

月经初潮年龄与疾病风险的孟德尔随机化研究进展

司振民¹, 常 惠^{2*}

¹黑龙江中医药大学研究生院, 黑龙江 哈尔滨

²黑龙江中医药大学附属第一医院妇科一科, 黑龙江 哈尔滨

收稿日期: 2024年10月14日; 录用日期: 2024年11月7日; 发布日期: 2024年11月14日

摘 要

月经初潮年龄是女性青春期第一次出现子宫内膜出血的年龄, 越来越多的研究表明月经初潮年龄与某些疾病风险有关系。孟德尔随机化研究是一种使用已知的暴露遗传决定因素来测试或估计暴露对疾病结果的因果影响的方法, 可用于提供这些关联是否存在因果关系的证据。本文总结了先前使用孟德尔随机化方法研究月经初潮年龄与某些疾病风险的关系的研究, 旨在描述孟德尔随机化研究如何帮助我们理解月经初潮年龄的因果关系, 以期为临床医生提供新的思考。

关键词

月经初潮年龄, 孟德尔随机化研究, 研究进展

Advances in Mendelian Randomization Studies on the Association between Age at Menarche and Disease Risk

Zhenmin Si¹, Hui Chang^{2*}

¹Graduate School, Heilongjiang University of Chinese Medicine, Harbin Heilongjiang

²Department of Gynecology, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin Heilongjiang

Received: Oct. 14th, 2024; accepted: Nov. 7th, 2024; published: Nov. 14th, 2024

Abstract

The age of menarche is the age at which endometrial bleeding first appears during female puberty,

*通讯作者。

文章引用: 司振民, 常惠. 月经初潮年龄与疾病风险的孟德尔随机化研究进展[J]. 临床医学进展, 2024, 14(11): 929-937. DOI: 10.12677/acm.2024.14112965

and more and more studies have shown that the age of menarche is associated with the risk of certain diseases. Mendelian randomization studies, a method that uses known genetic determinants of exposure to test or estimate the causal effect of exposure on disease outcomes, can be used to provide evidence of whether these associations are causal. This review summarizes previous studies using Mendelian randomization to study the relationship between age at menarche and the risk of certain diseases, and aims to describe how Mendelian randomization studies can help us understand the causality of age at menarche, with a view to providing new thinking for clinicians.

Keywords

Age at Menarche, Mendelian Randomization Studies, Research Progress

Copyright © 2024 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

月经初潮是女性青春期发育的一个关键标志,代表着女性生殖的开始[1]。许多研究[2]-[6]报告称,月经初潮年龄(age at menarche, AAM)的提前或推迟与某些因素互为因果。月经初潮年龄对于女性生活质量和健康来说是一个重大问题,因此必须了解 AAM 的危险因素和不良后果。随机对照试验是临床研究中确定疾病因果关系的“金标准”,然而随机对照试验存在样本量小、成本高、干预时间短、失败率高、伦理等问题。观察性研究虽然能反映因素与结局之间的关系,但是存在混杂因素和主观因素的影响。孟德尔随机化研究基于全基因组关联研究,弥补了随机对照试验和观察性研究的不足,以揭示因素与结局之间的关系。

2. 孟德尔随机化的介绍

孟德尔随机化(Mendelian randomization, MR)是基于遗传变异探索病因与疾病之间关系的方法[7],在 MR 分析中,遗传变异(通常是单核苷酸多态性)作为工具变量模拟暴露因素对疾病风险的影响,有效规避混杂因素和反向因果造成的偏倚[8] [9]。MR 依靠三个假设:(1) 工具变量与暴露因素强相关;(2) 工具变量与任何潜在的混杂因素无关;(3) 工具变量仅通过暴露因素影响结局[10]。

3. AAM 与疾病风险的 MR 研究

3.1. 内分泌疾病

一项 Meta 分析[11]显示早期 AAM 与 2 型糖尿病风险增加存在关联,Xing 等[12]研究发现晚期 AAM 与较低的 2 型糖尿病风险之间存在因果关系。Yuan 等[13]的研究发现 AAM 与降低 2 型糖尿病的风险相关。一项队列研究[14]显示早期 AAM 是妊娠期糖尿病的独立风险因素,同时一项 Meta 分析[15]显示 AAM 提前与妊娠期糖尿病风险增加密切相关,MR 研究[16]也验证了这一点,早期 AAM 与较高的妊娠期糖尿病风险呈因果正相关。

3.2. 心血管疾病

心血管疾病是女性发病和死亡的主要原因[17]。Fan 等[18]研究提示 AAM 提前对冠状动脉疾病风险的影响有 29%是由收缩压介导的,另外 Maddalena Ardisino 等[19]研究表明 AAM 提前会增加冠状动脉

疾病和心力衰竭的风险,这两种关联部分是由 BMI 来介导的,然而一项 MR 研究[20]发现几乎没有证据支持 AAM 对冠状动脉疾病风险的因果关系。Chen 等[21]通过双样本随机化,MR 分析揭示了 AAM 推迟与缺血性心脏病风险降低之间存在关系,并且这种关系是通过 BMI 介导的。因此 BMI 是妇女初级预防的重点。

