Sex and Gender Differences in Aortic Disease

Lauren V Huckaby, MD, MS and Bradley G Leshnower, MD

Division of Cardiac Surgery, Emory University, Atlanta, GA

Abstract

Dilatation of the thoracic or abdominal aorta can progress to dissection or rupture with significant associated morbidity and mortality. Aortic disease remains a treatable contributor to mortality in the US and its burden is likely underestimated. Recent clinical studies have uncovered sex and gender distinctions in the epidemiology, pathophysiology, and outcomes of aortic disease. Despite this, there has been little progress in the application of these findings to clinical practice. Improved understanding of the sex-specific mechanisms of aortic disease may inform personalized indications for elective repair and thus reduce the morbidity of aortic catastrophe. The objective of this review is to summarize known clinical and biological sex differences in both thoracic and abdominal aortic disease and highlight promising areas for future investigation.

Keywords

Thoracic aortic disease, abdominal aortic disease, aortic dissection, aortic aneurysm, sex differences

Disclosure: The authors have no conflicts of interest to declare.
Received: December 31, 2022 **Accepted:** July 6, 2023 **Citation:** *US Cardiology Review* 2023;17:e14. **DOI:** https://doi.org/10.15420/usc.2022.39
Correspondence: Bradley G Leshnower, Division of Cardiothoracic Surgery, Emory University School of Medicine, 1365 Clifton Rd, Suite A 2213, Atlanta, GA 30322. E: bleshno@emory.edu

The morbidity and mortality of aortic pathologies remain significant in the current era despite continued progress in understanding and treatment. Aortic aneurysm and dissection accounted for 9,317 deaths in 2020, a rate of 2.8 per 100,000 people, though this has been slowly trending down over the past two decades.[1] Despite this, the true impact of both thoracic and abdominal aortic disease may be underestimated as many of these patients expire without a diagnosis and prior to receiving care. Many of these deaths may be preventable, particularly for abdominal aortic aneurysm (AAA), with multiple large-scale studies demonstrating a mortality benefit from screening of at-risk patients.[2–4] Thus far, exploration of mechanistic factors contributing to both loss of aortic wall integrity and aneurysm formation have mostly considered both sexes together despite consistent clinical data demonstrating sex-specific differences. In some cases, this is limited by the prevalence of the disease, yet the formation of national registries and collaborative working groups has yielded large data sets with robust patient data allowing for exploration of nuances in aortic disease.

This review summarizes the current understanding of sex differences in both thoracic and abdominal aortic disease and highlights critical knowledge deficits, which merit further investigation. Improved understanding of the sexual dimorphism in aortic disease will contribute to tailored care for these patients and underscore the importance of considering sex as a key variable in future basic science, translational, and clinical studies in aortic disease.

When addressing sex differences that pertain to biological sex at birth or other biological factors (including discussion of chromosomes, sex organs, and endogenous hormonal profiles), we have adopted the SAGER guidelines for sex and gender reporting. As such, we will designate sex differences with the terms 'female' and 'male'. When addressing societal impact factors or in studies in which gender was self-reported, we will designate gender differences with the terms 'women' and 'men'. We acknowledge there are data limitations in this review as many historic studies did not ask participants to specify biological sex and self-designated gender.

Epidemiology and Clinical Presentation of Aortic Disease

Thoracic Aortic Disease

Unlike AAA, which is more common in men, the prevalence of thoracic aortic aneurysm (TAA) in patients with a normal (tricuspid) aortic valve appears to be equal between men and women. Population studies from a Minnesota county have demonstrated an equal incidence of TAA between the sexes; this is corroborated in a Swedish study of autopsy subjects.[5–7] Conflicting reports about TAA prevalence being higher in men may be attributed to the inclusion of aortic dissection and rupture cases, which appear be higher among men.[8] A consistent finding in TAA epidemiology has been a later age of presentation, by approximately one decade, in women with TAA compared to men. In the two Minnesota population studies previously described, the authors noted ages of presentation of 65 years and 62.8 years for men compared to 77 years and 75.9 years among women.[5,6] Older age of presentation in women is important to note for diagnosis and management considerations because increased age is associated with both non-operative and operative morbidity and mortality. Etiology of TAA includes both heritable causes, usually with strong familial association and younger age of presentation, as well as degenerative TAA, which occurs at a later age. Sexual dimorphism has also been observed in aneurysm growth rates. In a prospective study of 82 patients with degenerative and heritable TAA, both absolute and indexed aneurysm growth rates were over twofold greater in women compared to men.[9]

Further stratification by etiology determined that aortic growth in women with degenerative TAA was over three-times greater than in men (p=0.0009); this contrasts with women with heritable TAA, who displayed similar growth rates to men.[9] Aortic growth rates are an additional consideration in risk stratification for aortic complications and are, therefore, included in guidelines to guide timing of aortic intervention.

