

An umbrella review of genetic factors associated with diabetes complications

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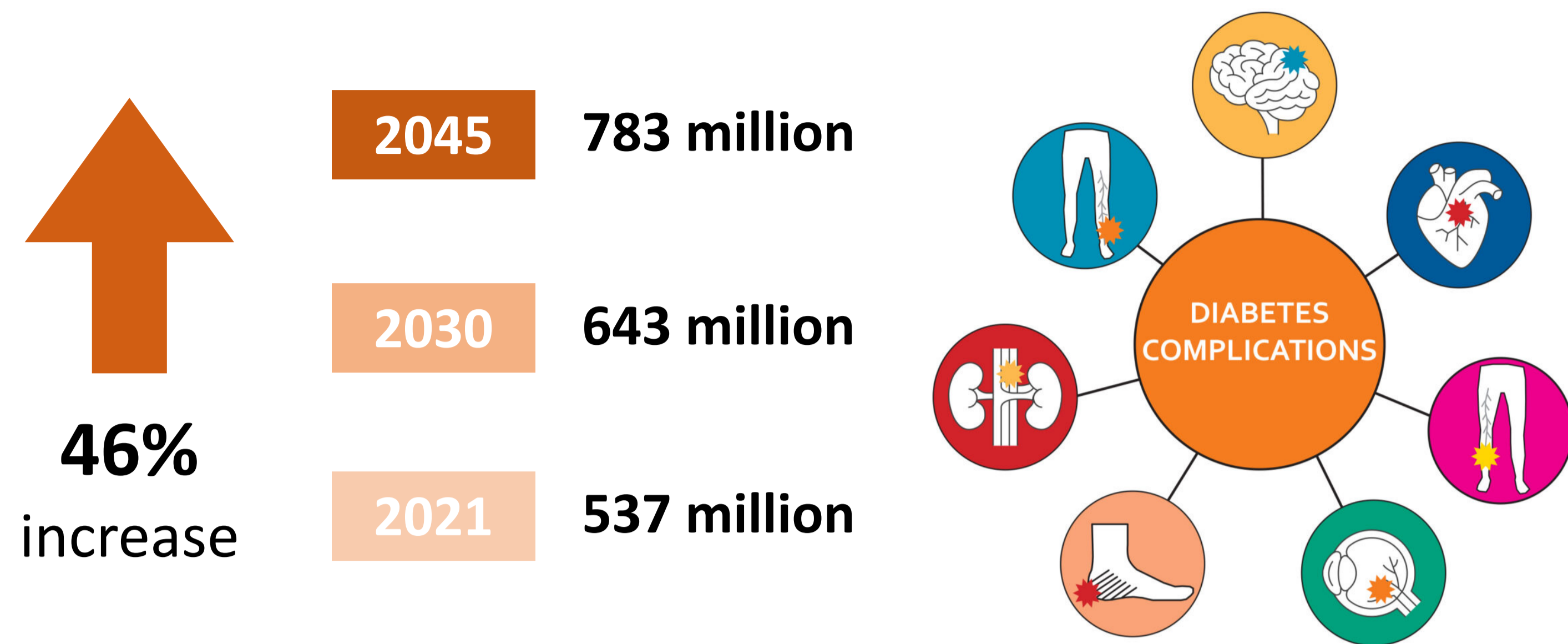
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Background



- **Diabetes mellitus** is a chronic condition characterized by high levels of blood glucose (**hyperglycaemia**).
- It is estimated that diabetes mellitus affects approximately **537 million** people worldwide, with a global prevalence rate of 10.5% in 2021, and is projected to increase to **643 million** by 2030 and **783 million** by 2045 [1].
- Irregular blood glucose levels put individuals with diabetes at higher risk of **microvascular complications** (i.e., retinopathy, nephropathy, and neuropathy) and **macrovascular complications** (i.e., cardiovascular diseases).