3.3. 心理疾病

观察性研究表明,女性一生中发生抑郁症的机率很高[22][23]。先前的研究[24]-[26]认为 AAM 越早,发生抑郁症的机率越高,一项队列研究[27]发现与 ≤ 12 岁月经初潮的女性相比, ≥ 15 岁月经初潮的女性患抑郁症的风险增加,尽管之前研究有争议,但都表明 AAM 与抑郁症密切相关。而在一项纵向研究中[28]中发现抑郁症与 AAM 无关。Raphael Hirtz 等[29]进行双样本 MR 研究,发现 AAM 对抑郁风险有显著的因果效应,Yu 等[30]等研究发现 AAM 较晚会降低抑郁症的风险,Maija-Eliina Sequeira 等[31]发现早发性月经初潮对青春期中期抑郁症状有因果关系,Wang 等[32]发现在单变量分析时,早期 AAM 与重度抑郁症风险增加有因果关系。然而在对一项中国南方队列进行 MR 研究[33]时,结果表明 AAM 与抑郁症状没有关联。神经性厌食症是一种以食物摄入限制、体重减轻和对体重增加恐惧为表现的精神疾病,MR 分析[34]表明 AAM 较小与早发性神经性厌食症之间存在因果关系。

3.4. 呼吸疾病

肺癌是女性癌症死亡的主要原因,来自国际肺癌联盟的汇总分析[35]显示没有发现 AAM 与肺癌相关的证据,而来自九个队列的[36]研究中发现在调整 BMI 后,AAM 推迟仍与子宫内膜癌、肝癌、黑色素瘤、膀胱癌和结肠癌、肺癌和乳腺癌风险减少存在关系,另一项研究[37]发现 AAM 提前与肺癌风险较高有关。一项 MR 分析[38]发现 BMI 可能是 AAM 与肺癌风险之间关联的重要介质,使得晚期 AAM 与肺癌风险降低有因果关系。

3.5. 妇科疾病

多囊卵巢综合征(Polycystic ovary syndrome, PCOS)是育龄妇女中最常见的疾病之一。在以前 AAM 与 PCOS 关系的研究中,仅有一项研究[39]表明早期 AAM 对 1 型糖尿病女性患者患 PCOS 有影响,然而有一项 MR 研究[40]证实晚期 AAM 可以降低 PCOS 的风险,在 Pu 等[41]研究中证实 AAM 与 PCOS 中氧化应激标志物存在因果关系。

子宫内膜异位症是一种激素依赖性慢性炎症性疾病,据报道[42][43],AAM 提前可以导致子宫内膜异位症的风险增加,这一观点在 MR 研究[44]研究中也得到了验证,其数据表明体重和 BMI 的降低是子宫内膜异位症遗传易感性的中介因素。此外,Lv 等[51]检测到 AAM 与子宫内膜异位症之间相关的微弱证据。

在 Qu 等[45]的 MR 研究中,结果表明子宫内膜异位症的年龄较晚会增加子宫平滑肌瘤的风险,PCOS 与之相反,并且此研究证实 AAM 提前是子宫平滑肌瘤的风险因素。Wang 等[46]采用双样本 MR 研究女性生殖因素、性激素与子宫平滑肌瘤的假定因果关系时,发现当使用 FinnGen GWAS 作为结局数据时,AAM 与子宫平滑肌瘤风险之间存在因果关系。

子宫内膜癌是一种常见的妇科癌症,一些研究[47][48]结果认为 AAM 推迟与子宫内膜癌风险呈负相关。Felix R Day 等[49]发现通过 MR 方法,在调整基因预测的 BMI 后,AAM 增加与子宫内膜癌和浆液性卵巢癌风险降低相关。Tracy A O'Mara 等[50]研究也证实了月经初潮晚龄对子宫内膜癌风险的保护作用。Lv 等[51]研究发现 AAM 对子宫内膜癌和乳腺癌具有强大的因果效应,Wang 等[52]采用多变量 MR 分析发现 AAM 对子宫内膜癌有显著影响,然而在 Shannon D'Urso 等[53]的研究中,发现用单变量 MR 分

析时, AAM 对子宫内膜癌风险具有因果效应, 用多变量 MR 分析时, AAM 与子宫内膜癌风险无关。

卵巢癌是全球最常见的妇科癌症之一, 上皮卵巢癌占卵巢癌病例的 95% [54]。一项 Meta 分析[55]显示 AAM 与卵巢癌风险呈负相关, 另一项研究[56]发现早期 AAM 与卵巢癌风险有关。James Yarmolinsky 等[57]发现在逆方差加权模型中, 有证据表明 AAM 较早与浸润性上皮性卵巢癌风险有关, 在检查浸润性上皮性卵巢癌组织型和低恶性潜在肿瘤的分析中, 有证据表明 AAM 较早与子宫内膜样癌有关。Yang 等[58]在对中国全基因组关联研究和欧洲血统女性的 MR 分析时, 显示 AAM 较早与上皮卵巢癌之间存在因果关系。

3.6. 产科疾病

先兆子痫是孕产妇和围产期死亡主要原因。研究[59] [60]表明 AAM 与先兆子痫有关, Lv 等[51]用 MR 研究进行了证明。自然流产是指在特定妊娠周之前失去胎儿。G Wyshak 等[61]发现 AAM 在 12 岁以下和 AAM 在 14 岁及以上的女性比 AAM 在 12 岁或 13 岁的女性有更多失败的妊娠结局, L A al-Ansary 等[62]发现 AAM 与自然流产风险呈正相关。MR 研究[63]证实晚期 AAM 与自然流产风险增加有关。

3.7. 骨科疾病

骨关节炎是最常见的关节疾病。前瞻性研究[64]表明 AAM 越早, 用于治疗骨关节炎的膝关节置换术的风险就会增加, 研究认为 AAM 较小可能代表了如年轻时的身体习惯等其他因素, 影响骨关节炎和关节置换术的发展。Wang 等[65]利用 MR 分析, 发现 AAM 对膝关节骨关节炎产生不利的因果影响。