Recent studies on gender-specific epidemiology of aortic dissection suggest that aortic dissection is more common among men, though, as in TAA, women tend to present at a later age. A study from the International Registry of Aortic Dissection (IRAD) database from 2004 found that men comprised 67.9% of enrollees, and that they were significantly younger than their women counterparts (60.3 years versus 66.7 years, p<0.001).[10] A 2022 IRAD study of 2,823 patients with acute type A dissection similarly found an approximately 2:1 ratio between genders (65.6% men), with women presenting later in life (65.4 years versus 58.6 years, p<0.001).[11] A German registry recently published data on 3,380 patients with similar patterns of acute type A dissection being twice as common in men with women presenting at a later age.[12] However, both the IRAD and German registries focus on patients undergoing surgical intervention and thus may not capture the full spectrum of patients with acute aortic dissection. This is particularly critical given that a more advanced age of presentation in women may result in a tendency to non-operative management. It is also important to note that the extent of dissection appears similar across genders, although the imaging findings, such as false lumen thrombosis and intramural hematoma, were significantly different between men and women.[11] Taken together, these findings suggest both sex- and gender-specific mechanisms may contribute not only to aortic wall integrity but also subsequent non-operative and surgical outcomes.

Prior studies have also noted sex and gender differences in inherited aortopathies including patients with a bicuspid aortic valve and those with connective tissue disorders. Both valvular disease and aortopathy display increased prevalence among males with a bicuspid aortic valve in comparison to females.[13,14] A recent epidemiological study of 1,887 bicuspid aortic valve patients from the Netherlands demonstrated a statistically significant difference in aortic dimensions, after adjustment for morphometric properties, at the level of the aortic annulus, the sinus of Valsalva, and the sinotubular junction, with males having larger diameters.[13] There is a paucity of data examining aortic dissection specifically in patients with a bicuspid aortic valve though large-scale studies powered to explore sex differences may further guide indications for prophylactic aortic replacement in these subgroups.

Marfan syndrome, a connective tissue disorder associated with a defect in the fibrillin-1 gene, displays equal gender distribution. However, a population study revealed that men carry a significantly increased risk of aortic events (HR 1.75) and that these events occur at an earlier age than in females (median 36.5 versus 39.2 years).[15] The risk of pregnancy-associated aortic events in patients with Marfan syndrome is also worth noting. Though data remain limited, observations of pregnancy-associated aortic dissection have resulted in consensus guidelines recommending a threshold for surgical intervention at an aortic diameter of 40 mm for women with Marfan syndrome contemplating pregnancy.[16–18] These patients warrant close monitoring and multidisciplinary follow-up as there is additional concern about postpartum and long-term risk of aortic events.

In patients with Ehlers-Danlos syndrome, particularly the vascular subtype resulting from a defect in collagen type III, men demonstrated lower median survival attributable to vascular rupture with men experiencing aortic complications at a mean age of 32.6 years compared to 41 years in women (p<0.01).[19] Other aortopathies, such as Loeys-Dietz syndrome and familial thoracic aortic aneurysm and dissection, are rare, but appear to be more common in men. Turner syndrome, a genetic disorder affecting females exclusively and characterized by complete or partial loss of one X chromosome (XO), is associated with a bicuspid aortic valve and carries a risk of acute aortic dissection that is almost 100-fold higher than in the general population.[20] Greater differentiation of sex-specific characteristics will likely result from multi-institutional, longitudinal data collection, which has the potential to provide key findings to guide management, reduce disease burden, and increase lifespan for both sexes in these younger patient populations.

Abdominal Aortic Disease

Variations in the cutoff diameter for diagnosis of AAA in the literature have led to inconsistent reporting of the prevalence of the disease overall. Despite this, multiple studies have confirmed the greater prevalence of AAA among men. In one study of patients screened regardless of risk, 4.6% of men had an AAA >3 cm compared to only 1.2% of women.[21] Following adjustment, the odds ratio for AAA in men was 3.24.[21] These ratios correlating male gender and the prevalence of AAA have been corroborated in other studies.[22–24] Similar gender differences, namely predominance among men, are noted in epidemiological studies of patients with ruptured AAA.[25,26] Older age and current or prior smoking have been associated with AAA across genders.[27] Similar to TAA, women are older at diagnosis with AAA. Current US Preventive Task Force (USPTF) guidelines recommend ultrasound screening only for men and particularly for men who have smoked.[2,28] The 2022 AHA/ACC guidelines for aortic disease suggest that screening for women ≥65 years of age who have ever smoked is reasonable.[28] The incorporation of gender into AAA management guidelines clearly reflects the abundance of evidence confirming the gender dimorphism of AAA.

