·综述·

不同性别动脉粥样硬化差异性研究进展

王亚伟 田锋

【摘要】 心脑血管病是病残和病死的主要原因，动脉粥样硬化是其重要病因。绝经前女性动脉粥样硬化发生率明显低于同龄男性，而绝经后女性动脉粥样硬化发生率显著升高甚至超过同龄男性，与雌激素水平密切相关。本文从影像学检查、危险因素、肠道微生物群和血管炎症反应对动脉粥样硬化影响等方面综述动脉粥样硬化的性别差异，为动脉粥样硬化的精准医疗提供依据。

【关键词】 动脉粥样硬化； 性别因素； 磁共振成像； 危险因素； 胃肠道微生物组； 炎症； 综述

Research progress on the difference of atherosclerosis between different sexes

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【Abstract】 Cardiovascular and cerebrovascular diseases are the main causes of disability and death, and atherosclerosis is an important cause. The incidence of atherosclerosis in premenopausal women is significantly lower than that in men of the same age, while the incidence of atherosclerosis in postmenopausal women is significantly higher than that in men of the same age, which is closely related to estrogen levels. In this paper, sex differences in atherosclerosis were reviewed from the aspects of imaging examination, risk factors, intestinal microbiome and vascular inflammatory effects on atherosclerosis, to provide evidence for precision medical treatment of atherosclerosis.

【Key words】 Atherosclerosis; Sex factors; Magnetic resonance imaging; Risk factors; Gastrointestinal microbiome; Inflammation; Review

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心脑血管病是全球死亡的主要原因，动脉粥样硬化是其主要危险因素。根据世界卫生组织数据显示，2019年逾1800万人死于心脑血管病，包括960万男性和890万女性[1-2]。值得注意的是，更多男性死于动脉粥样硬化性心脑血管病，平均发病年龄40～60岁，较女性早7～10年[3]，女性则通常于绝经后发病。动脉粥样硬化系血管内皮细胞激活引发的一系列事件如脂质沉积、纤维增生和钙质沉着，进而引发血管狭窄和炎症通路激活，最终导致心脑血管病。因此，预防动脉粥样硬化对预防与治疗心脑血管病具有重要意义。2006-2018年发表的动脉粥样硬化和心脑血管病相关动物实验中，18.8%的研究未报道动物性别，其余实验中仅24.1%同时对雄性和雌性动物进行研究[4]。鉴于此，本文拟从动脉粥样硬化影像学检查、危险因素及肠道微生物群和血管炎症反应对动脉粥样硬化影响等方面综述动脉粥样硬化的性别差异。

一、影像学检查的性别差异

动脉粥样硬化性病变早期通常无症状。急性脑血管病与血栓形成和动脉粥样硬化斑块破裂相关，而与颈动脉狭窄程度无明显关联性[5-6]。斑块内出血（IPH）和富脂坏死核心（LRNC）可增加斑块易损性[7]，二者在男性中更常见[8]。

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1.颈动脉超声 研究显示,动脉粥样硬化早期通过颈动脉超声评估颈动脉内-中膜厚度(IMT)和颈动脉斑块是缺血性卒中的重要预测因素[9]。无论是青少年还是中年人群,男性IMT厚度均明显高于同龄女性[10-11],且随年龄增长,男性IMT厚度每年增加约0.007毫米[12]。测量结果可能受血管管径的影响,校正管径因素后,IMT的性别差异仍存在[13]。基于巴西健康成人进行的纵向研究显示,无论是按照种族分层还是无传统心脑血管危险因素的低风险个体,男性IMT厚度均高于女性[14]。我国一项针对45岁以上且无脑卒中病史的农村居民的流行病学调查显示,男性平均IMT和颈动脉斑块发生率均高于女性,且随年龄增长而增加[15]。

2.MRI MRI对脑血管的成像优于超声,MR血管壁成像可清晰显示颈动脉斑块负荷、成分和表面状况[16]。研究显示,无论是男性还是女性,颈动脉狭窄程度和斑块体积均随年龄增长而增加,女性颈动脉狭窄程度较男性更严重、男性颈动脉斑块体积则较女性更大;而在狭窄程度相同情况下,女性发生颈动脉斑块的相对风险低于男性,因此,男性颈动脉斑块的负荷更严重[8]。国内一项MR血管壁成像评估近期发生缺血性卒中或短暂性脑缺血发作(TIA)患者颈动脉斑块易损性性别差异的研究显示,症状性颈动脉狭窄患者中,男性颈动脉管径较大,斑块内出血和富脂坏死核心发生率较高,但斑块负荷与女性相似;而无症状性颈动脉狭窄患者中,男性颈动脉斑块易损性更明显,表现为纤维帽破裂和更大的富脂坏死核心[17]。荷兰伊拉斯姆斯大学医学中心针对颈动脉斑块成分性别差异的研究亦得出相似结论[18]。

二、危险因素的性别差异

1.高血压 高血压是动脉粥样硬化的重要危险因素,颅内动脉粥样硬化则是缺血性卒中的主要病因[19]。首都医科大学附属北京朝阳医院与美国西达斯西奈医学中心共同参与一项前瞻性研究,纳入2015年10月至2021年3月合并高血压的颅内动脉粥样硬化性急性缺血性卒中患者,并行MR血管壁成像,结果显示,高血压与动脉粥样硬化发生率呈正相关关系,且高血压对男性动脉粥样硬化的负荷明显高于女性,但随年龄增长,男性和女性血压均升高,尤其是女性绝经后高血压发生率急剧增加,此时女性动脉粥样硬化的负荷高于男性,推测与女性绝经前雌激素的保护作用有关[20]。研究显示,内源性雌激素可以抑制绝经前女性血管内皮细胞增殖、炎症和血管收缩,与女性血压降低有关[21]。与绝经前女性相比,同龄患卵巢激素缺乏症(如绝经前卵巢早衰或行卵巢切除术)和绝经后女性高血压患病率增加[22]。雌激素主要通过雌激素受体(ER)和肾素-血管紧张素系统(RAS)介导血管扩张,调节血压[23-24]。动物模型显示,卵巢切除小鼠脑缺血急性期予以雌激素受体激动剂可以有效改善脑缺血,减少梗死灶面积[25];正常雌性大鼠血管紧张素Ⅱ(AngⅡ)水平低于卵巢切除的雌性大鼠,推测与雌激素抑制肾素和血管紧张素转换酶(ACE)活性有关[26]。临床研究显示,接受雌激素替代治疗的绝经后女性血浆肾素水平低于未接受雌激素治疗的绝经后女性[24]。

