
Epidemiologic Studies of MMR Vaccine and Autism

Michael A. Stoto, PhD

Sean D. Cleary, PhD

Virginia B. Foster, PhD

Department of Epidemiology and Biostatistics

George Washington University

Outline of presentation

- ◆ Epidemiology of
 - autism
 - inflammatory bowel disease
- ◆ Wakefield study
 - MMR vaccine, autism, and bowel disease
- ◆ Studies regarding MMR and autism
- ◆ Studies regarding MMR and bowel disease
- ◆ Summary and conclusions

Disclaimer

- ◆ GW authors are not experts in the substantive areas covered, but assessed the totality of the available epidemiologic evidence
 - comments and suggestions gratefully accepted!
- ◆ Although commissioned by the IOM, the conclusions in this paper are not binding on the IOM
 - other factors might enter into causality assessment
 - other factors might enter into conclusions and recommendations

Epidemiology of autism

- ◆ Pervasive developmental disorders (PPD)
 - Rett's disorder
 - childhood disintegrative disorder
 - autistic spectrum disorder (ASD)
 - » Asperger's disorder (ASP)
 - » autism (usually no period of “unequivocally normal development”)
 - » PPD not otherwise specified (PPD-NOS)
 - ◆ childhood disintegrative disorder (CDD)
 - ◆ atypical autism (later age of onset, atypical or subthreshold symptom)

Epidemiology of autism

- ◆ Prevalence of autism (per 10,000) (Fombonne)
 - Median: 5.2; Range: 0.7 to 31.0
 - Before 1988: 4.3; 1988-1999: 7.2
- ◆ Trends
 - Gillberg and Wing: 3.8% increase per calendar year
 - Kaye *et al.*: 8 to 29 in 2-5 year old boys between 1988 and 1993 in UK
 - CA Dept. of Developmental Services: 15.0 may reflect increased awareness of availability of services
- ◆ Etiology: not much known

Epidemiology of bowel disease

- ◆ Inflammatory bowel disease (IBD)
 - Crohn's disease (CD)
 - ulcerative colitis (UC)
- ◆ Incidence of IBD (per 100,000 person years)
 - CD: 0.08 to 7.0
 - UC: 0.5 to 12.8
 - higher in northern areas including UK
 - increasing in other countries to UK levels
 - compare with caution due to varying diagnostic criteria and access to medical care

Epidemiology of bowel disease

- ◆ Etiology generally unknown, but
 - family history is important
 - higher in urban than rural populations
 - smoking increases risk
 - » especially for women
 - » children exposed to passive smoking
 - other suggested factors
 - » oral contraceptives, paramyxovirus
 - » dietary habits, breast feeding
 - » inefficient immune system response

The Wakefield study

- ◆ Case series of 12 children
 - referred to pediatric gastroenterology department with intestinal symptoms
 - with history of PDD with loss of acquired skills
- ◆ 11/12 found to have non-specific colitis
 - not CD or UC
- ◆ PPD diagnoses
 - 8 with “definitive diagnosis of autism”
 - 1 “questionable and possible disintegrative disorder”
 - 1 “autistic spectrum disorder”
 - 2 “post-vaccinial encephalitis?”
 - » neither term nor ? discussed in paper

The Wakefield study

- ◆ Urinary methylmalonic acid excretion significantly elevated compared to controls
 - age-matched and from same site, but selection not described
- ◆ MMR was the “exposure identified by parents or a doctor” in 6/8 cases with definitive autism
 - other 2 did receive MMR, but not identified as the “primary exposure”
 - MMR also identified for 1 with questionable autism
 - MMR identified in 1/2 with “post-vaccinial encephalitis?”

The Wakefield Study

- ◆ No reported detection of measles virus RNA in intestinal tissue or otherwise
- ◆ Measles virus RNA was detected in peripheral blood mononuclear cells using RT-PCR/nested PCR from a subset (?) of the 12 autistic enterocolitis patients (3/9)
 - Kawashima (2000)
- ◆ Unknown significance of measles virus detection without comparable non-affected pediatric control group
 - control group not clearly described in paper

The Wakefield study

- ◆ Authors conclude that they have “identified a chronic enterocolitis in children that may be related to neuropsychiatric disfunction”
 - typically follows a period of apparent normal development after which children lose skills
 - “in most cases, onset of symptoms was after” MMR vaccination
- ◆ The study “did not prove an association” between MMR and the syndrome described

