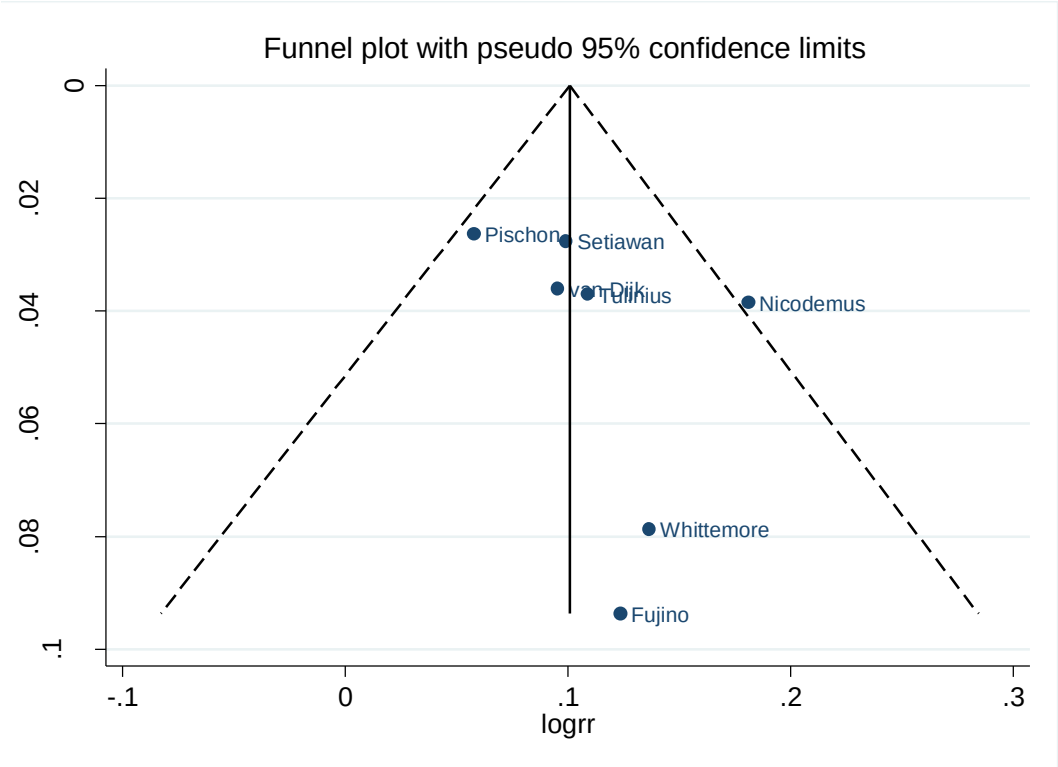


Figure 126 Dose-response graph of weight and kidney cancer

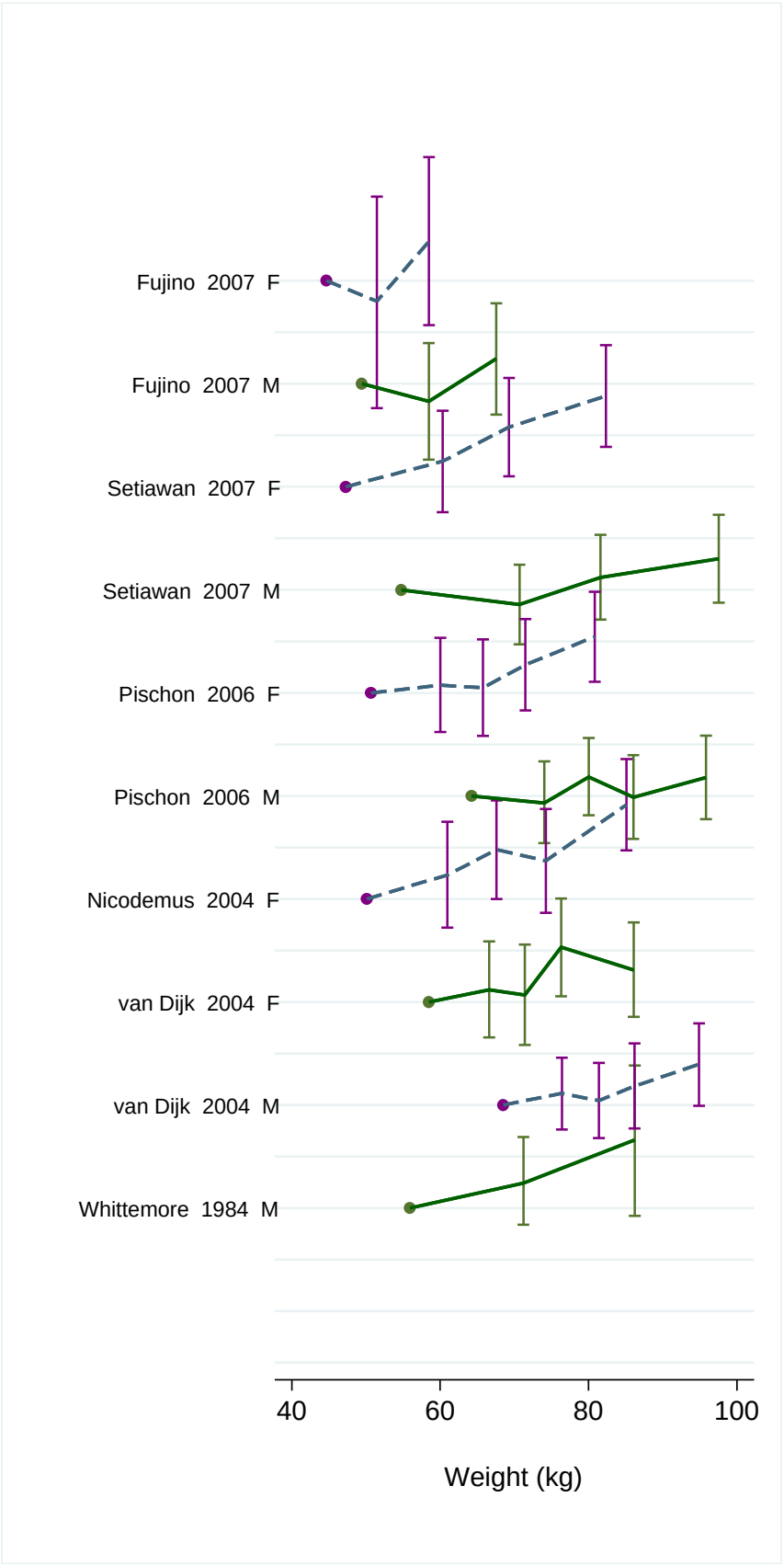


Figure 127 Dose-response meta-analysis of weight and kidney cancer, stratified by sex – per 5 kg

