WebLog Journal of Gerontology and Geriatrics

Commentary
Published: 25 Jul, 2026

Gender Differences of Morbidity and Mortality may be Age-Related: Partial Explanation by Hormonal Changes in Human Ontogeny

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Abstract

The connection between age-related dynamics and gender differences, as referred to morbidity and mortality, is outlined, suggesting the involvement of endocrine mechanisms in programming/imprinting and embedding phenomena, including the contribution of glucocorticoids and sex steroid hormones.

Keywords: Gender Differences; Morbidity; Mortality; Ontogeny

Introduction

The author of present article would like to begin it from well-known postulate: frequently new information is born on the boundaries between various disciplines. In fact, our main experience in the past was related principally to the use of experimental models on laboratory animals and cell cultures in biochemistry and pharmacology. However, since the first decade of current century we became interested also in epidemiologic investigations, largely due to our involvement in the paradigm of developmental origins of health and disease (DOHaD), with its well-established branch of life-course epidemiology [1, 2].

One of the consequences of such dramatic changes in our scientific trajectory was the necessity to maintain our knowledge base both in biochemistry and pharmacology, together with epidemiology and public/collective health, especially because another branch of DOHaD paradigm includes multidisciplinary (biochemistry, physiology, pharmacology, etc.) studies on mechanisms of the phenomena of programming/imprinting and embedding till adult state and even senescence, where hormonal bioregulators, and especially glucocorticoids appear to be involved [3, 4], thus paving the way for additional inclusion of endocrinology and gerontology, our long-dated interests since 1977.

The value of associative mode of thought

Just recently we began to organize our greater future involvement in age-related pharmacology, reading several articles on peculiarities of pharmacodynamics and pharmacokinetics (PK) in development and aging. We could not imagine beforehand that apparently disconnected paper on PK of mephobarbital [5] will have so profound impact on our mode of thinking in relation to life-course epidemiology. But it really happened! As a matter of fact, a short paragraph in discussion of this paper has clearly prompted us that we should pay much more attention to age-related dynamics of gender differences, the two aspects that previously were in general treated by us separately.

However, several events occured earlier that could facilitate the changes of our conceptual thinking. At first, we interpreted age-related alterations of feminine fraction of morbidity and mortality in postmenopausal period as accelerated aging [6, 7], attributing it to rapid decrease in ovarian production of estrogens with the onset of menopause. In addition, just recently we have revealed higher women's predisposition to anemias in fertile period of ontogeny, obviously limited by the events of menarche and menopause [8]. But what about males?

Here again, the same paper on mephobarbital PK [5] helped a lot: in fact, in its discussion the authors mentioned the article of Fujita S. et al. (1990), focusing attention on andropause related to much slower decrease in testicular production of androgens. Moreover, the same citation included also programming/imprinting of steroid hormone metabolism by cytochrome P450 in the liver during perinatal period, together with partial weakening of this phenomenon during andropause.

Exactly in this moment we should remember that on our opinion, the terms "programminig"

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Received Date: *01 Jun 2026*
Accepted Date: *23 Jul 2026*
Published Date: *25 Jul 2026*

Citation:
Goudochnikov VI. Gender Differences of Morbidity and Mortality may be Age-Related: Partial Explanation by Hormonal Changes in Human Ontogeny. WebLog J Gerontol Geriatr. wjgg.2026.g2502. https://doi.org/10.5281/zenodo.21740738

and "imprinting", as related to DOHaD paradigm, were used for the first time by Swedish biochemist Jan Ake Gustafsson in 1973-1974, when studying the long-term consequences of sex hormone exposure during perinatal period on liver metabolism of glucocorticoids in later life (see discussion in [9]). Here we must outline also the probable connection between the involvement of glucocorticoids and sex steroid hormones in programming/ imprinting and embedding phenomena [10], an aspect that had not received adequate attention till the present time.

Connections between gender differences and age-related dynamics of morbidity and mortality

Although we plan to perform in near future meticulous re-evaluation of our previous results obtained in life-course epidemiology, we are eager to give at least some examples just now.

In addition to already published and mentioned earlier in this article higher women's predisposition to anemias in fertile period and accelerated aging with onset of menopause, we may amplify also our considerations by higher feminine predominance in morbidity from affective disorders (depression, bipolar disorder, anxiety) and on the other hand, higher predisposition of males to schizophrenia. It is highly simptomatic that these neuropsychiatric pathologies occur largely in middle phase of human ontogeny (30-59 y) [11, 12].

Besides neuropsychiatric disorders, some gastro-intestinal diseases appear to be also age- and gender-dependent. Really, cholecystitis is much more frequent in females, whereas peptic ulcer is more characteristic to males. Moreover, these gastro-intestinal diseases occur also largely in middle phase of human ontogeny.

Finally, quite recently we have obtained some data allowing to subdivide senescent, late phase of human ontogeny (60-79 and more than 80 y) for elderly (> 60 y) and oldest-old (>80 y) subpopulations, according to morbidity and mortality from cardiometabolic disorders and Alzheimer disease respectively (in this journal, in press). It means that we should continue our epidemiologic investigations, amplifying them from earlier chronologic period 1998-2007 to more recent one, 2008-2023, in order to obtain much more evidence for interconnected age-related dynamics and gender differences of morbidity and mortality.

Conclusion

It appears that two principal branches of DOHaD paradigm help each other in revealing the phenomena of programminig/ imprinting and embedding in life-course epidemiology and their molecular and endocrine mechanisms in biochemistry, physiology and pharmacology. This is another manifestation of great power of associative mode of thinking that crosses the boundaries between disciplines by means of interdisciplinary approach.

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