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Precision Medicine, Healthy Living and the Complex Patient: Managing the Patient With Multimorbidity

Anne E. Holland [a,b,c,*], Annemarie L. Lee [c,d]

[a] Discipline of Physiotherapy, La Trobe University, Melbourne, Australia
[b] Department of Physiotherapy, Alfred Health, Melbourne, Australia
[c] Institute for Breathing and Sleep, Melbourne, Australia
[d] Department of Physiotherapy, Monash University, Australia

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ABSTRACT

Multimorbidity is the most common chronic health condition in adults and is associated with poor health outcomes. Optimal care for people with multimorbidity requires a person-centred approach that considers goals and preferences, improves quality of life and coordinates care across services. Because care is focused on patient outcomes, rather than disease outcomes, this provides an ideal setting for delivery of the Healthy Living Polypill (HLPP). Precision in delivery of the HLPP for people with multimorbidity involves active participation of patients in goal setting, strategies to address functional limitations and frailty, and support to develop the self-management skills necessary to adopt and sustain healthy behaviours. The multidisciplinary team is a key feature of integrated care for people with multimorbidity and all members should have the necessary skills to deliver the HLPP. Integration and continuity across health and social care sectors enhances outcomes and increases opportunities for personalised delivery of the HLPP.

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Multimorbidity, the co-existence of two or more chronic conditions, is the most common chronic health condition in adults, affecting >50% of older adults and 70% of Medicare beneficiaries.[1] Multimorbidity is present in 77% of those with cardiovascular disease (CVD), 90% of people with chronic obstructive pulmonary disease (COPD), 82% of those with cancer, 80% of stroke survivors, 79% with arthritis, and 80% of those with Parkinson's disease.[2,3] People with multimorbidity are 3.5 times more likely to have problems with activities of daily living and 6 times more likely to have physical function limitations than those without chronic diseases, after adjusting for socioeconomic status and depression.[4] The costs of health are 2.5 times higher than those with a single chronic disease.[5] People with multimorbidity have worse quality of life, increased general practice visits and hospitalisations, higher rates of polypharmacy and adverse drug events, and greater mortality than their peers with a single disease.[6]

The adverse impacts of multimorbidity vary with the number of co-existing conditions and the pattern of multimorbidity. When compared to people without multimorbidity the hazard ratio for death in people with two or more chronic conditions is 1.73 (95% confidence interval

Abbreviations and Acronyms: COPD, chronic obstructive pulmonary disease; CVD, Cardiovascular disease; HL, Healthy living; HLM, Healthy living medicine; HLPP, Healthy Living Polypill; NICE, National Institute for Health and Care Excellence; PA, physical activity; QoL, quality of life; US, United States.

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* Address reprint requests to Anne E Holland, Alfred Health Clinical School, La Trobe University, Level 4, The Alfred Centre, 99 Commercial Rd, Melbourne 3004, Australia.
E-mail address: a.holland@alfred.org.au (A.E. Holland).

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(CI) 1.41 to 2.13), rising to 2.72 (1.81 to 4.08) for those with three or more chronic conditions.[7] The risk of reduced functional independence is higher in those whose multimorbidity includes the combination of bone diseases and chronic pain, or CVD and metabolic disease.[8] Because it is ubiquitous and costly, multimorbidity is increasingly recognised as a critical health challenge for patients, health care providers and policy makers.

Why the Healthy Living (HL) Polypill (HLPP) matters in multimorbidity

The prevalence of multimorbidity is increasing, with only about half of this increase attributable to population ageing.[9] This suggests that other factors, including health behaviours and societal organisation, may play a role.

(HL) Medicine (HLM) emphasises: 1) Moving more and sitting less; 2) consuming a healthy diet at the appropriate caloric load; 3) maintaining a healthy bodyweight; and 4) not smoking.[10] There is consistent evidence linking multimorbidity to the targets of the HLPP - low physical activity (PA), poor diet, obesity and smoking. Some examples of this literature and the corresponding risks are in Table 1. In a study of over 120,000 people followed for over 10 years, incident cardiometabolic multimorbidity (developing at least two of type 2 diabetes, coronary heart disease and stroke) was twice as likely in those who were overweight, almost five times more likely in those who were obese and >14 times more likely in those with severe obesity.[11] Often lifestyle risk factors do not exist in isolation from each other. Compared to having no risk factors, having two or more unhealthy behaviours has been shown to increase the risk of multimorbidity by 42–166%.[12] Other authors reported that three or more risk factors almost doubled the odds of developing multimorbidity (odds ratio 1.91, 95% CI 1.57–2.33). Specific combinations may be particularly harmful; for instance, low PA and obesity increased the risk of multimorbidity by 187% (adjusted hazard ratio 2.87, 95% CI 1.55 to 5.3).[12] Importantly, these risk factors may be modifiable with personalised application of the HLPP, which emphasises moving more and sitting less, consuming a healthy diet at the appropriate caloric load, maintaining a healthy body weight, and not smoking.[10] As a result, the HLPP could have a critical role in both prevention and ongoing management of multimorbidity.

