Glyphosate: An Updated Meta-Analysis for Non-Hodgkin Lymphoma

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Glyphosate Overview

Photo: Scott's Miracle-Gro

- Most widely used herbicide in the world
  - Sold commercially as "Round-up" by Monsanto/Bayer
  - "Glyphosate technical" is combined with "inert ingredients" to form glyphosate-based herbicides (GBHs)
    - Adjuvants (e.g., POEA – polyethoxylated tallow amine, a surfactant) may be more toxic alone or combined with glyphosate
    - Seemingly identical Roundup products can have different adjuvants (e.g., the EU has restricted the use of POEA, but this is not evident from the packaging)
  - Also used as desiccant prior to harvest ("green burndown")
- A current controversy: carcinogenic or not?
  - IARC (2015): **Probably carcinogenic to humans** (Group 2A)
  - EFSA (2015):"glyphosate is **unlikely to pose a carcinogenic hazard** to humans and the evidence does not support classification with regard to its carcinogenic potential"
  - EPA (2016): "**not likely to be carcinogenic** to humans at doses relevant for human health risk assessment"

Why Did I Publish on Glyphosate?

- I served on 2016 EPA FIFRA Panel to evaluate the *carcinogenic potential* of glyphosate (i.e., is it carcinogenic?)
  - I replaced an epidemiologist who was removed from the Panel after objections from CropLife
  - One month to prepare:
    - 227 page "Issue Paper" technical report
    - Supporting information:
      - 67 confidential "10g" (trade secret) study reports
      - EPA's 2005 *Guidelines for Carcinogen Risk Assessment*
      - International Agency for Cancer Research's (IARC's) 2015 *Monograph 112* on glyphosate
      - Dozens of papers from the peer-review literature, including statements of concern about previous official assessments
      - Public docket with over 500 submissions
- I was concerned about EPA's approach to using the evidence and their conclusions
  - Joined two other FIFRA Panel members to address these concerns


My personal motivation:


At that time I believed Roundup was safe to use in my organic garden

My Glyphosate Publications

1. **Letter** to JNCI highlighting error in the Agricultural Health Study 2018 (AHS 2018) multiple imputation/exposure simulation that is known theoretically to bias results towards the null

   Sheppard, L., & Shaffer, R. M. (2019). Re: Glyphosate Use and Cancer Incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute*, 111:214-215.

2. **Review of glyphosate exposure studies** highlighting the limited exposure information available

   Gillezeau, C., van Gerwen, M., Shaffer, R. M., Rana, I., Zhang, L., Sheppard, L., & Taioli, E. (2019). The evidence of human exposure to glyphosate: a review. *Environmental Health*, *18*(1), 2.

3. **Updated meta-analysis** of glyphosate and Non-Hodgkin's lymphoma (NHL)

   Zhang, L., Rana, I., Shaffer, R. M., Taioli, E. & Sheppard, L. (2019). Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence. *Mutation Research/Reviews in Mutation Research,* 781:186-206.

Review of Meta-Analysis Paper

What We Did

- Asked whether or not glyphosate-based herbicides (GBHs such as Roundup) are associated with an increased risk of non-Hodgkin lymphoma (NHL)
- How
  - Combined the evidence from six published epidemiologic studies of workers using meta-analysis
    - One large cohort
    - Five case-control
  - Focused on the most highly exposed group in each study
- What was novel
  - Better approach to asking the question: ***Are GBHs carcinogenic in humans?***
  - Incorporated new evidence from the *Agricultural Health Study* (AHS 2018)
    - 11-12 additional years of follow-up
    - 5x as many NHL cases

Methods (Exposure Group Selection)

A priori selection of **highest exposure groups** when available

- Relationship may be more likely to be detected with higher exposures
- Less concern with confounding
- Prevents dilution of exposure groups; ensures adequate exposure contrast

High exposure category	Reason for selection
(1) Highest cumulative exposure & longest lag[1] or latency[2]	• Persistence of glyphosate in the environment • Chronic disease (ex: cancer) usually result from cumulative long term exposures
(2) Highest cumulative exposure	
(3) Longest exposure duration and longest lag or latency	• Decades may be needed for cancer to manifest
(4) Longest exposure duration	
(5) Longest lag or latency	
(6) Ever-exposed	• Avoid excluding relevant data, given so few published studies