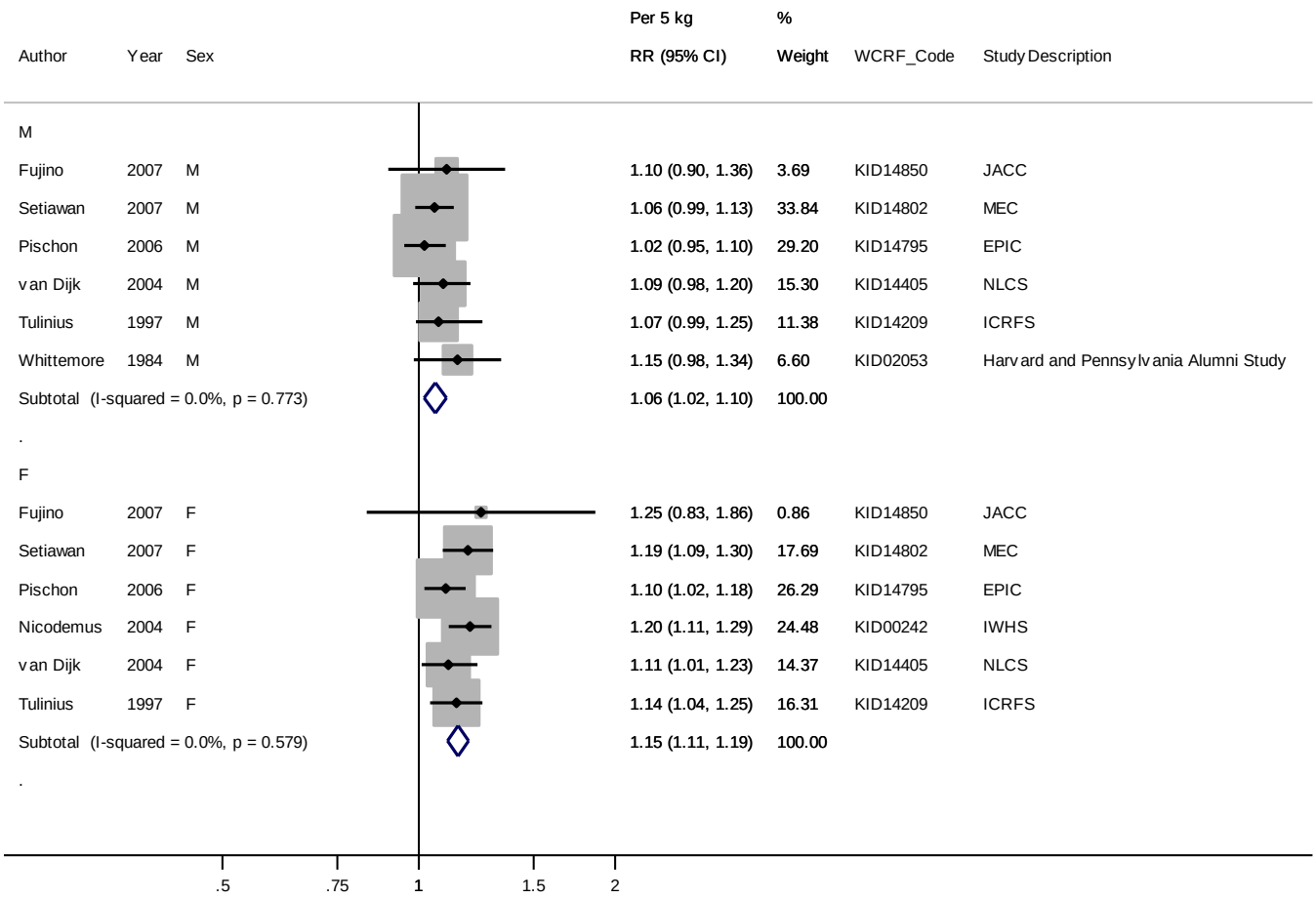
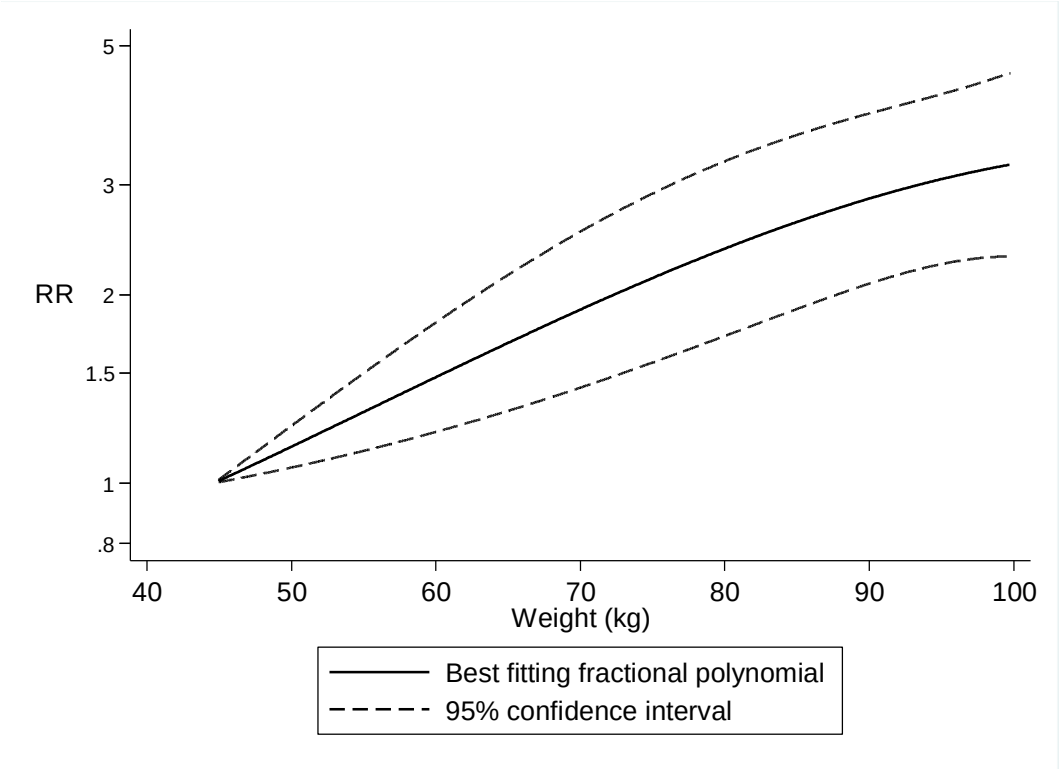


Figure 128 Nonlinear dose-response analysis of weight and kidney cancer



p for nonlinearity=0.39

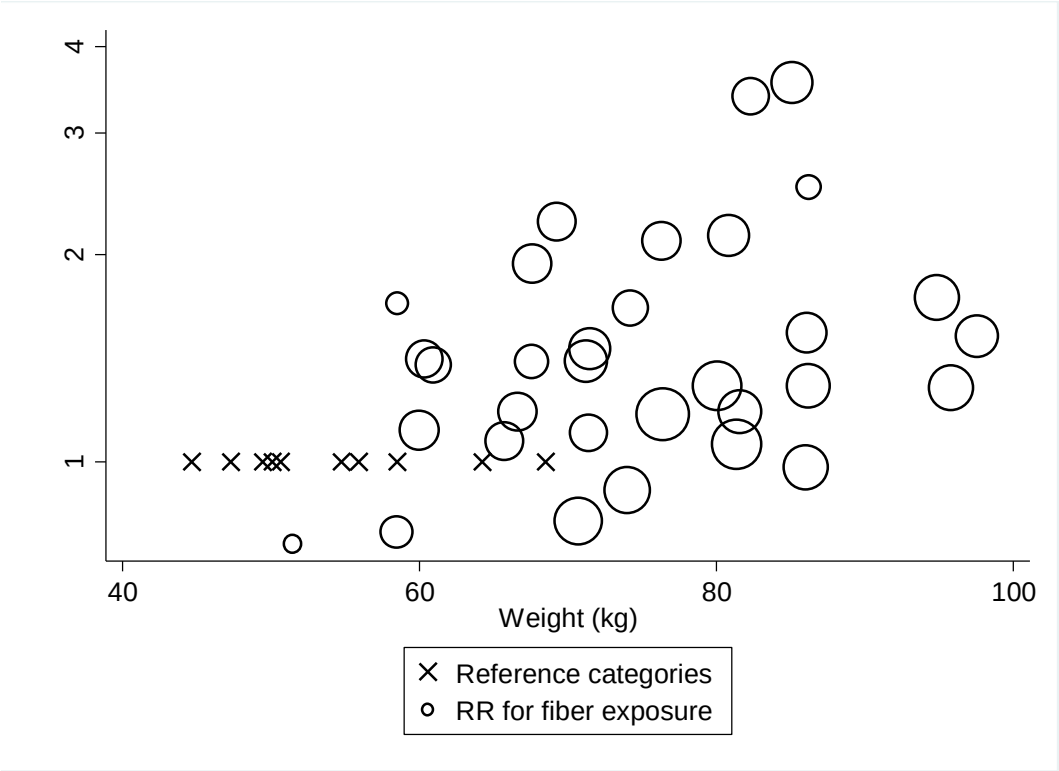


Table 146 RRs for nonlinear dose-response analysis

Weight	RR (95% CI)
44.8	1.00
45	1.01 (1.00-1.02)
50	1.14 (1.06-1.24)
55	1.30 (1.13-1.50)
60	1.48 (1.21-1.81)
65	1.68 (1.31-2.16)
70	1.89 (1.42-2.53)
75	2.13 (1.56-2.90)
80	2.37 (1.72-3.28)
85	2.62 (1.90-3.61)
90	2.85 (2.08-3.90)
95	3.07 (2.24-4.19)
100	3.24 (2.30-4.56)

8.2.1 Waist circumference

Methods

A total of 3 cohort studies of waist circumference and kidney cancer were identified, all in the CUP. Dose-response analyses of waist circumference and kidney cancer risk were conducted per 10 cm increase.

