What have we learned about eczema from routinely-collected health data?

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Why eczema?

Observational studies in dermatology

- The need for population-based studies
- Prolonged follow up times
- Large numbers to detect rare outcomes
- Cost and logistic implications

From individual patients to “ehealth”

Health records ‘An arsenal that the genius of English healers cannot fail to turn to account’

William Farr 1874
supplement to 35th annual report
of the Registrar General

“Routinely collected health data”

Data collected for non-research purposes and/or without an *a priori* research question in mind

<u>Examples</u>

Administrative or “claims” data

Medical record databases (EMR/EHR)

Disease registries (including cancer registries)

What have we learned about eczema from routinely-collected health data?

- Selected early life risk factors for eczema
- Long-term outcomes in people with eczema
- Particular challenges using routinely-collected health data for eczema

Search strategy to inform this talk

- PubMed
- EMBASE
- Web of Science

  -April 10, 2016 for studies using routinely collected data to identify cases of atopic dermatitis

- Map of systematic reviews of eczema, https://nottingham.ac.uk/research/groups/cebd/resources/eczema-systematic-reviews.aspx

Clues about early life exposures

Does Caesarian section increase the risk of eczema?

Data from West Midlands General Practice database (n=24,690, 7,758 with eczema)

-No increased risk observed with C Section OR 1.04 (0.98-1.10)

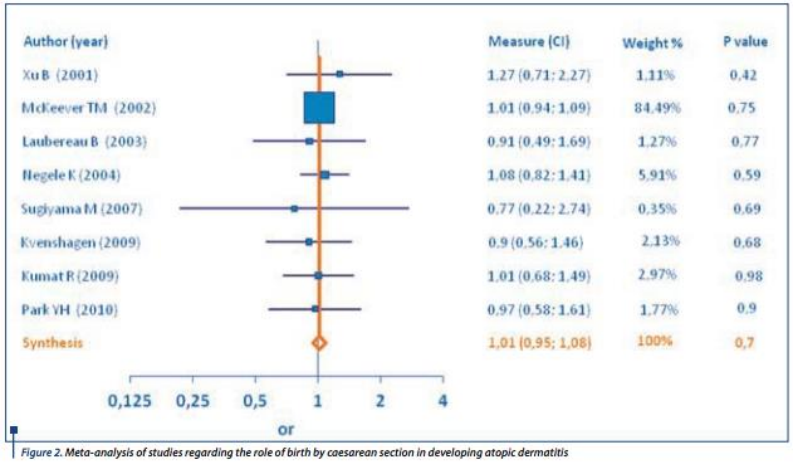


Figure 2. Meta-analysis of studies regarding the role of birth by caesarean section in developing atopic dermatitis

McKeever, Am J Respir Crit Care Med 2002

http://gineco.eu/system/revista/20/196-198.pdf

Clues about early life exposures

Does exposure to antibiotics in utero or in the first year of life increase the risk of eczema?

Data from West Midlands General Practice database (n=24,690)

In utero antibiotics	Risk of eczema
1	1.02 (0.96–1.07)
2	1.02 (0.93–1.10)
≥2	1.12 (1.02–1.24)

McKeever et al. Am. J. Respir. Crit. Care Med. 2002;166(6):827-832;

McKeever et al. J. Allergy Clin. Immunol. 2002;109(1):43-50

Infections and antibiotics in first year of life

Bacterial infections HR 1.33, 1.14-1.56

≥3 antibiotics increased the risk of eczema HR 1.54 (1.39-1.70); adjusting for consultations 1.25, 1.12-1.40

Clues about early life exposures

Does exposure to antibiotics in the first year of life increase the risk of eczema?