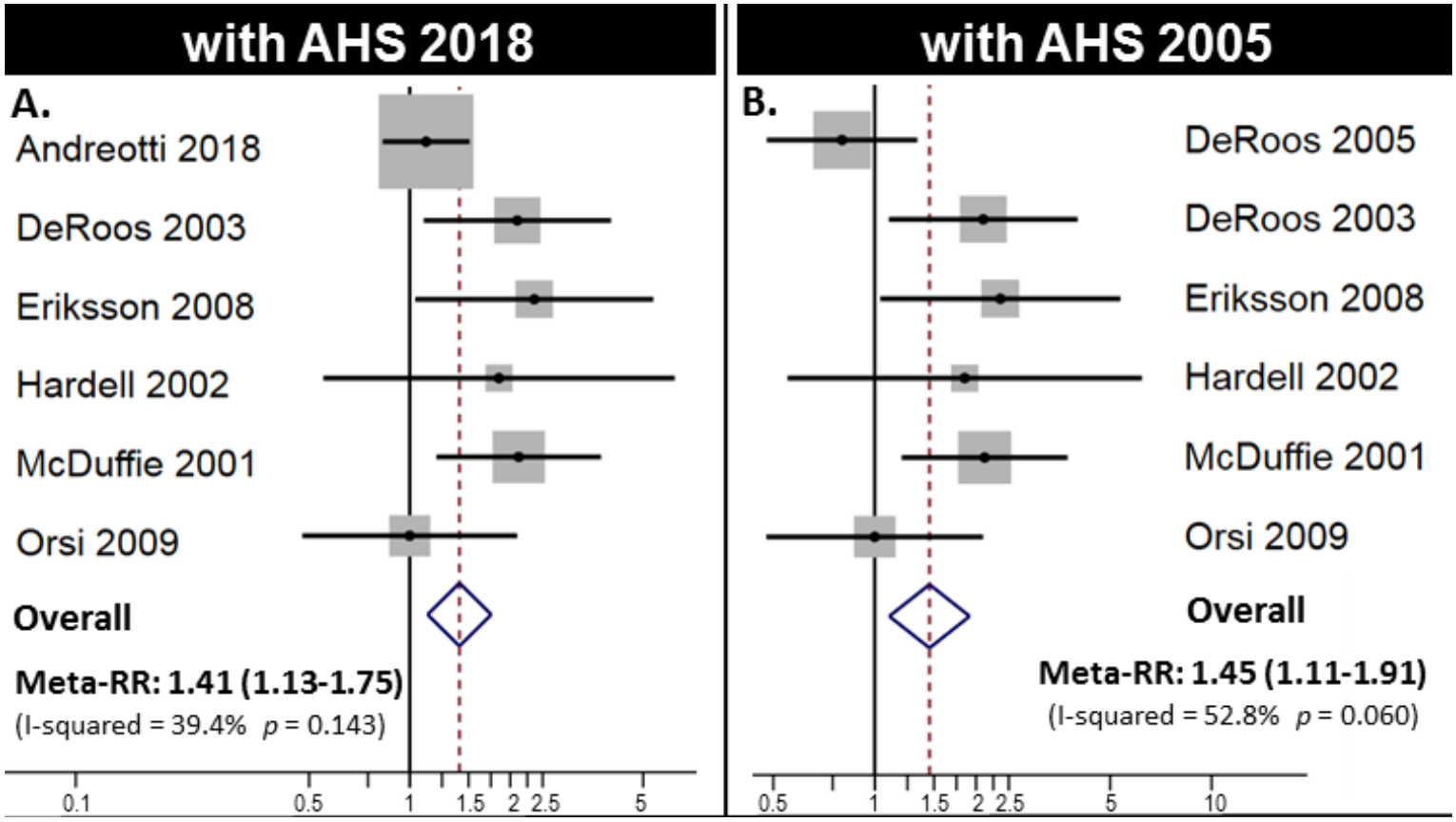
[1] Lag = time before NHL onset, excluded from exposure estimates
[2] Latency = time between first lifetime exposure & NHL diagnosis

Meta-Analysis Results

Our Result: The most highly exposed workers have a 41% increased relative risk (95% CI: 13 – 75%)

- Results robust to sensitivity analyses
- Comparison to previous meta-analyses:
  - Our result: **1.41** (1.13-1.75)
  - IARC: 1.30 (1.03-1.65)
  - Chang & Delzell: 1.27 (1.01-1.59)

Meta-Analysis Forest Plot



Meta-Analysis Strengths & Limitations

Strengths

- Included updated AHS results
- Focus on high exposure group to maximize ability to detect association