2.高胆固醇血症 血清总胆固醇升高是动脉粥样硬化的重要危险因素。绝经前女性高密度脂蛋白胆固醇(HDL-C)水平高于同龄男性,绝经后女性低密度脂蛋白胆固醇(LDL-C)水平高于绝经前女性和同龄男性[27-28],而卵巢切除女性的LDL-C水平升高,表明雌激素与LDL-C水平呈负相关[29]。雌激素调节胆固醇代谢的机制研究显示,雌激素通过上调肝脏低密度脂蛋白受体(LDLR)、下调前蛋白转化酶枯草杆菌蛋白酶Kexin9型和肝脂酶以调节甘油三酯和LDL-C的代谢[30]。动物模型显示,G蛋白耦联受体(*GPER*)基因敲除小鼠总胆固醇水平升高[31]。临床研究显示,携带*GPER* P16L低功能基因变异的人群LDL-C水平升高,尤以女性显著[32]。

3.肥胖 肥胖是高血压、高脂血症和2型糖尿病的常见危险因素,亦是动脉粥样硬化的独立危险因素[33-34]。既往40余年,全球肥胖率显著增加,自1975年的不足1%增至2016年的6%~8%,儿童肥胖率自3%增至11%,同期女性肥胖率自6%增至15%[35]。目前全球有超6亿成年肥胖患者[体重指数(BMI)≥30 kg/m^2],占全部成人的1/3[36]。体重指数与冠心病之间的关联性无明显性别差异,而男性体重指数增加相关脑卒中风险则高于女性[37-38]。一项前瞻性研究显示,体重指数每增加5 kg/m^2,女性患冠心病风险增加1.35倍(95%CI:1.280~1.430)、男性增加1.42倍(95%CI:1.350~1.480),二者无明显差异(P=0.200);女性患脑卒中风险增加1.30倍(95%CI:1.190~1.420)、男性增加1.50倍(95%CI:1.380~1.650),男性高于女性(P=0.020)[39]。与女性易囤积皮下脂肪相比,男性易沉积内脏脂肪,更

易导致动脉粥样硬化，增加心脑血管病风险[40]；亦有研究显示，肥胖仅是男性动脉粥样硬化斑块易损的独立危险因素，特别是70岁以下男性[41]，而对于女性，肥胖对动脉粥样硬化斑块影响并不显著[42]。

4.吸烟　吸烟是动脉粥样硬化的主要危险因素。2016年，全球共有710万人死于吸烟[43]。截至2020年，男性吸烟率达26%、女性为5%[44]。尽管男性吸烟者多于女性，但吸烟对女性心脑血管系统的损害更严重[45]，女性吸烟者患冠心病的风险较男性高25%[46]。吸烟可以导致血管内皮细胞损伤和血液循环中一氧化碳水平升高，女性吸烟通过升高血浆同型半胱氨酸（Hcy）和不对称二甲基精氨酸（ADMA）水平以影响血管内皮细胞功能，而男性吸烟仅升高血浆同型半胱氨酸水平且显著低于女性，吸烟仅增加女性血小板计数和单核细胞计数[47]。由于血管内皮功能和细胞计数增加的性别差异是心脑血管病的危险因素[48]，因此认为，吸烟对女性的危害大于男性[39]。

三、肠道微生物群对动脉粥样硬化影响的性别差异

越来越多的研究表明，肠道微生物群与动脉粥样硬化和心脑血管病的发生密切相关[49]，且肠道微生物群存在性别差异[50]。人类肠道微生物群由数万亿个共生生物组成，这些生物在胃肠道具有代谢功能，可生成具有生物活性的微生物代谢物，在机体营养、代谢和免疫功能中发挥重要作用[51]。肠道微生物群参与动脉粥样硬化发生机制的直接证据为氧化三甲胺（TMAO），这是一种肠道微生物群依赖性血浆代谢物，与心脑血管事件增加有关[52]。TMAO由三甲胺（TMA）氧化生成，后者由肠道微生物群代谢物中的胆碱和肉碱所合成，再经门静脉系统循环转移至血液中，在肝脏经含黄素单氧化酶3（FMO3）氧化生成TMAO[53]。TMAO可以增加血管壁炎症反应，抑制胆固醇逆向转运，促进胆固醇在血管内膜积聚，进而调节肝脏、肠道和动脉壁的胆固醇代谢[54]；TMAO水平升高触发促炎因子表达和白细胞募集，诱导血管炎症反应，加速动脉粥样硬化[55]。动物实验显示，FMO3受性激素的调节，睾丸切除的雄性小鼠FMO3 mRNA和TMAO水平分别升高100和7倍[56]；卵巢切除的雌性小鼠补充雌激素后，FMO3水平升高幅度较小，故认为雄激素是肝脏FMO3表达存在性别差异的主要因素[57]。此外，肠道微生物介导的高血压、高脂血症、肥胖和葡萄糖调节受损等心脑血管病危险因素分子机制也存在性别差异[50]。