Socioeconomic disadvantage has a strong and consistent relationship to multimorbidity. For instance Canadians in the lowest socioeconomic group had 3.7 times the odds of multimorbidity and onset was significantly younger than those who had more socioeconomic advantage.[13] The odds of developing multimorbidity in Scotland were 46% higher in those in the most deprived areas versus the least deprived areas, and lifestyle factors explained only 41% of this risk.[14] This reinforces the need for a comprehensive approach to HL that starts in childhood and considers health policy, the built environment and incorporates public health education.

Optimal care for people with multimorbidity – individualised and prevention-oriented

Improvements are needed in delivery of health care for people with multimorbidity. Using traditional disease-based models of care, patients with multimorbidity are at greater risk of adverse outcomes and treatment complications than their individual conditions would confer, and are more likely to receive ineffective care than those without multimorbidity.[15,16] This is reflected in the patient's experience of care, which has been described as 'overwhelming, draining and complicated' and that care is fragmented, 'like being split into pieces'.[17] Patients and carers report: 1) poor communication with and between health care providers; 2) a lack of care coordination; 3) long wait times for services; 4) difficulty making decisions about health care; and 5) being unsure how to prioritise; and feeling alone.[18] Family physicians describe similar concerns, along with insufficient time or reimbursement to deal with the complexities of multimorbidity in everyday practice.[18,19]

Individuals with multimorbidity identify individualised care planning and proactive, prevention-oriented care as the most important features of an optimal health care process.[20] This is consistent with the HLPP which has a strong emphasis on addressing individual healthy behaviours across the spectrum of prevention. People with multimorbidity define good health and wellbeing as enjoyment of life, maintenance of independence, having social relationships and participating in society.[20] An approach which emphasises an individual's function and participation is likely to deliver good outcomes for both patients and the health system. A population based study of 5771 Medicare-enrolled adults aged 65 and older showed that better daily function was a stronger determinant of lower

Table 1
Impact of lifestyle factors on risk of multimorbidity.

Risk factor	Author	n	Definition	Hazard ratio/odds ratio and 95% CI
Physical inactivity	Roberts 2015[13]	105,416	No leisure time physical activity	aOR 1.40 (1.30–1.60)
	Wikstrom 2015[45]	663	No leisure time physical activity, women	aHR 1.45 (1.03–2.52)
		586	No leisure time physical activity, men	aHR 1.84 (1.35–2.52)
	Dhalwani 2017[12]	5476	Hardly ever physically active	aHR 1.33 (1.03–1.73)
	Keats 2017[46]	18,709	<600 MET minutes/week	aOR 1.26 (1.10–1.44)
Inadequate diet	Roberts 2015[13]	105,416	<5 serves of fruit and vegetables/day	aOR 1.1 (1.0–1.2)
	Wikstrom 2015[45]	663	<3–5 serves of fruit and vegetables/week, women	aHR 1.53 (1.12–2.11)
		586	<3–5 serves of fruit and vegetables/week, men	aHR 1.51 (1.08–1.74)
	Dhalwani 2017[12]	2902	<5 serves of fruit and vegetables/day, women	aHR 1.65 (1.17–2.34)
		2574	<5 serves of fruit and vegetables/day, men	aHR 0.60 (0.43–0.86)
	Katkireddi 2017[14]	4510	Fruit and vegetables some days in last week	aOR 1.06 (0.95–1.19)
			Fruit and vegetables no days in last week	aOR 1.45 (1.24–1.70)
Obesity	Agborsangaya 2013[47]	4803	BMI ≥ 30 $kg \cdot m^{-2}$	aOR 2.2 (1.9–2.7)
	Roberts 2015[13]	105,416	BMI ≥ 30 $kg \cdot m^{-2}$	aOR 2.2 (1.9–2.4)
	Wikstrom 2015[45]	663	BMI per unit increase, women	aHR 1.10 (1.07–1.13)
		586	BMI per unit increase, men	aHR 1.12 (1.09–1.15)
	Dhalwani 2017[12]	5476	BMI ≥ 30 $kg \cdot m^{-2}$	aHR 1.28 (0.85–1.91)
	Katkireddi 2017[14]	4510	Obese BMI 30–34.9 $kg \cdot m^{-2}$	aOR 1.43 (1.21–1.68)
			Morbidly obese BMI > 34.9 $kg \cdot m^{-2}$	aOR 1.98 (1.50–2.62)
Smoking	Roberts 2015[13]	105,416	Current smoker, any amount	aOR 1.6 (1.4–1.8)
	Wikstrom 2015[45]	663	Current smoker, women	aHR 2.10 (1.37–3.22)
		586	Current smoker, men	aHR 1.65 (1.20–2.26)
	Dhalwani 2017[12]	5476	Current smoker	aHR 1.21 (0.65–2.27)
	Katkireddi 2017[14]	4510	Current smoker	aOR 1.57 (1.37–1.80)
			Ex smoker	aOR 1.35 (1.18–1.55)