German administrative health data (n=487)

Infections and antibiotics in first year of life

RTI No antibiotics	**RTI treated with antibiotics**
RR 0.69 (0.39-1.24)	Macrolides RR 2.15 (1.18–3.91)
	Cephalosporines RR: 1.93 (1.07–3.49)

Schmitt et al. Pediatric Allergy and Immunology 2010;21(2):292-300

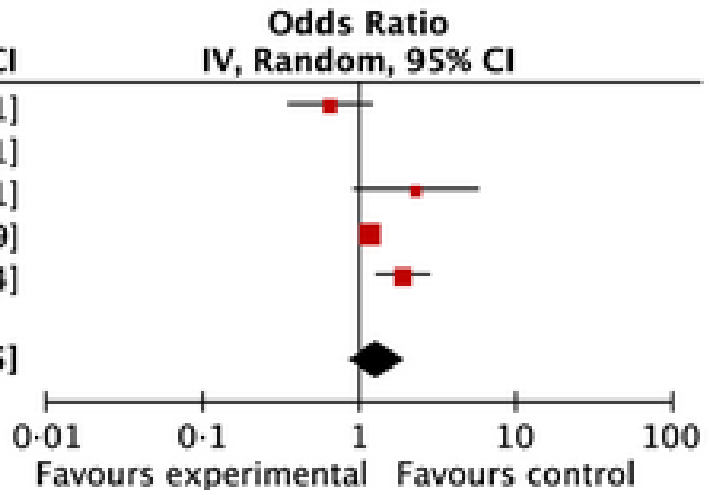
Does early life exposure to antibiotics increase the risk of eczema? A systematic review

Prenatal antibiotics

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Bisgaard 2009	−0·4308	0·3185	20·4%	0·65 [0·35, 1·21]
Dom 2010	0·5988	0·2399	0·0%	1·82 [1·14, 2·91]
Jedrychowski 2006	0·8329	0·4725	12·9%	2·30 [0·91, 5·81]
McKeever 2002b	0·157	0·0501	38·3%	1·17 [1·06, 1·29]
Sariachvili 2007	0·6419	0·2047	28·4%	1·90 [1·27, 2·84]
Total (95% CI)			**100·0%**	**1·30 [0·86, 1·95]**

Heterogeneity: $Tau^2 = 0·11$; $Chi^2 = 10·89$, df = 3 (P = 0·01); $I^2 = 72\%$

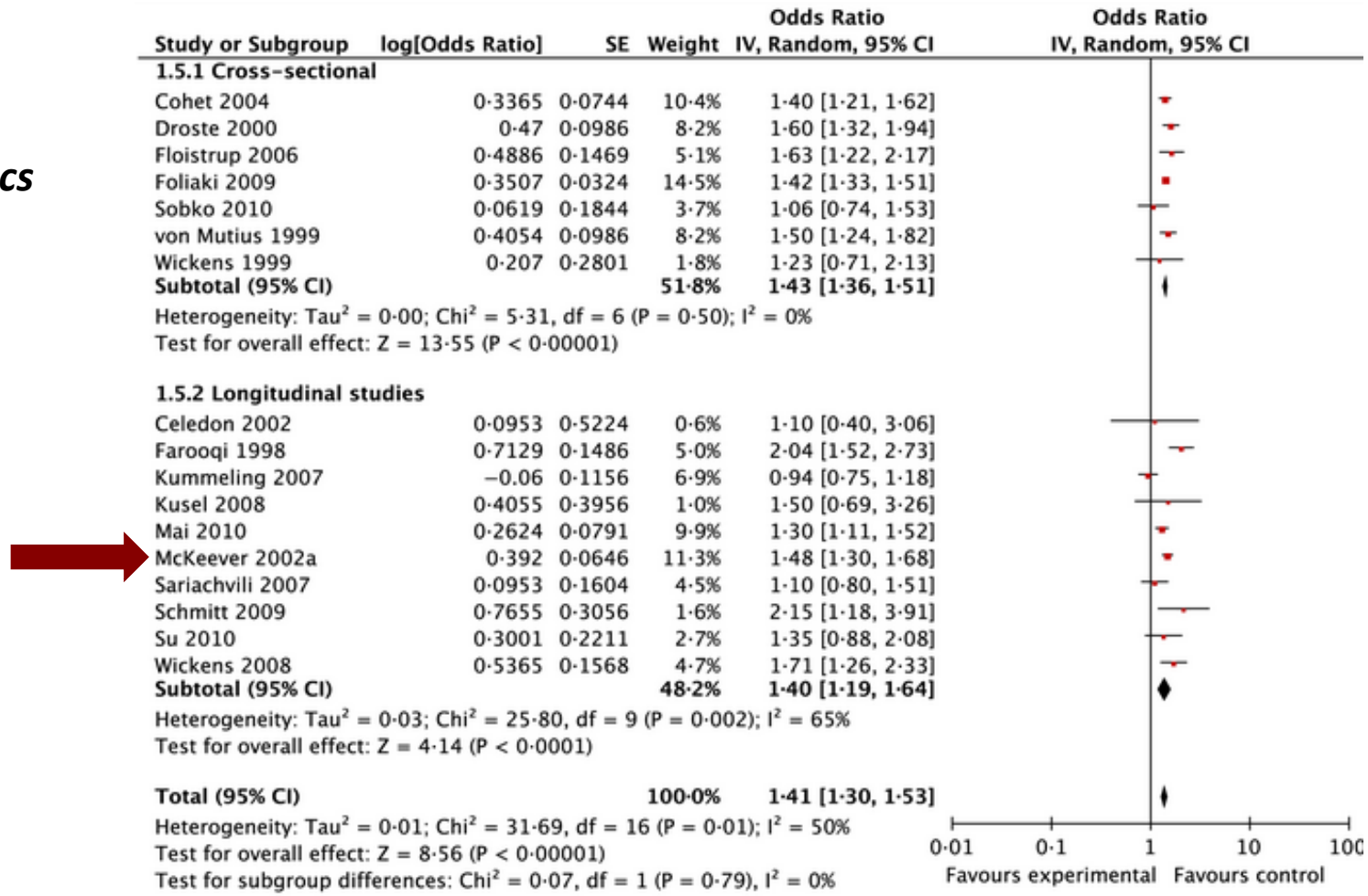
Test for overall effect: Z = 1·26 (P = 0·21)