Main results

The summary RR per 10 cm increase was 1.11 (95% CI: 1.05-1.19, I^2=0%, $p_{heterogeneity}$=0.83) (unadjusted for BMI). Analysing two studies (EPIC, NLCS) which also provided risk estimates adjusted for BMI or weight gave a summary RR of 1.11 (95% CI: 0.92-1.34, I^2=0%, $p_{heterogeneity}$=0.73).

Heterogeneity

There was no heterogeneity in the analyses, I^2=0%, $p_{heterogeneity}$=0.83.

Comparison with the Second Expert Report

In the SLR there were no studies on waist circumference and kidney cancer. No judgement was possible.

Table 147 Studies on waist circumference identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Hughes, 2009	Netherlands	Netherlands Cohort Study	195 cases	13.3 years	M/F	1.63 1.05	0.93 0.99	2.84 1.11	>103 vs. <50 cm Per trouser size
Luo, 2007	USA	Women's Health Initiative	269 cases	7.7 years	F	1.4 1.01	1.0 1.01	2.0 1.02	102.8 vs. 72.0 cm Per 1 cm
Pischon, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	287 cases	6.0 years	M F	1.27 1.67	0.74 0.94	2.19 2.98	≥103.0 vs. <86.3 cm ≥90 vs. <71.0 cm

Table 148 Overall evidence on waist circumference and kidney cancer

	Summary of evidence
2005 SLR	No studies were identified.
Continuous Update Project	Three studies were identified and two reported non-significant positive associations and one reported a significant positive association.

Table 149 Summary of results of the dose-response meta-analysis of waist circumference and kidney cancer

Kidney cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	751 cases
RR (95% CI)	-	1.11 (1.05-1.19)
Quantity	-	Per 10 cm
Heterogeneity (I^2, p-value)	-	I^2=0%, p=0.83

*No meta-analysis was conducted in the Second Expert Report

Table 150 Inclusion/exclusion table for meta-analysis of waist circumference and kidney cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14817	Hughes	2009	Case cohort study	Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints	-
KID14799	Luo	2007	Prospective cohort study	Women's Health Initiative	F	Incidence	No	Yes	Yes	-	-
KID14795	Pischon	2006	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-

Figure 129 Highest versus lowest forest plot of waist circumference and kidney cancer

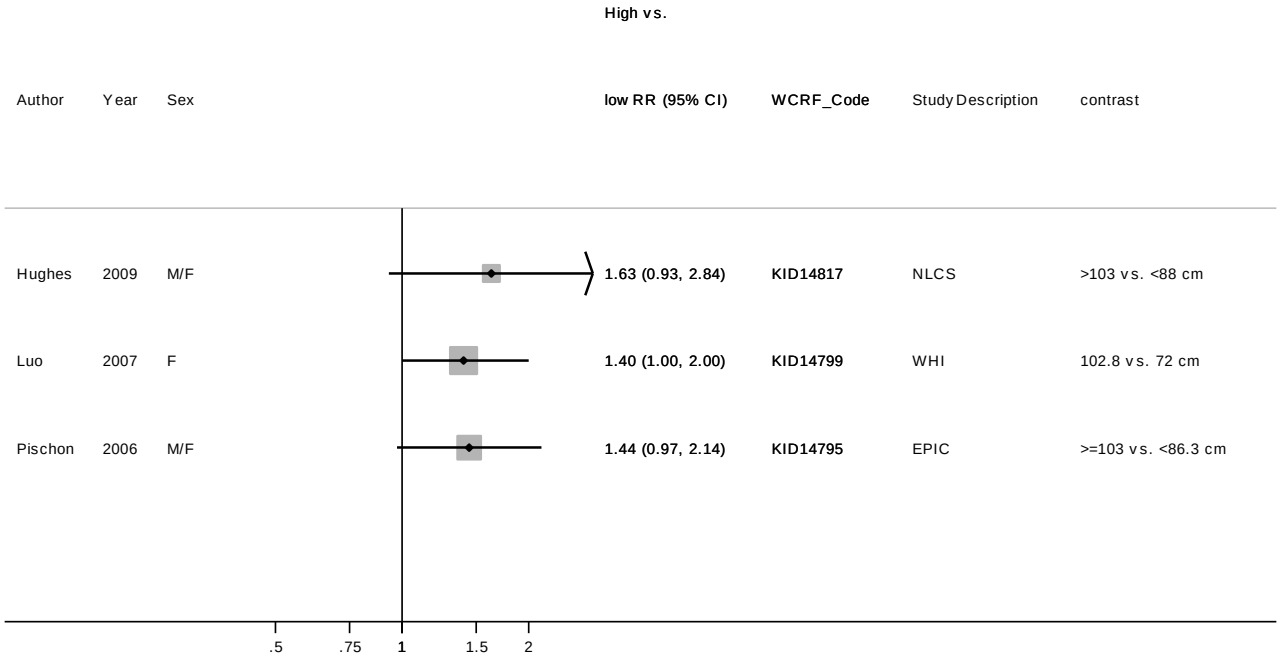


Figure 130 Dose-response meta-analysis of waist circumference and kidney cancer - per 10 cm

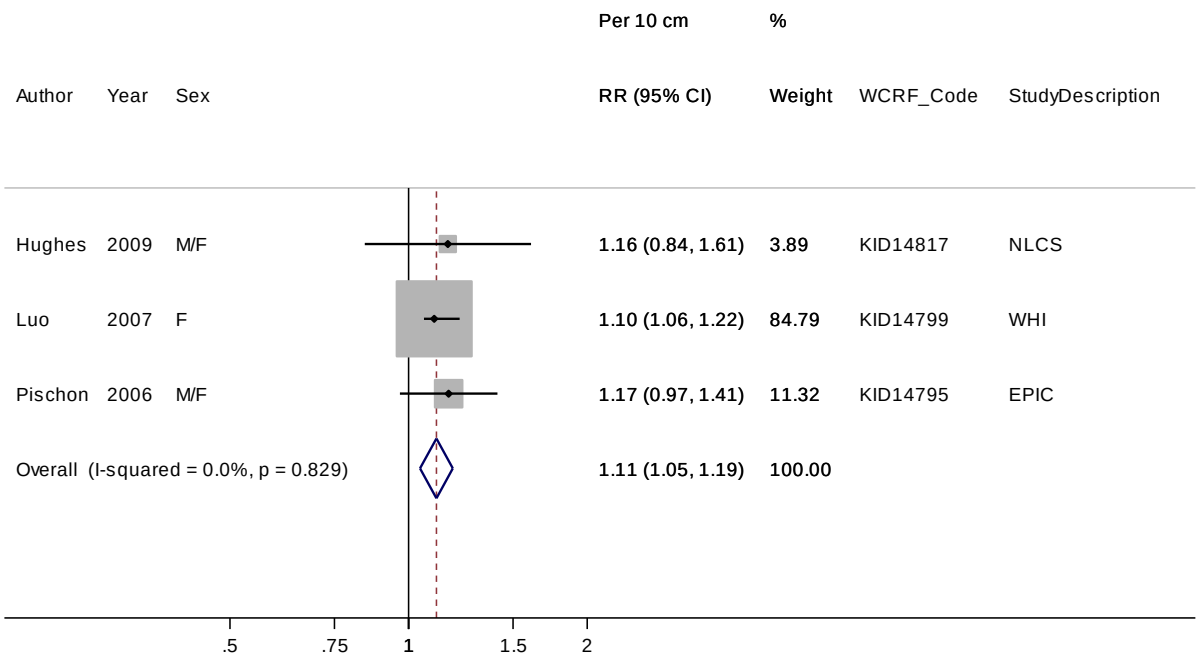
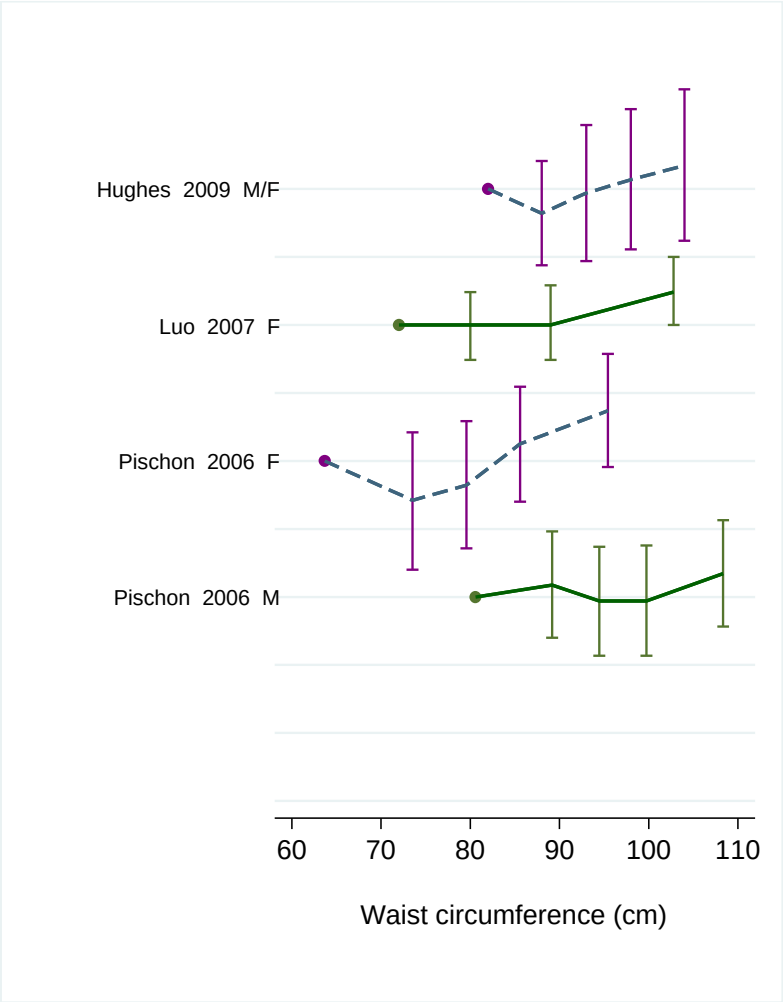