aHR – adjusted hazard ratio; aOR – adjusted odds ratio; BMI – body mass index; CI – confidence interval; MET – metabolic equivalent; MM – multimorbidity.

health care costs than any other demographic feature or combination of chronic diseases.[21]

Individualisation of the HLPP for people with multimorbidity

The number of possible disease combinations in people with multimorbidity is enormous, making any approach based on disease labels or 'clusters' unlikely to be broadly applicable. A population-based study in Canada has demonstrated 113 different combinations of diagnoses in people with two health conditions; 243 unique combinations captured only the first 50% of those with ≥5 health conditions.[22] This suggests it may not be practical to deliver comprehensive care that is targeted at disease clusters, as a large number of individuals will always fall outside them. Similarly, treatment of each disease as though it appeared in isolation is unlikely to be effective or acceptable to patients. Examination of United States (US) clinical guidelines for six common health conditions found that for patients with three chronic conditions, complying with all the guidelines would require taking a minimum of 6 to a maximum of 13 medications per day, visiting a health caregiver a minimum of 1.2 to a maximum of 5.9 times per month and spending an average of 50 to 71 h each month in health-related activities. The patient's workload increased greatly with increasing numbers of concomitant conditions.[23]

It has recently been proposed that multimorbidity should be seen as a complex adaptive response to biobehavioural and socioenvironmental networks, rather than the sum of individual diseases.[24] This holistic approach requires that we pay attention to both disease-specific mechanisms and the context in which disease is occurring, with the aim of strengthening resilience and enhancing social capital.[24] This is entirely consistent with both precision medicine and the principles of HLM[10] and has a strong focus on environment, lifestyle and patient goals. Whilst biomedical care remains critical (including reducing polypharmacy and eliminating ineffective treatments), personal health behaviours such as diet and exercise are of growing importance to the effective management of multimorbidity.

The National Institute for Health and Care Excellence (NICE, United Kingdom) has published a guideline on clinical assessment and management of multimorbidity.[25] The guideline recommends that care for multimorbidity should be directed by five principles: 1) how the person's health conditions and their treatments interact and how this affects QoL; 2) the person's individual needs, preferences for treatments, health priorities, lifestyle and goals; 3) the benefits and risks of following recommendations from guidance on single health conditions; 4) improving quality of life by reducing treatment burden, adverse events, and unplanned care; and 5) improving coordination of care across services. Key features of this person-centred care for people with multimorbidity are: 1) active participation of patients in goal-setting and decision-making about the care provided and self-management of their conditions; 2) involvement of informal carers; and 3) provision of coordinated multidisciplinary care.[26] These features are critical to underpin the delivery of the HLPP in people with multimorbidity.