AAA growth rates also appear to differ between men and women. Mofidi et al. examined expansion rates in more than 1,200 patients and found median annular growth rates of 3.67 mm/year in women compared to 2.03 mm/year in men, with gender independently predicting faster growth among women.[29] This dichotomy was particularly evident for aneurysms ≥60 mm.[29] Furthermore, increased rates of expansion have also been correlated with elevated rupture risk.[30] The addition of 3D modeling and longitudinal monitoring of changes in aortic shape, and not simply orthogonal diameter, may provide further insight into developing rupture risk.[31,32] With the higher mean annular growth rates, particularly at greater diameters, women may benefit from more frequent surveillance of their aneurysms.

Though there are clear data demonstrating a greater prevalence of AAA among men compared to women, there is some debate about the relative risk of rupture across genders.[33–35] In one study comparing aneurysms 5–5.9 cm, rupture risk was 0.01% per year in men and 0.15% in women, with a similar pattern holding for aneurysms >6 cm.[30] Others have astutely explored relative body size in relation to rupture risk with findings that an indexed aneurysm diameter was more predictive than diameter alone for determination of rupture risk among women.[36] In men, diameter alone was most predictive of rupture.[36] These gender differences are important to keep in mind in the development of screening guidelines, particularly if there is concern about higher morbidity associated with AAA in women despite the lower prevalence. Nevertheless, the lower prevalence of AAA in women has led to the underrepresentation of women in some screening trials, further contributing to the lag in understanding of AAA in women.[37]

Pathophysiology

Thoracic Aortic Disease

Current clinical knowledge deficits in thoracic aortic disease center largely around the inability to predict TAA formation, progression, and risk of aortic catastrophe. Guidelines dictate prophylactic aortic replacement at a threshold diameter, dependent upon TAA etiology, yet in one study, 59% of patients experiencing dissection fell below the diameter cut-off.[38] From a biological standpoint, much remains to be explored in the physiology and pathophysiology among the components of the aortic wall layers, including relevant cell types, the extracellular matrix, and local mediators.

One hallmark feature of the classic description of cystic medial degeneration observed in the pathologic evaluation of TAA is that of smooth muscle cell (SMC) apoptosis. As the key effector cells in the aortic media and primary mediators of extracellular matrix regulation, aortic SMCs play a vital role in aortic wall homeostasis; thus, regulation of cell turnover, differentiation, phenotypic switching, and proliferation may all contribute to pathogenesis. Clinical and basic science studies have associated TAA development in females with menopause, suggesting a potential protective role of sex hormones in aneurysm formation.[39–41] Control of SMC turnover may be at least partially explained by the effects of estrogen on SMC proliferation. SMC proliferation and migration have been shown to be inhibited by physiologically relevant concentrations of 17β-estradiol, an effect that was reversed by treatment with an estrogen receptor inhibitor.[42] Aside from the aortic media, cells in the aortic endothelium are also thought to contribute to TAA pathogenesis. Nitric oxide (NO), a potent vasodilator synthesized by NO synthase, promotes vasoprotection and may inhibit atherosclerosis.[43] Treatment of aortic endothelial cells with estrogen increased NO production through increased endothelial nitric oxide synthase (eNOS) expression; treatment with testosterone, in contrast, had no effect.[44] Estrogen-regulated eNOS expression has also been corroborated in an animal model.[45] Testosterone, on the other hand, has been shown to promote oxidative stress *in vitro* and may mitigate some of the protective effects of estrogens in vascular cells.[46,47] Despite these findings, there is a paucity of data on the influence of sex in other mechanisms implicated in thoracic aortic disease including transforming growth factor (TGF)-β signaling, extracellular matrix production, and mechanosensing, among others.

Abdominal Aortic Disease

Though both TAA and AAA are characterized by structural deterioration of the aortic wall resulting in dilatation, there are distinct pathophysiological processes that play a role in AAA disease but are not as prominent in TAA disease. In addition to oxidative stress, extracellular matrix degeneration, and smooth muscle cell changes that occur in TAA, inflammation is a key process in AAA pathophysiology.[48] Additionally, smoking is a major risk factor for AAA formation but appears to be less influential in TAA. The association of AAA with other aneurysms, such as popliteal aneurysms, also suggests global changes in vascular physiology.[24] Despite the strong clinical association between smoking and AAA, which is not prominent in TAA, the pathogenetic mechanism linking the two entities remains elusive. Furthermore, the influence of smoking on AAA formation appears to be stronger in men than in women. There are some data to suggest, however, that smoking induces changes in extracellular matrix production and degradation and may impact cellular responses to oxidative stress.[24] Thus, though similarities exist between TAA and AAA, vascular biology studies should always be extrapolated with caution given that the pathophysiology of aneurysmal disease in the aorta varies by region.