Tsakok et al Br J Dermatol 2013; 169 (5):983-991

Does early life exposure to antibiotics increase the risk of eczema? A systematic review

Postnatal antibiotics



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 Cross-sectional				
Cohet 2004	0·3365	0·0744	10·4%	1·40 [1·21, 1·62]
Droste 2000	0·47	0·0986	8·2%	1·60 [1·32, 1·94]
Floistrup 2006	0·4886	0·1469	5·1%	1·63 [1·22, 2·17]
Foliaki 2009	0·3507	0·0324	14·5%	1·42 [1·33, 1·51]
Sobko 2010	0·0619	0·1844	3·7%	1·06 [0·74, 1·53]
von Mutius 1999	0·4054	0·0986	8·2%	1·50 [1·24, 1·82]
Wickens 1999	0·207	0·2801	1·8%	1·23 [0·71, 2·13]
Subtotal (95% CI)			**51·8%**	**1·43 [1·36, 1·51]**
Heterogeneity: $Tau^2 = 0·00$; $Chi^2 = 5·31$, df = 6 (P = 0·50); $I^2 = 0\%$				
Test for overall effect: Z = 13·55 (P < 0·00001)				
1.5.2 Longitudinal studies				
Celedon 2002	0·0953	0·5224	0·6%	1·10 [0·40, 3·06]
Farooqi 1998	0·7129	0·1486	5·0%	2·04 [1·52, 2·73]
Kummeling 2007	−0.06	0·1156	6·9%	0·94 [0·75, 1·18]
Kusel 2008	0·4055	0·3956	1·0%	1·50 [0·69, 3·26]
Mai 2010	0·2624	0·0791	9·9%	1·30 [1·11, 1·52]
McKeever 2002a	0·392	0·0646	11·3%	1·48 [1·30, 1·68]
Sariachvili 2007	0·0953	0·1604	4·5%	1·10 [0·80, 1·51]
Schmitt 2009	0·7655	0·3056	1·6%	2·15 [1·18, 3·91]
Su 2010	0·3001	0·2211	2·7%	1·35 [0·88, 2·08]
Wickens 2008	0·5365	0·1568	4·7%	1·71 [1·26, 2·33]
Subtotal (95% CI)			**48·2%**	**1·40 [1·19, 1·64]**
Heterogeneity: $Tau^2 = 0·03$; $Chi^2 = 25·80$, df = 9 (P = 0·002); $I^2 = 65\%$				
Test for overall effect: Z = 4·14 (P < 0·0001)				
Total (95% CI)			**100·0%**	**1·41 [1·30, 1·53]**
Heterogeneity: $Tau^2 = 0·01$; $Chi^2 = 31·69$, df = 16 (P = 0·01); $I^2 = 50\%$				
Test for overall effect: Z = 8·56 (P < 0·00001)				
Test for subgroup differences: $Chi^2 = 0·07$, df = 1 (P = 0·79), $I^2 = 0\%$				