四、血管炎症反应对动脉粥样硬化影响的性别差异

血管炎症反应是导致动脉粥样硬化的关键环节，血管细胞（血管内皮细胞和血管平滑肌细胞）、免疫细胞为发生机制中的关键细胞。

1.血管细胞　（1）血管内皮细胞：血管炎症反应早期，低密度脂蛋白（LDL）进入血管内皮细胞间隙并沉积和迁移[58]。过量活性氧（ROS）与抗氧化剂的不平衡导致LDL氧化修饰，形成氧化修饰低密度脂蛋白（ox-LDL）[59]，经氧化低密度脂蛋白受体1（LOX-1）刺激血管内皮细胞和血管平滑肌细胞分泌单核细胞趋化蛋白-1（MCP-1）、巨噬细胞集落刺激因子（M-CSF）等趋化因子，以促进单核细胞、T淋巴细胞和B淋巴细胞的招募[60-61]。此外，ox-LDL诱导的血管内皮细胞LOX-1激活经信号转导通路上调细胞间黏附分子-1（ICAM-1）和血管细胞黏附分子-1（VCAM-1）表达，促进单核细胞粘附于血管内皮细胞[62-63]，发挥促炎症反应作用。血管内皮细胞中雌二醇可下调脂多糖或磷脂酰胆碱介导的ICAM-1和VCAM-1表达以及白细胞介素-1（IL-1）诱导的E选择素、ICAM-1和VCAM-1表达，发挥抗炎症反应作用[64]；而雄激素衍生物二氢睾酮通过诱导血管内皮细胞VCAM-1表达，促进单核细胞与血管内皮细胞粘附，发挥促炎症反应作用[65]。性别可影响血管内皮细胞功能，一项全球性调查研究显示，健康女性的血管内皮细胞功能优于男性，内皮舒血管因子（EDRF）水平亦高于男性[66]；肥胖和糖尿病可显著降低男性血管内皮细胞功能[67]。此外，绝经后女性血管内皮细胞功能降低[68]，体外予以雌激素后一氧化氮（NO）水平升高[69]，表明雌激素对调节血管扩张具有重要意义[70]。（2）血管平滑肌细胞：血管平滑肌细胞和细胞外基质（ECM）构成的血管壁中间层在维持血管结构和功能方面扮演重要角色[71]。血管平滑肌细胞转化为巨噬细胞吞噬脂质以形成平滑肌源性泡沫细胞[72]，后者增生迁移形成纤维帽，最终形成纤维斑块，导致动脉粥样硬化[73]。动物实验显示，雄性大鼠主动脉平滑肌细胞生长和迁移明显快于雌性大鼠[74]，究其原因，雌激素可减弱主动脉平滑肌细胞定向迁移和收缩能力[75]。目前关于性别对人类血管平滑肌细胞影响的研究相对较少。雌激素受体（ERα和ERβ）、孕激素受体（PR）和雄激

素受体(AR)表达于血管内皮细胞、血管平滑肌细胞和免疫细胞[76],其中ERβ主要表达于女性冠状动脉平滑肌细胞[77]。雌激素对男性和女性主动脉平滑肌细胞具有抗增殖作用[78],通过抑制AngⅡ介导血管平滑肌细胞舒张[79]。体外研究显示,雌激素和孕激素可下调主动脉平滑肌细胞胶原沉积,睾酮可上调基质金属蛋白酶(MMPs)表达[80]。血管平滑肌细胞在炎性因子作用下可产生黏附分子(ICAM-1、VCAM-1)和趋化因子,雌激素参与这一过程[81-82],通过ERβ依赖性信号转导通路抑制肿瘤坏死因子-α(TNF-α)介导的主动脉平滑肌细胞ICAM-1和VCAM-1[83]以及中性粒细胞和单核细胞选择性趋化因子和MCP-1的生成[84]。由此可见,雌激素在血管平滑肌细胞中发挥抗炎症反应和抗增殖作用,而雄激素对血管平滑肌细胞的影响尚待进一步研究。

