Chapter 8

Summary in English

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Chapter 1 provides a background on the demography of population ageing in Europe and Italy and the consequent emergence of age-related diseases as causes of disability and mortality. It illustrates how preserving homeostasis is crucial to delay functional and cognitive decline as well as mortality, and suggests that homeostasis may vary in old compared to young age. Furthermore, it highlights the controversies in scientific literature regarding optimal blood pressure and thyroid status in old age and the pitfalls of evidence derived from clinical trials and population-based studies. Finally, it introduces the Milan Geriatrics 75+ Cohort Study, which was conceived to provide novel evidence on older outpatients' populations, whom clinicians encounter in everyday clinical practice. It also describes PROSPER, a randomized controlled trial on statin use in a population of old adults at high cardiovascular risk, the second cohort on which the research work for this thesis has been done.

Chapter 2 presents findings on the association between blood pressure and cognition in the Milan Geriatrics 75+ Cohort Study, indicating that higher blood pressure was associated with better cognition especially in the oldest old and in those with impaired functional status. Both chronological age and biological age as defined as impaired functional status significantly modified the relationship between blood pressure and cognition.

In **Chapter 3**, we investigated the relationship between blood pressure and mortality risk in the Milan Geriatrics 75+ Cohort Study. We showed that the relationships of systolic and diastolic blood pressure with mortality risk were U-shaped; systolic blood pressure of 165 mmHg and diastolic blood pressure of 85 mmHg were associated with the lowest mortality risk. When focussing on older adults with systolic blood pressure below 180 mmHg, higher systolic blood pressure was associated with lower mortality risk in older adults with impaired functional and cognitive status but not in those with preserved functional and/or cognitive status.

Chapter 4 explores the association between thyroid status and mortality risk in a sample of euthyroid older adults of the Milan Geriatrics 75+ Cohort Study. It shows that higher TSH and lower fT4 were associated with decreased mortality risk in men, but not in women. Sex significantly modified the relationships of TSH and fT4 with mortality risk. In addition, the inverse relationship between TSH and mortality risk was most pronounced in men aged 85 years and over.

Chapter 5 presents novel findings on the association between resting heart rate, heart rate variability and functional decline in older adults at high cardiovascular risk. Higher resting heart rate and lower heart rate variability were associated with worse functional status and with higher risk of future functional decline. It also explores the pathophysiological mechanisms that may link these markers of cardiac autonomic function to functional decline.

Chapter 6 examines the relationship between visit-to-visit blood pressure variability and functional decline in older adults at high cardiovascular risk. It expands our current knowledge on the associations between blood pressure variability and adverse health outcomes, by showing that higher systolic blood pressure variability was associated with steeper functional decline. This association was independent of mean blood pressure, cardiovascular risk factors and comorbidities and cognition.

Chapter 7 summarises the key findings of this thesis, highlighting their novelty in the context of scientific literature. It was concluded that there is a need for hospital-based cohorts in which to explore whether the relationships between risk factors and health outcomes may vary across the wide spectrum of biological and chronological age. Moreover, findings from these cohorts should guide appropriate clinical trials that are needed to assess the benefits and harms of either introducing or withdrawing medications in older adults.