Global data for diabetes and obesity research

Global data for diabetes and obesity research

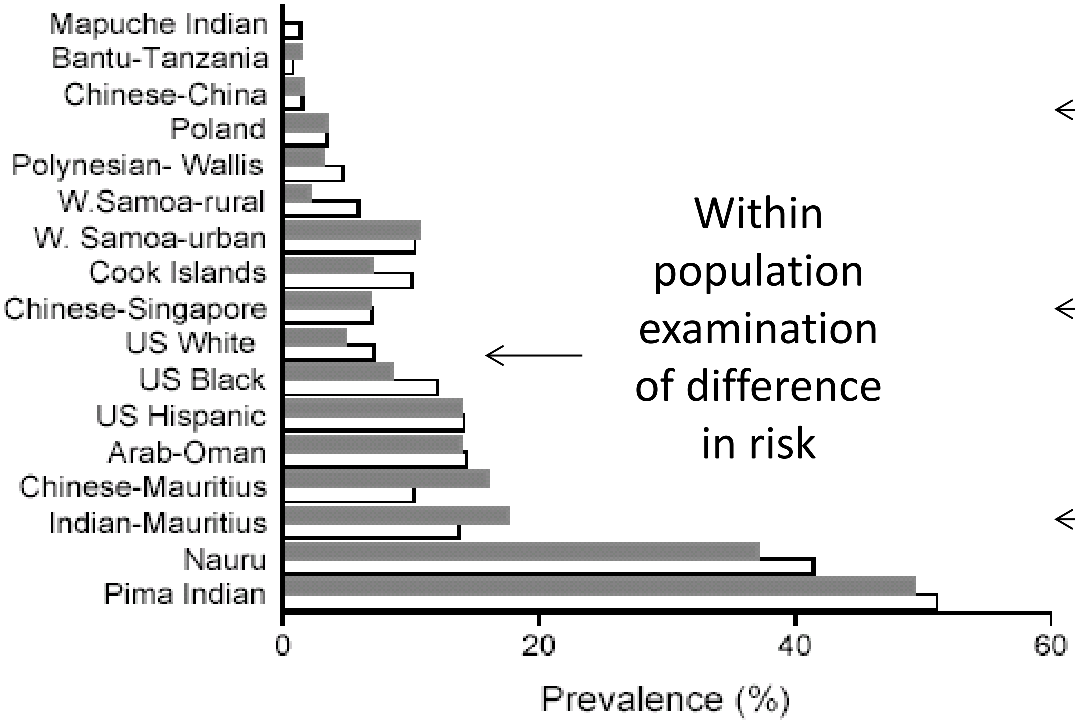
Host: Nick Wareham, InterConnect Co-ordinator & Director, MRC Epidemiology Unit, University of Cambridge, UK
Pre-EASD Symposium Lisbon, 11 September 2017

This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

InterConnect Goal

- Create the foundations for cross-cohort analyses
  - Move from explaining differences in risk within populations to explaining differences between populations

Moving from within-population investigation to the study of between-population differences



Within population examination of difference in risk

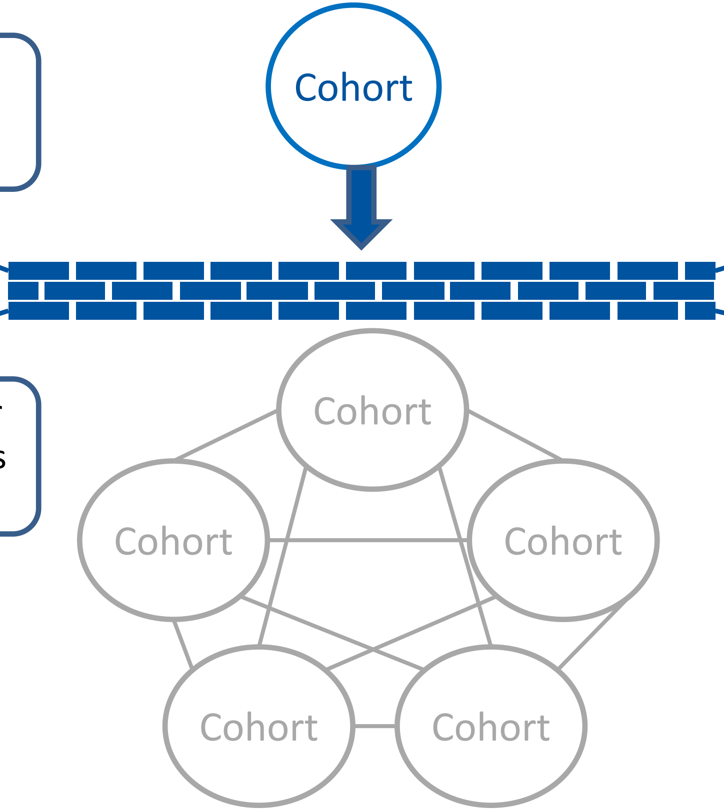
Between population examination of difference in risk

Barriers to cross-cohort analyses

Burden on collaborators of repeatedly preparing and analysing data

Collaborators fear loss of ownership of their data

RESULTS SHARING



DATA POOLING

Results sharing works well for some risk factors but can miss between cohort variation

Complex data-sharing or deposition agreements are needed

How to realise the vision?

- Create one large international cohort ✗
- Make better use of existing data ✓
- Align prospective studies with use of comparable metrics ✓

InterConnect contributing

Align prospective studies with use of comparable metrics

Steps to make better use of existing data

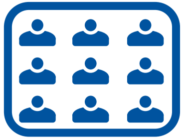
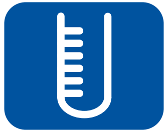
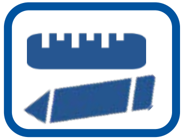
- Find relevant studies globally
- Find out what data the studies have collected
- Find an appropriate way of bringing data together
- Find a way of interpreting different forms of data that are brought together

InterConnect foundations

TOOLS & INFRASTRUCTURE

Identification of studies, design, data – **Registry**	**Harmonisation** of exposures and outcomes	Framework for **taking the analysis to the data**

Identification of studies, design, data – **Registry**	**Harmonisation** of exposures and outcomes	Framework for **taking the analysis to the data**

	A catalogue of studies relating to diabetes and obesity
	Populations recruited to the study
	Biological samples stored or analysed
	The study design that was employed

InterConnect: Live Study Registry

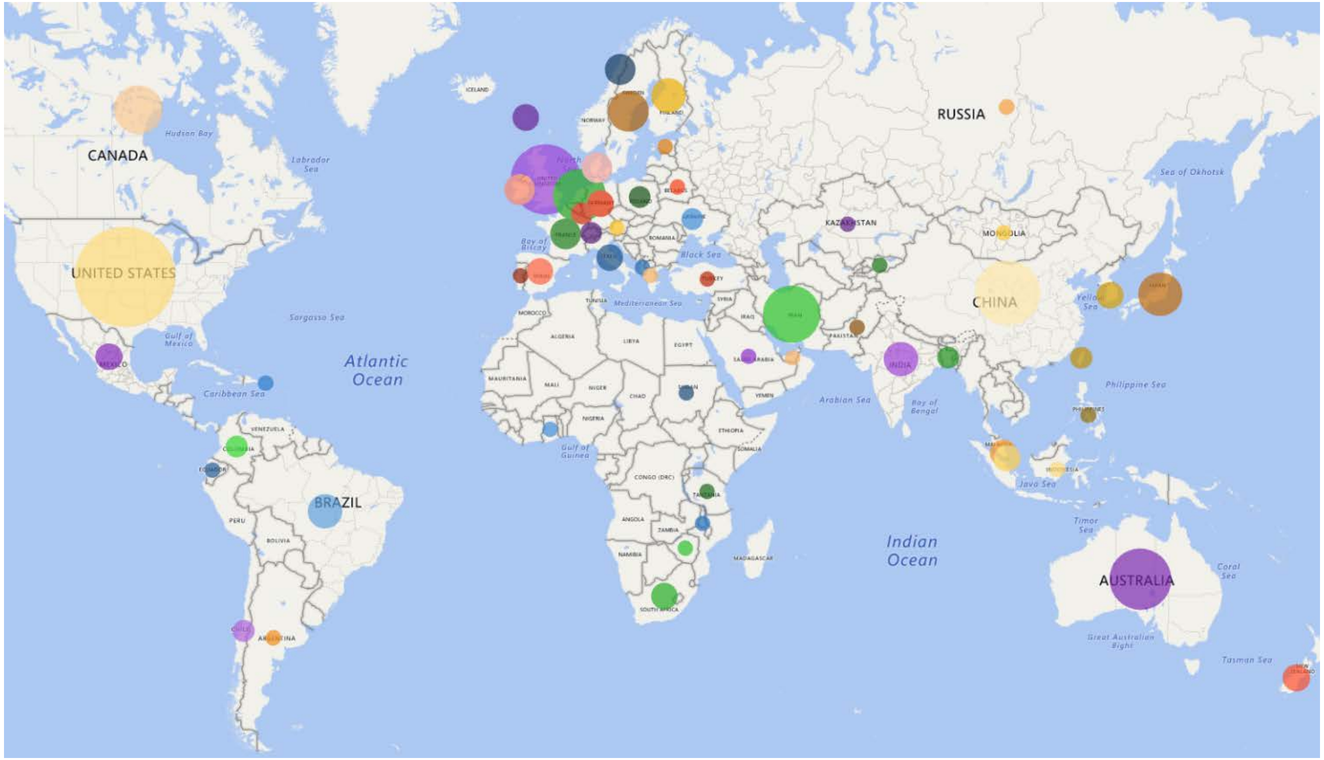
Short Name	Name	Study Design	Actual number of participants recruited to the study	Country of residence
MEC	Multiethnic Cohort Study	Prospective cohort study	215 251	United States
SWS	Southampton Women's Survey	Prospective cohort study	12 583	United Kingdom
	Healthy Start study	Prospective cohort study	2 820	United States
ALSPAC	Avon Longitudinal Study of Parents and Children	Prospective cohort study	14 541	United Kingdom
AHS	Agricultural Health Study	Prospective cohort study	89 655	United States
ARIC	Atherosclerosis Risk in Communities Study	Prospective cohort study	15 792	United States
DNBC	Danish National Birth Cohort	Prospective cohort study	101 042	Denmark
EPIC - Turin	European Prospective Investigation into Cancer and Nutrition - Turin	Prospective cohort study	10 604	Italy
NHS I	Nurses Health Study I	Prospective cohort study	121 700	United States
NOMAS	The NOrthern MAnhattan Study	Prospective cohort study	3 298	United States

1 2 3 4 5 6 7 8 9 … next ›

Geographic diversity

ALBANIA	1
ARGENTINA	1
AUSTRALIA	16
AUSTRIA	1
BANGLADESH	2
BELARUS	1
BRAZIL	5
CANADA	10
CHILE	2
CHINA	18
COLOMBIA	2
DENMARK	4
ECUADOR	1
ESTONIA	1
FAROE ISLANDS	3
FINLAND	5
FRANCE	4
GERMANY	3
GHANA	1
GREECE	1
INDIA	5
INDONESIA	1
IRAN	14
IRELAND	4
ITALY	3
JAPAN	8
KAZAKHSTAN	1
KOREA	3
KYRGYZSTAN	1
LUXEMBOURG	2

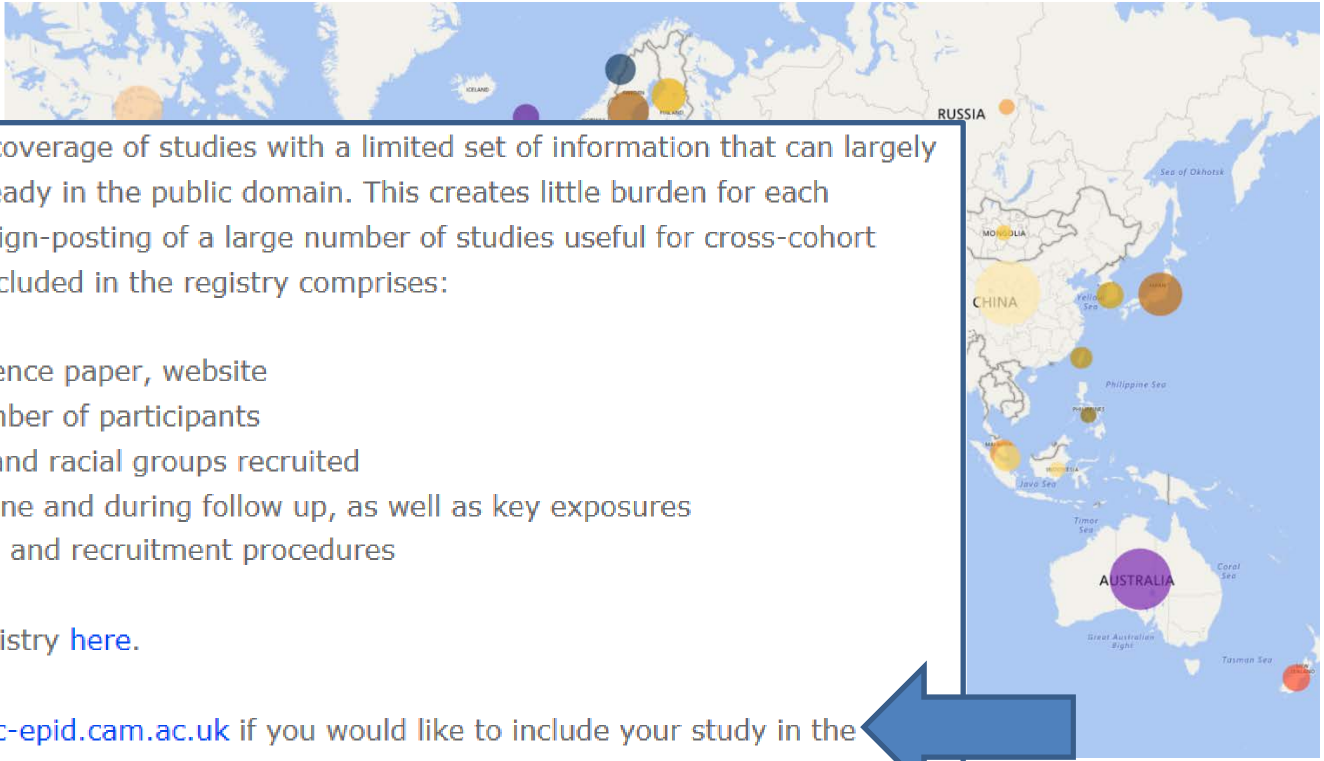
MALAWI	1
MALAYSIA	3
MEXICO	3
MONGOLIA	1
NETHERLANDS	12
NEW ZEALAND	3
NORWAY	4
PAKISTAN	1
PALESTINE	1
PHILIPPINES	1
POLAND	2
PORTUGAL	1
PUERTO RICO	1
RUSSIA	1
SAUDI ARABIA	1
SINGAPORE	3
SOUTH AFRICA	3
SPAIN	3
SUDAN	1
SWEDEN	7
SWITZERLAND	2
TAIWAN	2
TANZANIA	1
TURKEY	1
UKRAINE	2
UNITED ARAB EMIRATES	1
UNITED KINGDOM	21
UNITED STATES	43
ZIMBABWE	1



Adding to the registry

ALBANIA	1
ARGENTINA	1
AUSTRALIA	16
AUSTRIA	1
BANGLADESH	2

MALAWI	1
MALAYSIA	3
MEXICO	3
MONGOLIA	1
NETHERLANDS	12



Our approach is to enable wide coverage of studies with a limited set of information that can largely be collated from information already in the public domain. This creates little burden for each individual study while enabling sign-posting of a large number of studies useful for cross-cohort analyses. Meta-data currently included in the registry comprises:

- Study name, contact, reference paper, website
- Study design, timeline, number of participants
- Broad categories of ethnic and racial groups recruited
- Health information at baseline and during follow up, as well as key exposures
- Participant selection criteria and recruitment procedures

You can view and search the registry here.