Individualising the HLPP for people with multimorbidity requires consideration of both *function* and *frailty*. Functional limitations may include difficulty with physical mobility, activities of daily living, instrumental activities of daily living, social interaction, work or leisure activities. Functional limitation is present in around 45% of those with chronic conditions; the number of limitations increases with each additional chronic disease and with increasing age.[1] The US Department of Health and Human Services framework on multiple chronic conditions emphasises the importance of optimizing function, maintaining function, or preventing further decline in function of those who have multimorbidity.[27] The accumulation of multiple health deficits and functional impairments may manifest as frailty, which identifies a vulnerable subgroup who are at particularly high risk of poor outcomes such as falls, disability, loss of independence, hospitalisation and death.[28] Markers of frailty could include impairments in mobility, strength, balance, cognition, nutrition, endurance, mood and physical activity, with a variety of measurement tools available.[29,30] Whilst not all individuals with multimorbidity are frail, there is a substantial overlap. This is recognised in the recent NICE guidelines, which encourage assessment of frailty in people with multimorbidity using simple measures such as gait speed or self-reported health status.[25]

In people with multimorbidity who do not have functional limitations or frailty, delivering the HLPP may use similar approaches to those used in people with single chronic diseases. However, the added complexities and treatment burdens in people with multimorbidity require diligent attention to: 1) understanding the individual's goals and priorities; 2) minimising the burden of care; avoiding duplication of care; and 3) improving care coordination. The HLPP may therefore be best delivered in the context of a multidisciplinary team where a shared understanding of treatment priorities and responsibilities across patients, carers and health professionals can be developed. In recognition of the treatment burden imposed by multimorbidity, it may be necessary to work with patients to identify one or two elements of the HLPP that is of greatest significance to them. This may enable the establishment of achievable goals, the delivery of appropriate education and support, and achievement of good health outcomes. For instance, an individual who is well motivated to quit smoking could be supported to achieve this goal, acknowledging that obesity is present but not currently a priority, and the burden of care is such that the individual currently has little spare capacity to address this domain. As goals will alter over time alongside changes in health status and personal priorities, an individual's goals should be frequently revisited, with new opportunities to address other domains of HL.

For individuals with functional impairment, delivering the HLPP should additionally consider ways in which function could be improved. Individuals with physical mobility impairments that affect PA of daily living may be more motivated to set goals relevant to the physical activity domain, with opportunities to achieve gains that are meaningful for daily functioning. Where functional impairment includes social isolation, HL interventions must consider the important role of social supports and environment, such as group exercise classes, provision of transport to smoking cessation appointments and neighbourhood meal services. Interventions that target functional and PA limitations (e.g., multidisciplinary programs that include goal setting and prioritisation, muscle strengthening, balance, falls prevention and social support) are some of the more effective treatments available for individuals with multimorbidity[31] and provide an ideal setting to deliver the HLPP.

For individuals with frailty, the HLPP is critical to addressing the key phenotypic domains of slow walking speed, weakness, inactivity, exhaustion, and shrinking.[29] PA interventions, or interventions that combine nutrition and physical activity, may be effective to reduce frailty markers in this group.[32] People with frailty and multimorbidity have the greatest treatment burden and most significant risk from inappropriate treatment; thus excellent coordination of care and strong support from the multidisciplinary team will be required. A recent European study reported that frail older people were the most common subgroup addressed in interdisciplinary care programs for people with multimorbidity, in 45% of programs surveyed, suggesting that the high care needs of this group are increasingly recognised.

Existing chronic disease rehabilitation programs may provide an opportunity to individualise the HLPP in people with multimorbidity who have functional impairment or frailty. For instance, cardiac rehabilitation has a strong focus on management of risk factors and is highly effective for improving functional capacity, although its impact on frailty is yet to be determined.[33] There is emerging evidence that pulmonary rehabilitation programs can reduce frailty.[34] However, people with multimorbidity are less likely than their peers with a single health condition to take up a referral to rehabilitation, and are more likely to drop out before they complete the program.[35] New models of cardiac

rehabilitation that take a more person-centred approach are emerging (e.g., home-based rehabilitation or telerehabilitation, which overcome barriers related to transport and access) and appear to have equivalent outcomes to traditional centre-based programs.[36] Whether these models can improve uptake and outcomes in people with multimorbidity has yet to be determined.