Limitations

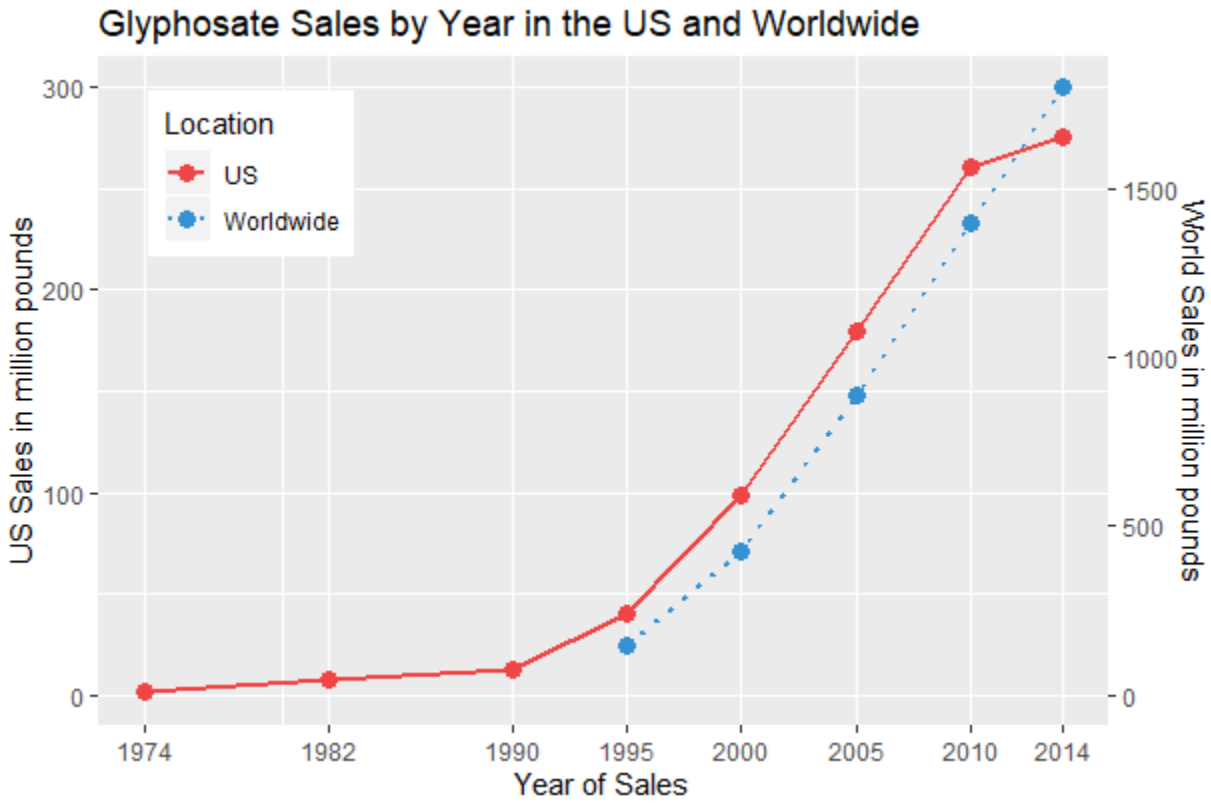
- Limited studies (n=6) available for inclusion
- Potential for publication bias
- Key differences between studies (ex: reference group) suggests caution in interpretation of numerical estimate
- None of the studies would have incorporated the increasing adoption of “green burndown” practices since mid-2000s

What Does This Evidence Mean?

- Supports IARC's conclusion that glyphosate is probably carcinogenic
- Findings apply to the most highly exposed workers; unclear how they translate to the general public
  - Note: With a ubiquitous exposure, even a small increase in risk means many more cases of NHL in the general population
- Currently there are no studies of GBHs impact on the public
  - These studies are much harder to do
  - The absence of studies does not imply no risk

There Is Much More to Learn!