3.8. 神经系统疾病

Giancarlo Pesce 等[66]研究发现 AAM < 12 岁或 AAM $\geq$ 14 岁的女性的帕金森病发病率高于 AAM 为 12~13 岁的女性。Benjamin Meir Jacobs 等[67]发现帕金森病与早期 AAM 存在强有力的关联。而一项 MR 研究[68]发现 AAM 与帕金森病不存在关联。多发性硬化症是一种中枢神经系统的自身免疫性疾病。以往的研究[69] [70]报告了 AAM 越早会增加多发性硬化症的风险。Amirreza Azimi 的 Meta 分析[71]也显示一样的结果。Lazaros Belbasis 等[72]发现用 MR 分析时, 发现基因决定的晚期 AAM 与较低的多发性硬化症风险相关, 与 Harroud 等人最近发表的 2 样本 AAM 的 MR 分析一致[73]。

3.9. 乳腺疾病

乳腺癌是女性中最常见的癌症。Chen 等[74]发现 AAM 较小与乳腺癌风险升高显著相关, Day 等[49]在 BMI 调整模型中, 发现增加 AAM 与较低的乳腺癌风险相关, Tom G Richardson 等[75]结果与此一致, 但仅限于考虑早期体型时。Stephen Burgess 等[76]研究结果显示 AAM 对乳腺癌风险的反向直接因果影响 (BMI 无关), 以及通过 BMI 的正向间接影响。Jia 等[77]进行双样本 MR 分析, 发现 AAM 对乳腺癌无影响。Maria Escala-Garcia 等[78]分析显示 AAM 与乳腺癌特异性生存率不存在关联。

3.10. 风湿免疫病

系统性红斑狼疮和类风湿关节炎是慢性自身免疫性疾病, Zhang 等[79]进行双样本 MR 分析, 证实了 AAM 与系统性红斑狼疮的负向因果关系。前瞻性队列研究[80]表明与 13 岁月经初潮相比, AAM > 14 岁与类风湿关节炎风险更高相关。而在 Zhu 等[81] MR 研究中发现没有证据支持 AAM 与类风湿关节炎风险存在因果关系。

3.11. 消化疾病

食管癌是一个患者癌症死亡的主要原因, 可以分为良性食管癌和恶性食管癌。Su 等[82]通过 MR 分

析探讨了 AAM 与良性食管癌和恶性食管癌之间的遗传因果关系, 结果发现 AAM 与良性食管癌呈负向遗传因果关系, 与恶性食管癌之间不存在遗传因果关系。结直肠癌的发病率在逐年上升, 前瞻性队列研究[83]和 Meta 分析[84]表明 AAM 与结直肠癌无关, MR 研究[85]证实了这一点。

3.12. 脑部疾病

Zou 等[86]进行双样本 MR 研究, 发现 AAM 与脑出血风险有因果关系。Wang 等[87]利用单变量 MR 分析和多变量 MR 分析, 未发现 AAM 对脑小血管疾病临床和神经影像学表现的因果关系。

4. 小结

笔者总结了迄今为止的关于 AAM 与疾病风险的 MR 研究, 以期待为公共卫生预防提供新的思考。一些研究将 AAM 作为暴露因素, 证实 AAM 与某些疾病的风险, 研究证实 AAM 的提前会导致妊娠期糖尿病, 肺癌, 子宫内膜异位症, 子宫平滑肌瘤, 上皮性卵巢癌, 神经性厌食症, 肌少症, 早期绝经等风险增加; AAM 的推迟会增加自然流产的风险, 降低 2 型糖尿病, 缺血性心脏病, 多囊卵巢综合征, 膝关节骨性关节炎, 多发性硬化症的风险; 几项研究证实 AAM 与类风湿关节炎, 结直肠癌, 缺血性脑卒中无关; 存在争议的研究结果有乳腺癌, 帕金森病, 子宫内膜癌, 抑郁症, 冠状动脉疾病。总的来说, MR 研究在 AAM 与疾病风险中的应用给公共卫生预防提供了新的思路。