Figure 131 Dose-response graphs of waist circumference and kidney cancer



8.2.3 Waist to hip ratio

Methods

A total of 4 cohort studies (5 articles) of waist-to-hip ratio and kidney cancer were identified and three of these studies were identified in the CUP. Dose-response analyses of waist-to-hip ratio and kidney cancer risk were conducted per 0.1 unit.

Main results

The summary RR per 0.1 unit was 1.26 (95% CI: 1.18-1.36, I^2=0%, $p_{heterogeneity}$=0.39) (one of these studies adjusted for weight in the multivariable analysis). Analysing results from two studies (EPIC, IWHS) that were further adjusted for weight gave a summary RR of 1.34 (95% CI: 1.11-1.61, I^2=25%, $p_{heterogeneity}$=0.25)

Heterogeneity

There was no heterogeneity in the analyses, I^2=0%, $p_{heterogeneity}$=0.39.

Comparison with the Second Expert Report

In the SLR there was only one study on waist-to-hip ratio and kidney cancer. No judgement was possible.

Table 151 Studies on waist to hip ratio identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Adams, 2008	USA	NIH-AARP Diet and Health Study	344 cases	8.2 years	M F	1.11 1.77	0.80 0.93	1.52 3.36	Quintile 5 vs. 1 Quintile 5 vs. 1
Luo, 2007	USA	Women's Health Initiative	269 cases	7.7 years	F	1.8 1.24	1.2 1.14	2.5 1.34	0.90 vs. 0.73 Per 0.1 unit
Pischon, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	287 cases	6.0 years	M F	1.72 1.26	0.97 0.71	3.02 2.25	≥0.990 vs. <0.888 ≥0.85 vs. <0.74

Table 152 Overall evidence on waist to hip ratio and kidney cancer

	Summary of evidence
2005 SLR	Only one study was identified.
Continuous Update Project	Three studies were identified and two reported non-significant positive associations and one reported a significant positive association.

Table 153 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and kidney cancer

Kidney cancer		
	SLR*	CUP
Studies (n)	-	3
Cases (n)	-	751 cases
RR (95% CI)	-	1.26 (1.18-1.36)
Quantity	-	Per 0.1 unit
Heterogeneity (I^2, p-value)	-	I^2=0%, p=0.39

*No meta-analysis was conducted in the Second Expert Report

Table 154 Inclusion/exclusion table for waist-to-hip ratio and kidney cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
KID14803	Adams	2008	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	No	Yes	-	No quantities provided
KID14799	Luo	2007	Prospective cohort study	Women's Health Initiative	F	Incidence	No	Yes	Yes	-	-
KID14795	Pischon	2006	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID00242	Nicodemus	2004	Prospective cohort study	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints, person-years	-
KID01081	Prineas	1997	Prospective cohort study	Iowa Women's Health Study	F	Incidence	Yes	No	No	-	Overlap with Nicodemus et al, 2004, KID 00242

Figure 132 Highest versus lowest forest plot of waist-to-hip ratio and kidney cancer

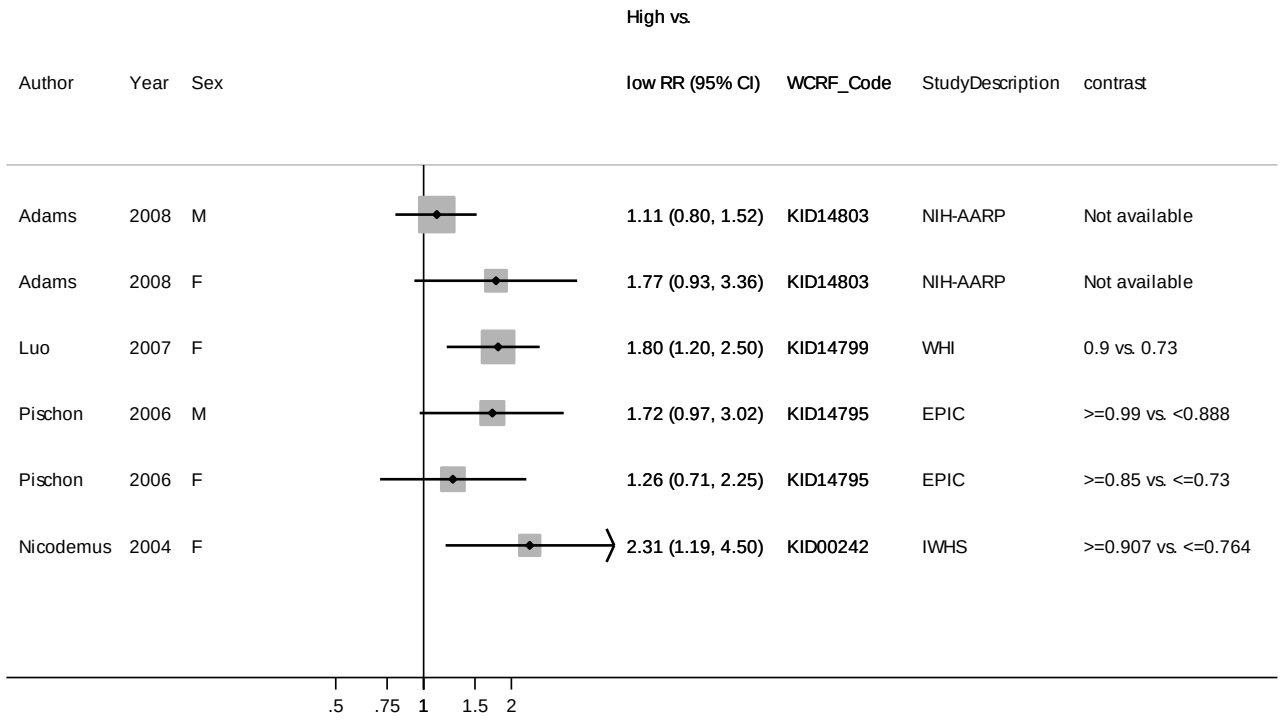


Figure 133 Dose-response meta-analysis of waist-to-hip ratio and kidney cancer - per 0.1 unit