Like TAA, a temporal relationship between AAA formation in females and menopause has been observed, potentially suggesting a role for sex hormones in AAA pathogenesis. Whereas androgens have been shown to promote inflammation, oxidative stress, and proteolysis in the aortic wall, estrogens appear to exert the opposite effect.[48] These findings are further supported by sex differences in the content and structure of the extracellular matrix in males and females.[48] In particular, female sex steroids when compared to testosterone have been demonstrated to reduce collagen deposition and increase elastin production *in vitro* as well as increase fibrillin-1 deposition.[49] Thus, it appears that not only the presence of male versus female sex hormones but also their physiological variations over time appear to modulate the key pathophysiological steps contributing to aneurysmal dilatation.

In addition to sex hormones, the contribution of genetic factors to aneurysmal disease has been explored. One study compared male and female mice, both with XY chromosomes, and found elevated rates of aneurysm development among female XY mice, thought to be driven by inflammation, extracellular matrix (ECM) degradation, and oxidative stress.[50] AAA pathophysiology is clearly multifactorial; however, it is important to consider the relative roles and nuances of the individual pathways as they relate to biological sex.

Management and Outcomes

Thoracic Aortic Disease

Reports on medical and surgical outcomes of women with acute aortic dissection have varied. Medical management of type A dissection is associated with high mortality, though patient preference may dictate this management course and it is certainly possible that the older age of female patients may play into decision-making for or against surgery. There have also been reports of differences in operative approach to type A dissection, although there are insufficient data to conclude whether this reflects surgeon experience or potential bias in management. It is also important to note that women are frequently underrepresented in many endovascular device trials and thus true understanding of sex-based outcomes may be limited.[37] In a Swedish study of patients with acute aortic dissection, there were no gender differences in rates of open operative management, although men were more likely to undergo thoracic endovascular aortic repair (TEVAR) than women.[51]

Data on postoperative outcomes for thoracic aortic disease are conflicting with one large study reporting no difference in 30-day mortality for descending thoracic aortic aneurysms.[52] Nienaber et al. described higher mortality among women with type A dissection compared to men but no significant difference for type B dissection.[10] More recent studies, however, demonstrate no differences in survival following operative repair of type A dissection between the sexes.[11,53] In a study examining outcomes following TEVAR, however, length of stay, 30-day, and 1-year mortality were significantly increased among women, and gender independently predicted worse outcomes.[54]

Abdominal Aortic Disease

Like TAA, elective repair of AAA is based on diameter thresholds, with features such as rapid growth also contributing to evidence-based indications for repair. Prior to widespread adoption of endovascular aortic repair (EVAR), gender was associated with increased mortality for both elective and ruptured AAA repair as well as increased length of stay among women.[55] The decision for open or endovascular repair is dictated by aneurysm anatomy and operative risk. Interestingly, variations in operative approach are evident between the sexes for both elective and

rupture repair.[25] With the adoption of endovascular approaches for elective AAA repair, the year 2010 marked a shift from a predominantly open approach to an endovascular approach among men in a Canadian study, though rates of open and endovascular repair remained similar among women through 2016.[25] A 2021 study of patients with AAA in the US found that women were 25% less likely to undergo surgery for AAA and, among those undergoing intervention, women were less likely to receive an endovascular compared to an open repair.[56] Both authors do note that the reduced rates of endovascular repair may be attributable to anatomic differences precluding EVAR in women. Nevertheless, it is important to better understand patterns in surgical referral, decision-making, patient preference, and surgical planning among genders to ensure equitable care.

These gender differences in AAA management are particularly critical, given that EVAR has been associated with lower mortality and shorter length of stay and thus may improve outcomes, which have historically been worse among women.[26] Among patients undergoing operative repair for ruptured AAA, one study found that women had a 48% increase in 30-day mortality compared to men, which they attributed to delays in intervention.[57] Interestingly, another investigation found that women displayed worse outcomes than men for elective EVAR though there were no gender differences in open repair or emergency repair using either approach.[58] The increased mortality in women was accompanied by greater blood loss, more frequent ischemic complications, and greater rates of intraoperative arterial rupture or endoleak requiring intervention.[58] Others have found inferior outcomes for both open and endovascular approaches among women undergoing elective AAA repair.[59,60] Further work will be critical to understand whether these disparities are driven by technical factors making aneurysm repair more complicated in women or physiological factors, such as the later age at presentation.