The Wakefield study

- ◆ Association in epidemiologic studies
 - compare individuals with and without a certain exposure (MMR) to see if the outcome (autism) is higher in the exposed group
 - compare cases (individuals with the outcome) to controls without the outcome to see if cases are more likely to have been exposed
- ◆ “Association” in this study reflects opinions of parents and physicians, not statistical association
 - difficult to assess unless proximate in time
 - might be better to call this “attribution”

The epidemiologic challenge

- ◆ Gathering epidemiologic evidence to support or refute Wakefield's hypothesis presents a serious challenge
 - the outcomes in question
 - » rare
 - » prevalence and diagnostic criteria vary
 - » may not have sharp onset or be diagnosed promptly
 - » etiologic factors are not well known
 - the exposure (MMR) is common

Studies of MMR and autism

- ◆ Case-control studies
 - UK: Miller et al. (1997)
- ◆ Case series
 - Finland: Peltola et al. (1998); Patja et al. (2000)
 - North East Thames (UK): Taylor et al. (1999)
- ◆ Ecological studies
 - UK: Kaye et al. (2001)
 - Sweden: Gilberg and Heijbel (1998)

UK: Miller et al.

- ◆ Based on National Childhood Encephalopathy Study (NCES), 1976-1979
- ◆ 770 cases of acute encephalopathy in “previously apparently neurologically normal” children
 - 16 had received measles vaccine 7 to 14 days prior
 - similar proportion in controls (RR 1.85; 95% CI 0.9 - 3.7)
- ◆ 10-year follow-up of 594 (77%) cases
 - including 11/16 with measles vaccine
 - 3/11 died or had neurological, educational, or behavioral dysfunction
 - similar proportion in controls (RR 0.84; 95% CI 0.2, 3.5)

Finland: Peltola et al.; Patja et al.

- ◆ Population-based passive surveillance data following nationwide MMR program
 - judgment of whether outcomes were causally related to MMR based on available clinical information and serum samples
 - 437 adverse events reported in 14 years (0 autism)
 - 31 cases of gastrointestinal symptoms
 - » 5 febrile seizures, 2 headaches, 1 ataxia
 - 173 serious adverse events (in 169 people)
 - » factors other than MMR account for up to 45%

NE Thames (UK): Taylor et al.

- ◆ Children with autistic disorders
 - born between 1979 and 1992; identified in 1998 from computerized specialized needs/disability registries
- ◆ Information extracted on
 - age at diagnosis
 - age at first parental concern
 - age at which regression first became obvious
- ◆ Diagnoses confirmed by checking available records
 - 82% of autism cases
 - 31% of atypical autism cases
 - 38% of Asperger's syndrome cases

NE Thames (UK): Taylor et al.

- ◆ Time series analysis to fit exponential trend to number of cases with core or atypical autism
 - no evidence of a “step up” after 1987, when MMR vaccine was introduced in the UK
- ◆ Mean age at diagnosis not statistically different among children who
 - received MMR before 18 months
 - never received MMR
 - received MMR after 18 months

NE Thames (UK): Taylor et al.

- ◆ Timing of diagnosis, first parental concern, and regression in children who received MMR
 - Clustering of parental concern within 6 months of diagnosis (RI 1.48; 95% CI 1.04 - 2.12) attributed to
 - » peak in recorded concern at 18 months (rounding?)
 - » peak in MMR vaccination at 13 months
 - No other statistically significant clustering
- ◆ New (unpublished) study with longer induction interval still finds no effect

UK: Kaye et al.

- ◆ Time trend analysis based on UK general practice research database (GPRD)
- ◆ 305 cases of autism < 12 years of age diagnosed between 1988 and 1999
 - analysis restricted to boys born before 1994 with first diagnosis between 2 and 5 years of age
 - 96% had received MMR
- ◆ Annual incidence of autism increased from 0.3 to 2.1 per 10,000 between 1988 and 1993
- ◆ 4-year risk of autism increased four-fold between 1988 and 1993, while prevalence of MMR remained constant

Sweden: Gilberg and Heijbel

- ◆ Children diagnosed between 1975 and 1984
 - 55 with autism by DSM-III-R criteria
 - 19 with autistic-like condition (atypical autism)
- ◆ Birth cohorts defined relative to introduction of MMR
 - 47 cases (34 autism, 13 atypical autism) born before July 1, 1980
 - 27 cases (21 autism, 6 atypical autism) born after July 1, 1980
- ◆ Since numbers in second period are much less than expected, the data does not support association between MMR and autism