2.免疫细胞　多项研究业已证实,性激素对动脉粥样硬化相关单核细胞/巨噬细胞和T淋巴细胞等免疫细胞具有免疫调节作用[85]。(1)单核细胞/巨噬细胞:动脉粥样硬化脂纹期,单核细胞经M-CSF分化为两种表型,即炎性M1型和调节性M2型巨噬细胞[86],其中M1型巨噬细胞通过分泌促炎因子如IL-12、IL-23、IL-6、IL-1和TNF-α以促进炎症反应的发生[87],M2型巨噬细胞通过分解细胞碎片和释放抗炎因子IL-10以调节炎症反应[88]。ox-LDL与巨噬细胞结合后被其摄取,并形成巨噬细胞源性泡沫细胞[89],诱发炎症反应。然而,单核细胞/巨噬细胞如何在性激素作用下发挥抗炎症反应或促炎症反应作用?以及如何解释绝经前后女性动脉粥样硬化的差异?既往研究显示,雌二醇对免疫细胞具有性别、剂量和时间依赖性调节作用[90],低剂量雌二醇可促进促炎因子TNF-α的生成,高剂量雌二醇则抑制其生成[83];同时,在外周血单个核细胞(PBMC)中,高剂量雌二醇可促进辅助性T细胞1(Th1)向Th2细胞转化[91]。动脉粥样硬化小鼠模型显示,雌二醇可抑制活化巨噬细胞MCP-1表达,表明在动脉粥样硬化性病变中雌二醇具有阻止巨噬细胞聚积的作用[92],提示激素替代疗法可降低绝经后女性MCP-1表达[93]。家兔模型亦观察到类似现象,正常喂养情况下,卵巢切除的雌性家兔降主动脉MCP-1 mRNA水平高于正常雌性家兔;高胆固醇饮食喂养6周后,卵巢切除的家兔降主动脉MCP-1 mRNA水平升高,但这种升高随着补充生理剂量的雌激素而消除[94]。因此推测,男性和雄性动物可能更易通过MCP-1诱发炎症反应[95]。雌二醇还可抑制脂多糖诱导的小鼠巨噬细胞TNF-α和IL-6生成[96],支持二者活性增强与绝经期卵巢功能减退相关的结论[83]。此外,雌激素以ERα依赖性方式促进M2型巨噬细胞极化[97],因此推测,绝经前女性巨噬细胞ERα水平较高与动脉粥样硬化发生率较低相关。体外研究显示,睾酮可促进单核细胞与血管内皮细胞的粘附[98],进而上调男性血管内皮细胞VCAM-1表达,而对女性无明显影响[99]。(2)T淋巴细胞:T淋巴细胞与巨噬细胞共同通过趋化因子和黏附分子聚集至血管壁[100],通过对ox-LDL产生抗原特异性免疫反应而激活[101],随后分化为Th1、Th2和Th17细胞,主要为Th1细胞[59]。Th1细胞分泌大量促炎因子如IL-2、IL-3、TNF-α和干扰素-γ(IFN-γ),激活巨噬细胞、血管内皮细胞和血管平滑肌细胞,加重局部炎症反应[102]。其中,IFN-γ通过激活核转录因子-κB(NF-κB)、信号转导与转录激活因子3(STAT3)上调血管平滑肌细胞分泌型磷脂酶A2(sPLA2)表达,诱导促炎因子生成[103],降低斑块稳定性。Th2细胞分泌抗炎因子如IL-4、IL-10和IL-13,可阻止动脉粥样硬化的发生[104]。Th17细胞分泌促炎因子如IL-17,可促进动脉粥样硬化的发生[105]。外周血单个核细胞中高剂量雌二醇可促使Th1细胞转化为Th2细胞,发挥抗炎症反应作用,而绝经后女性动脉粥样硬化发生率明显升高,提示动脉粥样硬化与雌激素水平密切相关[106]。另一方面,雄激素也被证实具有广泛抗炎症反应作用[107],但其免疫调节作用并未在动脉粥样硬化环境中获得,因此尚待进一步探究动脉粥样硬化性病变患者雄激素的免疫调节作用。

目前,心脑血管病仍是病残和病死的主要原因,动脉粥样硬化在其中扮演重要角色。绝经前女性动脉粥样硬化发生率明显低于同龄男性,而绝经后女性显著高于同龄男性,提示动脉粥样硬化的发生与雌激素的调节密切相关。本文综述动脉粥样硬化影像学检查、危险因素、肠道微生物群和血管炎症反应的性别差异,从而为男性和女性心脑血管病的一级预防以及个体化治疗方案的制定提供依据,从而最大限度改善患者预后,减轻家庭及社会负担。

利益冲突　无

参　考　文　献

[1] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ,

Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study[J]. J Am Coll Cardiol, 2020, 76:2982-3021.

[2] Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action[J]. J Am Coll Cardiol, 2020, 76:2980-2981.

[3] Vakhtangadze T, Singh Tak R, Singh U, Baig MS, Bezsonov E. Gender differences in atherosclerotic vascular disease: from lipids to clinical outcomes[J]. Front Cardiovasc Med, 2021, 8: 707889.

[4] Ramirez FD, Hibbert B. Letter by Ramirez and Hibbert regarding article, "Consideration of sex differences in design and reporting of experimental arterial pathology studies: a statement from the Arteriosclerosis, Thrombosis, and Vascular Biology Council"[J]. Arterioscler Thromb Vasc Biol, 2018, 38: e99-e100.

[5] Spagnoli LG, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS, Piepgras DG, Pistolese R, Ippoliti A, Holmes DR Jr. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke[J]. JAMA, 2004, 292:1845-1852.

[6] Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, Strecker C, Hempel JM, Yuan C, Malik R, Wollenweber FA, Boeckh-Behrens T, Cyran CC, Helck A, Harloff A, Ziemann U, Poli S, Poppert H, Dichgans M, Saam T. Complicated carotid artery plaques as a cause of cryptogenic stroke[J]. J Am Coll Cardiol, 2020, 76:2212-2222.

[7] Ikebe Y, Ishimaru H, Imai H, Abe K, Izumo T, Morofuji Y, Ideguchi R, Morikawa M, Uetani M. Quantitative susceptibility mapping for carotid atherosclerotic plaques: a pilot study[J]. Magn Reson Med Sci, 2020, 19:135-140.

[8] van Dam-Nolen DHK, van Egmond NCM, Dilba K, Nies K, van der Kolk AG, Liem MI, Kooi ME, Hendrikse J, Nederkoorn PJ, Koudstaal PJ, van der Lugt A, Bos D. Sex differences in plaque composition and morphology among symptomatic patients with mild-to-moderate carotid artery stenosis[J]. Stroke, 2022, 53:370-378.

[9] Zyriax BC, Dransfeld K, Windler E. Carotid intima-media thickness and cardiovascular risk factors in healthy volunteers[J]. Ultrasound J, 2021, 13:17.

[10] Böhm B, Hartmann K, Buck M, Oberhoffer R. Sex differences of carotid intima-media thickness in healthy children and adolescents[J]. Atherosclerosis, 2009, 206:458-463.

[11] Abeysuriya V, Perera BPR, Wickremasinghe AR. Regional and demographic variations of carotid artery intima and media thickness (CIMT): a systematic review and meta-analysis[J]. PLoS One, 2022, 17:e0268716.

[12] Bauer M, Möhlenkamp S, Lehmann N, Schmermund A, Roggenbuck U, Moebus S, Stang A, Mann K, Jöckel KH, Erbel R. The effect of age and risk factors on coronary and carotid artery atherosclerotic burden in males: results of the Heinz Nixdorf Recall Study[J]. Atherosclerosis, 2009, 205:595-602.