Future Directions

Clinical observations on sex and gender differences in aneurysm disease presentation, management, and outcomes reveal a multitude of areas for further investigation. It is clear that the treatment approach for these patients should incorporate all available data regarding sex and gender differences with respect to the epidemiology, pathophysiology and outcomes of TAA and AAA. It is plausible that future guidelines for TAA will be sex-specific, as in AAA, as more information is obtained about relative dissection risk and the benefit of elective repair. Furthermore, elucidation of specific perioperative complications following elective and emergent repair of aneurysmal disease among genders may guide operative approach and postoperative management to improve mortality. Ultimately, improved understanding of various contributors to aneurysmal degeneration, including sex- and gender-specific data, will inform personalized management and understanding of aortic catastrophe risk. Incorporation of biological sex, as well as self-identified gender, as key variables in clinical, translational, and basic science research studies on aortic disease ensures comprehensive understanding of the disease process and represents an initial step towards mitigating any disparities in treatment. The interplay between sex, genetics, environmental factors, gender-bias among patients and providers, and molecular and cellular pathophysiology is undoubtedly complex. Despite this, significant progress has been made in the past few decades to bridge the knowledge gap. Continued efforts, including multi-institution clinical databases, collaborative studies using translational research, and application of advanced statistical techniques will further delineate the role of sex in TAA and AAA and help to guide clinical practice.

Conclusion

A large body of research has focused on sex and gender differences in AAA; however, less work has been published exploring such differences in TAA. Accountability regarding inclusion of sex as a biological variable in all human studies was recently highlighted in a 2015 National Institutes of Health (NIH) notice, underscoring its importance for all human studies.[61] Additionally, a statement from the Arteriosclerosis Thrombosis Vascular Biology Council has recently issued guidelines specific to cardiovascular disease for experimental design to accurately account for sex in preclinical studies.[62] Given what is known and unknown from a clinical and biological standpoint about sex differences in thoracic and abdominal aortic disease, it is reasonable to question, for example, how the aortic wall biology and pathophysiology of a 60-year-old male relates to that of a 70-year-old female. Echoing the call to include sex and gender as a biological variable in experiments by the NIH, future work with a deliberate attention to and incorporation of sex and gender in experimental design will be necessary to further elucidate key pathogenic mechanisms that may provide insight into potential therapeutic targets. ❑

1. Centers for Disease Control and Prevention. *WONDER Online Databases*. 2023. https://wonder.cdc.gov/ (accessed October 17, 2022).
2. US Preventive Services Task Force. Screening for abdominal aortic aneurysm: US Preventive Services Task Force recommendation statement. *JAMA* 2019;322:2211–8. https://doi.org/10.1001/jama.2019.18928; PMID: 31821437.
3. Ali MU, Fitzpatrick-Lewis D, Miller J, et al. Screening for abdominal aortic aneurysm in asymptomatic adults. *J Vasc Surg* 2016;64:1855–68. https://doi.org/10.1016/j.jvs.2016.05.101; PMID: 27871502.
4. Thompson SG, Ashton HA, Gao L, et al. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. *Br J Surg* 2012;99:1649–56. https://doi.org/10.1002/bjs.8897; PMID: 23034729.
5. Bickerstaff LK, Pairolero PC, Hollier LH, et al. Thoracic aortic aneurysms: a population-based study. *Surgery* 1982;92:1103–8. https://doi.org/10.5555/uri:pii:003960608290174X; PMID: 7147188.
6. Clouse WD, Hallett JW, Schaff HV, et al. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA* 1998;280:1926–9. https://doi.org/10.1001/jama.280.22.1926; PMID: 9851478.
7. Svensjo S, Bengtsson H, Bergqvist D. Thoracic and thoracoabdominal aortic aneurysm and dissection: an investigation based on autopsy. *Br J Surg* 1996;83:68–71. https://doi.org/10.1002/bjs.1800830122; PMID: 8653370.
8. Olsson C, Thelin S, Ståhle E, et al. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14 000 cases from 1987 to 2002. *Circulation* 2006;114:2611–8. https://doi.org/10.1161/CIRCULATIONAHA.106.630400; PMID: 17145990.
9. Cheung K, Boodhwani M, Chan KL, et al. Thoracic aortic aneurysm growth: role of sex and aneurysm etiology. *J Am Heart Assoc* 2017;6. https://doi.org/10.1161/JAHA.116.003792; PMID: 28159818.
10. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation* 2004;109:3014–21. https://doi.org/10.1161/01.CIR.0000130644.78677.2C; PMID: 15197151.
11. Huckaby LV, Sultan I, Trimarchi S, et al. Sex-based aortic dissection outcomes from the international registry of acute aortic dissection. *Ann Thorac Surg* 2022;113:498–505. https://doi.org/10.1016/j.athoracsur.2021.03.100; PMID: 34090668.
12. Rylski B, Georgieva N, Beyersdorf F, et al. Gender-related differences in patients with acute aortic dissection type A. *J Thorac Cardiovasc Surg* 2021;162:528–535.e1. https://doi.org/10.1016/j.jtcvs.2019.11.039; PMID: 31926709.
13. Kong WKF, Regeer MV, Ng ACT, et al. Sex differences in phenotypes of bicuspid aortic valve and aortopathy: insights from a large multicenter, international registry. *Circ Cardiovasc Imaging* 2017;10:e005155. https://doi.org/10.1161/CIRCIMAGING.116.005155; PMID: 28251911.
14. Michelena HI, Suri RM, Katan O, et al. Sex differences and survival in adults with bicuspid aortic valves: verification in 3 contemporary echocardiographic cohorts. *J Am Heart Assoc* 2016;5. https://doi.org/10.1161/JAHA.116.004211; PMID: 27688238.
15. Groth KA, Stochholm K, Hove H, et al. Aortic events in a nationwide Marfan syndrome cohort. *Clin Res Cardiol* 2017;106:105–12. https://doi.org/10.1007/s00392-016-1028-3; PMID: 27550511.
16. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol* 2010;55:27–129:2009. https://doi.org/10.1016/j.jacc.2010.02.015; PMID: 20359588.
17. Rossiter JP, Repke JT, Morales AJ, et al. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995;173:1599–606. http://doi.org/10.1016/0002-9378(95)90655-x; PMID: 7503207.
18. Donnelly RT, Pinto NM, Kocolas I, Yetman AT. The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. *J Am Coll Cardiol* 2012;60:224–9. https://doi.org/10.1016/j.jacc.2012.03.051; PMID: 22789886.
19. Pepin MG, Schwarze U, Rice KM, et al. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genet Med* 2014;16:881–8. https://doi.org/10.1038/gim.2014.72; PMID: 24922459.
20. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation* 2007;116:1663–70. https://doi.org/10.1161/