Email InterConnectRegistry@mrc-epid.cam.ac.uk if you would like to include your study in the registry

Identification of studies, design, data – **Registry**	**Harmonisation** of exposures and outcomes	Framework for **taking the analysis to the data**

Exemplar question: Study A
In a typical week, how many glasses of red wine (6 ounces) do you drink per day?
[___] Number of drinks per day

Exemplar question: Study B
In general, how many glasses of red wine do you drink per day over a week and weekend?
Week: [___] Number/day
Weekend: [___] Number/day

Exemplar question: Study C
In a typical week, how many glasses of red wine do you drink per day?
❑ 1–3
❑ 4–6
❑ 7–9
❑ 10 or more

→ Align to give a single exposure where possible

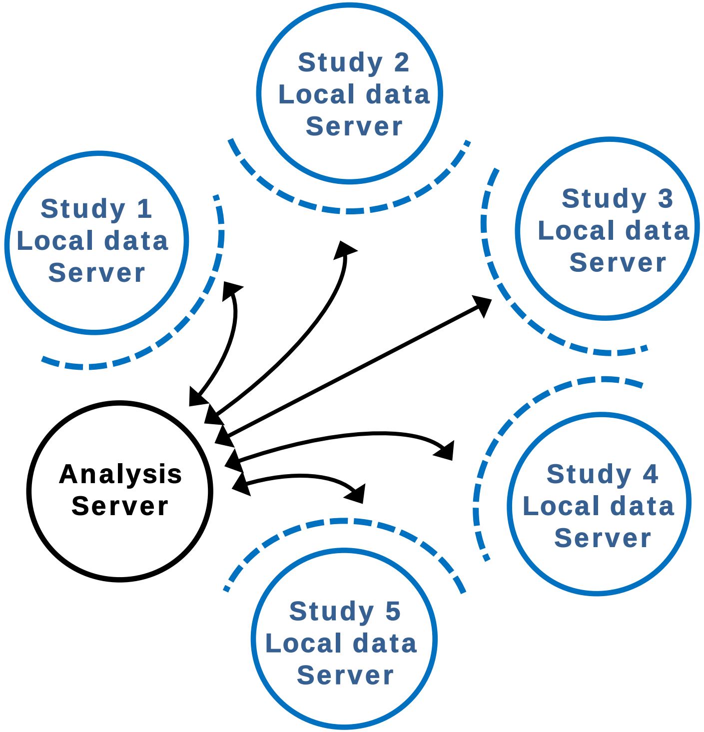
InterConnect software captures how the alignment is made so it is both explicit and re-usable

- Algorithms → study servers, catalogue
- Learning, guidance → DAPA toolkit

DAPA toolkit

- Also aids retrospective harmonisation
  - Harmonisation concepts and case studies
  - Principles, process and different techniques

Identification of studies, design, data – **Registry**	**Harmonisation** of exposures and outcomes	Framework for **taking the analysis to the data**



- Take the analysis to the data - federated analysis
- Data stay within the governance structure of the cohort
- Analytical instructions and non-identifying summary parameters allowed to pass between computers
- Users with log in credentials can remotely access the analysis server to run analyses

InterConnect: A bridging function

TOOLS & INFRASTRUCTURE

Identification of studies, design, data – **Registry**	**Harmonisation** of exposures and outcomes	Framework for **taking the analysis to the data**

Research driven 'Exemplar projects'

RESEARCH USE: APPLICATION TO FOCUS & REFINE

1. PA in pregnancy and neonatal anthropometric outcomes
2. Fish intake and risk of type 2 diabetes

Programme

- 14.30 Vision for the InterConnect approach
- 14.40 Resources for data harmonisation: DAPA toolkit (Matthew Pearce)
- 14.50 Relationship between maternal physical activity in pregnancy and off spring birth size (Silvia Pastorino)
- 15.05 Relationship between fish intake and type 2 diabetes (Nita Forouhi)
- 15.20 Discussion of changing landscape for cross-cohort analysis

InterConnect

Global data for diabetes and obesity research

Resources for data harmonisation – the DAPA toolkit

Matthew Pearce
MRC Epidemiology Unit, University of Cambridge, UK
Pre-EASD Symposium, Lisbon, 11 September 2017

This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Diet, Anthropometry and Physical Activity (DAPA) Measurement Toolkit

- www.measurement-toolkit.org

- Web-based resource to facilitate collection and interpretation of dietary, anthropometric and physical activity data

- Assists users when:
  - using and interpreting existing data
  - selecting methods that are fit-for purpose when planning new studies

DAPA Measurement Toolkit

NHS
National Institute for Health Research

MRC Medical Research Council

Welcome to the Diet, Anthropometry and Physical Activity (DAPA) Measurement Toolkit.

The DAPA Measurement Toolkit is a free web-based resource to assist researchers and public health or public end-users to identify methods for the assessment of diet, anthropometry and physical activity.

The toolkit does not recommend or promote any specific method or instrument (tool) but rather provides information for end-users to be better equipped at using and interpreting existing data or reaching an appropriate decision on choosing methods that are fit-for purpose when planning new studies.

Dietary Assessment

Physical Activity Assessment

Anthropometry

DAPA resources for data harmonisation

1. Inventory of subjective and objective methods
2. Dedicated harmonisation content
3. Instrument library

1 – Inventory of assessment methods

Diet

Subjective Methods

- Introduction
- Estimated food diaries
- Weighed food diaries
- 24-hour dietary recalls
- Food frequency questionnaires
- Diet checklists
- Diet histories

Objective Methods

- Introduction
- Direct observation
- Duplicate diets
- Nutritional biomarkers

Physical activity

Subjective Methods

- Introduction
- Questionnaires
- Diaries and logs

Objective Methods

- Introduction
- Pedometers
- Accelerometers
- Heart rate monitors
- Combined heart rate and motion sensors
- Direct observation
- Doubly labelled water
- GPS and other GNSS receivers

Anthropometry

Subjective Methods

- Introduction
- Birth weight
- Body shape
- Weight and height
- Waist and hip circumference

Objective Methods

- Introduction
- Anthropometric indices
- Simple measures - height
- Simple measures - weight
- Simple measures - circumference
- Simple measures - arm anthropometry
- Simple measures - skinfolds

1 – Inventory of assessment methods

- Each page contains information on:
  - What is assessed
  - How the measurement is conducted
  - When the method is used
  - Inferences used to convert raw data into estimates
  - Strengths and limitations
  - Considerations for use in different populations

1 – Inventory of assessment methods

Assists retrospective harmonisation:

- Describes measurement protocols
- Details the raw data generated and subsequent inferential steps
- Informs interpretation of data and development of algorithms

Assists prospective harmonisation:

- Supports uptake of methods by those without specialist knowledge
- Convergence of methods for variables, designs, populations

2 – Dedicated harmonisation content

- Provides background: what, when, why, how to harmonise?
- Explains key concepts
  - Inferential equivalence
  - Harmonisation vs. standardisation
  - Retrospective vs. prospective harmonisation
- Links to other harmonisation resources, e.g. Maelstrom Research
- Describes the process of retrospective harmonisation
  - Further outlined in 4 case studies

2 – Dedicated harmonisation content

Assists retrospective harmonisation:

- Explains the principles of harmonisation and why it is required
- Outlines the process and different techniques

Assists prospective harmonisation:

- Encourages consideration of inferential equivalence of data
- Informs method selection when planning new studies

3 – Instrument library

Instrument specific pages:

- Description
- Design
- Output variables
- Resources (e.g. PDF of instrument, processing code)
- Reliability/validity literature
- Examples of use in research

Description of instrument

The Recent Physical Activity Questionnaire (RPAQ) was based on the European Prospective Invest
Questionnaire (EPAQ2; see here), and inquires about PA across four domains (leisure time, occup
instrument is typically self-administered.

It is divided into 3 sections:

Section A asks about physical activity patterns in and around the house.

Section B is about travel to work and activity at work.

Section C asks about recreations engaged in during the last 4 weeks.

Resources

Resource	Link
Data entry template	External site
Guidelines	External site
Syntax (STATA)	External site
PDF of instrument (English, Basque, Danish, Dutch, French, German, Greek, Italian, Norwegian, Spanish, Swedish)	External site

Section B Activity at work

Travel to and from work in the last 4 weeks

What is the approximate distance from your home to your work?

☐☐☐ Miles *or* ☐☐☐ Kilometers

How many times a week did you travel from home to your main work? ☐☐
Count outward journeys only

Please tick (✓) one box **only** per line

How did you normally travel to work?	Always	Usually	Occasionally	Never or rarely
By car/motor vehicle				
By works or public transport				
By bicycle				
Walking				

What is the postcode for your main place of work during the last 4 weeks?

Postcode ☐☐☐☐ ☐☐☐

If not known please give your work address
Work address - ______________________________
____
____

What is the postcode for your home address?

Postcode ☐☐☐☐ ☐☐☐

3 – Instrument library

Assists retrospective harmonisation:

- Facilitates access to instruments and related resources

Assists prospective harmonisation:

- Discovery of existing instruments and evidence of validity
- Access to protocols, user guides and processing code
- Avoids unnecessary development of additional instruments

Summary

- The DAPA Measurement Toolkit facilitates both retrospective and prospective harmonisation
- Achieved directly by providing resources which assist interpretation of existing data and planning of new studies
- Also aims to have the broader, more indirect impact of promoting convergence of methods and compatibility of data

Work in progress….

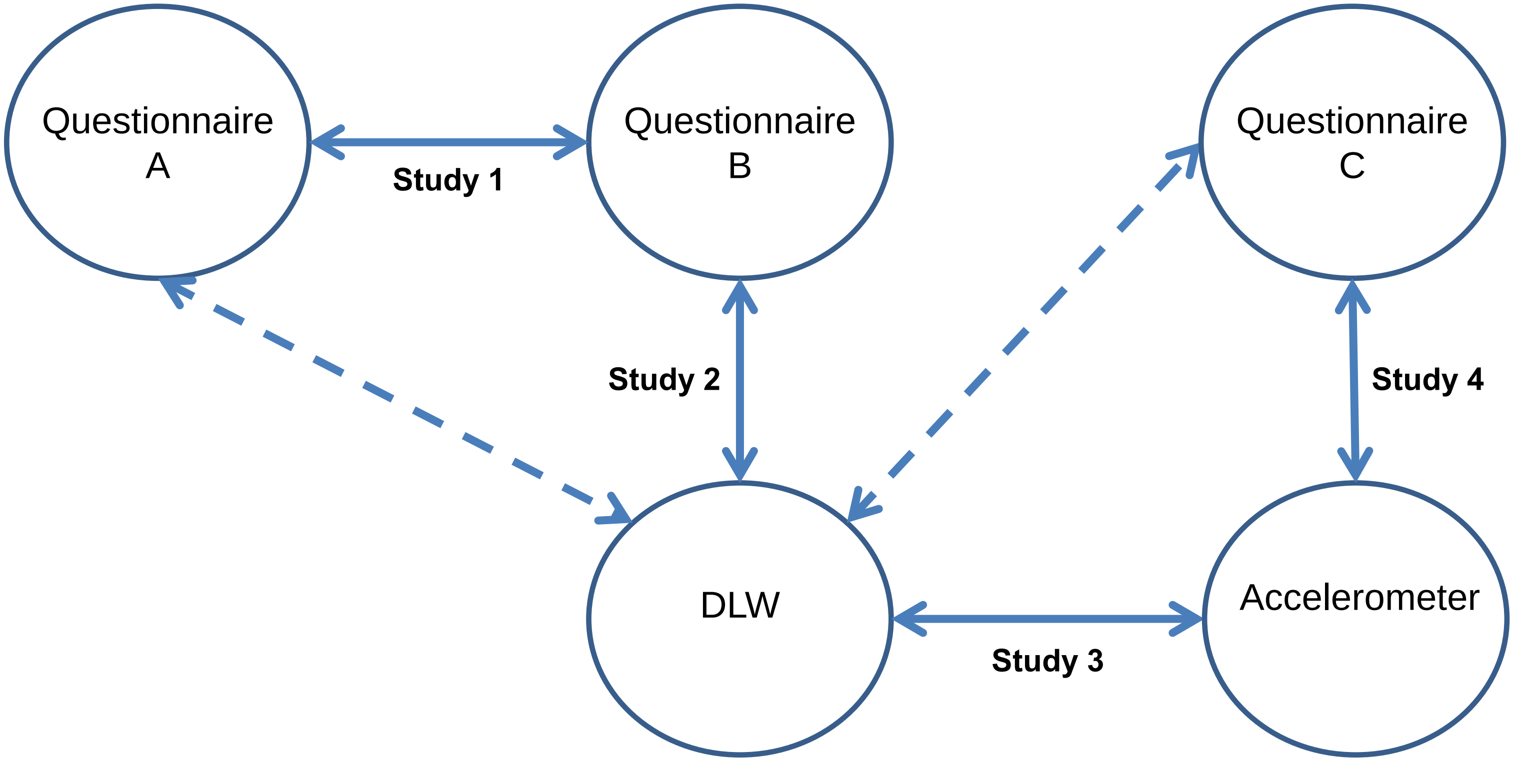
- Search/filter/sort functions for instrument library
  - Method types and subtypes
  - Variables
  - Populations
  - Settings