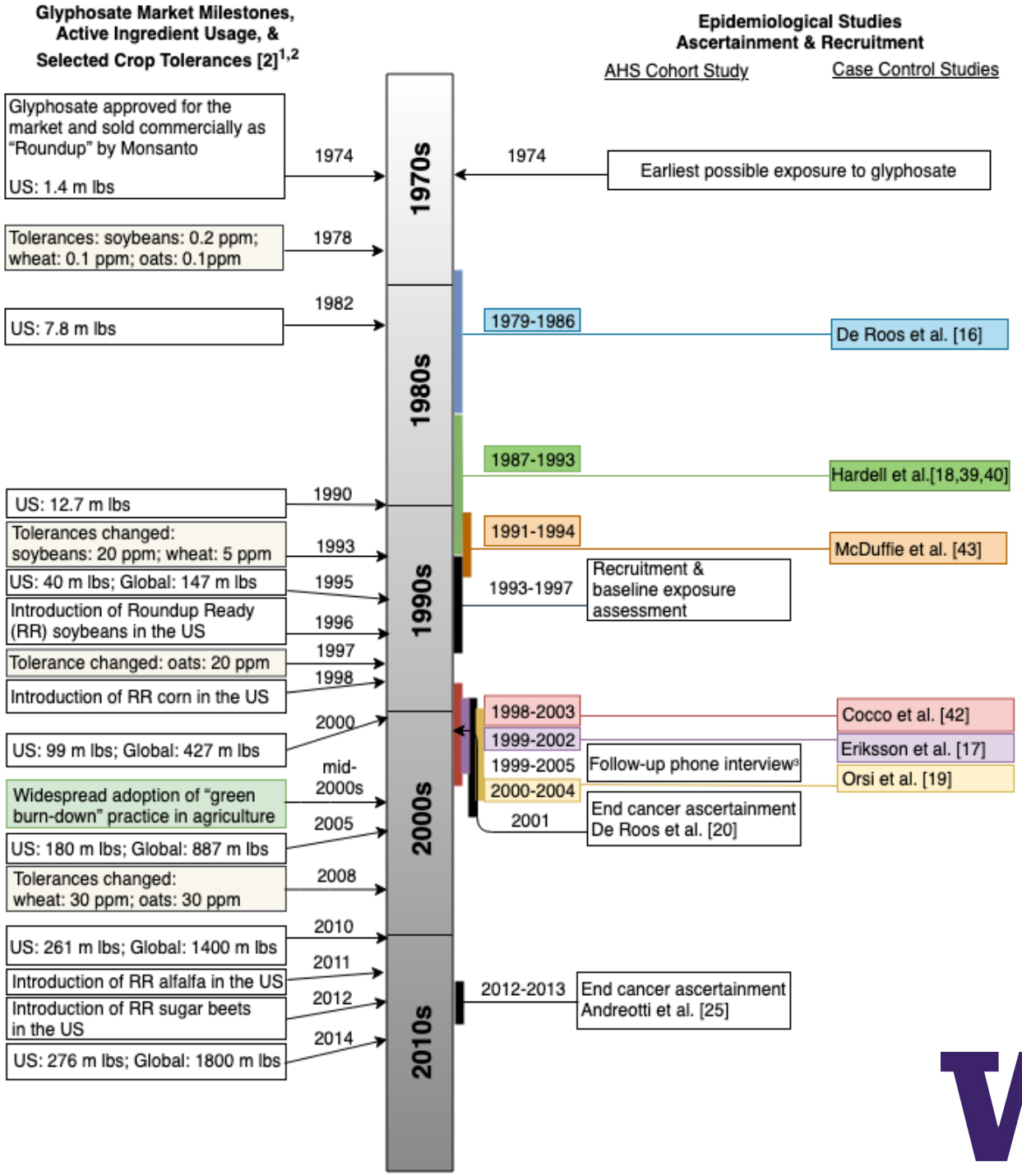
- These studies only know about exposures prior to 2005 (AHS 2018) or earlier
- Glyphosate sales have exploded in recent decades:



- Most intensively used herbicide in the world
  - For weed control AND as a desiccant prior to harvest (“green burndown”)

Timeline

Key point: Epidemiologic evidence was assembled prior to the explosion in glyphosate sales; we don't know the impact of this exposure trend on health



Experimental Evidence & Context

- ***In vivo* animal studies**
  - Supporting evidence from malignant lymphoma in mice and 7 other cancer endpoints in mice and rats (Portier 2020)
    - Evidence of dose-response associations in pooled analyses
  - Challenges & limitations
    - Insufficient follow-up time
      - 80% of cancers occur after the age of 60, but a 2-year rat assay approximates age 60-65
    - Pure glyphosate, rather than "real-world" glyphosate-based herbicides (GBHs)
      - GBHs have been shown to be more toxic
- **Potential mechanisms**
  - Immunosuppression & inflammation
  - Endocrine disruption
  - Genetic alterations
  - Oxidative stress

New Animal Study Evidence

Table 6 Summary of level of evidence[a] for tumors observed to have a significant trend in 13 rodent carcinogenicity studies in male and female, mice and rats[b]

Tumor	Males				Females			
	CD-1 Mouse	Swiss Mouse	SD Rat	Wistar Rat	CD-1 Mouse	Swiss albino mouse	SD Rat	Wistar Rat
Adrenal cortical carcinoma								
Adrenal pheochromocytoma								
Alviolar-Bronchiolar tumor	NE							
Harderian gland tumor								
Hemangioma								
Hemangiosarcomas	CE							
Kidney tumor	CE	SE						
Liver adenoma								
Mammary tumor								
Malignant lymphoma	CE	SE			CE	SE		
Pancreas Islet Cell tumor								
Pituitary adenomas								
Skin basal-cell tumor								
Skin keratoacanthoma								
Thyroid C-cell tumor								
Thyroid follicular-cell tumor			EE					
Testis interstitial-cell Tumor			SE					