Summary: MMR and autism

- ◆ Focus of Miller study was on measles vaccine
- ◆ Most studies not focused on atypical autism or regression
- ◆ Analysis limited by
 - trends in diagnosis of developmental disorders and possible background changes in prevalence
 - difficulty of finding a time connection between vaccination and onset of autism
- ◆ Limited evidence about the Wakefield hypothesis

Studies of MMR and bowel disease

◆ Cohort studies

- UK: Montgomery et al. (1999)
- Olmstead County, MN: Pardi et al. (2000)
- UK: Morris et al. (2000)
- UK: Thompson et al. (1996)

◆ Case-control studies

- East Dorset, UK: Feeny et al. (1997)
- CA, OR, WA: Davis et al. (2001)

UK: Montgomery et al.

- ◆ Based on the 1970 British Cohort Study
 - 7019 individuals born in April 1970 followed through age 26
- ◆ 37 individuals with IBD (17 UC, 20 CD)
 - all but one diagnosed at age 16 or older
- ◆ Measles infection < 2 years associated with UC but not significant (OR 3.7; 95% CI 0.97 - 13.8)
- ◆ Measles infection in same year associated with
 - UC (OR 7.5; 95% CI 2.4 - 23.0)
 - CD (OR 4.3; 95% CI 1.2 - 14.5)

Olmstead County, MN: Pardi et al.

- ◆ Eligible cohort: children seen for measles < age 5 at the Mayo or Olmsted County medical centers from 1950 through 1966
 - follow-up questionnaire or telephone survey (57% complete)
 - Standardized incidence rates based on Olmsted County
- ◆ Association between early measles infection and IBD
 - IBD and measles < 2 years (SIR 4.4; 95% CI 1.1 - 8.7)
 - IBD and measles > 2 years (SIR 1.9; 95% CI 0.5 - 4.9)

UK: Morris et al.

- ◆ Based on the 1970 British Cohort Study
 - 7616 individuals born in April 1970 followed through age 26
 - measles vaccination history at age 5 based on home parental survey
- ◆ No association found between measles vaccination by age 5 and later diagnosis with
 - UC (OR 0.57; 95% CI 0.2, 1.6)
 - CD (OR 0.67; 95% CI 0.3, 1.6)

UK: Thompson et al.

- ◆ Study of children in 1964 measles vaccine trial
 - annual mailed follow-up surveys through 1994 (n=3967)
 - compared to 1958 birth cohort (NCDS)
- ◆ Increase in vaccinated individuals
 - UC (RR 2.05; p = 0.21)
 - CD (RR 2.95; p = 0.01)
- ◆ No significant difference in age at vaccination for UC or CD cases compared to all individuals vaccinated

East Dorset, UK: Feeny et al.

- ◆ 140 cases in individuals born in East Dorset between 1968 and 1991 with definite diagnosis of IBD
 - two controls randomly selected from same GP, matched on gender and year of birth
 - vaccination history through age 5 obtained from GP records
- ◆ No association between measles vaccination and
 - IBD (OR 0.97; 95% CI 0.6 - 1.5)
 - UC (OR 0.84; 95% CI 0.4 - 1.6)
 - CD (OR 1.08; 95% CI 0.6 - 1.8)

CA, OR, WA: Davis et al.

- ◆ Vaccine Safety Datalink study in children enrolled in HMOs from 6 months of age or younger between 1958 and 1989
- ◆ 142 cases diagnosed as definite, probably, possible, or questionable IBD (75 CD and 67 UC)
 - up to 5 controls matched by HMO, gender, birth year
 - MMR exposure based on medical review of lifetime vaccination history
- ◆ No statistically significant association between MMR and IBD

Viral detection

- ◆ Haga (1996), Afzal (1998), and Chadwick (1998) find no detectable measles virus in intestinal tissue and peripheral blood mononuclear cells
 - using RT-PCR/nested PCR techniques
 - adults (ages 17-65) with UC, CD, and indeterminate colitis
 - no individuals diagnosed with autism and enterocolitis are included in these studies