参考文献

- [1] Hinojosa-Gonzalez, D.E., Ramonfaur, D., Morales-Palomino, K.L., Tellez-Giron, V.C., Latapi, X., Insua, J., *et al.* (2023) Relationship of Age at Menarche, Coitarche and First Gestation: A Retrospective Cohort Analysis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*: X, **18**, Article ID: 100189. <https://doi.org/10.1016/j.eurox.2023.100189>
- [2] Gaudino, R., Dal Ben, S., Cavarzere, P., Volpi, S., Piona, C., Boner, A., *et al.* (2020) Delayed Age at Menarche in Chronic Respiratory Diseases. *European Journal of Clinical Investigation*, **51**, e13461. <https://doi.org/10.1111/eci.13461>
- [3] Kim, H.S., Ng, D.K., Matheson, M.B., Atkinson, M.A., Warady, B.A., Furth, S.L., *et al.* (2020) Delayed Menarche in Girls with Chronic Kidney Disease and the Association with Short Stature. *Pediatric Nephrology*, **35**, 1471-1475. <https://doi.org/10.1007/s00467-020-04559-7>
- [4] Šaffa, G., Kubicka, A.M., Hromada, M. and Kramer, K.L. (2019) Is the Timing of Menarche Correlated with Mortality and Fertility Rates? *PLOS ONE*, **14**, e0215462. <https://doi.org/10.1371/journal.pone.0215462>
- [5] Lu, Z., Aribas, E., Geurts, S., Roeters van Lennep, J.E., Ikram, M.A., Bos, M.M., *et al.* (2022) Association between Sex-Specific Risk Factors and Risk of New-Onset Atrial Fibrillation among Women. *JAMA Network Open*, **5**, e2229716. <https://doi.org/10.1001/jamanetworkopen.2022.29716>
- [6] Ergin, A., Türkay, Ü., Özdemir, S., Taşkın, A., Terzi, H. and Özşürmeli, M. (2021) Age at Menarche: Risk Factor for Gestational Diabetes. *Journal of Obstetrics and Gynaecology*, **42**, 680-686. <https://doi.org/10.1080/01443615.2021.1929116>
- [7] Birney, E. (2021) Mendelian Randomization. *Cold Spring Harbor Perspectives in Medicine*, **12**, a041302. <https://doi.org/10.1101/cshperspect.a041302>
- [8] Ference, B.A., Holmes, M.V. and Smith, G.D. (2021) Using Mendelian Randomization to Improve the Design of Randomized Trials. *Cold Spring Harbor Perspectives in Medicine*, **11**, a040980. <https://doi.org/10.1101/cshperspect.a040980>
- [9] Skrivankova, V.W., Richmond, R.C., Woolf, B.A.R., Davies, N.M., Swanson, S.A., VanderWeele, T.J., *et al.* (2021) Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. *BMJ*, **375**, n2233. <https://doi.org/10.1136/bmj.n2233>
- [10] Sekula, P., Del Greco M, F., Pattaro, C. and Köttgen, A. (2016) Mendelian Randomization as an Approach to Assess Causality Using Observational Data. *Journal of the American Society of Nephrology*, **27**, 3253-3265. <https://doi.org/10.1681/asn.2016010098>
- [11] Janghorbani, M., Mansourian, M. and Hosseini, E. (2014) Systematic Review and Meta-Analysis of Age at Menarche and Risk of Type 2 Diabetes. *Acta Diabetologica*, **51**, 519-528. <https://doi.org/10.1007/s00592-014-0579-x>
- [12] Xing, W., Lv, Q., Li, Y., Wang, C., Mao, Z., Li, Y., *et al.* (2023) Genetic Prediction of Age at Menarche, Age at Natural

- Menopause and Type 2 Diabetes: A Mendelian Randomization Study. *Nutrition, Metabolism and Cardiovascular Diseases*, **33**, 873-882. <https://doi.org/10.1016/j.numecd.2023.01.011>
- [13] Yuan, S. and Larsson, S.C. (2020) An Atlas on Risk Factors for Type 2 Diabetes: A Wide-Angled Mendelian Randomisation Study. *Diabetologia*, **63**, 2359-2371. <https://doi.org/10.1007/s00125-020-05253-x>
- [14] Li, H., Shen, L., Song, L., Liu, B., Zheng, X., Xu, S., *et al.* (2017) Early Age at Menarche and Gestational Diabetes Mellitus Risk: Results from the Healthy Baby Cohort Study. *Diabetes & Metabolism*, **43**, 248-252. <https://doi.org/10.1016/j.diabet.2017.01.002>
- [15] Sun, X., Yang, L., Pan, J., Yang, H., Wu, Y., Chen, Z., *et al.* (2018) Age at Menarche and the Risk of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Endocrine*, **61**, 204-209. <https://doi.org/10.1007/s12020-018-1581-9>
- [16] Lu, L., Wan, B. and Sun, M. (2022) Mendelian Randomization Identifies Age at Menarche as an Independent Causal Effect Factor for Gestational Diabetes Mellitus. *Diabetes, Obesity and Metabolism*, **25**, 248-260. <https://doi.org/10.1111/dom.14869>