8 tumors show clear evidence (CE) in at least one species, strain and sex combination

3 additional tumors show some evidence (SE)

[a] *CE* Clear evidence, *SE* Some evidence, *EE* Equivocal evidence, *NE* No evidence: [b]a blank space indicates there is no positive finding in any study for this tumor in this sex/species

Portier 2020 *Environmental Health*

Discussion

Broader Context of Unconstrained Herbicide Use

- Herbicide-resistant (HR) crops are 85% of the world's GM crop acreage
  - Vast majority (~80-90%) are Roundup Ready
- Development of superweeds (herbicide-resistant weeds)
  - 49% of US farmers surveyed reported glyphosate-resistant weeds on their farm (Fraser, 2013)
  - From Heap & Duke 2017:
    - Thirty-eight weed species have now evolved resistance to glyphosate, distributed across 37 countries and in 34 different crops and six non-crop situations
    - Glyphosate-resistant weeds present the greatest threat to sustained weed control in major agronomic crops
- Reduced populations and diversity:
  - Milkweed & monarchs
  - Insects
  - Birds???
- May affect soil health

Glyphosate in Context

- Other herbicides (dicamba, 2,4-D) are more acutely toxic
  - Application requirements are stricter, more regulations that protect workers and off-target effects
- Glyphosate was considered safe for decades
  - Lower worker protection standards
  - Increased tolerances (residues allowed in foods) over time
  - Single most used agricultural chemical in the world (including fertilizers)
- Recently approved: New herbicide-resistant crops for glyphosate AND other herbicides (e.g., 2,4-D, dicamba)
  - "New era" of more pesticide pollution
  - Anticipate no reduction in glyphosate usage
  - Other pesticides (dicamba) are more volatile and drift to neighbors
  - Weeds are developing stacked resistance

My Conclusions

- **Glyphosate is likely to be carcinogenic to humans**
  - Positive evidence in animal studies in multiple species, sex, strain,and tumor site
  - Strengthened by other lines of evidence
    - Suggestive evidence in human studies
    - Genotoxicity evidence
- **We need a new paradigm for scientific review of registrant-funded studies that are used as a basis for policy**
  - Registrants have a vested interest in certain scientific results
- **It is important to reduce pesticide usage and population exposure**
  - We know from air pollution research that a ubiquitous exposure with small adverse effects can harm millions of people

Further Reading & References

1. My work

Sheppard, L., & Shaffer, R. M. (2019). Re: Glyphosate Use and Cancer Incidence in the Agricultural Health Study. JNCI: Journal of the National Cancer Institute, 111:214-215

Gillezeau, C., van Gerwen, M., Shaffer, R. M., Rana, I., Zhang, L., Sheppard, L., & Taioli, E. (2019). The evidence of human exposure to glyphosate: a review. *Environmental Health*, *18*(1), 2.

Zhang, L., Rana, I., Shaffer, R. M., Taioli, E. & Sheppard, L. (2019). Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence. *Mutation Research/ Reviews in Mutation Research,* 781:186-206.

2. Selected scientific papers

Myers, John Peterson, et al. "Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement." *Environmental Health* 15.1 (2016): 19.

Portier, Christopher J., et al. "Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)." J *Epidemiol Community Health* 70.8 (2016): 741-745.

Benbrook, Charles M. "Trends in glyphosate herbicide use in the United States and globally." *Environmental Sciences Europe* 28.1 (2016): 3.

Mills, Paul J., et al. "Excretion of the herbicide glyphosate in older adults between 1993 and 2016." *JAMA* 318.16 (2017): 1610-1611.

3. A very readable book

Gillam, Carey. *Whitewash: The story of a weed killer, cancer, and the corruption of science*. 2017 Island Press

4. Useful website

US Right to Know. Usrtk.org.

See e.g. their glyphosate fact sheet usrtk.org/pesticides/glyphosate-health-concerns

Thank you!

Questions?

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Additional Slides

Methods (Study Selection + Analysis)

- Literature search followed *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guidelines
  - Updated August 2018
- Eligible studies & participants
  - 1 cohort & 5 case-control studies
  - ~65,000 individuals
  - Locations: US, Canada, Sweden, France
- Statistical methods: Meta-risk estimation
  - Averages study estimates; gives higher weight to studies with more cases
  - Fixed effects inverse variance method (*primary results*)
  - Random effects method (*secondary results*)