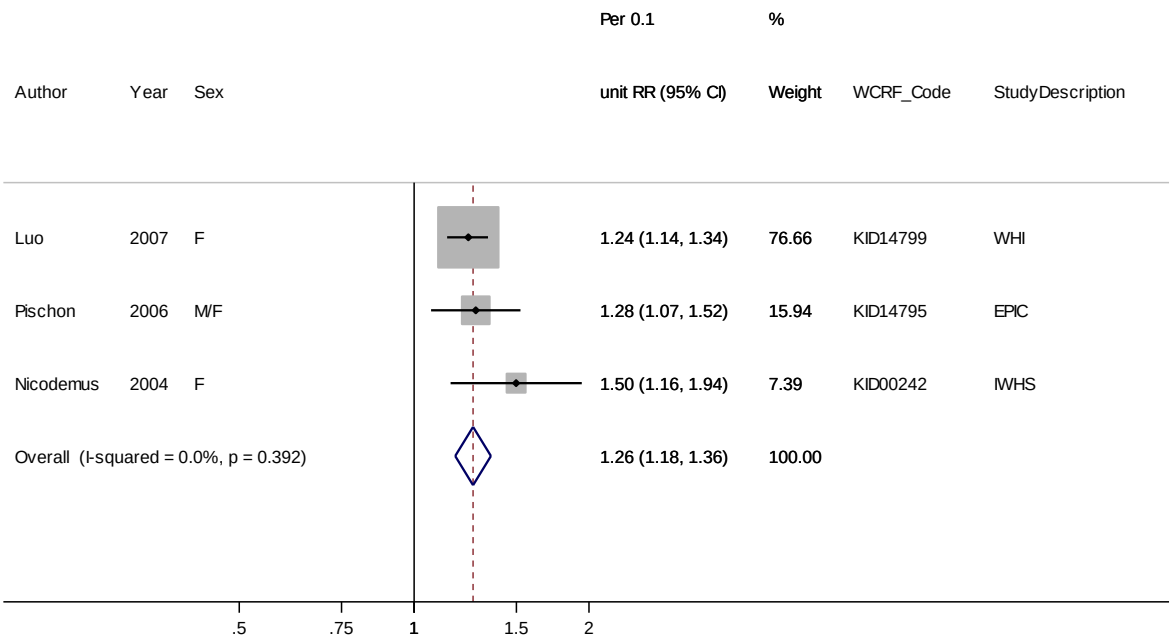
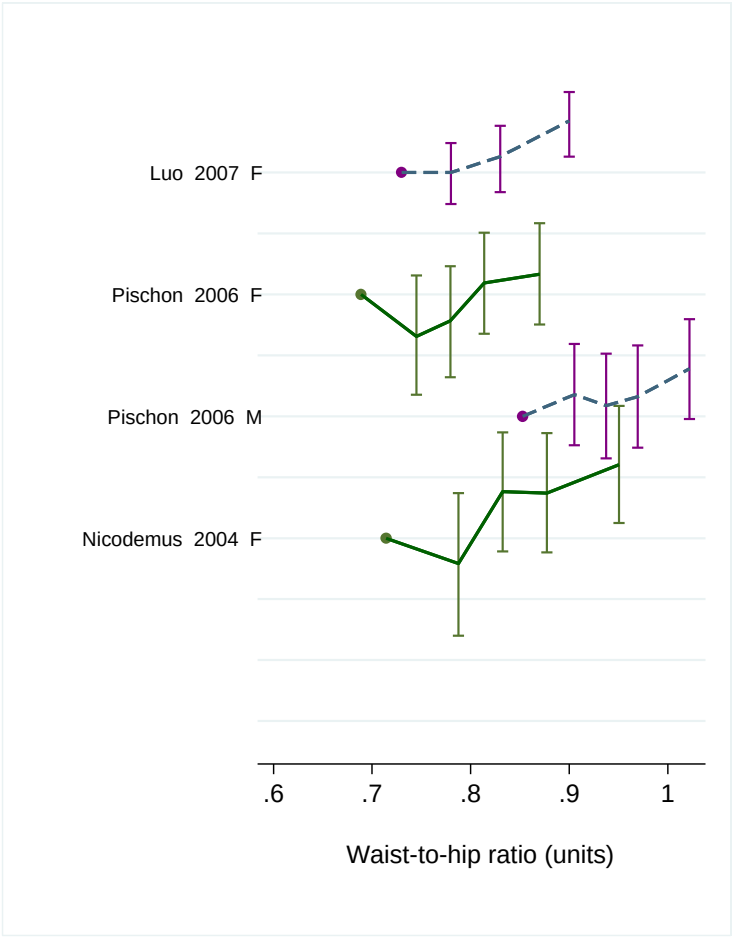


Figure 134 Dose-response graph of waist-to-hip ratio and kidney cancer



8.3.1 Height

Methods

A total of 11 cohort studies of height and kidney cancer were identified. Six studies were identified in the CUP. Dose-response analyses of height and kidney cancer risk were conducted per 5 cm.

Main results

The summary RR per 5 cm was 1.10 (95% CI: 1.08-1.12, I^2=0%, $p_{heterogeneity}$=0.45, n=10) and there was a similar association in men and women, summary RR = 1.10 (95% CI: 1.06-1.13, I^2=5%, $p_{heterogeneity}$=0.39, n=9) for men and summary RR = 1.10 (95% CI: 1.07-1.14, I^2=11%, $p_{heterogeneity}$=0.35, n=6) for women. There was no evidence for a nonlinear association between height and kidney cancer, $p_{nonlinearity}$=0.62.

Heterogeneity

There was no heterogeneity in the analyses, I^2=0%, $p_{heterogeneity}$=0.45. There was no indication of publication bias with Egger's test, p=0.54.

Comparison with the Second Expert Report

In the SLR the evidence relating height to kidney cancer risk was considered to be limited and no conclusion was possible.

Published pooled analysis

A pooled analysis of 38 Asian cohort studies on height and kidney cancer mortality reported a hazard ratio of 1.04 (95% CI: 0.83-1.31) for men and 1.21 (95% CI: 0.81-1.83) for women for a 6 cm increase in height (Batty, 2010).

Table 155 Studies on height identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Kabat, 2013	USA	Canadian National Breast Screening Study	196	16.2 years	F	1.28	1.02	1.60	Per 10 cm
Green, 2011	United Kingdom	Million Women's Study	1665	9.4 years	F	1.29	1.15	1.45	Per 10 cm
Fujino, 2007	Japan	Japan Collaborative Cohort Study	57	~14 years	M/F	0.83 0.85	0.39 0.14	1.76 4.93	≥165 vs. <160 cm ≥154 vs. <149

									cm
Setiawan, 2007	USA	Multiethnic Cohort Study	347 cases	8.3 years	M F	1.56 1.30	0.89 0.70	2.73 2.42	≥177.8 vs. <167.6 cm ≥165.1 vs. <154.9 cm
Pischon, 2006	8 European Countries	European Prospective Investigation into Cancer and Nutrition	287 cases	6.0 years	M F	1.33 1.12 1.02 1.03	0.77 0.99 0.53 0.89	2.30 1.27 1.98 1.19	≥180.5 vs. <168.0 cm Per 5 cm ≥167.7 vs. <156.0 cm Per 5 cm
Batty, 2006	United Kingdom	The Whitehall Study	62 deaths	Up to 35 years	M	2.55 1.20	0.89 0.99	7.27 1.46	≥181.0 vs. <171.0 cm Per 5 cm

Table 156 Overall evidence on height and kidney cancer

	Summary of evidence
2005 SLR	Five prospective studies were identified, four of which provided risk estimates. Three studies reported significant positive associations (although in one of them the positive association was only seen in women), and one reported no association.
Continuous Update Project	Of the six additional cohort studies identified in the CUP, all apart from one study reported significant or non-significant positive associations (the associations were significant in two studies).

Table 157 Summary of results of the dose-response meta-analysis of height and kidney cancer

Kidney cancer		
	SLR	CUP
Studies (n)	2	10
Cases (n)	424	9874
RR (95% CI)	1.13 (0.96-1.33)	1.10 (1.08-1.12)
Quantity	Per 10 cm	5 cm
Heterogeneity (I^2, p-value)	0%, p=0.86	0%, p=0.45
By gender		
Men	-	1.10 (1.06-1.13)
Heterogeneity (I^2, p-value)	-	5.1%, p=0.39
Women	-	1.10 (1.07-1.14)
Heterogeneity (I^2, p-value)	-	10.6%, p=0.35