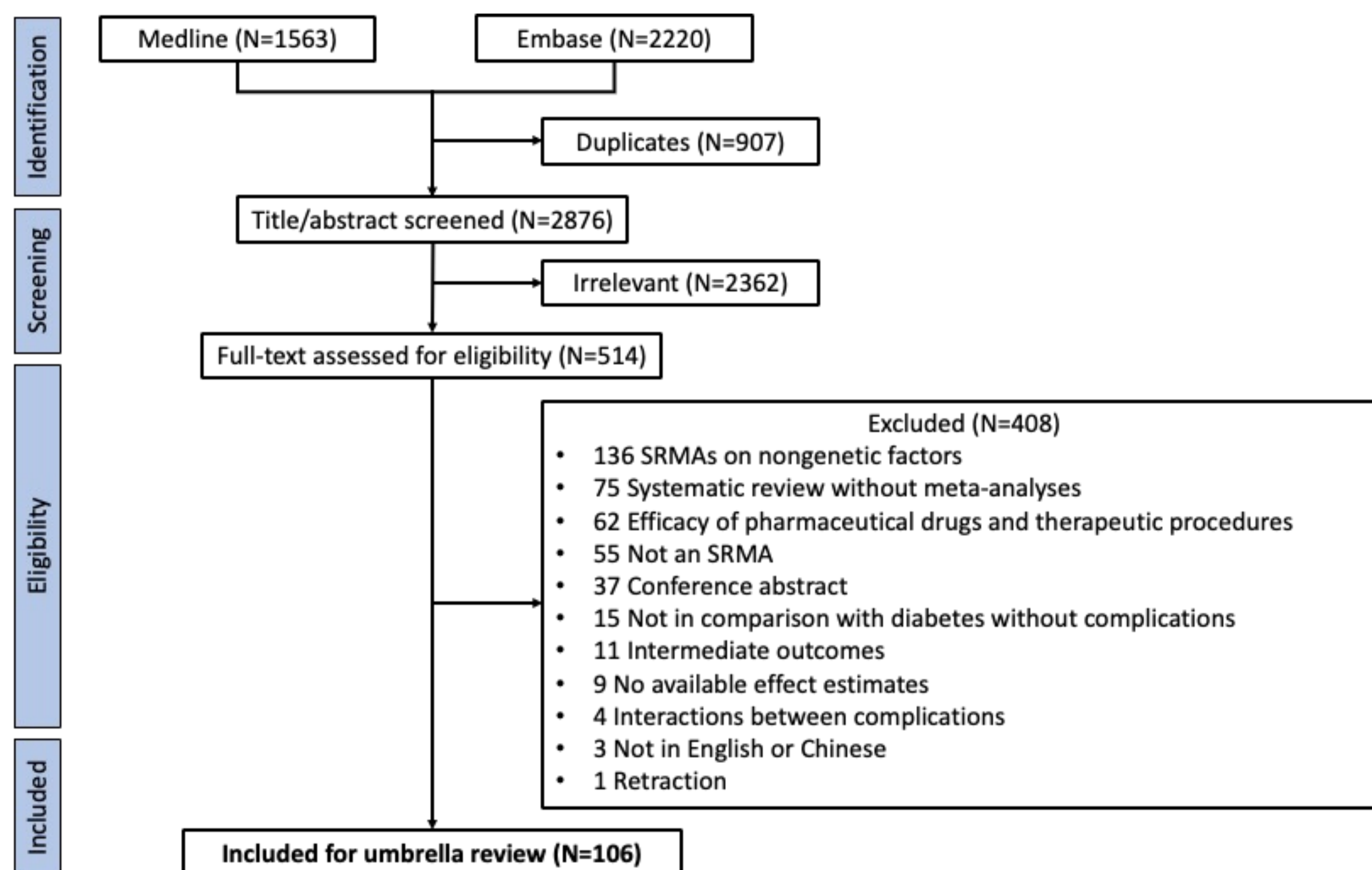
Methods



An **umbrella review** systematically **collects** and **evaluates** currently available evidence from **multiple systematic reviews and meta-analyses (SRMAs)**, providing a bird eye's view of published evidence [2].