- [17] Vogel, B., Acevedo, M., Appelman, Y., Bairey Merz, C.N., Chieffo, A., Figtree, G.A., *et al.* (2021) The Lancet Women and Cardiovascular Disease Commission: Reducing the Global Burden by 2030. *The Lancet*, **397**, 2385-2438. [https://doi.org/10.1016/s0140-6736\(21\)00684-x](https://doi.org/10.1016/s0140-6736(21)00684-x)
- [18] Fan, H., Huang, Y., Chen, Y., Hsu, J.B., Li, H., Su, T., *et al.* (2023) Systolic Blood Pressure as the Mediator of the Effect of Early Menarche on the Risk of Coronary Artery Disease: A Mendelian Randomization Study. *Frontiers in Cardiovascular Medicine*, **9**, Article ID: 1023355. <https://doi.org/10.3389/fcvm.2022.1023355>
- [19] Ardissino, M., Slob, E.A.W., Carter, P., Rogne, T., Girling, J., Burgess, S., *et al.* (2023) Sex-Specific Reproductive Factors Augment Cardiovascular Disease Risk in Women: A Mendelian Randomization Study. *Journal of the American Heart Association*, **12**, e027933. <https://doi.org/10.1161/jaha.122.027933>
- [20] Cao, M. and Cui, B. (2019) Negative Effects of Age at Menarche on Risk of Cardiometabolic Diseases in Adulthood: A Mendelian Randomization Study. *The Journal of Clinical Endocrinology & Metabolism*, **105**, 515-522. <https://doi.org/10.1210/clinem/dgz071>
- [21] Chen, J., Chen, H., Zhu, Q., Liu, Q., Zhou, Y., Li, L., *et al.* (2022) Age at Menarche and Ischemic Heart Disease: An Update Mendelian Randomization Study. *Frontiers in Genetics*, **13**, Article ID: 942861. <https://doi.org/10.3389/fgene.2022.942861>
- [22] Steiner, M. (2003) Hormones and Mood: From Menarche to Menopause and beyond. *Journal of Affective Disorders*, **74**, 67-83. [https://doi.org/10.1016/s0165-0327\(02\)00432-9](https://doi.org/10.1016/s0165-0327(02)00432-9)
- [23] Piccinelli, M. and Wilkinson, G. (2000) Gender Differences in Depression. *British Journal of Psychiatry*, **177**, 486-492. <https://doi.org/10.1192/bjp.177.6.486>
- [24] Mendle, J., Ryan, R.M. and McKone, K.M.P. (2018) Age at Menarche, Depression, and Antisocial Behavior in Adulthood. *Pediatrics*, **141**, e20171703. <https://doi.org/10.1542/peds.2017-1703>
- [25] Shen, Y., Varma, D.S., Zheng, Y., Boc, J. and Hu, H. (2019) Age at Menarche and Depression: Results from the NHANES 2005-2016. *PeerJ*, **7**, e7150. <https://doi.org/10.7717/peerj.7150>
- [26] Hirtz, R., Libuda, L., Hinney, A., Föcker, M., Bühlmeier, J., Holterhus, P., *et al.* (2022) Age at Menarche Relates to Depression in Adolescent Girls: Comparing a Clinical Sample to the General Pediatric Population. *Journal of Affective Disorders*, **318**, 103-112. <https://doi.org/10.1016/j.jad.2022.08.092>
- [27] Kim, H., Jung, J.H., Han, K., Lee, D., Fava, M., Mischoulon, D., *et al.* (2023) Ages at Menarche and Menopause, Hormone Therapy, and the Risk of Depression. *General Hospital Psychiatry*, **83**, 35-42. <https://doi.org/10.1016/j.genhosppsych.2023.04.001>
- [28] Prince, C., Joinson, C., Kwong, A.S.F., Fraser, A. and Heron, J. (2023) The Relationship between Timing of Onset of Menarche and Depressive Symptoms from Adolescence to Adulthood. *Epidemiology and Psychiatric Sciences*, **32**, e60. <https://doi.org/10.1017/s2045796023000707>
- [29] Hirtz, R., Hars, C., Naresh, R., Laabs, B., Antel, J., Grasemann, C., *et al.* (2022) Causal Effect of Age at Menarche on the Risk for Depression: Results from a Two-Sample Multivariable Mendelian Randomization Study. *Frontiers in Genetics*, **13**, Article ID: 918584. <https://doi.org/10.3389/fgene.2022.918584>
- [30] Yu, Y., Hou, L., Wu, Y., Yu, Y., Liu, X., Wu, S., *et al.* (2023) Causal Associations between Female Reproductive Behaviors and Psychiatric Disorders: A Lifecourse Mendelian Randomization Study. *BMC Psychiatry*, **23**, Article No. 799. <https://doi.org/10.1186/s12888-023-05203-y>
- [31] Sequeira, M., Lewis, S.J., Bonilla, C., Smith, G.D. and Joinson, C. (2017) Association of Timing of Menarche with Depressive Symptoms and Depression in Adolescence: Mendelian Randomisation Study. *British Journal of Psychiatry*, **210**, 39-46. <https://doi.org/10.1192/bjp.bp.115.168617>
- [32] Wang, Z., Lu, J., Weng, W., Fu, J. and Zhang, J. (2023) Women's Reproductive Traits and Major Depressive Disorder:

- A Two-Sample Mendelian Randomization Study. *Journal of Affective Disorders*, **326**, 139-146. <https://doi.org/10.1016/j.jad.2023.01.063>
- [33] Au Yeung, S.L., Jiang, C., Cheng, K.K., Xu, L., Zhang, W., Lam, T.H., *et al.* (2018) Age at Menarche and Depressive Symptoms in Older Southern Chinese Women: A Mendelian Randomization Study in the Guangzhou Biobank Cohort Study. *Psychiatry Research*, **259**, 32-35. <https://doi.org/10.1016/j.psychres.2017.09.040>
- [34] Watson, H.J., Thornton, L.M., Yilmaz, Z., *et al.* (2021) Common Genetic Variation and Age of Onset of Anorexia Nervosa. *Biological Psychiatry: Global Open Science*, **2**, 368-378.
- [35] Ben Khedher, S., Neri, M., Papadopoulos, A., Christiani, D.C., Diao, N., Harris, C.C., *et al.* (2017) Menstrual and Reproductive Factors and Lung Cancer Risk: A Pooled Analysis from the International Lung Cancer Consortium. *International Journal of Cancer*, **141**, 309-323. <https://doi.org/10.1002/ijc.30750>
- [36] Fuhrman, B.J., Moore, S.C., Byrne, C., Makhoul, I., Kitahara, C.M., Berrington de González, A., *et al.* (2021) Association of the Age at Menarche with Site-Specific Cancer Risks in Pooled Data from Nine Cohorts. *Cancer Research*, **81**, 2246-2255. <https://doi.org/10.1158/0008-5472.can-19-3093>
- [37] Zhang, Y., Liang, H., Cheng, J., *et al.* (2023) Associations between Sex-Specific Reproductive Factors and Risk of New-Onset Lung Cancer Among Women. *Chest*.
- [38] Denos, M., Sun, Y., Jiang, L., Brumpton, B.M. and Mai, X. (2023) Age at Menarche, Age at Natural Menopause, and Risk of Lung and Colorectal Cancers: A Mendelian Randomization Study. *Journal of the Endocrine Society*, **7**, bvad077. <https://doi.org/10.1210/jendso/bvad077>
- [39] Lebkowska, A., Adamska, A., Krentowska, A., Uruska, A., Rogowicz-Frontczak, A., Araszkiewicz, A., *et al.* (2021) The Influence of Prepubertal Onset of Type 1 Diabetes and Age of Menarche on Polycystic Ovary Syndrome Diagnosis. *The Journal of Clinical Endocrinology & Metabolism*, **106**, 1811-1820. <https://doi.org/10.1210/clinem/dgab062>
- [40] Ma, Y., Cai, J., Liu, L., Hou, W., Wei, Z., Wang, Y., *et al.* (2023) Age at Menarche and Polycystic Ovary Syndrome: A Mendelian Randomization Study. *International Journal of Gynecology & Obstetrics*, **162**, 1050-1056. <https://doi.org/10.1002/ijgo.14820>
- [41] Yifu, P. (2023) Evidence for Causal Effects of Polycystic Ovary Syndrome on Oxidative Stress: A Two-Sample Mendelian Randomisation Study. *BMC Medical Genomics*, **16**, Article No. 141. <https://doi.org/10.1186/s12920-023-01581-0>
- [42] Lu, M., Niu, J. and Liu, B. (2022) The Risk of Endometriosis by Early Menarche Is Recently Increased: A Meta-Analysis of Literature Published from 2000 to 2020. *Archives of Gynecology and Obstetrics*, **307**, 59-69. <https://doi.org/10.1007/s00404-022-06541-0>
- [43] Nnoaham, K.E., Webster, P., Kumbang, J., Kennedy, S.H. and Zondervan, K.T. (2012) Is Early Age at Menarche a Risk Factor for Endometriosis? A Systematic Review and Meta-Analysis of Case-Control Studies. *Fertility and Sterility*, **98**, 702-712.e6. <https://doi.org/10.1016/j.fertnstert.2012.05.035>
- [44] Garitazelaia, A., Rueda-Martínez, A., Arauzo, R., de Miguel, J., Cilleros-Portet, A., Mari, S., *et al.* (2021) A Systematic Two-Sample Mendelian Randomization Analysis Identifies Shared Genetic Origin of Endometriosis and Associated Phenotypes. *Life*, **11**, Article No. 24. <https://doi.org/10.3390/life11010024>
- [45] Qu, Y., Chen, L., Guo, S., Liu, Y. and Wu, H. (2023) Genetic Liability to Multiple Factors and Uterine Leiomyoma Risk: A Mendelian Randomization Study. *Frontiers in Endocrinology*, **14**, Article ID: 1133260. <https://doi.org/10.3389/fendo.2023.1133260>
- [46] Wang, H., Li, C., Chen, L., Zhang, M., Ren, T. and Zhang, S. (2024) Causal Relationship between Female Reproductive Factors, Sex Hormones and Uterine Leiomyoma: A Mendelian Randomization Study. *Reproductive BioMedicine Online*, **48**, Article ID: 103584. <https://doi.org/10.1016/j.rbmo.2023.103584>
- [47] Gong, T., Wang, Y. and Ma, X. (2015) Age at Menarche and Endometrial Cancer Risk: A Dose-Response Meta-Analysis of Prospective Studies. *Scientific Reports*, **5**, Article No. 14051. <https://doi.org/10.1038/srep14051>
- [48] Katagiri, R., Iwasaki, M., Abe, S.K., Islam, M.R., Rahman, M.S., Saito, E., *et al.* (2023) Reproductive Factors and Endometrial Cancer Risk among Women. *JAMA Network Open*, **6**, e2332296. <https://doi.org/10.1001/jamanetworkopen.2023.32296>
- [49] Day, F.R., Thompson, D.J., Helgason, H., *et al.* (2018) Genomic Analyses Identify Hundreds of Variants Associated with Age at Menarche and Support a Role for Puberty Timing in Cancer Risk. *Yearbook of Paediatric Endocrinology*, **49**, 834-841. <https://doi.org/10.1530/ey.15.7.5>
- [50] O'Mara, T.A., Glubb, D.M., Amant, F., *et al.* (2018) Identification of Nine New Susceptibility Loci for Endometrial Cancer. *Nature Communications*, **9**, Article No. 3166.
- [51] Lv, Y., Xia, X., Lei, L., Xiang, W., Wu, X., Xie, S., *et al.* (2023) Health Outcomes of Age at Menarche in European Women: A Two-Sample Mendelian Randomization Study. *Postgraduate Medical Journal*, **99**, 993-999. <https://doi.org/10.1093/postmj/qgad023>