[13] Juonala M, Kähönen M, Laitinen T, Hutri-Kähönen N, Jokinen E, Taittonen L, Pietikäinen M, Helenius H, Viikari JS, Raitakari OT. Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: the cardiovascular risk in Young Finns Study[J]. Eur Heart J, 2008, 29:1198-1206.

[14] Santos IS, Bittencourt MS, Oliveira IR, Souza AG, Meireles DP, Rundek T, Foppa M, Bezerra DC, Freire CM, Roelke LH, Carrilho S, Benseñor IM, Lotufo PA. Carotid intima-media thickness value distributions in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)[J]. Atherosclerosis, 2014, 237:227-235.

[15] Pan J, Liu J, Wang H, Li W, Du X, Lin Q, Zhang X, Qi D, Tu J, Ning X, Yang Q, Wang J. Association of carotid atherosclerosis with lipid components in asymptomatic low-income Chinese: a population-based cross-sectional study[J]. Front Neuro, 2020, 11:276.

[16] Bos D, Arshi B, van den Bouwhuijsen QJA, Ikram MK, Selwaness M, Vernooij MW, Kavousi M, van der Lugt A. Atherosclerotic carotid plaque composition and incident stroke and coronary events[J]. J Am Coll Cardio, 2021, 77:1426-1435.

[17] Zhang L, Zhu L, Lu M, Zhao X, Li F, Cai J, Yuan C; CARE-Ⅱ Investigators. Comparison of carotid plaque characteristics between men and women using magnetic resonance vessel wall imaging: a Chinese atherosclerosis risk evaluation study[J]. J Magn Reson Imaging, 2021, 54:646-654.

[18] van Dam-Nolen DHK, van Egmond NCM, Koudstaal PJ, van der Lugt A, Bos D. Sex differences in carotid atherosclerosis: a systematic review and meta-analysis[J]. Stroke, 2023, 54:315-326.

[19] Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanas F, Oguz A, Kruger IM, Diaz R, Yusoff K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Khatib R, Rahman O, Zatonska K, Iqbal R, Wei L, Bo H, Rosengren A, Kaur M, Mohan V, Lear SA, Teo KK, Leong D, O'Donnell M, McKee M, Dagenais G. Modifiable risk factors, cardiovascular disease, and mortality in 155, 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study[J]. Lancet, 2020, 395:795-808.

[20] Song JW, Xiao J, Cen SY, Liu X, Wu F, Schlick K, Li D, Yang Q, Song SS, Fan Z. Sex differences in intracranial atherosclerosis in patients with hypertension with acute ischemic stroke[J]. J Am Heart Assoc, 2022, 11:e025579.

[21] Feldman RD. Sex-specific determinants of coronary artery disease and atherosclerotic risk factors: estrogen and beyond[J]. Can J Cardiol, 2020, 36:706-711.

[22] Song JJ, Ma Z, Wang J, Chen LX, Zhong JC. Gender differences in hypertension[J]. J Cardiovasc Transl Res, 2020, 13:47-54.

[23] Ogola BO, Clark GL, Abshire CM, Harris NR, Gentry KL, Gunda SS, Kilanowski-Doroh I, Wong TJ, Visniauskas B, Lawrence DJ, Zimmerman MA, Bayer CL, Groban L, Miller KS, Lindsey SH. Sex and the G protein-coupled estrogen receptor impact vascular stiffness[J]. Hypertension, 2021, 78: e1-e14.

[24] Medina D, Mehay D, Arnold AC. Sex differences in cardiovascular actions of the renin-angiotensin system[J]. Clin Auton Res, 2020, 30:393-408.