CIRCULATIONAHA.106.685487; PMID: 17875973.
21. Summers KL, Kerut EK, Sheahan CM, Sheahan MG. Evaluating the prevalence of abdominal aortic aneurysms in the United States through a national screening database. *J Vasc Surg* 2021;73:61–8. https://doi.org/10.1016/j.jvs.2020.03.046; PMID: 32330595.
22. Khashram M, Jones GT, Roake JA. Prevalence of abdominal aortic aneurysm (AAA) in a population undergoing computed tomography colonography in Canterbury, New Zealand. *Eur J Vasc Endovasc Surg* 2015;50:199–205. https://doi.org/10.1016/j.ejvs.2015.04.023; PMID: 26072194.
23. Wanhainen A, Björck M, Boman K, et al. Influence of diagnostic criteria on the prevalence of abdominal aortic aneurysm. *J Vasc Surg* 2001;34:229–35. https://doi.org/10.1067/mva.2001.115801; PMID: 11496273.
24. Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. Pathophysiology and epidemiology of abdominal aortic aneurysms. *Nat Rev Cardiol* 2011;8:92–102. https://doi.org/10.1038/nrcardio.2010.180; PMID: 21079638.
25. Salata K, Hussain MA, de Mestral C, et al. Prevalence of elective and ruptured abdominal aortic aneurysm repairs by age and sex from 2003 to 2016 in Ontario, Canada. *JAMA Netw Open* 2018;1:e185418. https://doi.org/10.1001/jamanetworkopen.2018.5418; PMID: 30646400.
26. Dua A, Kuy S, Lee CJ, et al. Epidemiology of aortic aneurysm repair in the United States from 2000 to 2010. *J Vasc Surg* 2014;59:1512–7. https://doi.org/10.1016/j.jvs.2014.01.007; PMID: 24560865.
27. Jahangir E, Lipworth L, Edwards TL, et al. Smoking, sex, risk factors and abdominal aortic aneurysms: a prospective study of 18 782 persons aged above 65 years in the Southern Community Cohort Study. *J Epidemiol Community Health* 2015;69:481–8. https://doi.org/10.1136/jech; PMID: 25563744.
28. Isselbacher EM, Preventza O, Hamilton Black J, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease. *J Am Coll Cardiol* 2022;80:e223–393. https://doi.org/10.1016/j.jacc.2022.08.004; PMID: 36334952.
29. Mofidi R, Goldie VJ, Kelman J, et al. Influence of sex on expansion rate of abdominal aortic aneurysms. *Br J Surg* 2007;94:310–4. https://doi.org/10.1002/bjs.5573; PMID: 17262754.
30. Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg* 2003;37:280–4. https://doi.org/10.1067/mva.2003.119; PMID: 12563196.
31. Malkawi AH, Hinchliffe RJ, Xu Y, et al. Patient-specific biomechanical profiling in abdominal aortic aneurysm development and rupture. *J Vasc Surg* 2010;52:480–8. https://doi.org/10.1016/j.jvs.2010.01.029; PMID: 20395107.
32. Shum J, Martufi G, di Martino E, et al. Quantitative assessment of abdominal aortic aneurysm geometry. *Ann Biomed Eng* 2011;39:277–86. https://doi.org/10.1007/s10439-010-0175-3; PMID: 20890661.
33. Skibba AA, Evans JR, Hopkins SP, et al. Reconsidering gender relative to risk of rupture in the contemporary management of abdominal aortic aneurysms. *J Vasc Surg* 2015;62:1429–36. https://doi.org/10.1016/j.jvs.2015.07.079; PMID: 26409846.
34. Norman PE, Powell JT. Abdominal aortic aneurysm: the prognosis in women is worse than in men. *Circulation* 2007;115:2865–9. https://doi.org/10.1161/CIRCULATIONAHA.106.671859; PMID: 17548742.
35. Talvitie M, Stenman M, Roy J, et al. Sex differences in rupture risk and mortality in untreated patients with intact abdominal aortic aneurysms. *J Am Heart Assoc* 2021;10:e019592. https://doi.org/10.1161/JAHA.120.019592; PMID: 33619974.