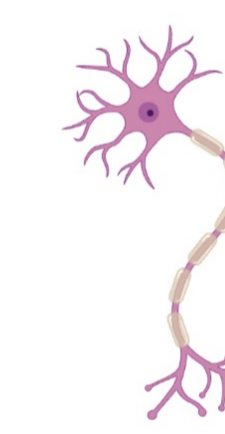
- Step 1:** Study selection and data extraction
- Step 2:** Re-conduct the meta-analyses on random-effects models
- Step 3:** Assess the heterogeneity, small-study effects, and excess significance
- Step 4:** Calculate the statistical power
- Step 5:** Assess the credibility of evidence (Highly credible/Credible/Not credible)
 - Venice criteria [3]
 - i) Amount of evidence, statistical power
 - ii) Extent of replication, heterogeneity
 - iii) Protection from bias, small-study effects
 - Bayesian false-discovery probability (BFDP) [4]
 - i) a medium/low prior level (0.05 to 10^{-3})
 - ii) a very low prior level (10^{-4} to 10^{-6})

Results



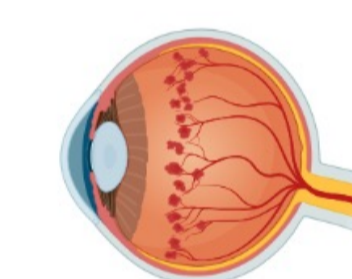
- 106 SRMAs on genetic factors associated with diabetes complications were eligible for inclusion, among which 63 non-overlapping ones were finally included in the umbrella review.

➤ Highly credible associations in type 1 diabetes

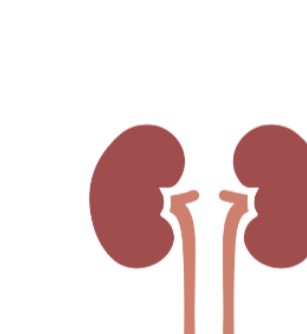


Diabetic peripheral neuropathy
SOD2 rs4880

➤ Highly credible associations in type 2 diabetes

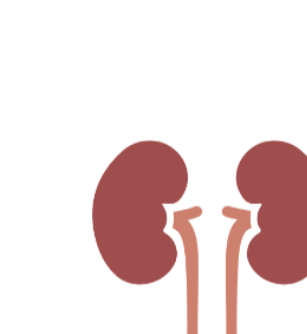


Diabetic retinopathy
MCP-1 rs1024611, *VEGF* rs3025039

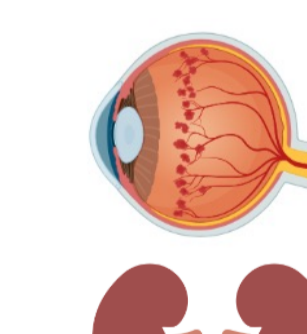


Diabetic kidney disease
ACACB rs2268388, *ACE* Ins/Del,
MTHFR rs1801133, *TCF7L2* rs7903146

➤ Highly credible associations in mixed types of diabetes



Diabetic kidney disease
ACE Ins/Del, *AKR1B1* rs759853,
ENPP1 rs1044498



Comorbidity of diabetic retinopathy and kidney disease
EPO rs1617640

Discussion

- This umbrella review provided a robust and significant synthesis of available evidence on the genetic basis of diabetes complications.
- This umbrella review highlighted ten candidate genes that are involved in nutrient metabolism, inflammation, oxidative stress, angiogenesis, and nuclear transduction pathways.
- It should be noted that none of these highly credible associations were replicated in the latest genome-wide association studies (GWASs) for diabetic complications.
- Molecular biology studies are warranted to confirm the findings from the observation studies.

References

- [1] IDF Atlas 10th Edition. 2021.
- [2] Lazaros B, Vanesa B, John PAI. Conducting umbrella reviews. *BMJ Medicine*. 2022;1(1):e000071.
- [3] Ioannidis JPA, Boffetta P, Little J, O'Brien TR, Uitterlinden AG, Vineis P, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. *International Journal of Epidemiology*. 2008;37(1):120-32.
- [4] Wakefield J. A Bayesian measure of the probability of false discovery in genetic epidemiology studies. *Am J Hum Genet*. 2007;81(2):208-27.