Table 158 Inclusion/exclusion table of height and kidney cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
KID14848	Kabat	2013	Prospective cohort	Canadian National Breast Screening Study	F	Incidence	No	Yes	No	-	Only continuous estimate
KID14824	Green	2011	Prospective cohort	Million Women's Study	F	Incidence	No	Yes	No	-	Only continuous estimate
KID14850	Fujino	2007	Prospective cohort	Japan Collaborative Cohort Study	M/F	Mortality	No	Yes	Yes	Midpoints	-
KID14802	Setiawan	2007	Prospective cohort	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14867	Batty	2006	Prospective cohort	The Whitehall Study	M	Mortality	No	Yes	Yes	Midpoints, person-years	-
KID14795	Pischon	2006	Prospective cohort	European Prospective Investigation into Cancer and Nutrition	M/F	Incidence	No	Yes	Yes	Midpoints, person-years	-
KID14404	Bjørge	2004	Prospective cohort	Norwegian Tuberculosis Screening Study	M/F	Incidence	Yes	Yes	Yes	Midpoints, person-years	-
KID00119	Giovannucci	2004	Prospective cohort	Health Professionals Follow-up Study	M/F	Incidence	Yes	Yes	No	-	Only continuous estimate
KID14405	Van Dijk	2004	Case cohort	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	-	-
KID14209	Tulinius	1997	Prospective cohort	Icelandic Cardiovascular Risk Factor Study	M	Incidence	Yes	Yes	No	-	Only continuous estimate
KID02039	Whittemore	1985	Prospective cohort	Harvard Alumni Study	M	Incidence	Yes	No	No	-	No risk estimates