- [52] Wang, X., Kho, P.F., Ramachandran, D., Bafligil, C., Amant, F., Goode, E.L., *et al.* (2023) Multi-Trait Genome-Wide Association Study Identifies a Novel Endometrial Cancer Risk Locus That Associates with Testosterone Levels. *iScience*, **26**, Article ID: 106590. <https://doi.org/10.1016/j.isci.2023.106590>
- [53] D'Urso, S., Arumugam, P., Weider, T., Hwang, L., Bond, T.A., Kemp, J.P., *et al.* (2022) Mendelian Randomization Analysis of Factors Related to Ovulation and Reproductive Function and Endometrial Cancer Risk. *BMC Medicine*, **20**, Article No. 419. <https://doi.org/10.1186/s12916-022-02585-w>
- [54] Jayson, G.C., Kohn, E.C., Kitchener, H.C. and Ledermann, J.A. (2014) Ovarian Cancer. *The Lancet*, **384**, 1376-1388. [https://doi.org/10.1016/s0140-6736\(13\)62146-7](https://doi.org/10.1016/s0140-6736(13)62146-7)
- [55] Gong, T., Wu, Q., Vogtmann, E., Lin, B. and Wang, Y. (2012) Age at Menarche and Risk of Ovarian Cancer: A Meta-analysis of Epidemiological Studies. *International Journal of Cancer*, **132**, 2894-2900. <https://doi.org/10.1002/ijc.27952>
- [56] Lee, J., Lee, Y.A., Shin, C.H., Suh, D.I., Lee, Y.J. and Yon, D.K. (2022) Long-Term Health Outcomes of Early Menarche in Women: An Umbrella Review. *QJM: An International Journal of Medicine*, **115**, 837-847. <https://doi.org/10.1093/qjmed/hcac187>
- [57] Yarmolinsky, J., Relton, C.L., Lophatananon, A., Muir, K., Menon, U., Gentry-Maharaj, A., *et al.* (2019) Appraising the Role of Previously Reported Risk Factors in Epithelial Ovarian Cancer Risk: A Mendelian Randomization Analysis. *PLOS Medicine*, **16**, e1002893. <https://doi.org/10.1371/journal.pmed.1002893>
- [58] Yang, H., Dai, H., Li, L., Wang, X., Wang, P., Song, F., *et al.* (2019) Age at Menarche and Epithelial Ovarian Cancer Risk: A Meta-Analysis and Mendelian Randomization Study. *Cancer Medicine*, **8**, 4012-4022. <https://doi.org/10.1002/cam4.2315>
- [59] Jaatinen, N., Jääskeläinen, T., Laivuori, H. and Ekholm, E. (2021) The Non-Traditional and Familial Risk Factors for Preeclampsia in the FINNPEC Cohort. *Pregnancy Hypertension*, **23**, 48-55. <https://doi.org/10.1016/j.preghy.2020.11.001>
- [60] K R, Gandhi S, Rao V. (2014) Socio-Demographic and Other Risk Factors of Pre-Eclampsia at a Tertiary Care Hospital, Karnataka: Case Control Study. *Journal of Clinical and Diagnostic Research*, **8**, JC01-JC04. <https://doi.org/10.7860/jcdr/2014/10255.4802>
- [61] Wyshak, G. (1983) Age at Menarche and Unsuccessful Pregnancy Outcome. *Annals of Human Biology*, **10**, 69-73. <https://doi.org/10.1080/03014468300006191>
- [62] Al-Ansary, L.A., Oni, G. and Babay, Z.A. (1995) Risk Factors for Spontaneous Abortion among Saudi Women. *Journal of Community Health*, **20**, 491-500. <https://doi.org/10.1007/bf02277065>
- [63] Wang, Q., Liu, F., Tuo, Y., Ma, L. and Feng, X. (2023) Associations between Obesity, Smoking Behaviors, Reproductive Traits and Spontaneous Abortion: A Univariable and Multivariable Mendelian Randomization Study. *Frontiers in Endocrinology*, **14**, Article ID: 1193995. <https://doi.org/10.3389/fendo.2023.1193995>
- [64] Liu, B., Balkwill, A., Cooper, C., Roddam, A., Brown, A. and Beral, V. (2008) Reproductive History, Hormonal Factors and the Incidence of Hip and Knee Replacement for Osteoarthritis in Middle-Aged Women. *Annals of the Rheumatic Diseases*, **68**, 1165-1170. <https://doi.org/10.1136/ard.2008.095653>
- [65] Wang, B., Wu, J., Li, H., Jin, X., Sui, C. and Yu, Z. (2022) Using Genetic Instruments to Estimate the Causal Effect of Hormonal Reproductive Factors on Osteoarthritis. *Frontiers in Public Health*, **10**, Article ID: 941067. <https://doi.org/10.3389/fpubh.2022.941067>
- [66] Pesce, G., Artaud, F., Roze, E., Degaey, I., Portugal, B., Nguyen, T.T.H., *et al.* (2022) Reproductive Characteristics, Use of Exogenous Hormones and Parkinson Disease in Women from the E3N Study. *Brain*, **146**, 2535-2546. <https://doi.org/10.1093/brain/awac440>
- [67] Jacobs, B.M., Belete, D., Bestwick, J., Blauwendraat, C., Bandres-Ciga, S., Heilbron, K., *et al.* (2020) Parkinson's Disease Determinants, Prediction and Gene-Environment Interactions in the UK Biobank. *Journal of Neurology, Neurosurgery & Psychiatry*, **91**, 1046-1054. <https://doi.org/10.1136/jnnp-2020-323646>
- [68] Kusters, C.D.J., Paul, K.C., Duarte Folle, A., Keener, A.M., Bronstein, J.M., Bertram, L., *et al.* (2021) Increased Menopausal Age Reduces the Risk of Parkinson's Disease: A Mendelian Randomization Approach. *Movement Disorders*, **36**, 2264-2272. <https://doi.org/10.1002/mds.28760>
- [69] Ramagopalan, S.V., Valdar, W., Crisiculi, M., DeLuca, G.C., Dymont, D.A., Orton, S., *et al.* (2009) Age of Puberty and the Risk of Multiple Sclerosis: A Population Based Study. *European Journal of Neurology*, **16**, 342-347. <https://doi.org/10.1111/j.1468-1331.2008.02431.x>
- [70] Nielsen, N.M., Harpsøe, M., Simonsen, J., Stenager, E., Magyari, M., Koch-Henriksen, N., *et al.* (2017) Age at Menarche and Risk of Multiple Sclerosis: A Prospective Cohort Study Based on the Danish National Birth Cohort. *American Journal of Epidemiology*, **185**, 712-719. <https://doi.org/10.1093/aje/kww160>
- [71] Azimi, A., Hanaei, S., Sahraian, M.A., Mohammadifar, M., Ramagopalan, S.V. and Ghajarzadeh, M. (2019) Age at Menarche and Risk of Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis. *BMC Neurology*, **19**, Article