- Web-form for researchers to upload instruments and resources

- Interactive map of relationships between different methods

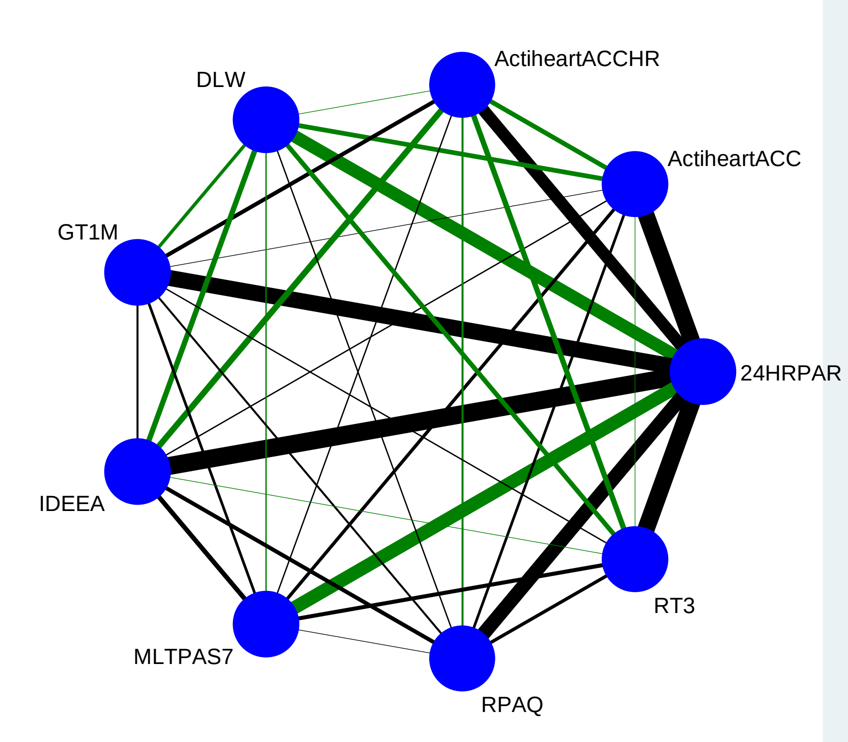
- Long term goal: integrate instrument library with interactive validity map

Work in progress – validity map



Work in progress – validity map

- Network meta-analysis
- Mean difference in PAEE (kJ/kg/day)
- Thicker line = greater difference
- Green lines = direct mapping from published data
- Black lines = indirect mapping from network meta analysis



Acknowledgments

Toolkit co-ordination team

Fumiaki Imamura, Emanuella De Lucia Rolfe, Soren Brage, Nita Forouhi

Toolkit technical team

David Vaughan, Adam Dickinson

Toolkit section contributors

Birdem Amoutzopoulos, Tom Bishop, Soren Brage, Emanuella De Lucia Rolfe, Ulf Ekelund, Anouar Fanidi, Nita Forouhi, Stefanie Hollidge, Fumiaki Imamura, Andy Jones, Saman Khalatbari-Soltani, Youngwon Kim, Sherly Li, Alexander Mok, Grainne O'Donohue, David Ogilvie, Ken Ong, Jenna Panter, Silvia Pastorino, Matthew Pearce, Richard Powell, Paul Scherer, Alison Sleigh, Antonia Smith, Marinka Steur, Tammy Tong, Eirini Trichia, Michelle Venables, Laura Watson, Kate Westgate, Tom White, Katrien Wijndaele, Eleanor Winpenny, Zheng Ye, Jusheng Zheng

Toolkit Principal Investigators

Nita Forouhi, Soren Brage, Nick Wareham

InterConnect

Global data for diabetes and obesity research

Acknowledgement

- This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Connect with us

- InterConnect@mrc-epid.cam.ac.uk
- www.interconnect-diabetes.eu

InterConnect

Global data for diabetes and obesity research

Physical activity during pregnancy and offspring birth size

Silvia Pastorino, Career Development Fellow
MRC Epidemiology Unit, University of Cambridge, UK

This project is funded by the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Why physical activity during pregnancy?

- Potential intervention target to lower the risk for large offspring birth size (LGA and macrosomia)
- In turn, benefits for pregnancy (obstetric) outcomes and longer-term obesity risks (for mother & child)

Systematic reviews: RCTs

- *Two recent meta-analyses of maternal PA interventions suggest modest decreases in birth weight and risk of LGA
- High heterogeneity in effect sizes
- Unable to summarise effects of Volume / Intensity of PA

**Wiebe et al, 2015*
**Sanabria-Martínez et al, 2015*

Systematic review: Observational Studies

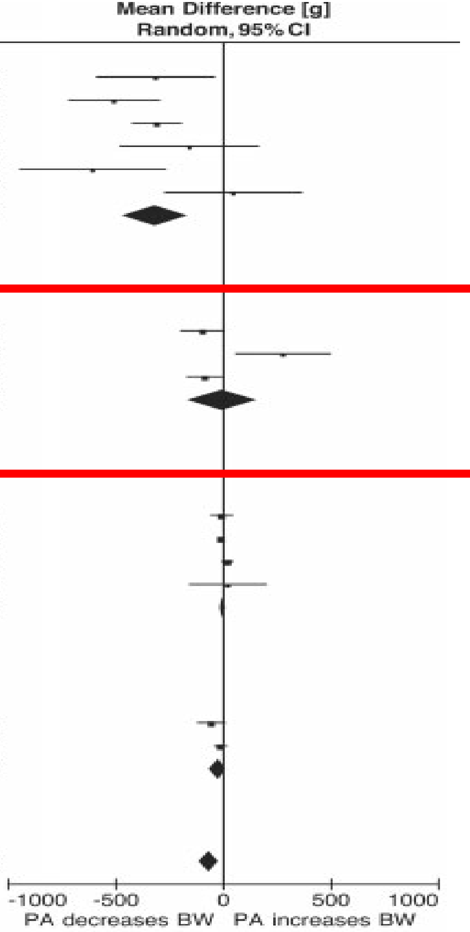
Study finding (N)	Birth weight (BW)	LGA or Macrosomia	% Body Fat
Negative association	8	8	2
No association	25	5	
Positive association	4		

- Most studies found no association with BW (continuous outcome)
- LTPA associated with lower OR of LGA/Macrosomia, and lower %Body Fat
- 19 of 42 studies did not adjust for any confounder
- Discordant associations with *high vs. moderate PA volume* and between confounder *adjusted vs. non-adjusted* studies…

**Bison et al, 2016*

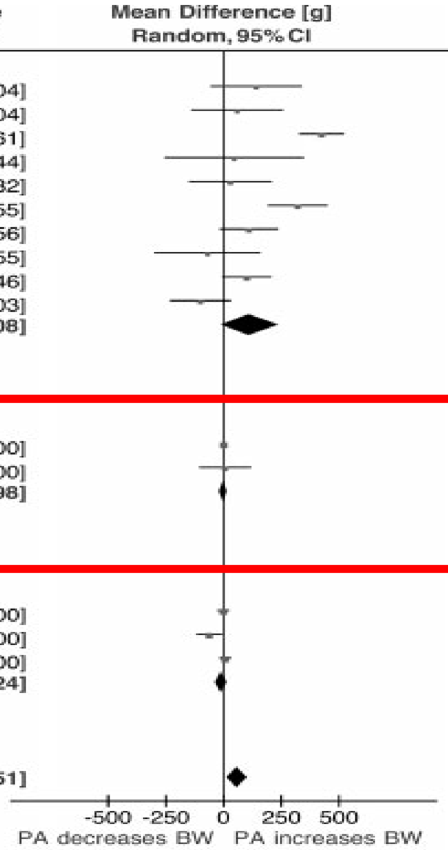
Association between pregnancy PA and offspring BW – High PA levels

Study or Subgroup	Mean Difference [g]	SE	High level Total	Low level Total	Weight	Mean Difference Random, 95% CI
2.1 High volume vs low volume - crude						
Bell 1995	-315	141	58	41	2.2%	-315.00 [-591.35, -38.65]
Clapp 1984	-509	108.8	29	152	3.3%	-509.00 [-722.35, -295.65]
Clapp and Capeless 1990	-310	59.5	77	55	7.0%	-310.00 [-426.62, -193.38]
Duncombe 2006	-158.6	165.1	27	17	1.7%	-158.60 [-482.38, 165.18]
Perkins 2007	-608	174.4	12	13	1.5%	-608.00 [-949.82, -266.18]
Rice 1991	45.4	163.5	12	11	1.7%	45.40 [-275.05, 365.85]
Subtotal (95% CI)			**215**	**289**	**17.4%**	**-319.33 [-472.21, -166.45]**
Heterogeneity: Tau² = 19373.36; Chi² = 11.71, df = 5 (P = 0.04); I² = 57%						
Test for overall effect: Z = 4.09 (P < 0.0001)						
2.2 High volume vs low volume - adjusted						
Harrod 2014 [a]	-97	52.9	206	206	7.7%	-97.00 [-200.68, 6.68]
Hatch 1993	276	113	15	185	3.1%	276.00 [54.52, 497.48]
Magann 2001	-86.5	43.7	238	217	8.9%	-86.50 [-172.15, -0.85]
Subtotal (95% CI)			**459**	**608**	**19.7%**	**-5.00 [-161.86, 151.86]**
Heterogeneity: Tau² = 14416.18; Chi² = 9.70, df = 2 (P = 0.008); I² = 79%						
Test for overall effect: Z = 0.06 (P = 0.95)						
2.3 High duration vs low duration						
Hegaard 2010	-9	27.0	289	3672	11.1%	-9.00 [-62.00, 44.00]
Juhl 2010	-11	9.4	2236	49929	12.8%	-11.00 [-29.42, 7.42]
Nieuwenjuijsen 2002 [b]	16.7	14.4	1131	6744	12.5%	16.70 [-11.52, 44.92]
Sternfeld 1995	20	92.6	25	122	4.2%	20.00 [-161.49, 201.49]
Subtotal (95% CI)			**3681**	**60467**	**40.5%**	**-3.06 [-17.82, 11.70]**
Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
2.4 High intensity vs low-moderate intensity						
Jukic 2012	-57	34.1	224	367	10.1%	-57.00 [-124.00, 10.00]
Rose 1991 [c]	-13	16.3	1281	17927	12.3%	-13.00 [-44.95, 18.95]
Subtotal (95% CI)			**1505**	**18294**	**22.4%**	**-24.74 [-62.88, 13.40]**
Heterogeneity: Tau² = 250.87; Chi² = 1.35, df = 1 (P = 0.25); I² = 26%						
Test for overall effect: Z = 1.27 (P = 0.20)						
Total (95% CI)			**5860**	**79658**	**100.0%**	**-69.85 [-114.75, -24.96]**
Heterogeneity: Tau² = 4006.44; Chi² = 80.59, df = 14 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 3.05 (P = 0.002)						
Test for subgroup differences: Chi² = 17.10, df = 3 (P = 0.0007), I² = 82.5%						



Association between pregnancy PA and offspring BW – Moderate PA levels

Study or Subgroup	Mean Difference [g]	SE	Moderate level Total	Low level Total	Weight	Mean Difference Random, 95% CI
3.1 Moderate volume vs low volume - crude						
Botkin 1991	140.5	101.3	19	25	3.6%	140.50 [-58.04, 339.04]
Clapp 1984	59	101.5	47	152	3.6%	59.00 [-140.04, 258.04]
Downs 2007	424.4	49.6	41	18	7.6%	424.40 [327.19, 521.61]
Duncombe 2006	45.6	153.4	24	17	1.9%	45.60 [-255.24, 346.44]
Horns 1996	29	92	48	53	4.1%	29.00 [-151.32, 209.32]
Jahromi 2011	320	66.1	70	62	6.0%	320.00 [190.45, 449.55]
Johnson 1994	109.2	64.9	139	95	6.1%	109.20 [-18.16, 236.56]
Melzer 2010	-70	117.6	27	17	2.9%	-70.00 [-300.55, 160.55]
Morgan 2014	100	54.8	126	144	7.1%	100.00 [-7.46, 207.46]
Portela 2014 [a]	-100	67.3	37	19	5.9%	-100.00 [-232.03, 32.03]
Subtotal (95% CI)			**578**	**602**	**48.7%**	**115.30 [-6.48, 237.08]**
Heterogeneity: $Tau^2 = 30923.55$; $Chi^2 = 58.39$, $df = 9$ ($P < 0.00001$); $I^2 = 85\%$						
Test for overall effect: $Z = 1.86$ ($P = 0.06$)						
3.2 Moderate volume vs low volume - adjusted						
Juhl 2010	0	7.1	4447	49929	11.7%	0.00 [-14.00, 14.00]
Sternfeld 1995	6	57.6	95	122	6.8%	6.00 [-107.00, 119.00]
Subtotal (95% CI)			**4542**	**50051**	**18.5%**	**0.09 [-13.80, 13.98]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, $df = 1$ ($P = 0.92$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.01$ ($P = 0.99$)						
3.3 Moderate intensity vs low intensity						
Hegaard 2010 [b]	-1	13.2	2384	1998	11.4%	-1.00 [-27.00, 25.00]
Jukic 2012	-62	28.5	527	367	10.0%	-62.00 [-118.00, -6.00]
Rose 1991	7	12.7	17927	2134	11.4%	7.00 [-18.00, 32.00]
Subtotal (95% CI)			**20838**	**4499**	**32.8%**	**-9.13 [-38.50, 20.24]**
Heterogeneity: $Tau^2 = 383.21$; $Chi^2 = 4.90$, $df = 2$ ($P = 0.09$); $I^2 = 59\%$						
Test for overall effect: $Z = 0.61$ ($P = 0.54$)						
Total (95% CI)			**25958**	**55152**	**100.0%**	**61.45 [16.40, 106.51]**
Heterogeneity: $Tau^2 = 4461.44$; $Chi^2 = 110.80$, $df = 14$ ($P < 0.00001$); $I^2 = 87\%$						
Test for overall effect: $Z = 2.67$ ($P = 0.008$)						
Test for subgroup differences: $Chi^2 = 3.81$, $df = 2$ ($P = 0.15$), $I^2 = 47.5\%$						



Limitations of literature-based reviews

- High heterogeneity due to:
  - Different consideration of confounding (many studies were unadjusted)
  - Different PA exposures:
    - Different domains: total PA, LTPA, occupational PA
    - Different volume or intensity
    - Categorisation not standardised
    - Different timings of PA during pregnancy
- Publication bias not tested