Figure 135 Highest versus lowest forest plot of height and kidney cancer

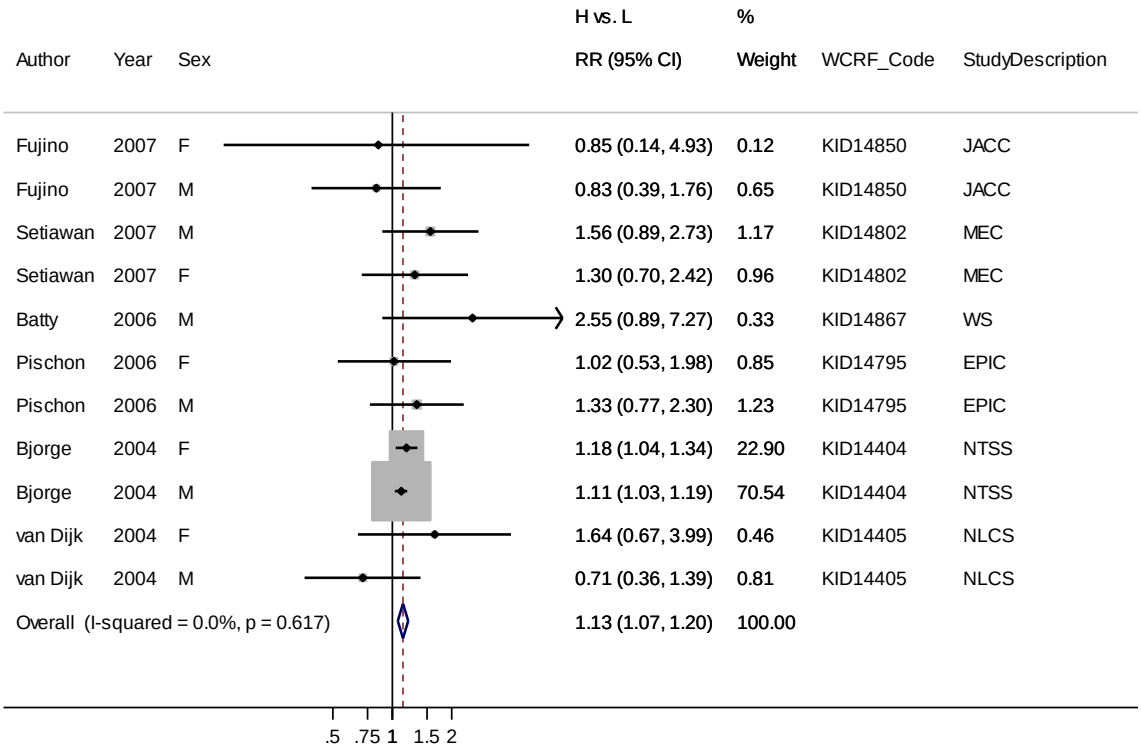


Figure 136 Dose-response meta-analysis of height and kidney cancer - per 5 cm

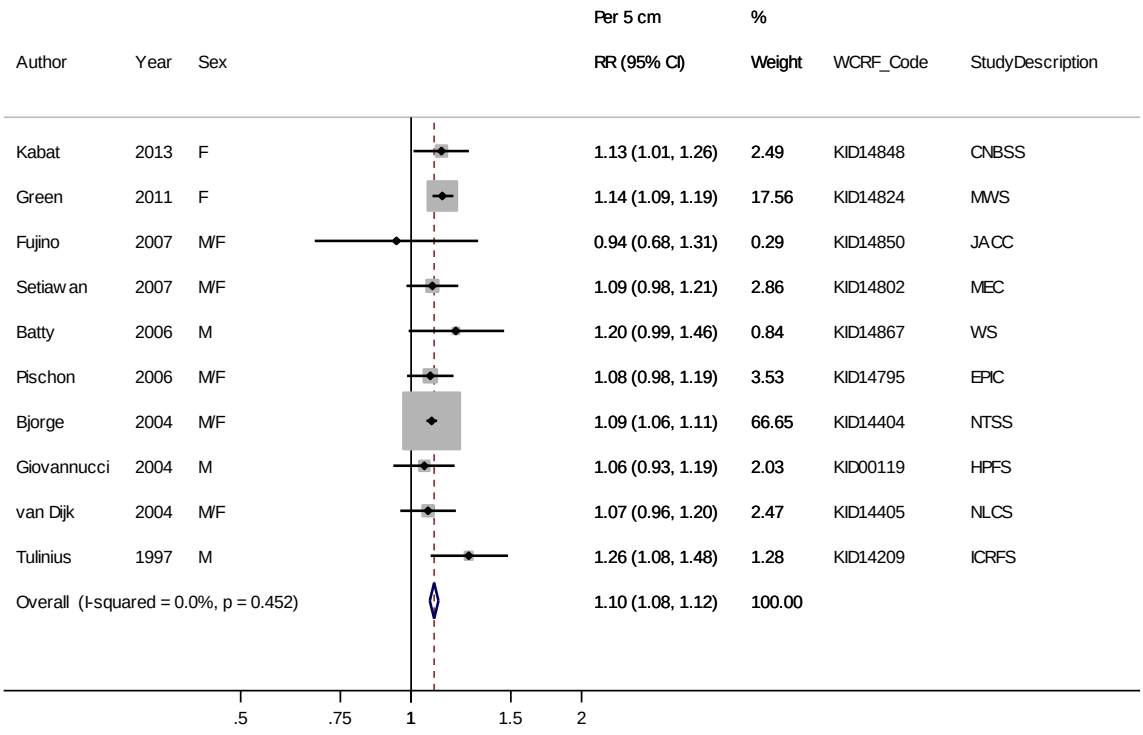


Figure 137 Funnel plot of height and kidney cancer

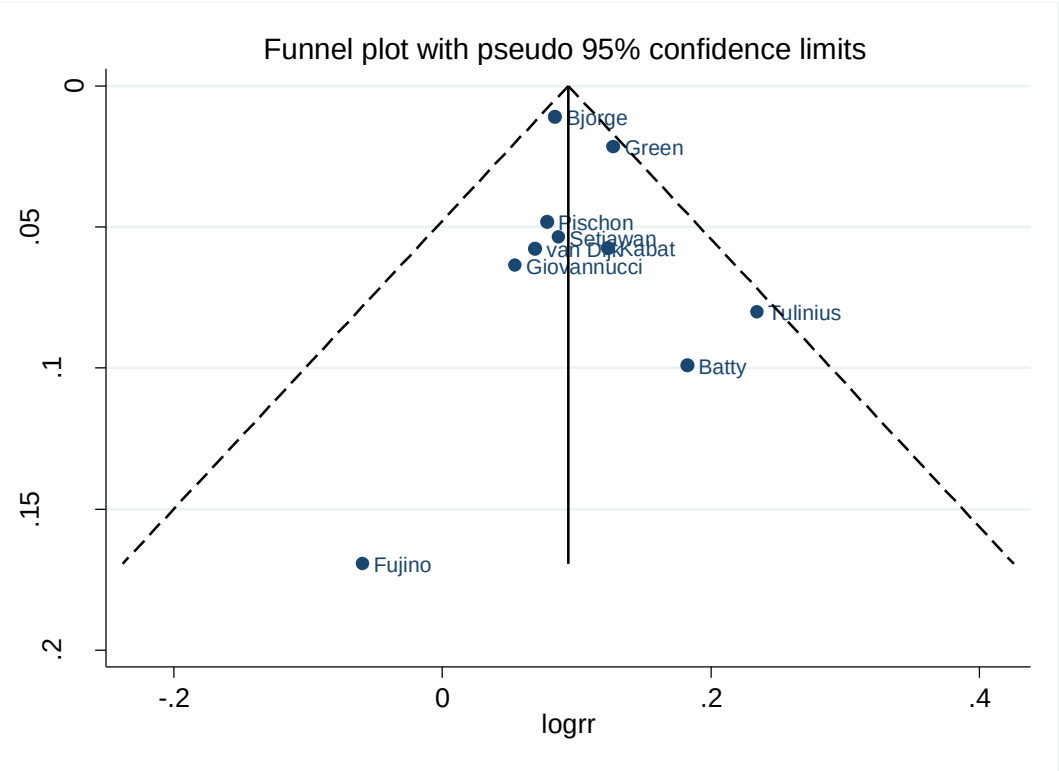


Figure 138 Dose-response graph of height and kidney cancer

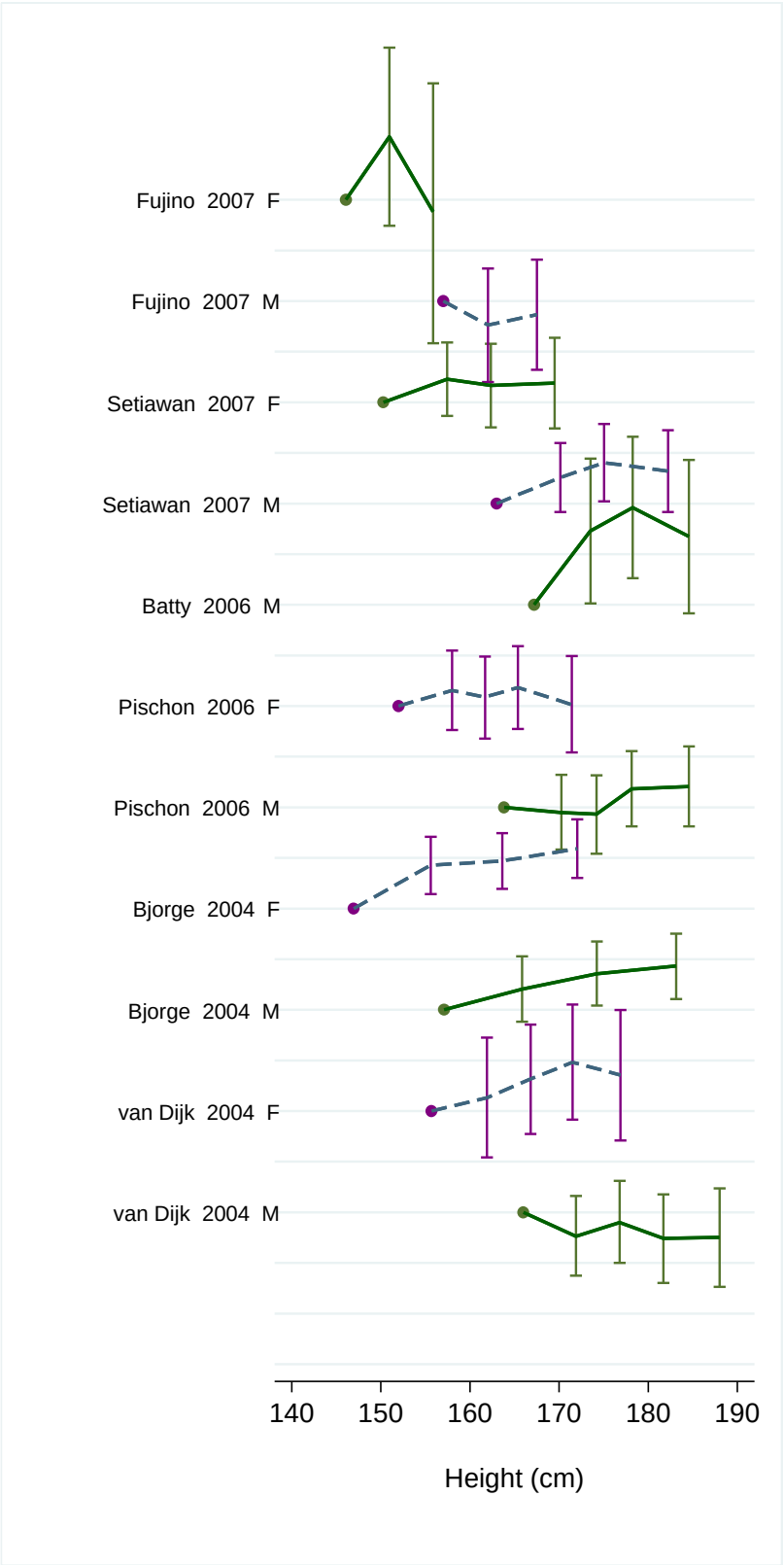


Figure 139 Dose-response meta-analysis of height and kidney cancer, stratified by sex - per 5 cm

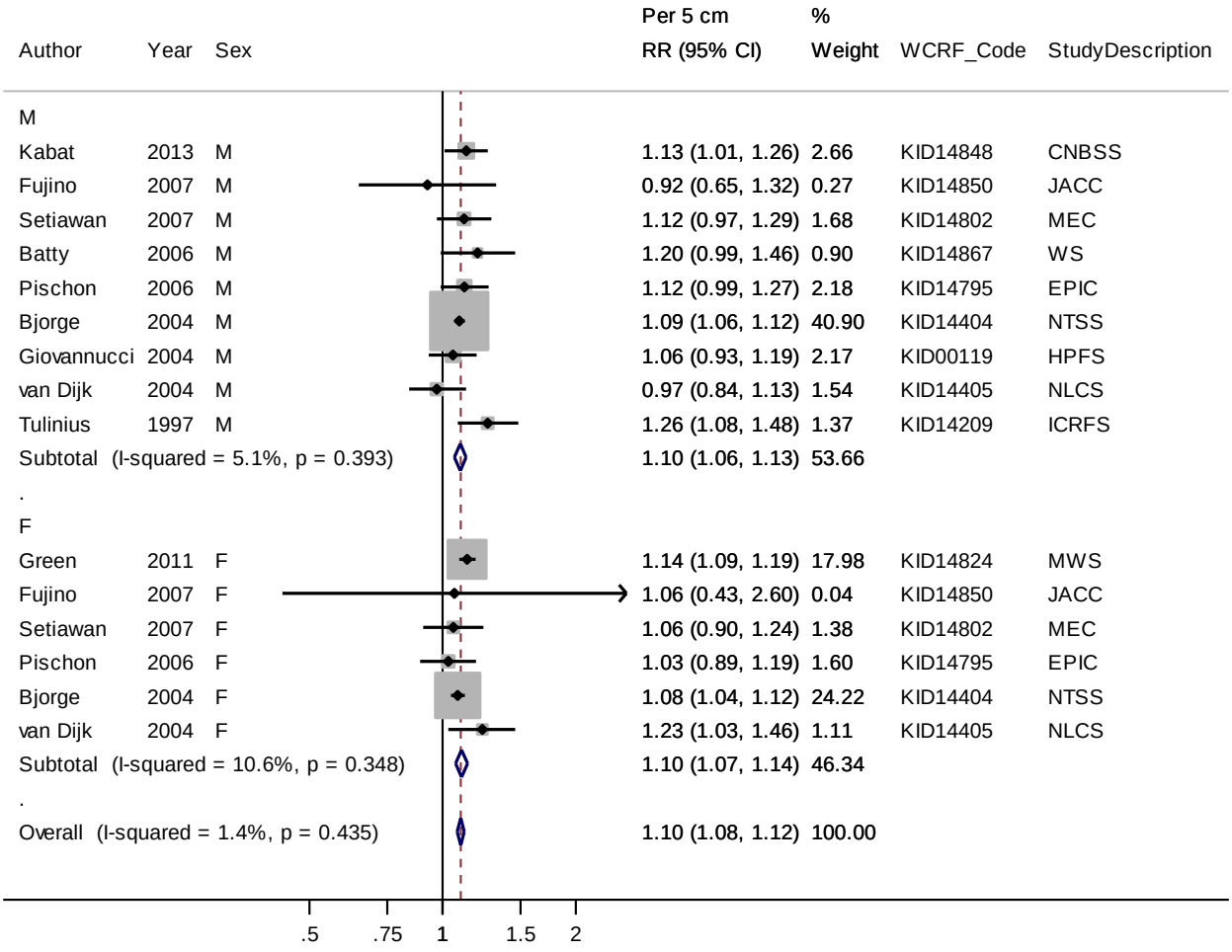
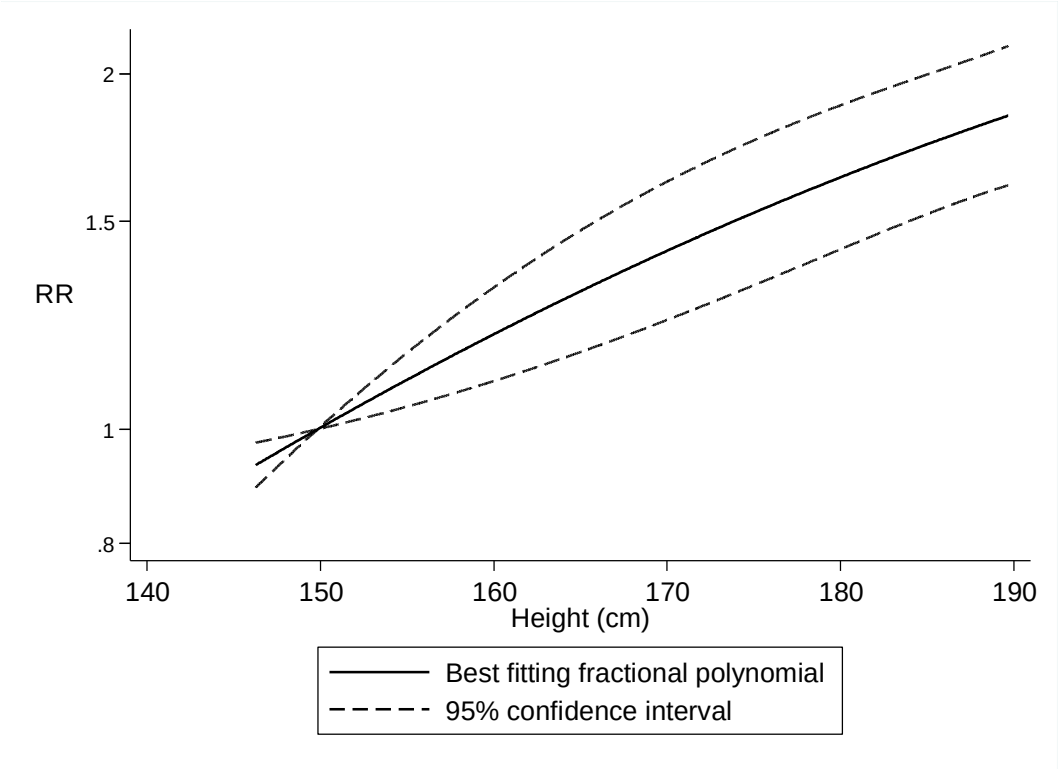