- No. 286. <https://doi.org/10.1186/s12883-019-1473-5>
- [72] Belbasis, L., Bellou, V., Tzoulaki, I. and Evangelou, E. (2020) Early-Life Factors and Risk of Multiple Sclerosis: An MR-EWAS. *Neuroepidemiology*, **54**, 433-445. <https://doi.org/10.1159/000508229>
- [73] Harroud, A., Morris, J.A., Forgetta, V., Mitchell, R., Smith, G.D., Sawcer, S.J., *et al.* (2019) Effect of Age at Puberty on Risk of Multiple Sclerosis. *Neurology*, **92**, e1803-e1810. <https://doi.org/10.1212/wnl.00000000000007325>
- [74] Chen, F., Wen, W., Long, J., Shu, X., Yang, Y., Shu, X., *et al.* (2022) Mendelian Randomization Analyses of 23 Known and Suspected Risk Factors and Biomarkers for Breast Cancer Overall and by Molecular Subtypes. *International Journal of Cancer*, **151**, 372-380. <https://doi.org/10.1002/ijc.34026>
- [75] Richardson, T.G., Sanderson, E., Elsworth, B., Tilling, K. and Davey Smith, G. (2020) Use of Genetic Variation to Separate the Effects of Early and Later Life Adiposity on Disease Risk: Mendelian Randomisation Study. *BMJ*, **369**, m1203. <https://doi.org/10.1136/bmj.m1203>
- [76] Qi, G. and Chatterjee, N. (2019) Mendelian Randomization Analysis Using Mixture Models for Robust and Efficient Estimation of Causal Effects. *Nature Communications*, **10**, Article No. 1941. <https://doi.org/10.1038/s41467-019-09432-2>
- [77] Jia, L., Lv, W., Liang, L., Ma, Y., Ma, X., Zhang, S., *et al.* (2023) The Causal Effect of Reproductive Factors on Breast Cancer: A Two-Sample Mendelian Randomization Study. *Journal of Clinical Medicine*, **12**, Article No. 347. <https://doi.org/10.3390/jcm12010347>
- [78] Escala-Garcia, M., Morra, A., Canisius, S., Chang-Claude, J., Kar, S., Zheng, W., *et al.* (2020) Breast Cancer Risk Factors and Their Effects on Survival: A Mendelian Randomisation Study. *BMC Medicine*, **18**, Article No. 327. <https://doi.org/10.1186/s12916-020-01797-2>
- [79] Zhang, Y., Fang, Y., Xu, N., Tian, L., Min, X., Chen, G., *et al.* (2023) The Causal Effects of Age at Menarche, Age at First Live Birth, and Estradiol Levels on Systemic Lupus Erythematosus: A Two-Sample Mendelian Randomization Analysis. *Lupus*, **32**, 928-935. <https://doi.org/10.1177/09612033231180358>
- [80] Jiang, L., Zhang, R., Musonye, H.A., Zhao, H., He, Y., Zhao, C., *et al.* (2024) Hormonal and Reproductive Factors in Relation to the Risk of Rheumatoid Arthritis in Women: A Prospective Cohort Study with 223526 Participants. *RMD Open*, **10**, e003338. <https://doi.org/10.1136/rmdopen-2023-003338>
- [81] Zhu, J., Niu, Z., Alfredsson, L., Klareskog, L., Padyukov, L. and Jiang, X. (2021) Age at Menarche, Age at Natural Menopause, and Risk of Rheumatoid Arthritis—A Mendelian Randomization Study. *Arthritis Research & Therapy*, **23**, Article No. 108. <https://doi.org/10.1186/s13075-021-02495-x>
- [82] Su, Y., Hu, Y., Xu, Y., Yang, M., Wu, F. and Peng, Y. (2023) Genetic Causal Relationship between Age at Menarche and Benign Oesophageal Neoplasia Identified by a Mendelian Randomization Study. *Frontiers in Endocrinology*, **14**, Article ID: 1113765. <https://doi.org/10.3389/fendo.2023.1113765>
- [83] Gausman, V., Liang, P.S., O'Connell, K., Kantor, E.D. and Du, M. (2022) Evaluation of Early-Life Factors and Early-Onset Colorectal Cancer among Men and Women in the UK Biobank. *Gastroenterology*, **162**, 981-983.e3. <https://doi.org/10.1053/j.gastro.2021.11.023>
- [84] Li, C., Song, B., Wang, Y., Meng, H., Guo, S., Liu, L., *et al.* (2013) Age at Menarche and Risk of Colorectal Cancer: A Meta-Analysis. *PLOS ONE*, **8**, e65645. <https://doi.org/10.1371/journal.pone.0065645>
- [85] Neumeyer, S., Banbury, B.L., Arndt, V., Berndt, S.I., Bezieau, S., Bien, S.A., *et al.* (2018) Mendelian Randomisation Study of Age at Menarche and Age at Menopause and the Risk of Colorectal Cancer. *British Journal of Cancer*, **118**, 1639-1647. <https://doi.org/10.1038/s41416-018-0108-8>
- [86] Zou, X., Wang, L., Wang, S. and Zhang, L. (2023) Mendelian Randomization Study and Meta-Analysis Exploring the Causality of Age at Menarche and the Risk of Intracerebral Hemorrhage and Ischemic Stroke. *CNS Neuroscience & Therapeutics*, **29**, 3043-3052. <https://doi.org/10.1111/cns.14245>
- [87] Wang, Z., Lu, J., Weng, W. and Zhang, J. (2023) Women's Reproductive Traits and Cerebral Small-Vessel Disease: A Two-Sample Mendelian Randomization Study. *Frontiers in Neurology*, **14**, Article ID: 1064081. <https://doi.org/10.3389/fneur.2023.1064081>