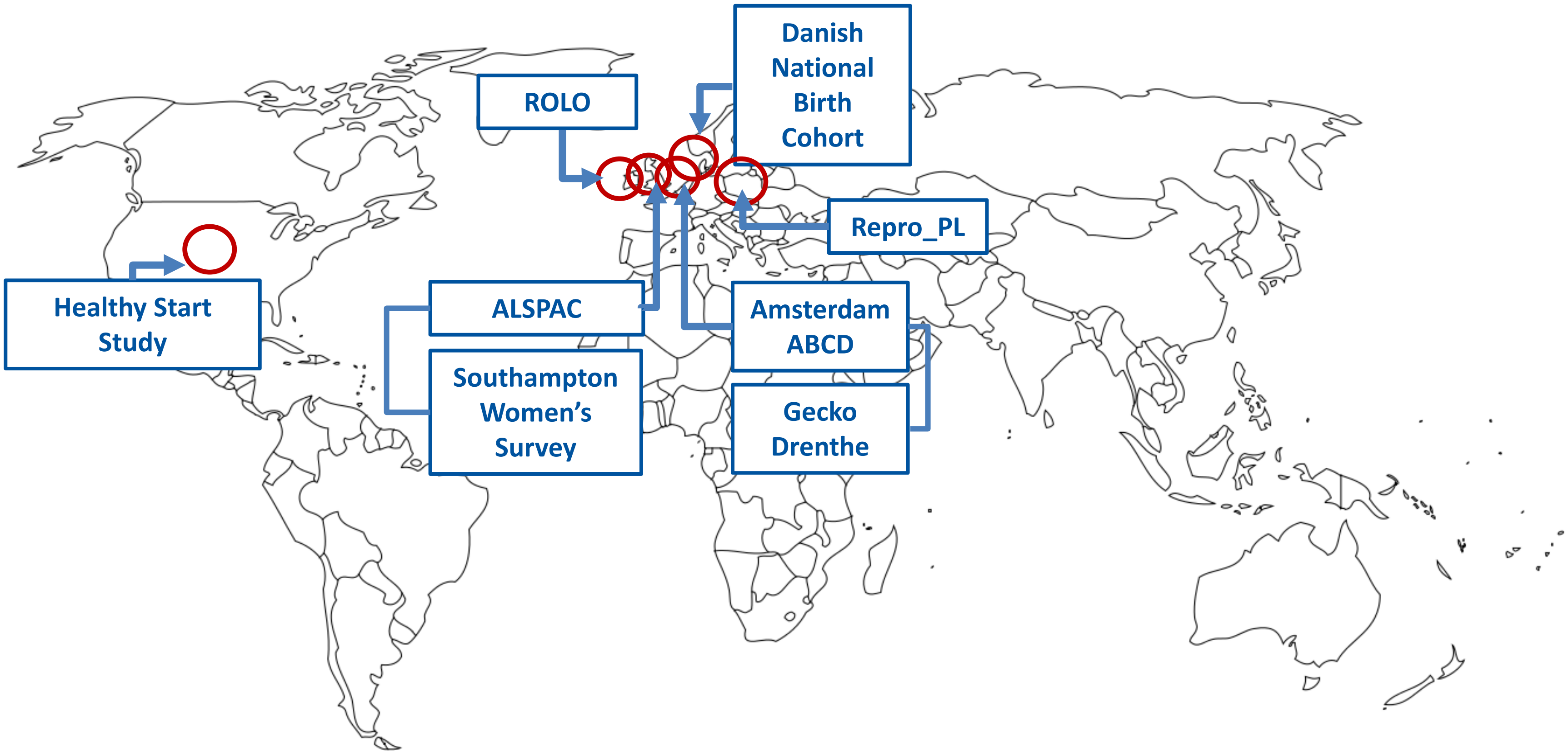
Alternative approaches

- Results sharing
  - Burden on study investigators and analysts to prepare and analyse data
  - Difficult to harmonise measures across studies
- Data pooling
  - Study investigators fear loss of ownership of their data
  - Complex data-sharing agreements
- Federated meta-analyses
  - Data stay within the governance structure of the cohorts
  - Only analytical instructions and non-identifying summary parameters are allowed to pass between computers

Why use federated meta-analysis?

- Allows individual participant-level meta-analysis without physical data pooling
- Reduces heterogeneity by allowing:
  - Harmonisation of exposure and outcome variables
  - Consistent consideration of confounders
- Allows investigation of:
  - Modifying factors
  - Different PA domains
  - Shape of the association and thresholds
  - Timing of the exposure (i.e. PA during early or late pregnancy)
- Avoids publication bias

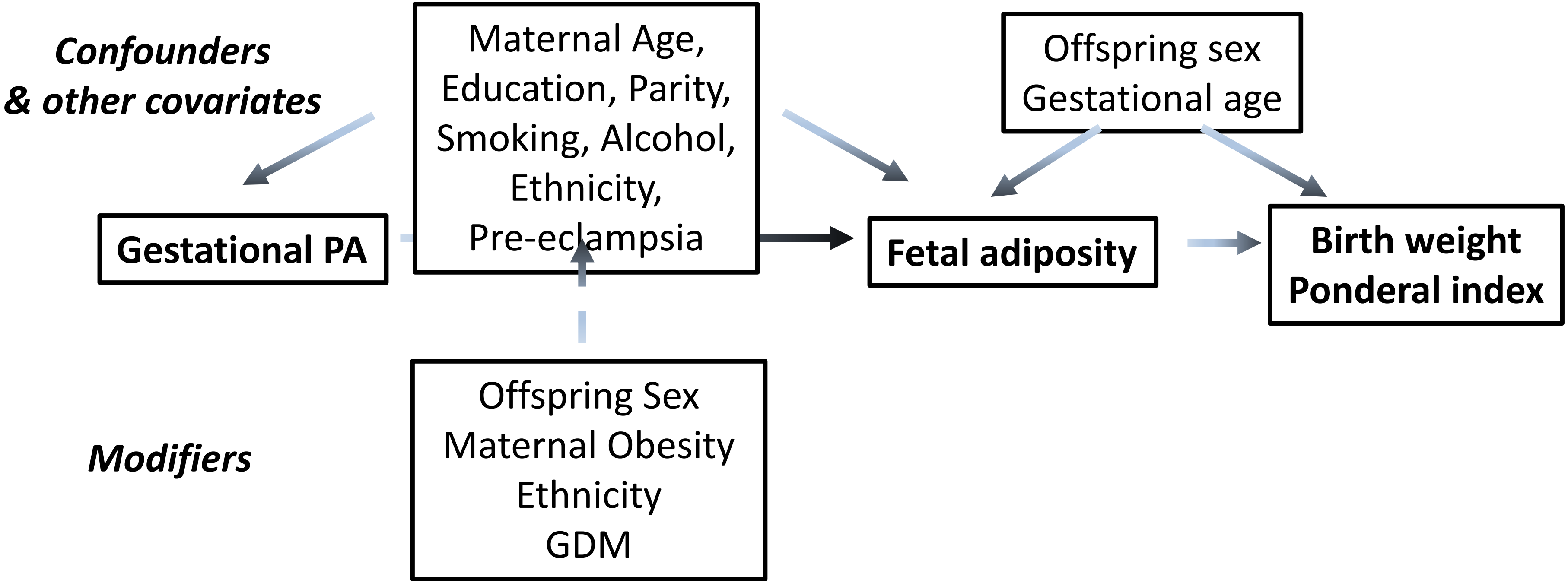
InterConnect PA in pregnancy exemplar project



Analysis plan

- **Population:**
  - **Include:** Live births, singleton, full term babies
  - **Exclude**: Preterm (< 37 weeks gestation), multiple births
- **Exposures:**
  - Duration of LTPA
  - Duration of LT moderate/vigorous physical activity (MVPA)
  - MET-h/week for LTPA = duration*intensity (coded by Compendium of PAs)
- **Outcomes:**
  - Birth weight, BW (g); Macrosomia (BW >4000 g); LGA, large for gestational age (BW >90^{th} centile)
  - Ponderal index (BW/Length^3)
  - %body fat in newborns (by DXA, skinfold thickness, or PeaPod)

DAG



Confounders
& other covariates
Maternal Age,
Education, Parity,
Smoking, Alcohol,
Ethnicity,
Pre-eclampsia
Offspring sex
Gestational age
Gestational PA
Fetal adiposity
Birth weight
Ponderal index
Modifiers
Offspring Sex
Maternal Obesity
Ethnicity
GDM

Study descriptions – birth size outcomes

	ALSPAC	ABCD	DNBC	GECKO	HSS	REPRO_PL	ROLO	SWS
N[1]	9,058	6,464	53,671	1,335	1,054	982	617	1,902
Birth weight, g -Male, mean (SD)	3,551 (479)	3,572 (491)	3,709 (503)	3,708 (505)	3,356 (432)	3,490 (440)	4,135 (481)	3,589 (480)
Birth weight, g - Female, mean (SD)	3,424 (447)	3,435 (456)	3,575 (481)	3538 (490)	3,217 (420)	3,316 (432)	3,963 (423)	3,445 (458)
Macrosomia, n (%)	1,158 (12.7)	871 (13.4)	11,681 (21.7)	289 (21.6)	60 (5.6)	84 (8.5)	320 (51.8)	267 (14)
LGA, n (%)	1,888 (20.8)	1,222 (18.9)	15,052 (28)	405 (30.3)	121 (8.7)	183 (18.6)	381 (61.7)	369 (19.4)
SGA, n (%)	418 (4.6)	311 (4.8)	1,849 (3.4)	59 (6.4)	100 (9.4)	58 (5.9)	5 (0.8)	101 (5.3)
Ponderal Index, median (IQR)	26.2 (24.7-27.8)		24.9 (23.5-26.5)		26.9 (24.9-29.2)	20.2 (18.9- 21.6)	27.1 (25.3-29.3)	27.8 (26.3-29.2)
% body fat[3], median (IQR)					10 (8-12)		16 (14-18)	11 (10-13)

Study descriptions – leisure time physical activity

	ALSPAC	ABCD	DNBC	GECKO	HSS	REPRO_PL	ROLO	SWS
Early pregnancy PA median (IQR)								
LTPA (h/w)	4.0 (0.5-5.5)	2.0 (0.5-4.3)	0.0 (0.0-1.0)		3.0 (1.0-5.8)	4.0 (0.0-7.0)	1.7 (1.0-2.3)	6.5 (3.2-11.5)
MVPA (h/w)	4.0 (0.5–5.0)	1.5 (0.0-3.5)	0.0 (0.0-1.0)		1.5 (0.0-3.5)	0.0 (0.0-0.0)	0.3 (0.0-1.0)	1.2 (0.3-3.0)
LTPA EE (Met-h/w)	15.2 (3.0-25.2)	8.1 (1.7-19.3)	0.0 (0.0-6.0)		10.2 (3.1-23.6)	16.5 (0.0-33.0)	4.5 (2.0-7.8)	17.5 (8.7-32.1)
Late pregnancy PA median (IQR)								
LTPA (h/w)			0.0 (0.0-1.0)	1.0 (1.0-1.0)	2.0 (0.5-3.6)	5.0 (0.0-8.0)		7.0 (3.4-12.0)
MVPA (h/w)			0.0 (0.0-1.0)	0.3 (0.0-1.0)	0.0 (0.0-1.5)	0.0 (0.0-00.0)		0.8 (0.1-2.3)
LTPA EE (Met-h/w)			0.0 (0.0-3.0)	1.0 (0.0-4.0)	6.3 (1.5-11.9)	19.8 (0.0-33.0)		16.7 (8.5-31.1)

Adjustment for confounding

- Tested models **BEFORE** and **AFTER** adjustment for potential confounders (Maternal SES, Age, Parity, Smoking, Alcohol, Ethnicity)
- Adjustment for confounding **reduced heterogeneity**

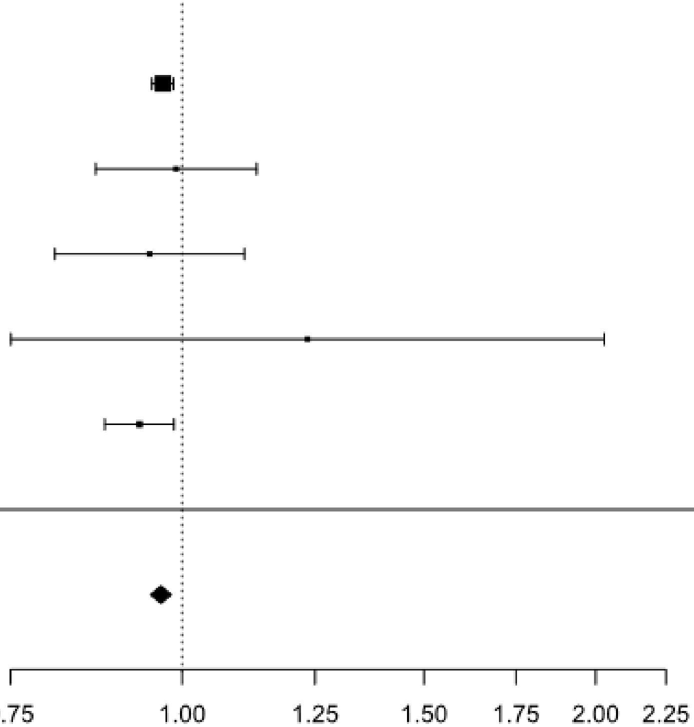
Results: Early pregnancy LTPA → offspring birth size

	BW (grams)	Macrosomia	LGA	Ponderal Index	SGA
Unadjusted	Beta, 95% CI I^2	RR, 95% CI I^2	RR, 95% CI I^2	Beta, 95% CI I^2	Beta, 95% CI I^2
LTPA (h/w)	0.30 (-3.39, 3.99)	0.99 (0.97, 1.02)	0.99 (0.97, 1.01)	0.00 (-0.02, 0.02)	0.98 (0.96, 1.00)
	86%	82%	80%	71%	41%
MVPA (h/w)	-0.18 (-5.46, 5.09)	1.00 (0.97 1.03)	0.99 (0.97, 1.02)	-0.01 (-0.02, 0.01)	0.98 (0.95, 1.01)
	86%	82%	81%	37%	47%
Adjusted					
LTPA (h/w)	-0.86 (-2.33, 0.61)	0.99 (0.98, 1,01)	0.99 (0.98, 1,00)	0.0 (-0.01, 0.01)	0.99 (0.98, 1.01)
	23%	51%	46%	0%	0%
MVPA (h/w)	-1.38 (-3.77, 1.01)	1.00 (0.98, 1,01)	1.00 (0.98, 1,01)	0.00 (-0.01, 0.01)	0.99 (0.98, 1.00)
	41%	52%	43%	0%	0%

Results: Late pregnancy MVPA → offspring BW (g)

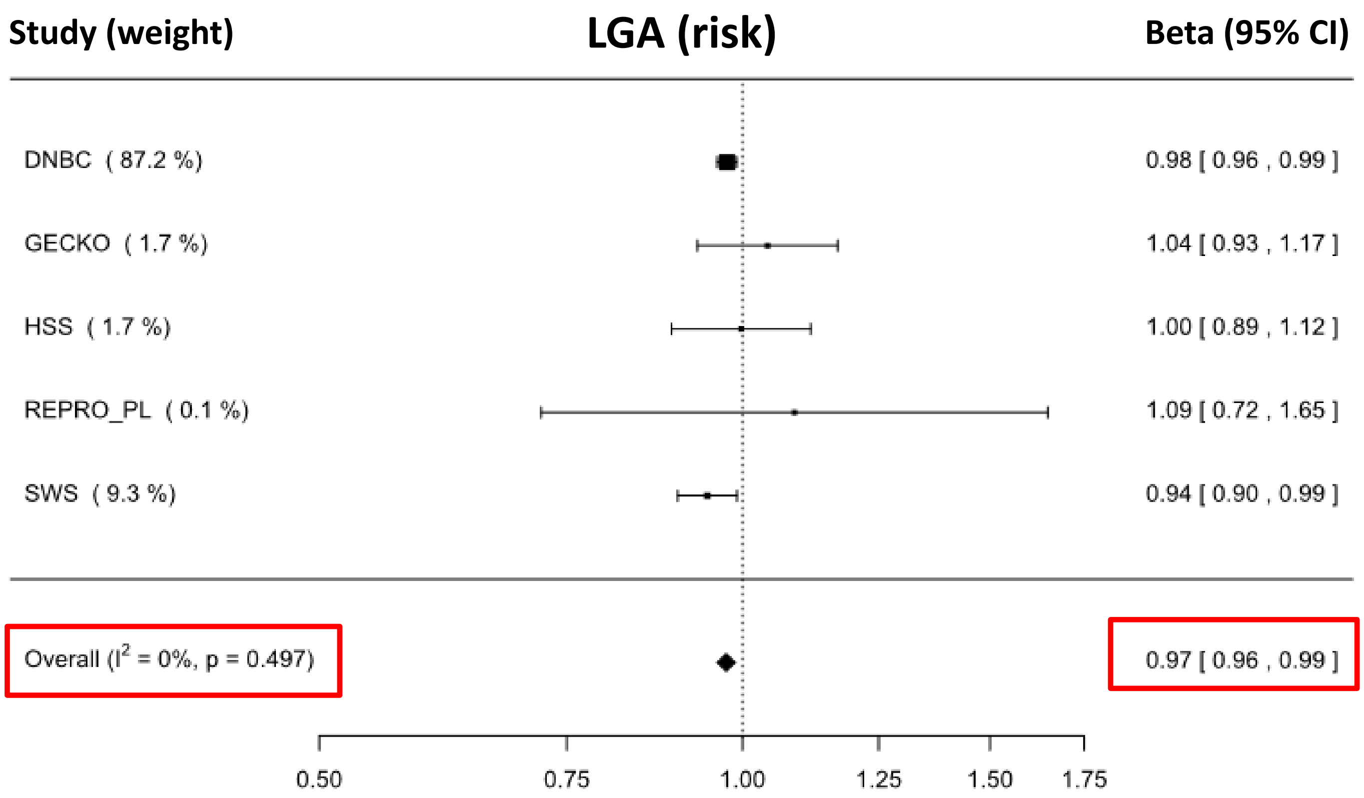
Birth weight (g)