[25] Dworatzek E, Mahmoodzadeh S. Targeted basic research to

highlight the role of estrogen and estrogen receptors in the cardiovascular system[J]. Pharmacol Res, 2017, 119:27-35.
[26] Sabbatini AR, Kararigas G. Estrogen-related mechanisms in sex differences of hypertension and target organ damage[J]. Biol Sex Differ, 2020, 11:31.
[27] Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, Erkkola R, Goulis DG, Hirschberg AL, Kiesel L, Lopes P, Pines A, van Trotsenburg M, Lambrinoudaki I, Rees M. Menopause symptom management in women with dyslipidemias: an EMAS clinical guide[J]. Maturitas, 2020, 135:82-88.
[28] Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis[J]. Menopause, 2019, 26:1327-1333.
[29] Buniam J, Chukijrungroat N, Khamphaya T, Weerachayaphorn J, Saengsirisuwan V. Estrogen and voluntary exercise attenuate cardiometabolic syndrome and hepatic steatosis in ovariectomized rats fed a high-fat high-fructose diet[J]. Am J Physiol Endocrinol Metab, 2019, 316:E908-E921.
[30] Jia F, Fei SF, Tong DB, Xue C, Li JJ. Sex difference in circulating PCSK9 and its clinical implications[J]. Front Pharmacol, 2022, 13:953845.
[31] Meyer MR, Fredette NC, Howard TA, Hu C, Ramesh C, Daniel C, Amann K, Arterburn JB, Barton M, Prossnitz ER. Erratum: G protein-coupled estrogen receptor protects from atherosclerosis[J]. Sci Rep, 2015, 5:13510.
[32] Hussain Y, Ding Q, Connelly PW, Brunt JH, Ban MR, McIntyre AD, Huff MW, Gros R, Hegele RA, Feldman RD. G-protein estrogen receptor as a regulator of low-density lipoprotein cholesterol metabolism: cellular and population genetic studies[J]. Arterioscler Thromb Vasc Biol, 2015, 35: 213-221.
[33] Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study[J]. Eur Heart J, 2020, 41:221-226.
[34] Ferreira J, Cunha P, Carneiro A, Vila I, Cunha C, Silva C, Longatto-Filho A, Mesquita A, Cotter J, Correia-Neves M, Mansilha A. Is obesity a risk factor for carotid atherosclerotic disease: opportunistic review[J]? J Cardiovasc Dev Dis, 2022, 9:162.
[35] Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, Mozaffarian D, Swinburn B, Ezzati M. The obesity transition: stages of the global epidemic[J]. Lancet Diabetes Endocrinol, 2019, 7:231-240.
[36] GBD 2015 Obesity Collaborators; Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health effects of overweight and obesity in 195 countries over 25 years[J]. N Engl J Med, 2017, 377:13-27.
[37] Emerging Risk Factors Collaboration; Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies[J]. Lancet, 2011, 377:1085-1095.
[38] Tabara Y, Nakatani E, Miyachi Y. Body mass index, functional disability and all-cause mortality in 330000 older adults: the Shizuoka study[J]. Geriatr Gerontol Int, 2021, 21:1040-1046.
[39] Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention[J]. Atherosclerosis, 2015, 241:211-218.
[40] Varlamov O, Bethea CL, Roberts CT Jr. Sex-specific differences in lipid and glucose metabolism[J]. Front Endocrinol (Lausanne), 2015, 5:241.
[41] Stoberock K, Debus ES, Atlihan G, Daum G, Larena-Avellaneda A, Eifert S, Wipper S. Gender differences in patients with carotid stenosis[J]. Vasa, 2016, 45:11-16.
[42] Rovella V, Anemona L, Cardellini M, Scimeca M, Saggini A, Santeusanio G, Bonanno E, Montanaro M, Legramante IM, Ippoliti A, Di Daniele N, Federici M, Mauriello A. The role of obesity in carotid plaque instability: interaction with age, gender, and cardiovascular risk factors[J]. Cardiovasc Diabetol, 2018, 17:46.
[43] Centner AM, Bhide PG, Salazar G. Nicotine in senescence and atherosclerosis[J]. Cells, 2020, 9:1035.
[44] Thomson NC, Polosa R, Sin DD. Cigarette smoking and asthma[J]. J Allergy Clin Immunol Pract, 2022, 10:2783-2797.
[45] Shi H, Leventhal AM, Wen Q, Ossip DJ, Li D. Sex differences in the association of e-cigarette and cigarette use and dual use with self-reported hypertension incidence in US adults[J]. Nicotine Tob Res, 2023, 25:478-485.
[46] Gallucci G, Tartarone A, Lerose R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation[J]. J Thorac Dis, 2020, 12:3866-3876.
[47] Campesi I, Carru C, Zinellu A, Occhioni S, Sanna M, Palermo M, Tonolo G, Mercuro G, Franconi F. Regular cigarette smoking influences the transsulfuration pathway, endothelial function, and inflammation biomarkers in a sex-gender specific manner in healthy young humans[J]. Am J Transl Res, 2013, 5:497-509.
[48] Bacon SL, Lavoie KL, Arsenault A, Dupuis J, Pilote L, Laurin C, Gordon J, Gautrin D, Vadeboncoeur A. The Research on Endothelial Function in Women and Men at Risk for Cardiovascular Disease (REWARD) study: methodology[J].