Adherence, persistence and the challenge of complexity in multimorbidity

Inadequate adherence and persistence are major challenges to precision in delivery of the HLPP.[10] These challenges are especially apparent in the context of multimorbidity. For instance, the presence of multimorbidity is a strong predictor of non-adherence to cardiovascular medications,[37] which is not surprising given the complexity of managing multiple treatments, the experience of side-effects and lack of clear benefits.[38] It is likely that adherence to the components of the HLPP will be similarly challenging. For health professionals, delivering evidence-based care to people with multimorbidity is perceived as difficult due to fragmentation of care, insufficient consultation time and inadequacy of single-disease guidelines to inform decisions.[39]

Self-management support for patients and caregivers is emphasised in frameworks for multimorbidity care, acknowledging that patients are required to execute complex care regimens outside the clinical setting, many of which involve non-pharmaceutical interventions such as those in the HLPP.[40] Self-management interventions for people with multimorbidity vary in content and mode of delivery, but have had positive effects on physical function, PA and diet.[31] Many include elements of behavioural counselling (e.g. health coaching, cognitive behavioural therapy). Behavioural counselling has been identified as the 'enteric coating' for the HLPP, used to optimise the time and location of delivery.[10] Care providers will require training to ensure that effective self-management support and behavioural counselling can be delivered. Similarly, patients and caregivers should be provided with training and support to improve self-management, tailored to their preferences and competencies.[40]

Precision delivery of the HLPP in multimorbidity requires active involvement of patients and caregivers in treatment decisions. Shared decision making aims to empower patients to take a central role in decisions about their care, including identification of priorities, goals and desired outcomes.[41] Shared decision making is especially important where there is uncertainty regarding which treatment option is superior, if there may be associated benefits and harms, or whether decision is likely to be strongly influenced by a patient's values and preferences.[42] This is exactly the situation in which patients with multimorbidity and their health professionals are making decisions. Shared decision making increases knowledge and understanding of risks.[43] Although evidence for the impact of shared decision making on adherence is not yet available, it has become a key element of multimorbidity care frameworks.[27,40,44] Precision delivery of the HLPP may benefit from this approach, to optimise engagement in HL behaviours in the setting of complex care.

Organisation of care for people with multimorbidity – Where does the HLPP fit?

Traditionally, health services have been organised around single medical conditions. The rising prevalence of multimorbidity means that new ways of organising care are required. Around the world new frameworks of integrated care for people with multimorbidity are being developed,[27,40,44] to guide health service providers and policy makers. Consistent with precision medicine and the principles of the HLPP these frameworks are person centred, with the individual and their environment placed centrally. Health is understood as going beyond physical, mental and social wellbeing, to include the ability to self-manage, adapt and cope.[44] The individual's environment includes their social network, their financial, housing arrangements and physical surroundings, as well as access to community services and transport. Consideration of these environmental facilitators is key to successful implementation of the HLPP; for instance, an individual is more likely to sit less and move more if there is a safe place to walk outside.

Shared features of multimorbidity frameworks that are relevant to precision delivery of the HLPP are in Table 2. Extending care and teamwork across health, social care and volunteer networks provides new opportunities to encourage healthy behaviours outside the health care setting. The emphasis on multidisciplinary teamwork and coordination of care requires that each team member is skilled in delivery of the HLPP, understands the patient's goals and preferences, can teach the required self- management skills, and can communicate progress to the rest of the team. All the frameworks emphasise the potential of technology to share information, provide integrated and coordinated care, stratify risk and empower patients; wearable devices provide opportunities for self- management and can encourage patients to undertake HL behaviours. Although widespread integrated care for people with multimorbidity remains an aspiration, models of care that embody some of these principles are emerging,[26] with great potential for effective, individualised delivery of the HLPP.

In conclusion, a person-centred, precision medicine approach is critical for optimal care of people with multimorbidity. Individualization of the HLPP for individuals with multimorbidity requires a shared understanding of goals and preferences; addressing functional impairment and frailty; support for self-management; multidisciplinary teamwork; and coordination of care. Emerging models of integrated care for multimorbidity will provide an ideal platform for delivery of the HLPP.

Table 2
Features of multimorbidity care frameworks that facilitate individualised delivery of the healthy living polypill.
Adapted from references [27,40,44].

Feature	Characteristics
Person centred care	Holistic understanding of the individual within their environment
Regular and comprehensive assessment	Assess medical psychological, social and functional capabilities
Individualised care plan	Person centred, focused on patient outcomes rather than disease outcomes
	Consider patient goals and preferences
Service delivery	Tailored and flexible
	Smooth transitions between providers
	Involve informal caregivers
Multidisciplinary team	Across health, social care and volunteer work boundaries
Coordination of care	Named individual to facilitate communication and continuity of care
Organisational integration	Across health and social care sectors
Self management	Facilitates the behavioural and lifestyle changes necessary for optimal wellbeing
Technology	ICT to facilitate integrated and coordinated care – e.g. EMRs and patient portals
	Telehealth and remote monitoring
	Wearables
Integration with environment and community	Support access to community and social resources

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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