Study (weight)	Beta (95% CI)
DNBC (88.5 %)	0.97 [0.95 , 0.99]
GECKO (1.6 %)	0.99 [0.87 , 1.13]
HSS (1.1 %)	0.95 [0.81 , 1.11]
REPRO_PL (0.1 %)	1.23 [0.75 , 2.03]
SWS (8.6 %)	0.93 [0.88 , 0.99]
Overall (I^2 = 0%, p = 0.606)	0.97 [0.95 , 0.98]



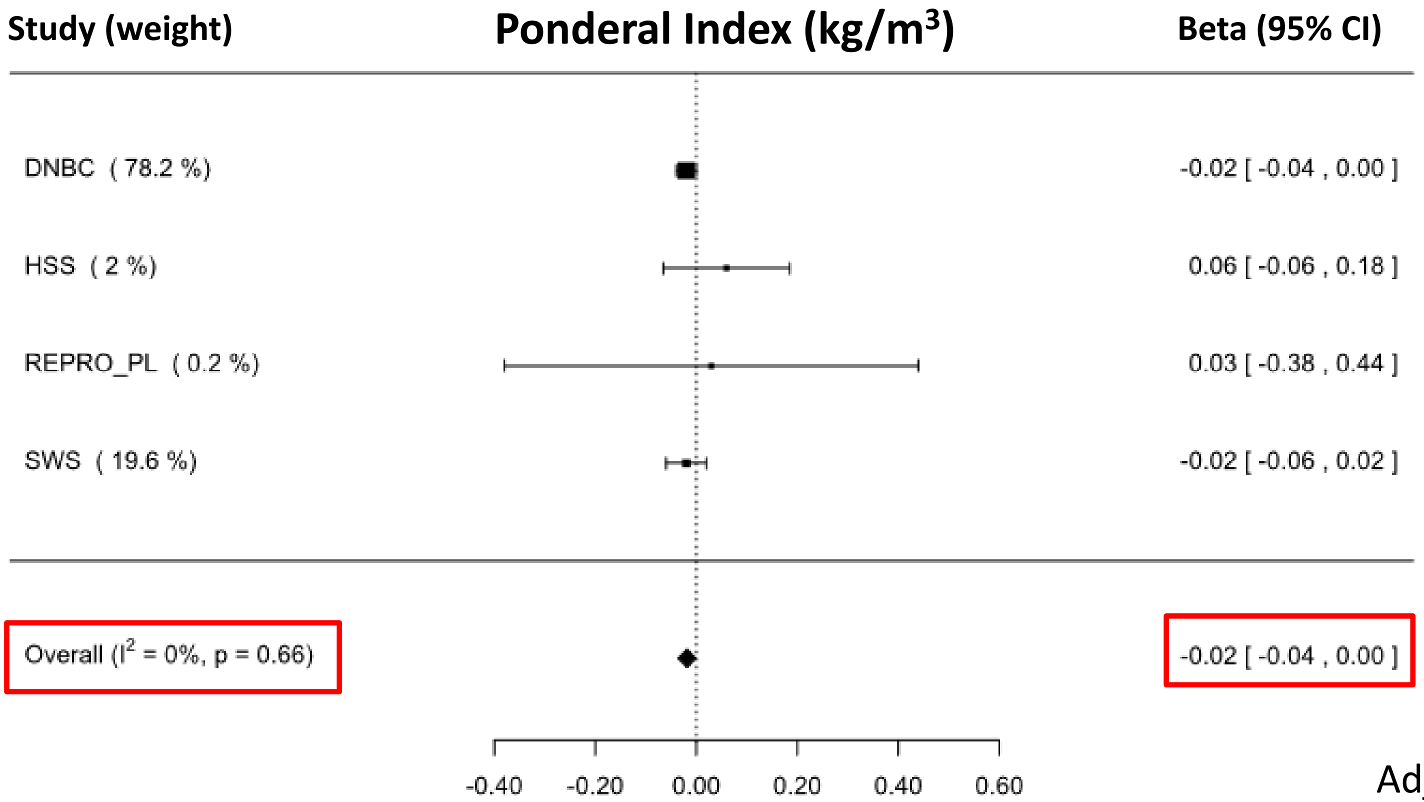
Adjusted models

Results: Late pregnancy MVPA → offspring LGA



Adjusted models

Results: Late pregnancy MVPA → offspring Ponderal Index



Adjusted models

Summary

- Heterogeneity between studies was substantially reduced by consistent adjustment for confounders
- Leisure time moderate-vigorous physical activity during late, but not early, pregnancy has a small but significant inverse association with offspring birth size (BW, large BW, ponderal index)
- No association with higher risk of low birth weight (SGA)

InterConnect

Global data for diabetes and obesity research

Silvia Pastorino, Tom Bishop, Sarah R. Crozier, Charlotta Granström, Katarzyna Kordas, Leanne K. Küpers, Eileen O'Brien, Kinga Polanska, Katherine A Sauder, Mohammad Hadi Zafarmand, Becca Wilson, Paul R. Burton, Eva Corpeleijn, Dana Dabelea, Wojciech Hanke, Hazel M. Inskip, Fionnuala McAuliffe, Sjurdur Frodi Olsen, Tanja G. Vrijkotte, Soren Brage, Aileen Kennedy, Donal O'Gorman, Paul Scherer, Katrien Wijndaele, Nick J. Wareham, Gernot Desoye, Ken K. Ong

www.InterConnect-diabetes.eu

This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Global data for diabetes and obesity research

Acknowledgement

- This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Connect with us

- InterConnect@mrc-epid.cam.ac.uk
- www.interconnect-diabetes.eu

InterConnect

Global data for diabetes and obesity research

Fish intake and new-onset type 2 diabetes

Nita Forouhi, Silvia Pastorino and the InterConnect Team
MRC Epidemiology Unit
11th September 2017

This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

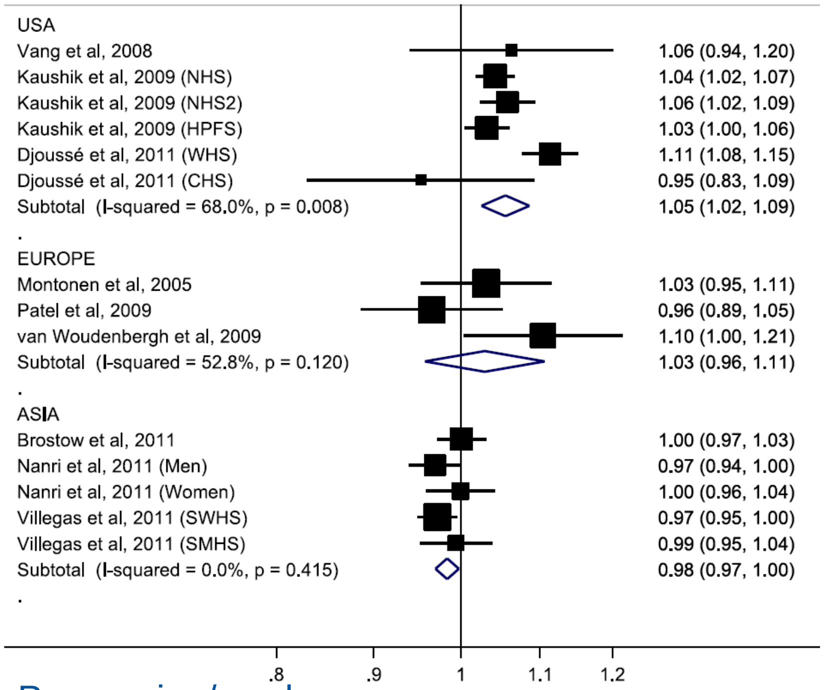
What is known

- It is proposed that fish intake is likely to be beneficial for the prevention of type 2 diabetes, based on the benefits for cardiovascular health

Meta analyses of fish and type 2 diabetes

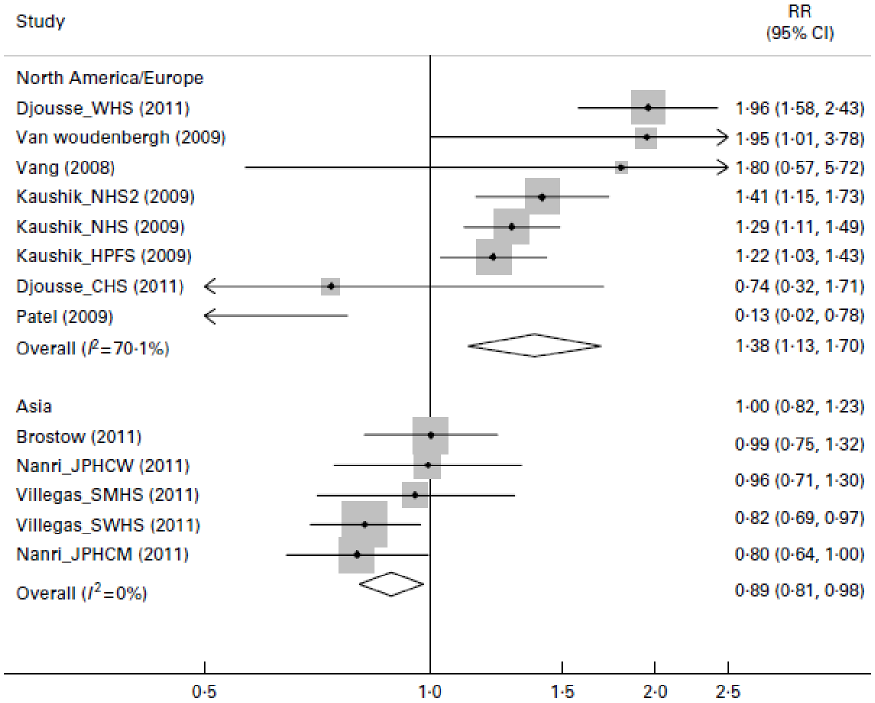
Meta analyses	Wallin, Diabetes Care, 2012,	Wu, Br J Nutr, 2012	Xun, Diabetes Care, 2012	Zhou, Br J Nutr, 2012	Zheng, PLOS ONE, 2012
	13 studies 21,173 T2D	13 studies 20,830 T2D	12 studies 18,711 T2D	9 studies 18,272 T2D	11 studies 18,047 T2D
Overall Relative risk (95% CI)	1.01 0.99, 1.03 Per serving/week	1.12 0.94, 1.34 Per 100g/day	1.00 0.85, 1.18 Highest/lowest	1.15 0.98, 1.35 Highest/lowest	1.07 0.91, 1.25 Highest/lowest

Fish and T2D: Location matters



Per serving/week

Wallin A *Diabetes Care*, 2012, 35:



Per 100 g/d

Wu HY *BJN* 2012, 107:

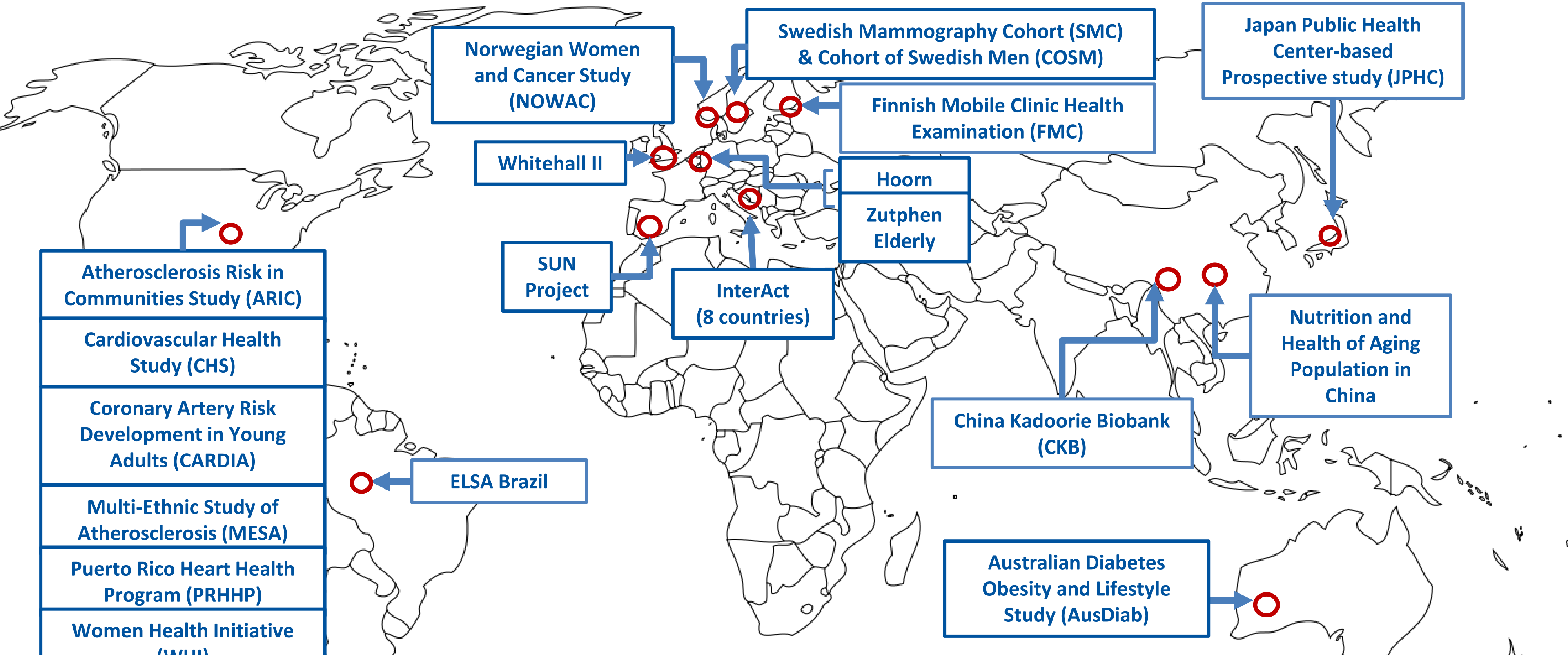
What are the research gaps?