Tsakok et al Br J Dermatol 2013; 169 (5):983-991

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Long-term outcomes in people with eczema

Overview of systematic reviews *Deckert et al. Allergy 2014;69:37-45*

Eczema and cancer- decreased risk of glioma (pooled OR 0.69, 0.58-0.82), meningioma (0.75, 0.65-0.87) and acute lymphoblastic leukaemia (6 reviews)

Eczema and ADHD- increased risk (1 review)

Associations also observed in recent SRs

https://nottingham.ac.uk/research/groups/cebd/resources/eczema-systematic-reviews.aspx

Recent emerging evidence of associations in individual studies between eczema and cardiovascular disease, fractures, renal outcomes

Is eczema associated with cardiovascular outcomes?

- Mechanistic work suggests that eczema may be associated with increased platelet activation and decreased fibrinolysis
- Cross-sectional studies in adults and US children suggest associations between eczema and acute vascular outcomes

- *Is there convincing evidence to support these observations*
- *Is the association causal?*

Is eczema associated with cardiovascular outcomes?

- German insurance data (n=1.2m)
- Associations observed with angina RR 1.17 (1.12-1.23) and PVD RR 1.15 (1.11-1.19) after adjusting for age, sex, SES, healthcare access
- Stronger associations with severe eczema
- No associations with MI and stroke
- No lifestyle factors available

Standl et al. J Inv Dermatol 2017

Is eczema associated with cardiovascular outcomes?

- Danish registry data (reference pop 145,372, mild AD 26,898, severe AD 2,527)
- Associations with stroke (1.51, 1.08-2.10), CVD death (1.46, 1.07-2.02) and MACE (1.53, 1.23-1.91) in severe eczema after adjusting for age and sex; none significant after adjusting for possible mediators

Anderson 2017 J Aller Clin Immunol

Is eczema associated with cardiovascular outcomes?

- Taiwan National Health Insurance database (n=20,323 AD patients and 20,323 comorbidity-matched subjects)
- HR=1.33 (1.12-1.59) increased incidence of ischemic stroke
- Gradient with increased severity
- Findings persisted after adjusting for confounders and mediators

Is eczema associated with cardiovascular outcomes?

- UK CPRD (n=469,453 eczema patients matched to 2.3m patients without eczema)
- Increased risk of acute coronary syndrome, stroke and coronary revascularisation in moderate and severe eczema
- Stronger associations with increased disease severity

Is eczema associated with cardiovascular outcomes?

- Signals from studies
- SR coming soon to summarise and meta-analyse key findings
- Routinely collected data allowed sufficient numbers and prospective follow up
- Many data sources lack lifestyle information, hence are subject to residual confounding

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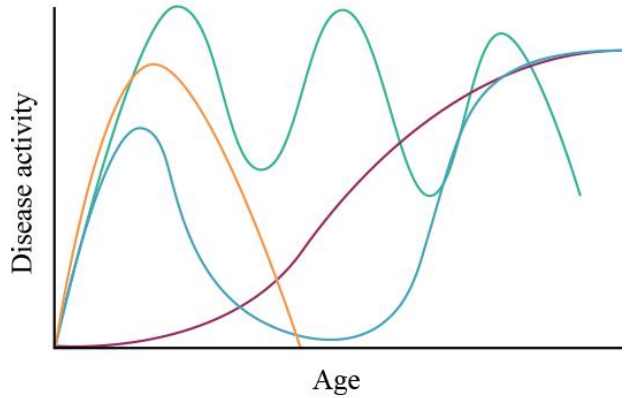
Particular challenges using routinely-collected health data for eczema

- Relapsing and remitting disease
- Non-specific terminology
- Validity of diagnostic algorithms



Are we measuring eczema?

- Develop and validate a diagnostic algorithm for atopic eczema that identifies cases based on medical record and pharmacy codes.
- The Health Improvement Network
- Sent survey to physicians of 100 children and 100 adults

Abuabara et al. JID 2017

Algorithm ‘test characteristics’

	Total	Confirmed	PPV (%)	95%CI
One eczema code + at least 2 treatment codes (selection criteria)	177	154	87%	(81%-92%)
Two eczema codes + at least 2 treatment codes	86	79	92%	(84%-97%)
Two eczema codes + at least one steroid/TCI codes	85	78	92%	(84%-97%)

Algorithm ‘test characteristics’

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Can routinely collected data be used to estimate burden related to eczema?