BMC Cardiovasc Disord, 2011, 11:50.
[49] Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease[J]. Circ Res, 2020, 127:553-570.
[50] Ahmed S, Spence JD. Sex differences in the intestinal microbiome: interactions with risk factors for atherosclerosis and cardiovascular disease[J]. Biol Sex Differ, 2021, 12:35.
[51] Astudillo AA, Mayrovitz HN. The gut microbiome and cardiovascular disease[J]. Cureus, 2021, 13:e14519.
[52] Zhu Y, Li Q, Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide[J]. APMIS, 2020, 128:353-366.
[53] Simó C, García - Cañas V. Dietary bioactive ingredients to modulate the gut microbiota - derived metabolite TMAO: new opportunities for functional food development[J]. Food Funct, 2020, 11:6745-6776.
[54] Janeiro MH, Ramírez MJ, Milagro FI, Martínez JA, Solas M. Implication of trimethylamine N - oxide (TMAO) in disease: potential biomarker or new therapeutic target[J]. Nutrients, 2018, 10:1398.
[55] Liu X, Shao Y, Tu J, Sun J, Li L, Tao J, Chen J. Trimethylamine - N - oxide - stimulated hepatocyte - derived exosomes promote inflammation and endothelial dysfunction through nuclear factor-kappa B signaling[J]. Ann Transl Med, 2021, 9:1670.
[56] Bennett BJ, de Aguiar Vallim TQ, Wang Z, Shih DM, Meng Y, Gregory J, Allayee H, Lee R, Graham M, Crooke R, Edwards PA, Hazen SL, Lusis AJ. Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation[J]. Cell Metab, 2013, 17:49-60.
[57] Razavi AC, Potts KS, Kelly TN, Bazzano LA. Sex, gut microbiome, and cardiovascular disease risk[J]. Biol Sex Differ, 2019, 10:29.
[58] Mundi S, Massaro M, Scoditti E, Carluccio MA, van Hinsbergh VWM, Iruela - Arispe ML, De Caterina R. Endothelial permeability, LDL deposition, and cardiovascular risk factors: a review[J]. Cardiovasc Res, 2018, 114:35-52.
[59] Nasser SA, Afify EA, Kobeissy F, Hamam B, Eid AH, El-Mas MM. Inflammatory basis of atherosclerosis: modulation by sex hormones[J]. Curr Pharm Des, 2021, 27:2099-2111.
[60] Marchini T, Mitre LS, Wolf D. Inflammatory cell recruitment in cardiovascular disease[J]. Front Cell Dev Biol, 2021, 9: 635527.
[61] Akhmedov A, Sawamura T, Chen CH, Kraler S, Vdovenko D, Lüscher TF. Lectin - like oxidized low - density lipoprotein receptor - 1 (LOX - 1): a crucial driver of atherosclerotic cardiovascular disease[J]. Eur Heart J, 2021, 42:1797-1807.
[62] Sharma T, Romeo F, Mehta JL. LOX - 1: implications in atherosclerosis and myocardial ischemia[J]. EXCLI J, 2022, 21:273-278.
[63] Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Döring Y. Sex - specific and hormone - related differences in vascular remodelling in atherosclerosis[J]. Eur J Clin Invest, 2023, 53:e13885.
[64] Simoncini T, Garibaldi S, Fu XD, Pisaneschi S, Begliuomini S, Baldacci C, Lenzi E, Goglia L, Giretti MS, Genazzani AR. Effects of phytoestrogens derived from red clover on atherogenic adhesion molecules in human endothelial cells[J]. Menopause, 2008, 15:542-550.
[65] Death AK, McGrath KC, Sader MA, Nakhla S, Jessup W, Handelsman DJ, Celermajer DS. Dihydrotestosterone promotes vascular cell adhesion molecule - 1 expression in male human endothelial cells via a nuclear factor - kappa B - dependent pathway[J]. Endocrinology, 2004, 145:1889-1897.
[66] Holder SM, Brislane Á, Dawson EA, Hopkins ND, Hopman MTE, Cable NT, Jones H, Schreuder THA, Sprung VS, Naylor L, Maiorana A, Thompson A, Thijssen DHJ, Green DJ. Relationship between endothelial function and the eliciting shear stress stimulus in women: changes across the lifespan differ to men[J]. J Am Heart Assoc, 2019, 8:e010994.
[67] Steinberg HO, Paradisi G, Cronin J, Crowde K, Hempfling A, Hook G, Baron AD. Type Ⅱ diabetes abrogates sex differences in endothelial function in premenopausal women[J]. Circulation, 2020, 101:2040-2046.
[68] Meng Q, Li Y, Ji T, Chao Y, Li J, Fu Y, Wang S, Chen Q, Chen W, Huang F, Wang Y, Zhang Q, Wang X, Bian H. Estrogen prevent atherosclerosis by attenuating endothelial cell pyroptosis via activation of estrogen receptor α - mediated autophagy[J]. J Adv Res, 2020, 28:149-164.
[69] Best PJ, Berger PB, Miller VM, Lerman A. The effect of estrogen replacement therapy on plasma nitric oxide and endothelin - 1 levels in postmenopausal women[J]. Ann Intern Med, 1998, 128:285-288.
[70] Kuczmarski AV, Shoemaker LN, Hobson JC, Edwards DG, Wenner MM. Altered endothelial ETB receptor expression in postmenopausal women[J]. Am J Physiol Heart Circ Physiol, 2020, 319:H242-H247.
[71] Rzucidlo EM, Martin KA, Powell RJ. Regulation of vascular smooth muscle cell differentiation[J]. J Vasc Surg, 2007, 45 Suppl A:A25-A32.
[72] Miao G, Zhao X, Chan SL, Zhang L, Li Y, Zhang Y, Zhang L, Wang B. Vascular smooth muscle cell c-Fos is critical for foam cell formation and atherosclerosis[J]. Metabolism, 2022, 132: 155213.
[73] Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease[J]. Int J Mol Sci, 2022, 23:12906.
[74] Bacáková L, Kunes J. Gender differences in growth of vascular smooth muscle cells isolated from hypertensive and normotensive rats[J]. Clin Exp Hypertens, 2000, 22:33-44.
[75] Straface E, Vona R, Gambardella L, Ascione B, Marino M, Bulzomi P, Canu S, Coinu R, Rosano G, Malorni W, Franconi F. Cell sex determines anoikis resistance in vascular smooth muscle cells[J]. FEBS Lett, 2009, 583:3448-3454.
[76] Fairweather D. Sex differences in inflammation during atherosclerosis[J]. Clin Med Insights Cardiol, 2015, 8(Suppl 3): 49-59.
[77] Hodges YK, Tung L, Yan XD, Graham JD, Horwitz KB, Horwitz LD. Estrogen receptors alpha and beta: prevalence of estrogen receptor beta mRNA in human vascular smooth muscle and transcriptional effects[J]. Circulation, 2000, 101: 1792-1798.
[78] Xia X, Zhou C, He X, Liu C, Wang G, Sun X. The relationship between estrogen - induced phenotypic transformation and proliferation of vascular smooth muscle and hypertensive intracerebral hemorrhage[J]. Ann Transl Med, 2020, 8:762.
[79] Shuang T, Fu M, Yang G, Huang Y, Qian Z, Wu L, Wang R. Interaction among estrogen, IGF-1, and H2S on smooth muscle cell proliferation[J]. J Endocrinol, 2021, 248:17-30.
[80] Natoli AK, Medley TL, Ahimastos AA, Drew BG, Thearle DJ, Dilley RJ, Kingwell BA. Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloproteinase expression[J]. Hypertension, 2005, 46:1129-1134.
[81] Hartman RJG, Owsiany K, Ma L, Koplev S, Hao K, Slenders L, Civelek M, Mokry M, Kovacic JC, Pasterkamp G, Owens G, Björkegren JLM, den Ruijter HM. Sex-stratified gene regulatory networks reveal female key driver genes of atherosclerosis