- Systematic reviews analysed total fish and did not distinguish between types of fish (e.g. fatty fish, lean fish and shellfish) or cooking methods;
- Systematic reviews did not include unpublished results
- High heterogeneity in meta-analyses might be caused by:
  - Different confounding structures of included studies
  - Different fish exposures (portions sizes varied across studies)

Advantages of InterConnect

- Individual participant meta-analysis without physical pooling of data
- Reduce heterogeneity by:
  - Including the same types of confounders
  - Harmonising exposures and outcome to a common format
- Include studies that have not yet published on the association between fish and T2D

Map of participating studies



Participating studies: Europe

Study name	Country	N, sex
EPIC-InterAct	8 European countries	28,460 m/w
Finnish Mobile Clinic Health Examination (FMC)	Finland	4,304 m/w
Hoorn Study	Netherlands	6000 m/w
Norwegian Women and Cancer Study (NOWAC)	Norway	33,740 w
Swedish Mammography Cohort (SMC) & Cohort of Swedish Men (COSM)	Sweden	66,651 w & 45,906 m
SUN Project	Spain	22,340 m/w
Whitehall II	UK	10,308 m/w
Zutphen Elderly	Netherlands	876 m/w

Participating studies: Asia and Australia

Study name	Country	N, sex
The Australian Diabetes Obesity and Lifestyle Study (AusDiab)	Australia	6537 m/w
Japan Public Health Center-based Prospective study (JPHC)	Japan	52,680 m/w
Nutrition and Health of Aging Population in China	China	4,526 m/w
China Kadoorie Biobank	China	>500,000 m/w

Participating studies: North and South America

Study name	Country	N, sex
Atherosclerosis Risk in Communities Study (ARIC)	US	15,792 m/w
Cardiovascular Health Study (CHS)	US	5,210 m/w
Coronary Artery Risk Development in Young Adults (CARDIA)	US	5,115 m/w
Multi-Ethnic Study of Atherosclerosis (MESA)	US	6,814 m/w
Puerto Rico Heart Health Program (PRHHP)	US	9,824 m
Women Health Initiative (WHI)	US	93,676 w
ELSA Brazil	Brazil	15,105 m/w

Exposure: harmonised variables

- **Total fish**
- **Fatty/oily fish (EPIC classification: fat content > 4%)**
- **Lean fish**
- **Fried fish**
- Shellfish (crustaceans and molluscs)
- Saltwater fish
- Freshwater fish
- Smoked or salted fish

Units:

  - Harmonised to g/day; results presented as 120g serving/week

Outcome: harmonised variables

Primary outcome: clinically incident type 2 diabetes

A confirmed clinical case is considered as fulfilling any one or more of the following criteria:

- ascertained by linkage to a registry or medical record, OR
- self-report of physician diagnosis or use of antidiabetic medication verified by at least one additional source including:
  - a) linkage to a registry or medical record, OR
  - b) biochemical measurement (glucose or HbA1c), OR
  - c) if validated in a validation study with high concordance

Outcome: harmonised variables

Secondary outcome: incident type 2 diabetes

Presence of any of the following criteria:

- self-report of physician diagnosis or use of antidiabetic medication (reported or confirmed use of medication), OR
- ascertained by linkage to a registry or medical record, OR
- biochemical measurement (glucose or HbA1c)

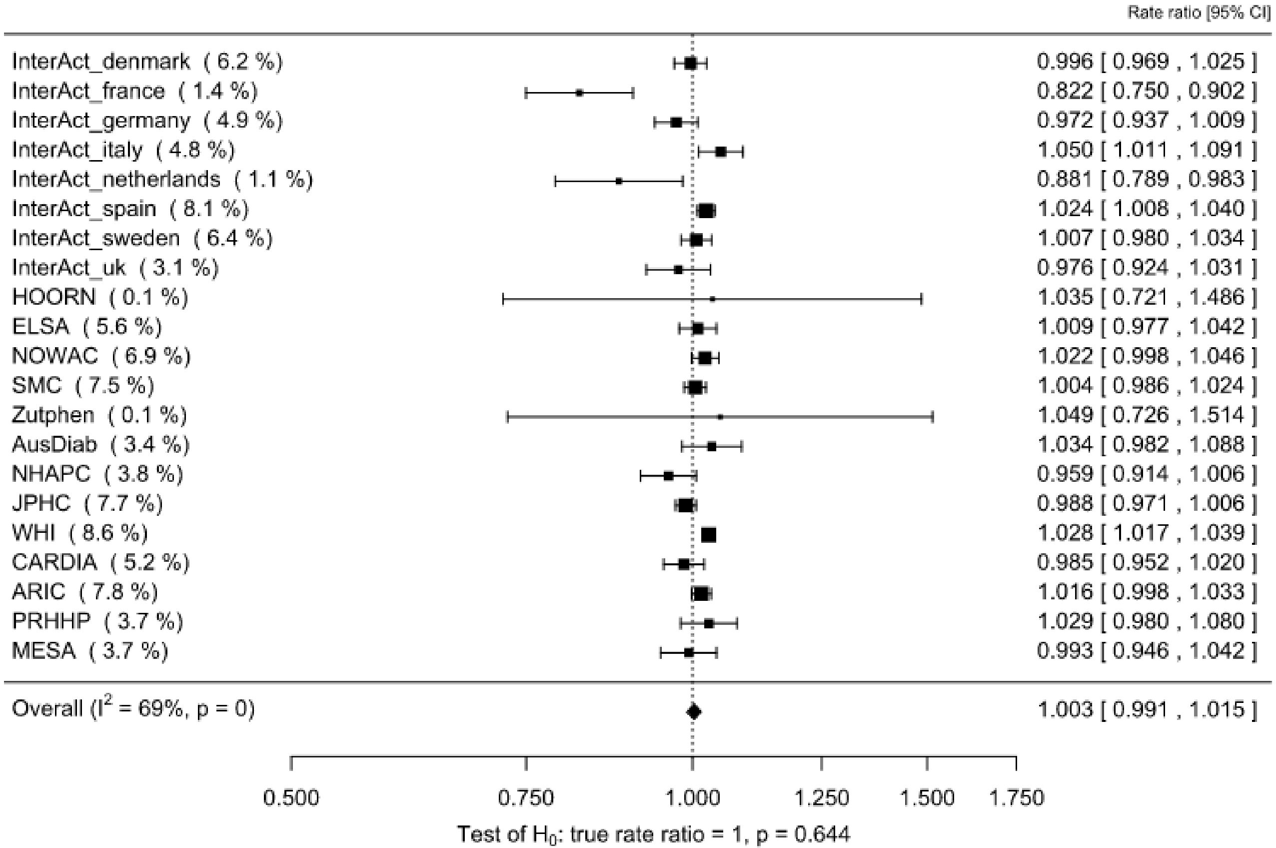
Confounders

- **Demographic:**
  - Age
  - education (highest educational level or years of education)
- **Lifestyle:**
  - Smoking (mostly equivalent to smoking history: current, never, former)
  - Physical activity
  - Alcohol (g/d or categorical variables)
- **Health:**
  - BMI; Waist circumference
  - Family history of diabetes
  - Co-morbidity (diagnosed with: MI OR stroke OR cancer OR hypertension)
- **Dietary:**
  - Total energy intake; Fibre
  - Red and processed meat; Fruits; Vegetables; Sugary beverages
  - Fish-oil supplement

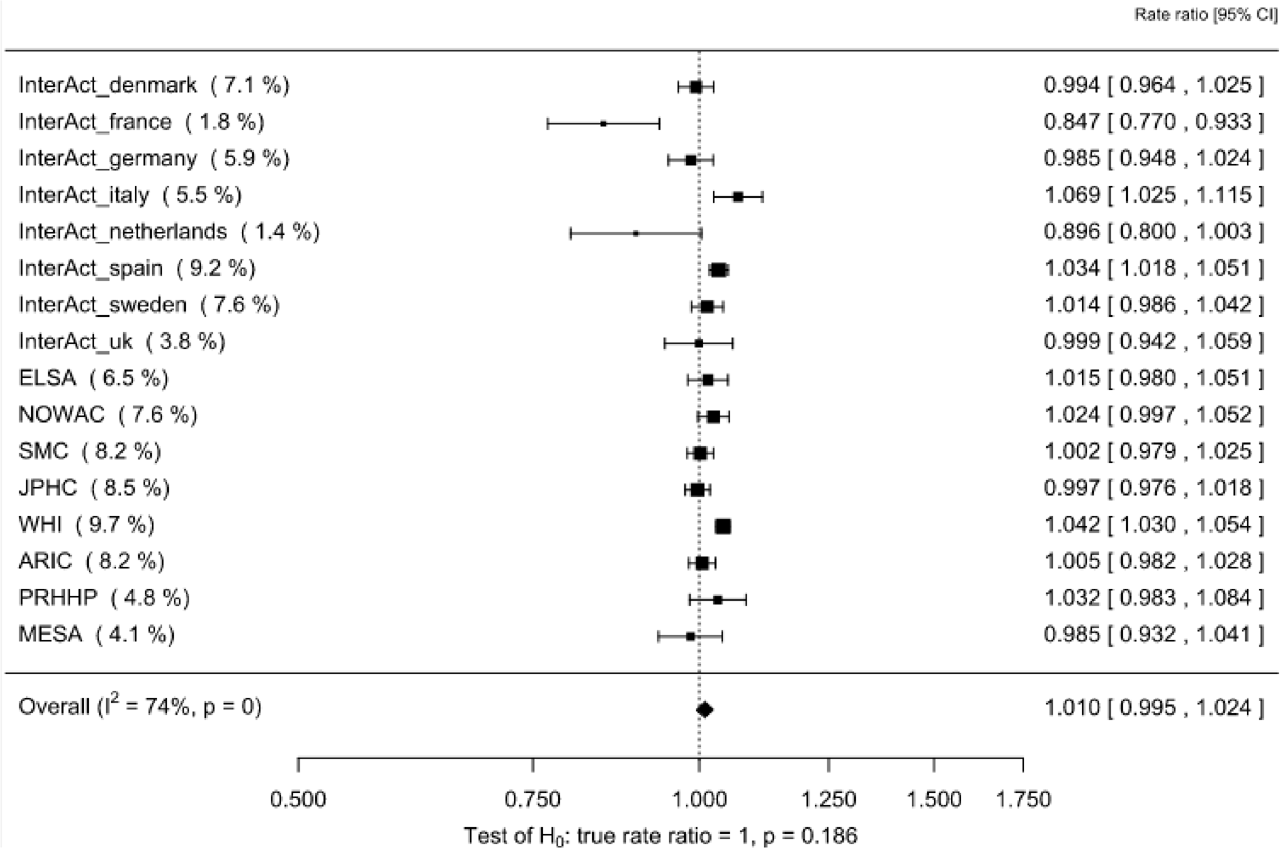
Study	Country	Age (years) Median (IQR)	Mean follow up (years)	Total N	Men (%)	Cases N – clinically incident T2D	Cases N–incident T2D
InterAct	Various EU	54.1 (48.2, 60.0)	9.8	26,771	43	11,433	11,433
HOORN	Netherlands	60.7 (55.1, 67.5)	6.4	2,247	46	17	131
ELSA Brazil	Brazil	51.0 (45.0, 58.0)	3.9	12,367	44	342	693
NOWAC	Norway	50.0 (46.0, 54.0)	6.3	45,965	0	703	703
SMC/COSM	Sweden	60.0 (53.0, 69.0)	10.9	76,020	52	5,245	7,854
Zutphen	Netherlands	71.3 (67.6, 75.8)	9.0	745	100	11	71
AusDiab	Australia	49.0 (40.0, 60.0)	9.6	9,682	44	204	404
NHAPC	China	58.0 (53.0, 64.0)	5.5	2,740	42	415	514
JPHC	Japan	55.0 (50.0, 62.0)	4.8	52,301	45	845	845
WHI	USA	64.0 (58.0, 69.0)	10.5	90,627	0	10,693	10,693
CARDIA	USA	25.0 (22.0, 28.0)	20.6	4,066	42	279	279
ARIC	USA	53.0 (49.0, 59.0)	15.9	9,745	44	734	2,028
PRHHP	Puerto Rico	52.0 (47.0, 57.0)	5.5	8,382	100	310	862
MESA	USA	62.0 (53.0, 70.0)	4.1	5,275	46	230	702
Whitehall	UK	49.4 (44.9, 55.5)	14.0	8,058	69	298	1,038

Study	Dietary assessment method	Total Fish Median (IQR)	Lean Median (IQR)	Fatty Median (IQR)	Fried Median (IQR)
InterAct	FFQ	32.3 (19.0, 51.0)	10.2 (4.6, 20.1)	6.9 (2.2, 14.3)	2.6 (0.8, 5.5)
HOORN	FFQ	12.0 (1.0, 27.0)	3.6 (0.0, 10.0)	1.0 (0.0, 9.0)	0.0 (0.0, 0.0)
ELSA Brazil	FFQ	33.0 (18.0, 58.0)	N/A	N/A	0.0 (0.0, 13.0)
NOWAC	FFQ	87.3 (57.6, 126.0)	23.7 (11.0, 42.9)	11.4 (4.2, 21.5)	N/A
SMC/COSM	FFQ	29.0 (19.0, 41.0)	10.0 (8.0, 25.0)	10.0 (6.0, 15.0)	16.4 (8.2, 16.4)
Zutphen	Cross-check dietary history	13.0 (0.0, 27.0)	9.0 (0.0, 18.0)	0.0 (0.0, 8.0)	0.0 (0.0, 14.0)
AusDiab	FFQ	25.3 (13.5, 44.0)	N/A	N/A	3.2 (1.2, 10.8)
NHAPC	Open-ended FFQ	26.6 (9.6, 55.0)	N/A	N/A	N/A
JPHC	FFQ	78.8 (49.8, 120.7)	8.0 (4.0, 19.3)	27.1 (15.3, 48.3)	N/A
WHI	FFQ	23.0 (11.8, 40.8)	3.9 (0.0, 9.2)	0.0 (0.0, 5.9)	0.0 (0.0, 3.9)
CARDIA	Diet history interview	34.5 (9.2, 80.5)	18.4 (0.0, 46.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
ARIC	FFQ interview	60.1 (38.4, 96.4)	7.7 (1.9, 16.4)	7.7 (7.7, 16.4)	N/A
PRHHP	FFQ	0.0 (0.0, 0.0)	N/A	N/A	N/A
MESA	FFQ	23.6 (11.0, 46.6)	1.7 (0.0, 9.2)	3.5 (0.0, 9.2)	3.5 (0.0, 9.2)
Whitehall	FFQ	35.0 (17.5, 52.5)	17.5 (8.8, 26.3)	8.8 (0.0, 17.5)	0.0 (0.0, 8.8)