- Systematic review (in submission) assessing how studies using routinely collected data defined eczema
- Prevalence measured in 40/59 (68%) of studies- estimates ranged from 0.18% to 32.49%

Why are prevalence estimates so different?

- Different countries, ages etc.
- Terminology/measuring different things- studies including seborrheic and contact dermatitis codes reported higher prevalences- 10% vs. 5%
- Algorithms which included prescription data- median prevalence 16% if included compared to 4%
- **One major caveat-** Algorithms need to be context specific

Key issues to watch out for

Why were data collected?

- Clinical care
- Billing

Who is the population?

- Selection bias
- Generalisability

What information are we missing?

- Limited data on disease severity
- Mostly no “over the counter” drugs
- Residual confounding

Pitfalls

- Changes in how diseases/drugs are coded
- Changes in healthcare systems leading to artefactual findings
- Ascertainment issues with repeated measures

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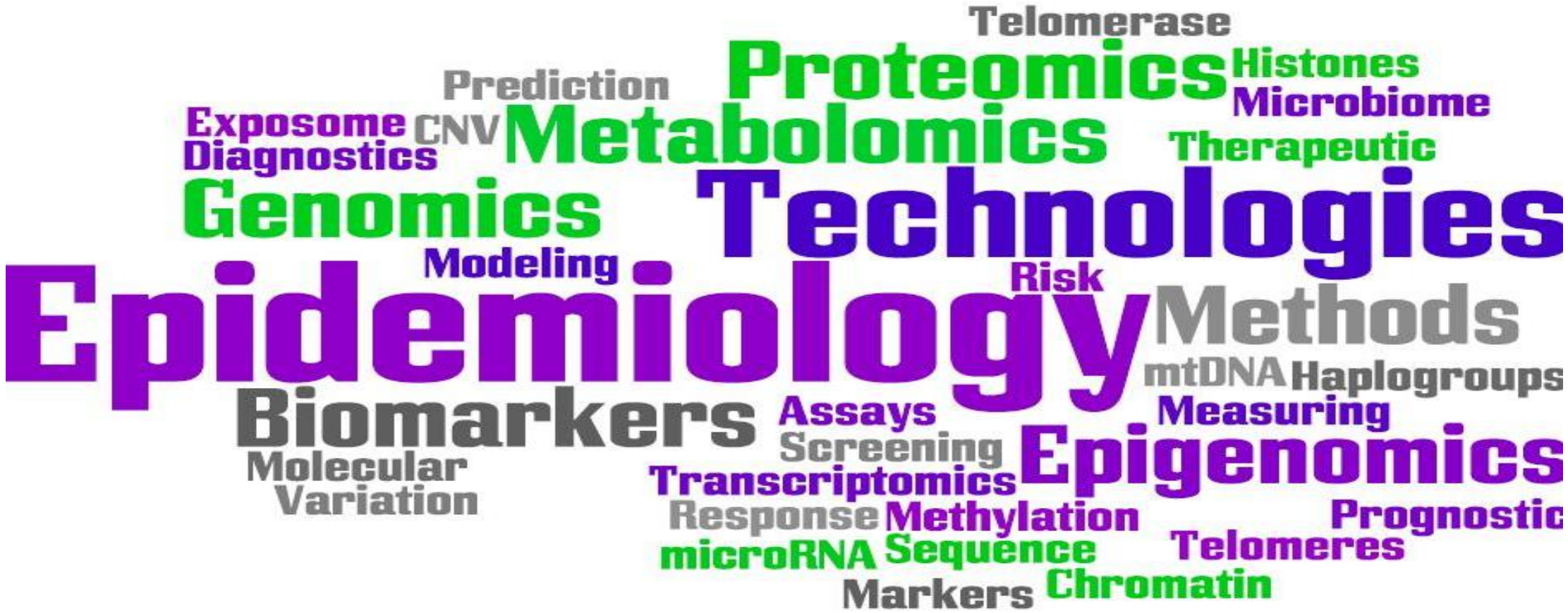
New opportunities



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