Figure 140 Nonlinear dose-response analysis of height and kidney cancer



$P_{nonlinearity}$=0.62

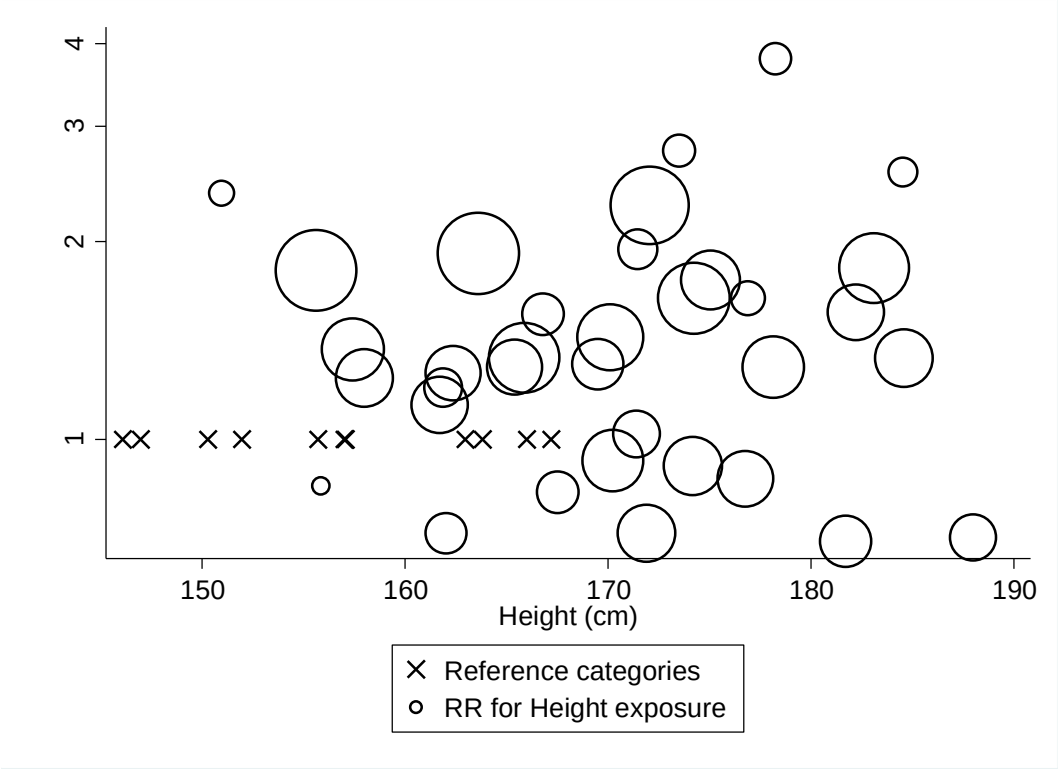


Table 159 RRs for nonlinear dose-response analysis

Height (cm)	RR (95% CI)
146	0.93 (0.89-0.97)
150	1.00
155	1.10 (1.05-1.16)
160	1.21 (1.10-1.32)
165	1.31 (1.16-1.48)
170	1.42 (1.24-1.63)
175	1.53 (1.32-1.76)
180	1.64 (1.42-1.88)
185	1.75 (1.53-2.00)
190	1.85 (1.62-2.12)

Annex . Anthropometric characteristics investigated by each study

Several studies investigated BMI, height, weight, waist circumference and waist-to-hip ratio. The anthropometric characteristics investigated by each study are indicated with a cross in the list below:

			Anthropometric characteristic				
First author	Year	Study name	BMI	Weight	Height	Waist	WHR
Kabat	2013	Canadian National Breast Screening Study			x		
Southard Wilson Hirvonen	2012 2009 2001	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	x				
Smits van Dijk Hughes	2010 2004 2009	Netherlands Cohort Study	x	x	x	x	
Sawada	2010	Japan Public Health Centre-based Prospective Study	x				
Andreotti	2010	Agricultural Health Study	x				
Prentice Luo	2009 2007	Women's Health Initiative	x			x	x
Song Jee Oh	2008 2008 2005	National Health Insurance Corporation Study	x				
Adams	2008	NIH-AARP Diet and Health Study	x				x
Setiawan	2007	Multiethnic Cohort Study	x	x	x		
Batty	2006	The Whitehall Study			x		
Fujino Washio	2007 2005	Japan Collaborative Cohort Study	x	x	x		
Green Reeves	2011 2007	Million Women's Study	x		x		
Samanic Chow	2006 2000	Swedish Construction Workers' Cohort Study	x				
Pischon	2006	European Prospective Investigation into Cancer and Nutrition	x	x	x	x	x
Lukanova	2006	Northern Sweden Health and Disease Cohort Study	x				
Rapp	2005	The Vorarlberg Health Monitoring and Promotion Program	x				
Kuriyama	2005	Miyagi Cohort Study	x				
Flaherty	2005	Nurses' Health Study	x	x			
Flaherty Giovannucci	2005 2004	Health Professionals Study	x	x	x		x
Nicodemus Prineas	2004 1997	Iowa Women's Health Study	x	x			x

Bjorge	2004	Norwegian Tuberculosis Screening Study	x		x
Calle	2003	Cancer Prevention Study 2	x		
Ali	2003	New York University Women's Health Study	x		
Bergström	2001	NA	x		
Kurttio	1999	Finland 1967-1980	x		
Tulinius	1997	Icelandic Cardiovascular Risk Factor Study	x		x
Gamble	1996	New Jersey Refineries	x		
Tulinius	1997	Reykjavik Study	x	x	
Hiatt	1994	Kaiser Permanente Medical Care Program	x		
Fraser	1990	Adventist Health Study	x		
Whittemore	1984	Harvard and Pennsylvania Alumni Study 1916-1950	x	x	x

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