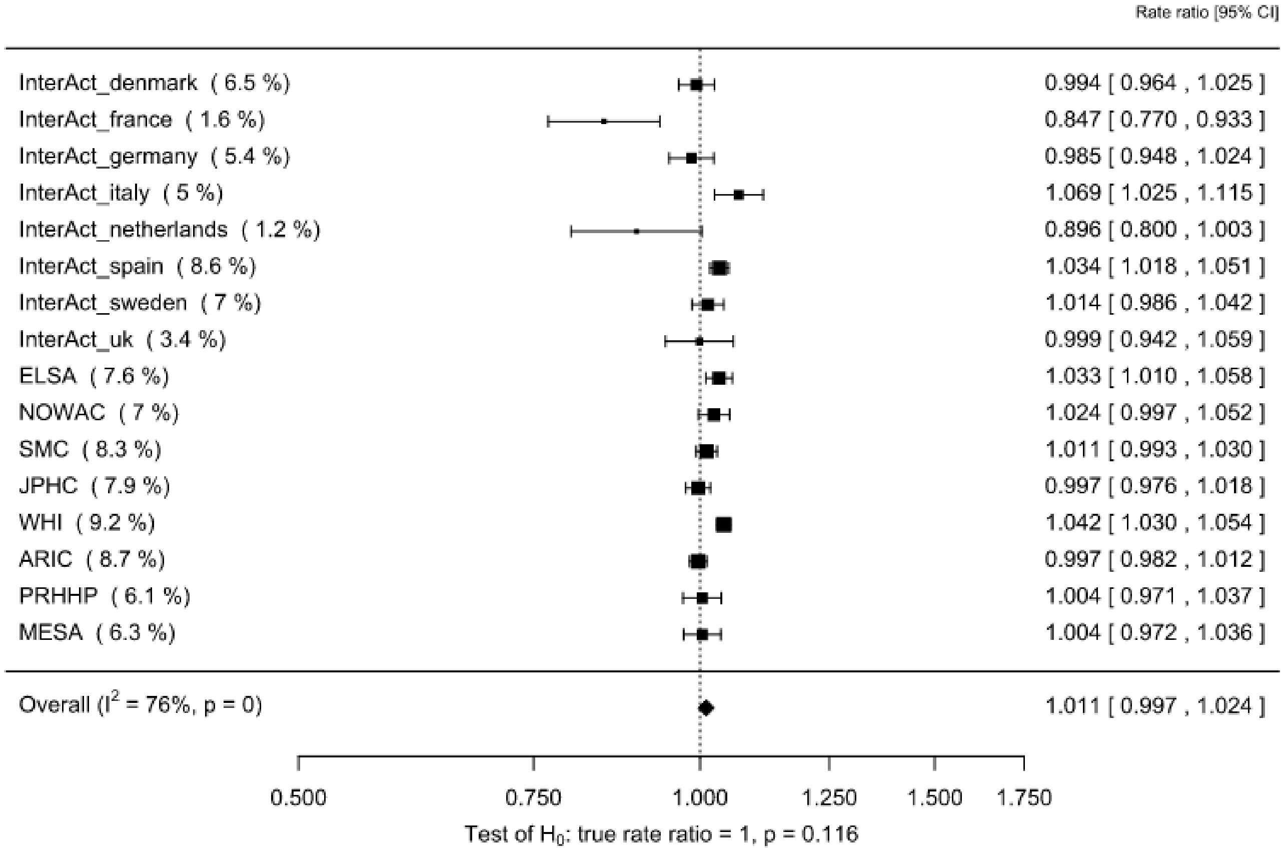
RESULTS– Model 1: Total fish adjusted for age, sex, education, smoking, physical activity, BMI, co-morbidities



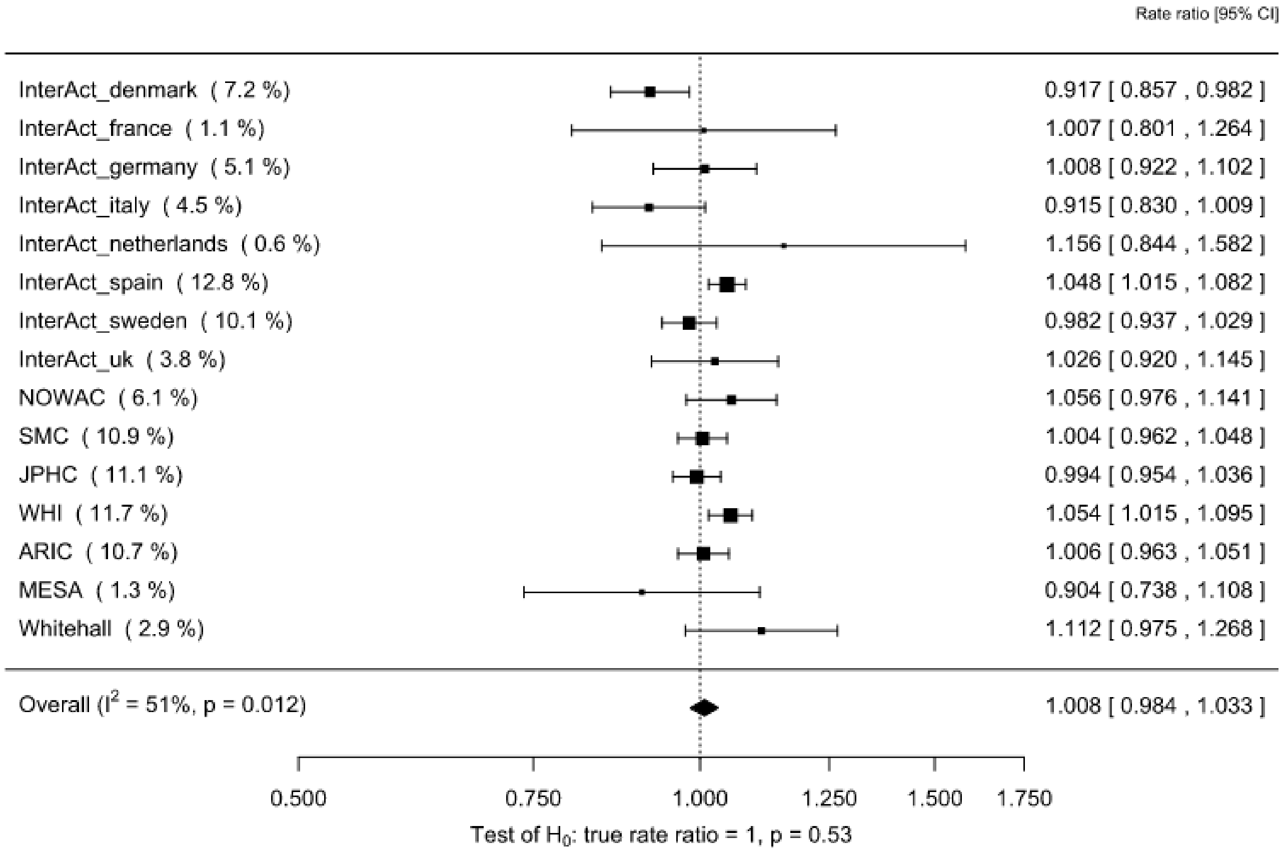
RESULTS – Model 2: As model 1 + adjusted for energy intake, alcohol, fibre, red and processed meat, fruit, vegetables, and sugary drinks



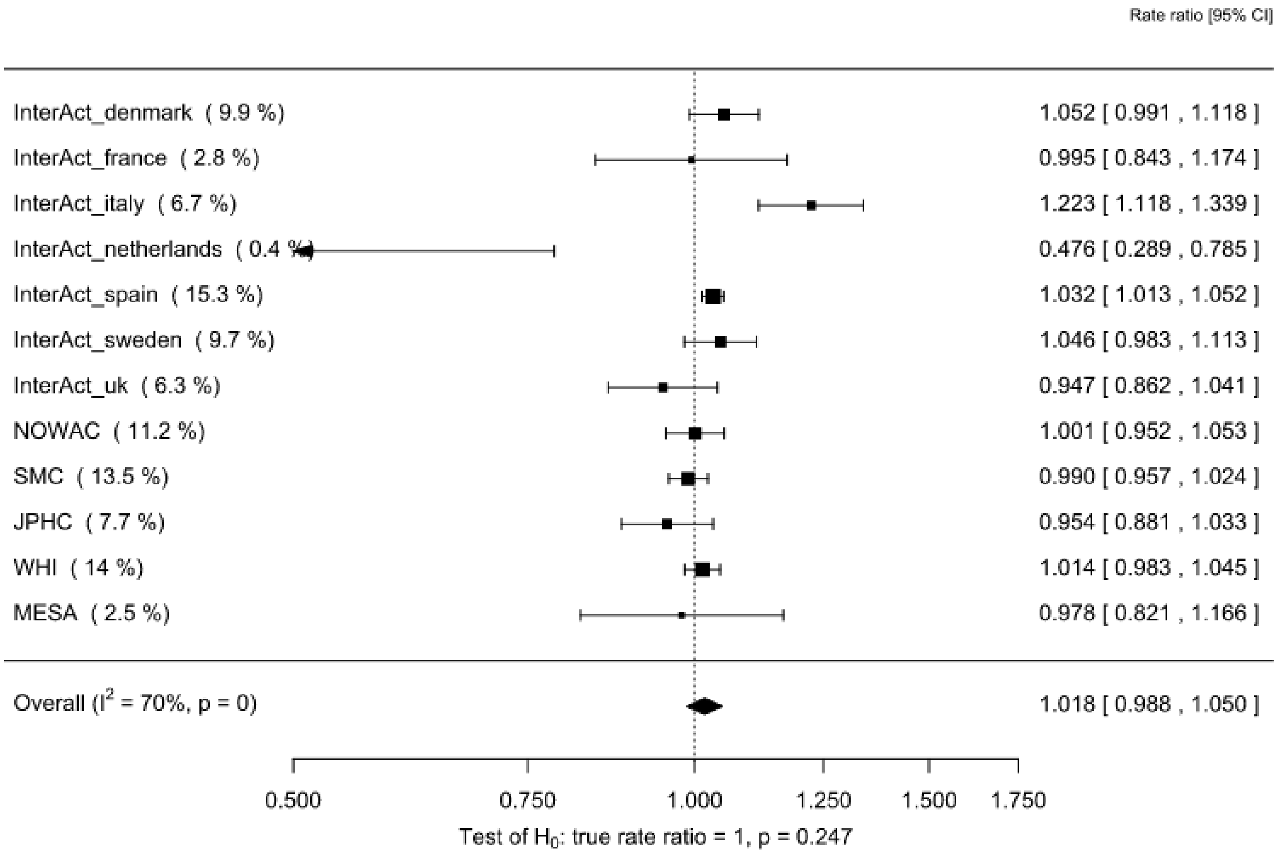
RESULTS – Model 2 using secondary outcome (incident T2D)



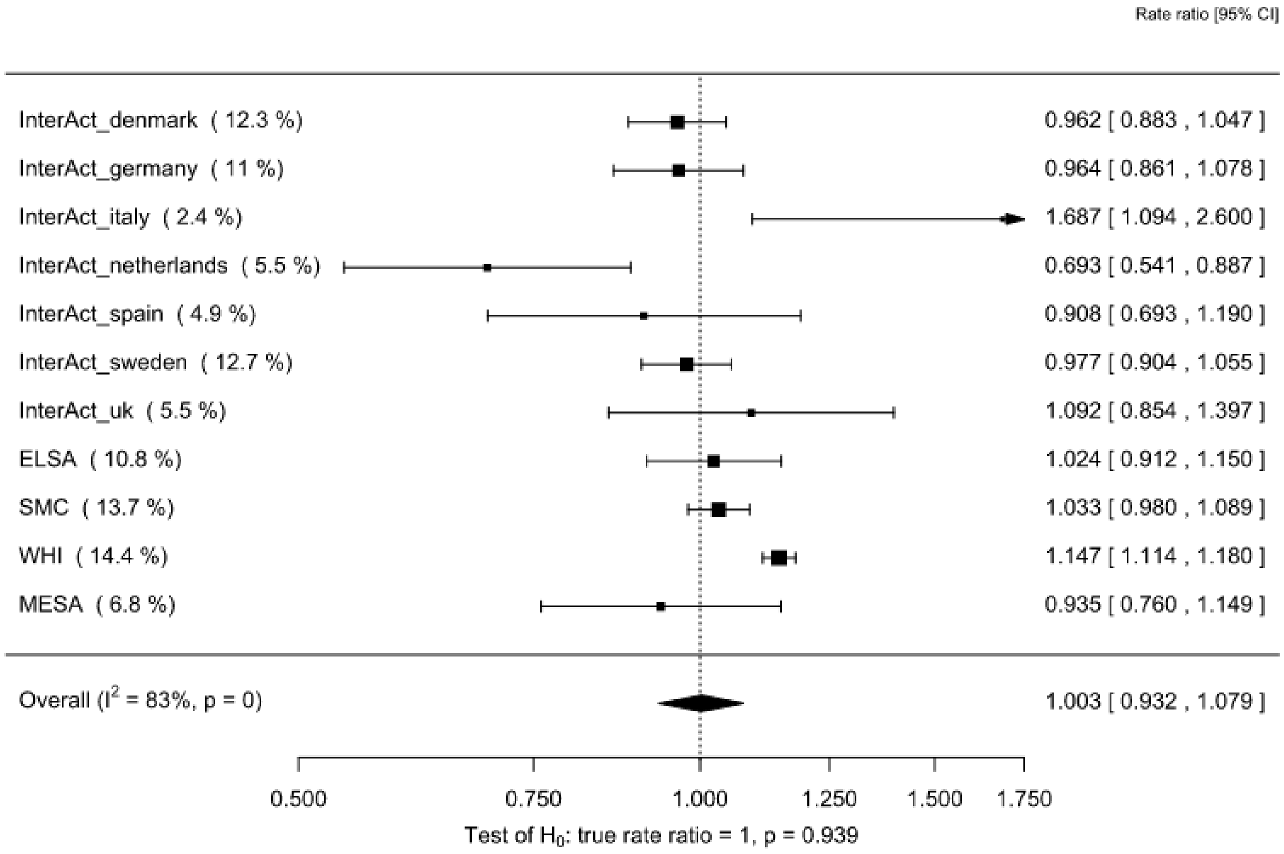
RESULTS for type of fish – Fatty fish Model 2