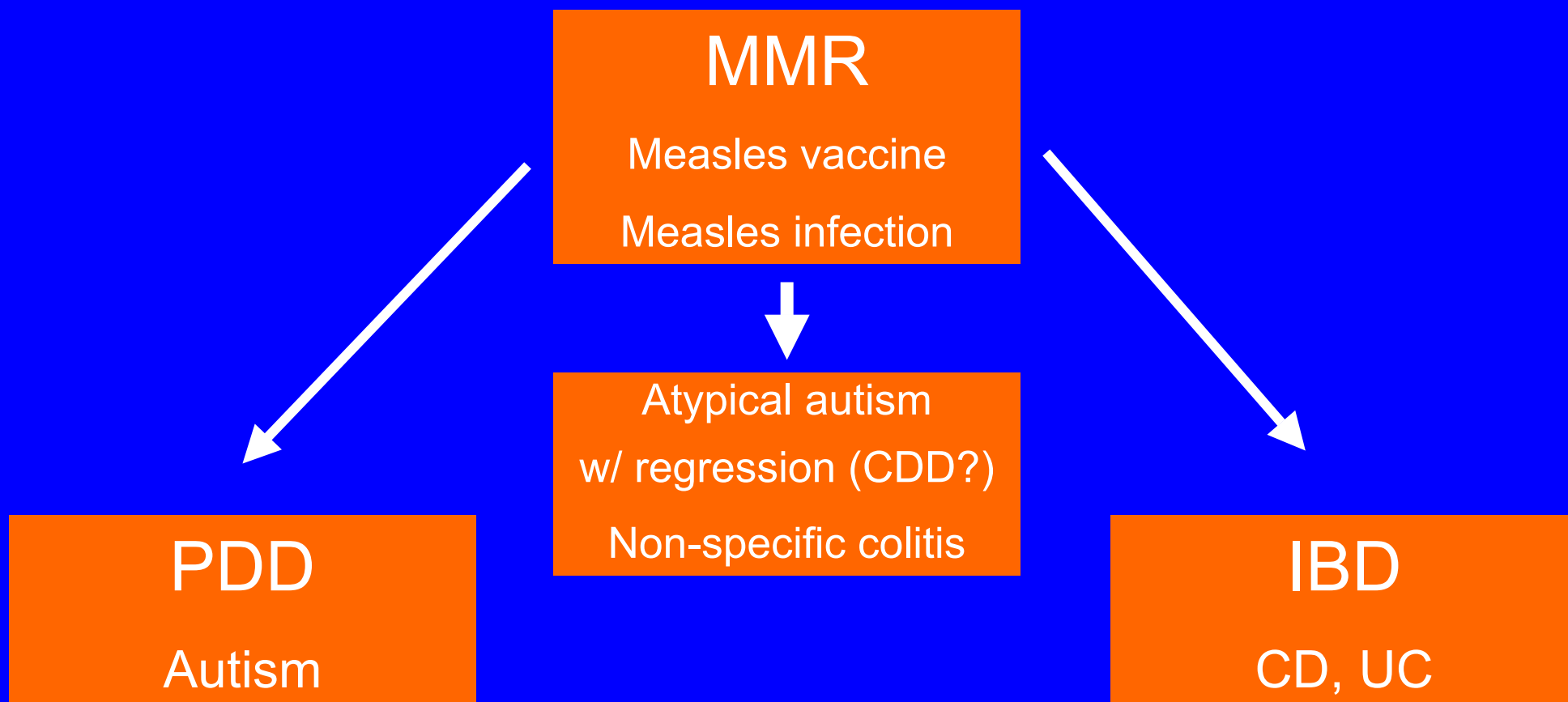
Summary: MMR and IBD

- ◆ Limited evidence of an association between measles vaccine or infection and IBD
 - Measles vaccine or measles infection, not MMR
 - IBD (UC and CD), not non-specific colitis
- ◆ Analysis limited by
 - accuracy of retrospective diagnoses
 - differing definitions of IBD
- ◆ Almost no evidence about the Wakefield hypothesis