involved in smooth muscle cell phenotype switching [J]. Circulation, 2021, 143:713-726.
[82] Zhang ML, Zhang MN, Wang WL, Chen H, Wang X, Li X, Li L, Tong F. 17β-estradiol reduces NF-κB expression induced by increased crosstalk between KLF5 and ERα in murine vascular smooth muscle cells[J]. Biochem Biophys Res Commun, 2022, 625:181-187.
[83] Evans BR, Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Döring Y. Inflammatory mediators in atherosclerotic vascular remodeling [J]. Front Cardiovasc Med, 2022, 9:868934.
[84] Xing D, Feng W, Miller AP, Weathington NM, Chen YF, Novak L, Blalock JE, Oparil S. Estrogen modulates TNF-alpha-induced inflammatory responses in rat aortic smooth muscle cells through estrogen receptor-beta activation [J]. Am J Physiol Heart Circ Physiol, 2007, 292:H2607-H2612.
[85] Bhatia A, Sekhon HK, Kaur G. Sex hormones and immune dimorphism[J]. Scientific World Journal, 2014, 2014:159150.
[86] Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, Seifi B, Mohammadi A, Afshari JT, Sahebkar A. Macrophage plasticity, polarization, and function in health and disease[J]. J Cell Physiol, 2018, 233: 6425-6440.
[87] Bernardi S, Toffoli B, Tonon F, Francica M, Campagnolo E, Ferretti T, Comar S, Giudici F, Stenner E, Fabris B. Sex differences in proatherogenic cytokine levels[J]. Int J Mol Sci, 2020, 21:3861.
[88] Butcher MJ, Galkina EV. Phenotypic and functional heterogeneity of macrophages and dendritic cell subsets in the healthy and atherosclerosis-prone aorta [J]. Front Physiol, 2012, 3:44.
[89] Duan Y, Zhang X, Zhang X, Lin J, Shu X, Man W, Jiang M, Zhang Y, Wu D, Zhao Z, Sun D. Inhibition of macrophage-derived foam cells by Adipsin attenuates progression of atherosclerosis[J]. Biochim Biophys Acta Mol Basis Dis, 2022, 1868:166533.
[90] Gilmore W, Weiner LP, Correale J. Effect of estradiol on cytokine secretion by proteolipid protein-specific T cell clones isolated from multiple sclerosis patients and normal control subjects[J]. J Immunol, 1997, 158:446-451.
[91] Matalka KZ. The effect of estradiol, but not progesterone, on the production of cytokines in stimulated whole blood, is concentration-dependent[J]. Neuro Endocrinol Lett, 2003, 24: 185-191.
[92] Dama A, Baggio C, Boscaro C, Albiero M, Cignarella A. Estrogen receptor functions and pathways at the vascular immune interface[J]. Int J Mol Sci, 2021, 22:4254.
[93] Störk S, Baumann K, von Schacky C, Angerer P. The effect of 17 beta-estradiol on MCP-1 serum levels in postmenopausal women[J]. Cardiovasc Res, 2002, 53:642-649.
[94] Pervin S, Singh R, Rosenfeld ME, Navab M, Chaudhuri G, Nathan L. Estradiol suppresses MCP-1 expression in vivo: implications for atherosclerosis[J]. Arterioscler Thromb Vasc Biol, 1998, 18:1575-1582.
[95] Gosling J, Slaymaker S, Gu L, Tseng S, Zlot CH, Young SG, Rollins BJ, Charo IF. MCP-1 deficiency reduces susceptibility to atherosclerosis in mice that overexpress human apolipoprotein B[J]. J Clin Invest, 1999, 103:773-778.
[96] Deshpande R, Khalili H, Pergolizzi RG, Michael SD, Chang MD. Estradiol down-regulates LPS-induced cytokine production and NFkB activation in murine macrophages[J]. Am J Reprod Immunol, 1997, 38:46-54.
[97] Keselman A, Fang X, White PB, Heller NM. Estrogen signaling contributes to sex differences in macrophage polarization during asthma[J]. J Immunol, 2017, 199: 1573-1583.
[98] Man JJ, Beckman JA, Jaffe IZ. Sex as a biological variable in Atherosclerosis[J]. Circ Res, 2020, 126:1297-1319.
[99] McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1[J]. Circulation, 1999, 99: 2317-2322.
[100] Wolf D, Gerhardt T, Winkels H, Michel NA, Pramod AB, Ghosheh Y, Brunel S, Buscher K, Miller J, McArdle S, Baas L, Kobiyama K, Vassallo M, Ehinger E, Dileepan T, Ali A, Schell M, Mikulski Z, Sidler D, Kimura T, Sheng X, Horstmann H, Hansen S, Mitre LS, Stachon P, Hilgendorf I, Gaddis DE, Hedrick C, Benedict CA, Peters B, Zirlik A, Sette A, Ley K. Pathogenic autoimmunity in atherosclerosis evolves from initially protective apolipoprotein B_{100}-reactive $CD4^+$ T-regulatory cells[J]. Circulation, 2020, 142:1279-1293.
[101] Wolf D, Ley K. Immunity and inflammation in atherosclerosis [J]. Circ Res, 2019, 124:315-327.
[102] Ait-Oufella H, Lavillegrand JR, Tedgui A. Regulatory T cell-enhancing therapies to treat atherosclerosis[J]. Cells, 2021, 10: 723.
[103] Saigusa R, Winkels H, Ley K. T cell subsets and functions in atherosclerosis[J]. Nat Rev Cardiol, 2020, 17:387-401.
[104] Lee S, Bartlett B, Dwivedi G. Adaptive immune responses in human atherosclerosis[J]. Int J Mol Sci, 2020, 21:9322.
[105] Comeau KD, Shokoples BG, Schiffrin EL. Sex differences in the immune system in relation to hypertension and vascular disease[J]. Can J Cardiol, 2022, 38:1828-1843.
[106] Kassi E, Spilioti E, Nasiri-Ansari N, Adamopoulos C, Moutsatsou P, Papapanagiotou A, Siasos G, Tousoulis D, Papavassiliou AG. Vascular Inflammation and atherosclerosis: the role of estrogen receptors[J]. Curr Med Chem, 2015, 22: 2651-2665.
[107] Huang CK, Lee SO, Chang E, Pang H, Chang C. Androgen receptor (AR) in cardiovascular diseases [J]. J Endocrinol, 2016, 229:R1-R16.

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