36. Lo RC, Lu B, Fokkema MTM, et al. Relative importance of aneurysm diameter and body size for predicting abdominal aortic aneurysm rupture in men and women. *J Vasc Surg* 2014;59:1209–16. https://doi.org/10.1016/j.jvs.2013.10.104; PMID: 24388278.
37. Marcaccio CL, O'Donnell TFX, Dansey KD, et al. Disparities in reporting and representation by sex, race, and ethnicity in endovascular aortic device trials. *J Vasc Surg* 2022;76:1244–52.e2. https://doi.org/10.1016/j.jvs.2022.05.003; PMID: 35623599.
38. Pape LA, Tsai TT, Isselbacher EM, et al. Aortic diameter ≥5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation* 2007;116:1120–7. https://doi.org/10.1161/CIRCULATIONAHA.107.702720; PMID: 17709637.
39. Schuster V, Eggersmann TK, Eifert S, et al. Ascending aortic disease is associated with earlier menopause and shorter reproductive life span. *J Womens Health (Larchmt)* 2016;25:912–9. https://doi.org/10.1089/jwh.2015.5559; PMID: 27532245.
40. Xing D, Nozell S, Chen YF, et al. Estrogen and mechanisms of vascular protection. *Arterioscler Thromb Vasc Biol* 2009;29:289–95. https://doi.org/10.1161/ATVBAHA.108.182279; PMID: 19221203.
41. Stefanadis C, Tsiamis E, Dernellis J, Toutouzas P. Effect of estrogen on aortic function in postmenopausal women. *Am J Physiol* 1999;276:658–62. https://doi.org/10.1152/ajpheart.1999.276.2.H658; PMID: 9950868.
42. Dubey RK, Jackson EK, Gillespie DG, et al. Clinically used estrogens differentially inhibit human aortic smooth muscle cell growth and mitogen-activated protein kinase activity. *Arterioscler Thromb Vasc Biol* 2000;20:964–72. https://doi.org/10.1161/01.ATV.20.4.964; PMID: 10764660.
43. Li H, Xia N, Förstermann U. Nitric oxide synthesis in vascular physiology and pathophysiology. In: Schmidt M, Liebner S, eds. *Endothelial Signaling in Development and Disease*. New York, NY: Springer, 2015;381–97. https://doi.org/10.1007/978-1-4939-2907-8_16.
44. Hishikawa K, Nakaki T, Marumo T, et al. Up-regulation of nitric oxide synthase by estradiol in human aortic endothelial cells. *FEBS Lett* 1995;360:291–3. https://doi.org/10.1016/0014-5793(95)00124-r; PMID: 7533729.
45. Gonzales RJ, Walker BR, Kanagy NL. 17β-estradiol increases nitric oxide-dependent dilation in rat pulmonary arteries and thoracic aorta. *Am J Physiol Lung Cell Mol Physiol* 2001;280:L555–64. https://doi.org/10.1152/ajplung.2001.280.3.L555; PMID: 11159040.
46. Costa TJ, Ceravolo GS, dos Santos RA, et al. Association of testosterone with estrogen abolishes the beneficial effects of estrogen treatment by increasing ROS generation in aorta endothelial cells. *Am J Physiol Heart Circ Physiol* 2015;308:H723–32. https://doi.org/10.1152/ajpheart.00681.2014; PMID: 25637546.
47. Chignalia AZ, Schuldt EZ, Camargo LL, et al. Testosterone induces vascular smooth muscle cell migration by NADPH oxidase and c-Src-dependent pathways. *Hypertension* 2012;59:1263–71. https://doi.org/10.1161/HYPERTENSIONAHA.111.180620; PMID: 22566500.
48. Boese AC, Chang L, Yin KJ, et al. Sex differences in abdominal aortic aneurysms. *Am J Physiol Heart Circ Physiol* 2018;314:1137–52. https://doi.org/10.1152/ajpheart.00519.2017; PMID: 29350999.
49. Natoli AK, Medley TL, Ahimastos AA, et al. Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloproteinase expression. *Hypertension* 2005;46:1129–34. https://doi.org/10.1161/01.HYP.0000187016.06549.96; PMID: 16230520.