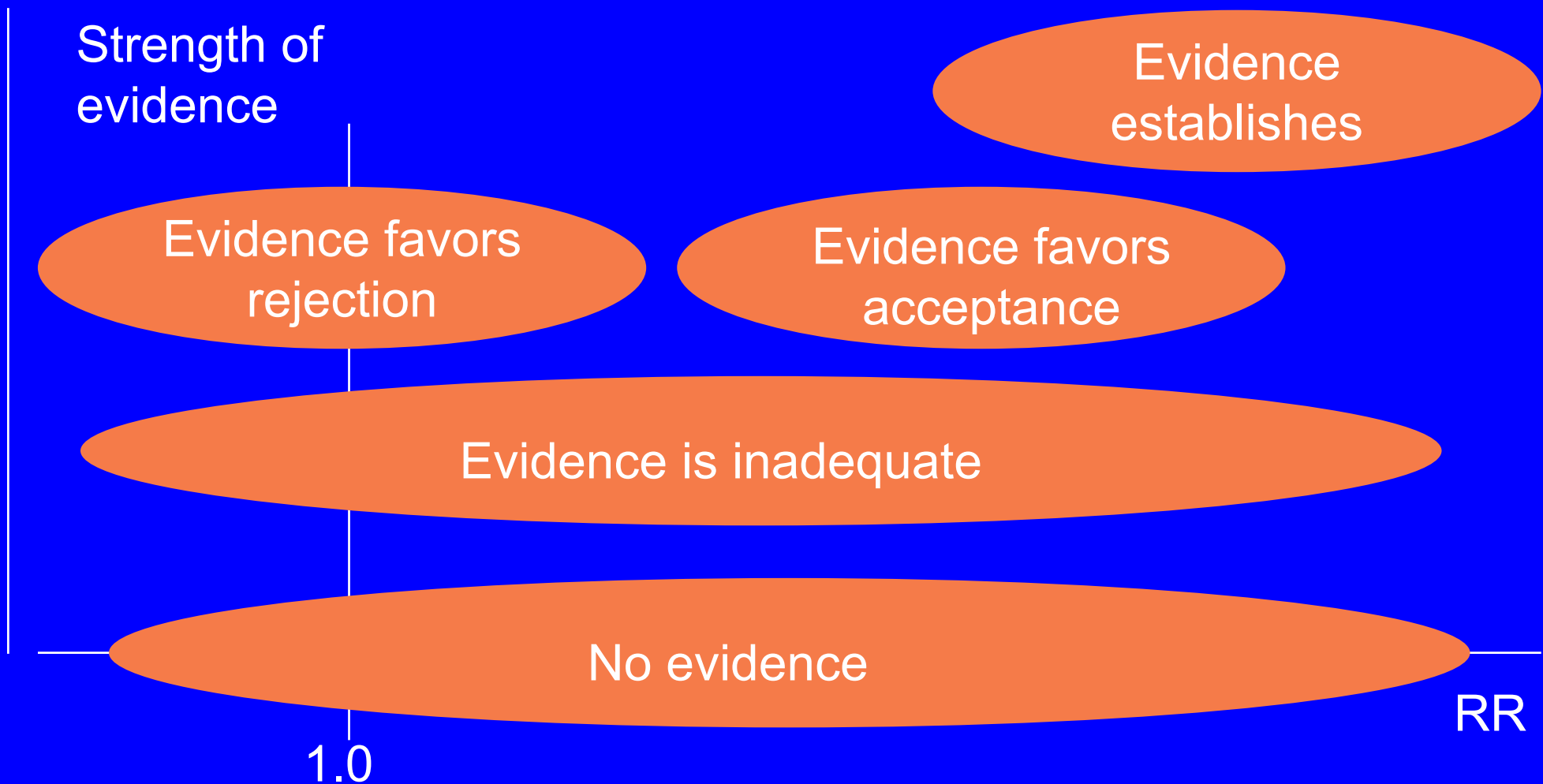
Conclusions

- ◆ Wakefield hypothesis
 - focused on 3-way relationship among MMR, atypical autism with regression, and non-specific colitis
 - based on “attribution” of cause by physicians and parents
- ◆ Other epidemiologic studies
 - focused on 2-way relationship between MMR and PDD or IBD
 - different outcomes and sometimes different exposures
 - difficulties of studying rare outcomes
- ◆ Epidemiological evidence reviewed here is inadequate to accept or reject a causal relationship between MMR and autism

MMR and autism evidence model



Categories of evidence for a causal relation (Source: IOM, 1991, 1994)



Disclaimer

- ◆ GW authors are not experts in the substantive areas covered, but assessed the totality of the available epidemiologic evidence
 - comments and suggestions gratefully accepted!
- ◆ Although commissioned by the IOM, the conclusions in this paper are not binding on the IOM
 - other factors might enter into causality assessment
 - other factors might enter into conclusions and recommendations