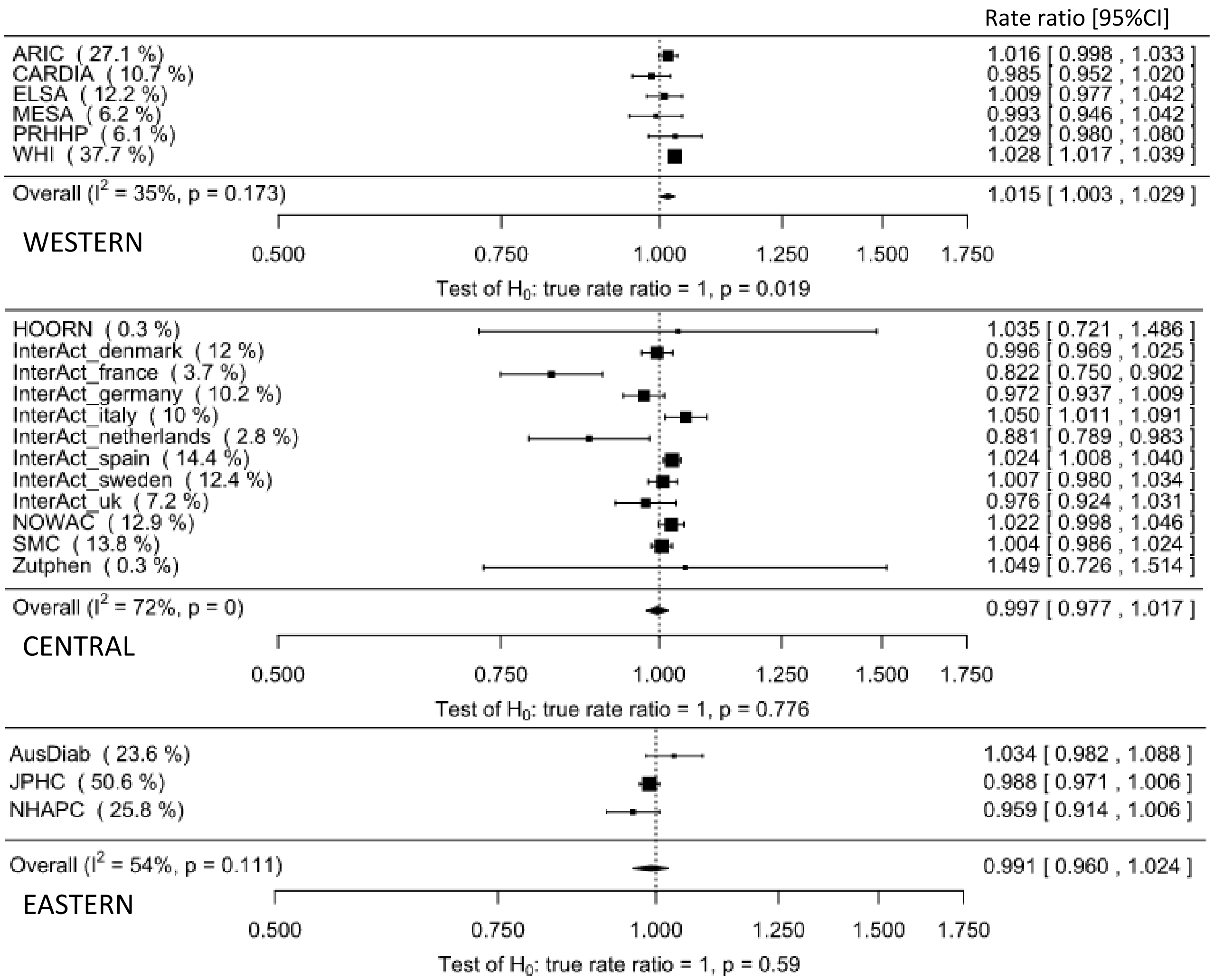
RESULTS for type of fish – Lean fish Model 2



RESULTS for type of fish – Fried fish Model 2

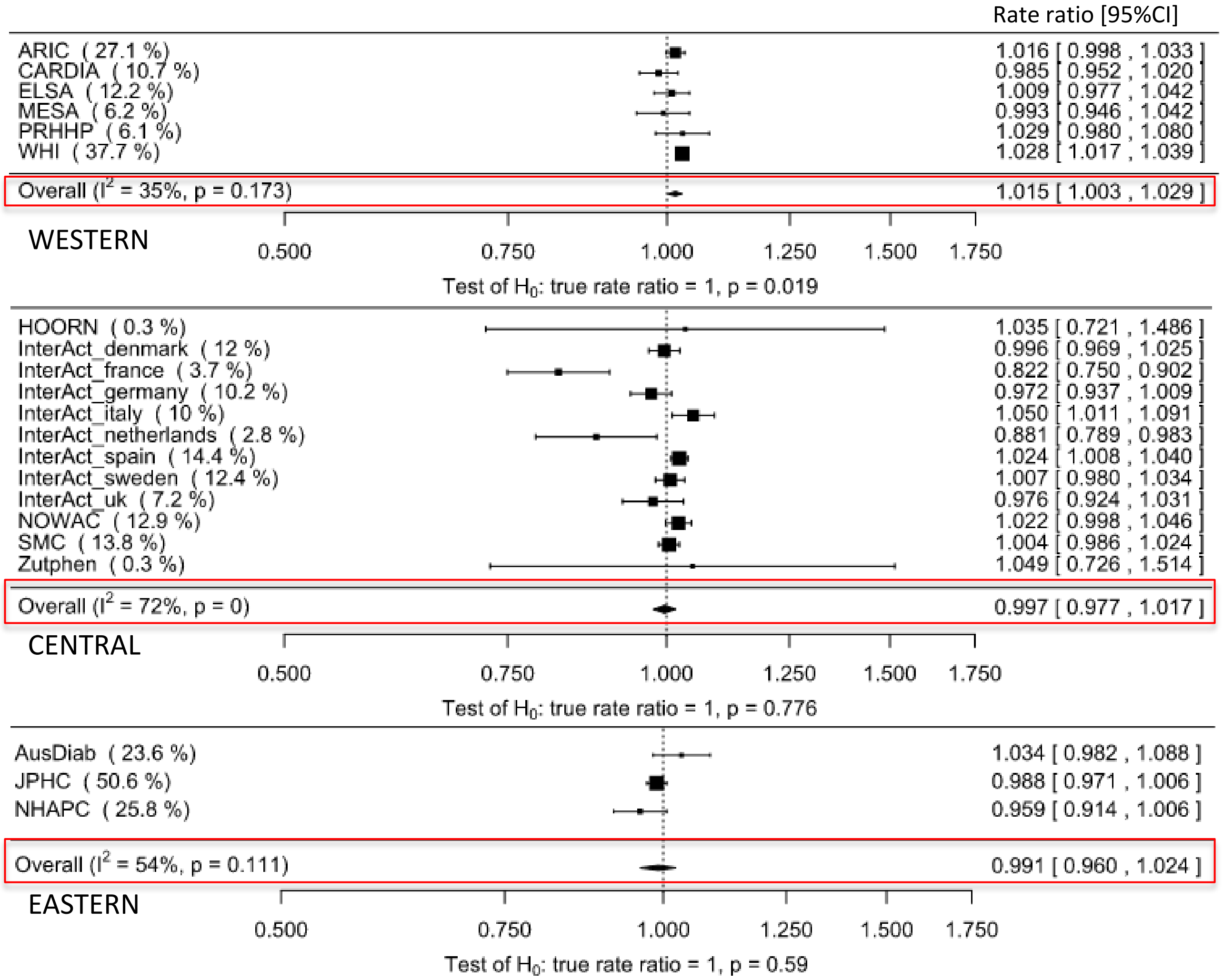


RESULTS stratified by geographical location – Model 1



RESULTS stratified by geographical location – Model 1

- Heterogeneity reduced in Western and Eastern countries
- Risk increased in US countries



Summary

- No association between total fish, types of fish (fatty and lean) or cooking method (fried fish) and type 2 diabetes

Summary – effect of geographic location

- Heterogeneity was reduced when results stratified by geographical location (I^2=35% for US, I^2=54% among Eastern countries)
- Higher T2D risk among US studies (HR for 120g/week=1.015, p=0.01)
- Null associations for European countries
- Tendency for lower risk among Asian countries but not Australia

Next Steps

- More studies will be added to the analyses:
  - China Kadoorie Biobank (China), N>500,000 m/w
  - Shanghai Women's Health Study (China), N>70,000 w
  - SUN Project (Spain), N=22,340 m/w
  - Finnish Mobile Clinic Health Examination (Finland), N=4,304 m/w
- Sensitivity analyses:
  - Models including waist circumference, family history of diabetes and fish oil supplements
  - Test interaction for sex and BMI

InterConnect

Global data for diabetes and obesity research

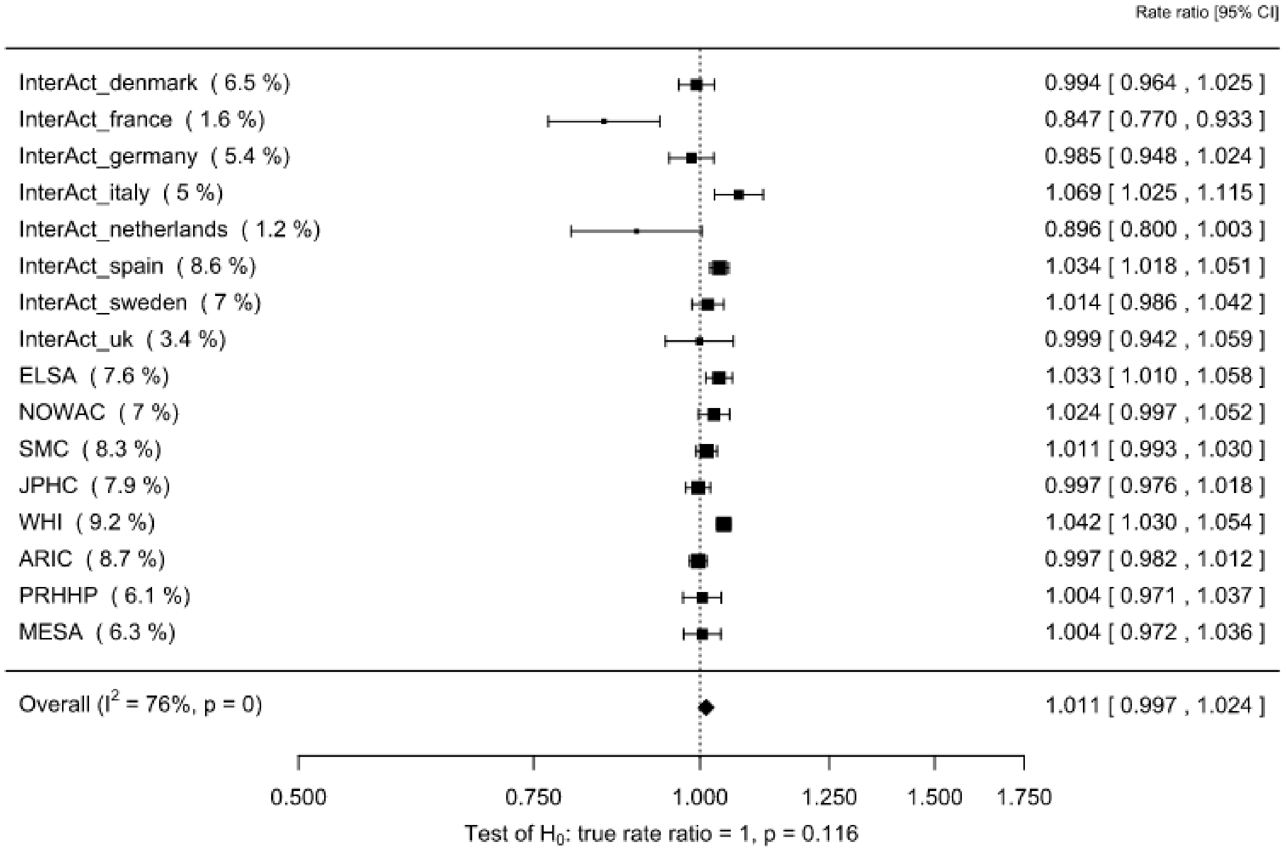
Acknowledgement

- This project is funded by the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Connect with us

- InterConnect@mrc-epid.cam.ac.uk
- www.interconnect-diabetes.eu

RESULTS for highest quartile of total fish intake compared to lowest quartile



Exclusions

Exclude:

- Type 2 diabetes prevalent cases (i.e. cases at baseline)
- Energy intake misreporters :
  - <500 or >3500 kcal/d for women
  - <800 or >4,200 kcal/d for men
- Type 1 diabetes cases
- Those with missing values for any of the variables (complete case analysis)

Changing the landscape for cross-cohort analysis

- Creating change requires many actors
  - Researchers – to see need, think useful, demonstrate value
  - Stakeholders who are users of research evidence – create pull
  - Funders – infrastructure, incentives for re-use of data

InterConnect focus on researchers

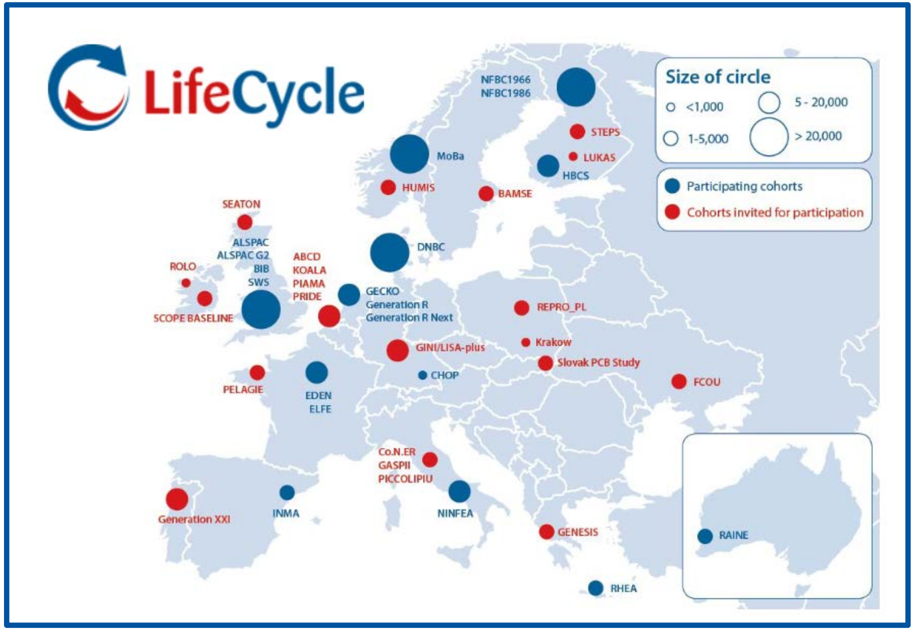
- Researchers – to see need, think useful, demonstrate value

Research driven 'Exemplar projects'

1. PA in pregnancy and neonatal anthropometric outcomes
2. Fish intake and risk of type 2 diabetes

3. Additional diet-related research questions
4. Birthweight and childhood central fat deposition

Wider pull beginning?



- EU Child Cohort Network
- Data sharing platform based on federated meta-analysis using DataSHIELD

InterConnect

Global data for diabetes and obesity research

Acknowledgement

- This project is funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602068.

Connect with us

- InterConnect@mrc-epid.cam.ac.uk
- www.interconnect-diabetes.eu