50. Alsiraj Y, Thatcher SE, Charnigo R, et al. Female mice with an XY sex chromosome complement develop severe angiotensin II-induced abdominal aortic aneurysms. *Circulation* 2017;135:379–91. https://doi.org/10.1161/CIRCULATIONAHA.116.023789; PMID: 27815372.
51. Smedberg C, Steuer J, Leander K, Hultgren R. Sex differences and temporal trends in aortic dissection: a population-based study of incidence, treatment strategies, and outcome in Swedish patients during 15 years. *Eur Heart J* 2020;41:2430–8. https://doi.org/10.1093/eurheartj/ehaa446; PMID: 32558879.
52. Ulug P, Powell JT, Warschkow R, von Allmen RS. Editor's choice – sex specific differences in the management of descending thoracic aortic aneurysms: systematic review with meta-analysis. *Eur J Vasc Endovasc Surg* 2019;58:503–11. https://doi.org/10.1016/j.ejvs.2019.04.022; PMID: 31371067.
53. Sabashnikov A, Heinen S, Deppe AC, et al. Impact of gender on long-term outcomes after surgical repair for acute Stanford A aortic dissection: a propensity score matched analysis. *Interact Cardiovasc Thorac Surg* 2017;24:702–7. https://doi.org/10.1093/icvts/ivw426; PMID: 28453793.
54. Deery SE, Shean KE, Wang GJ, et al. Female sex independently predicts mortality after thoracic endovascular aortic repair for intact descending thoracic aortic aneurysms. *J Vasc Surg* 2017;66:2–8. https://doi.org/10.1016/j.jvs.2016.12.103; PMID: 28259576.
55. Dillavou ED, Muluk SC, Makaroun MS. A decade of change in abdominal aortic aneurysm repair in the United States: have we improved outcomes equally between men and women? *J Vasc Surg* 2006;43:230–8. https://doi.org/10.1016/j.jvs.2005.09.043; PMID: 16476592.
56. McGinigle KL, Browder SE, Strassle PD, et al. Sex-related disparities in intervention rates and type of intervention in patients with aortic and peripheral arterial diseases in the National Inpatient Sample Database. *J Vasc Surg* 2021;73:2081–9.e7. https://doi.org/10.1016/j.jvs.2020.11.034; PMID: 33301865.
57. Wang LJ, Locham S, Dakour-Aridi H, et al. Sex disparity in outcomes of ruptured abdominal aortic aneurysm repair driven by in-hospital treatment delays. *Ann Surg* 2019;270:630–8. https://doi.org/10.1097/SLA.0000000000003482; PMID: 31356266.
58. Mehta M, Byrne WJ, Robinson H, et al. Women derive less benefit from elective endovascular aneurysm repair than men. *J Vasc Surg* 2012;55:906–13. https://doi.org/10.1016/j.jvs.2011.11.047; PMID: 22322123.
59. Sciria CT, Osorio B, Wang J, et al. Sex-based disparities in outcomes with abdominal aortic aneurysms. *Am J Cardiol* 2021;155:135–48. https://doi.org/10.1016/j.amjcard.2021.06.023; PMID: 34294407.
60. Deery SE, Soden PA, Zettervall SL, et al. Sex differences in mortality and morbidity following repair of intact abdominal aortic aneurysms. *J Vasc Surg* 2017;65:1006–13. https://doi.org/10.1016/j.jvs.2016.08.100; PMID: 27986477.
61. National Institutes of Health. *Consideration of sex as a biological variable in NIH-funded Research.* 2015. https://grants.nih.gov/grants/guide/notice-files/not-od-15-102.html (accessed April 21, 2018).
62. Robinet P, Milewicz DM, Cassis LA, et al. Consideration of sex differences in design and reporting of experimental arterial pathology studies-statement from ATVB council. *Arterioscler Thromb Vasc Biol* 2018;38:292–303. https://doi.org/10.1161/ATVBAHA.117.309524; PMID: 29301789.