Abstract: The main objective of this essay is to illustrate the state-of-the-art on ‘mental health-sensitive’ open space design in the built environment. Urban Green Blue Infrastructure can contribute to urbanites’ mental health and wellbeing as well as healthy aging, while providing co-benefits balancing the negative impacts of climate change, through the provision of integrated ecosystem services. There are a number of ways that exposure to and affiliation with Nature have shown to support mental health, but we are still missing the necessary evidence of the actual benefits achieved, as well as the key performance indicators and metrics to monitor and adapt our open space to the growing urban challenges. After introducing the key concepts of degenerative mental disorders as they are growing in the urban environment, and the emerging green blue infrastructure design approach, the authors present international case studies describing how evidence-based design and Nature-based Solutions have been found to be beneficial, especially to those diagnosed with mental disorders. Subsequently, in a comparative critical analysis, the authors look closer at a number of design solutions capable, at different scales, to support healthy aging through exposure to, and affiliation with, biodiversity.

Keywords: healthy public space design; healing gardens; dementia-friendly cities; Alzheimer; elderly people; evidence-based design; age-sensitive landscape design

1. Introduction

The United Nations Sustainable Development Goal 3 (2015) states that “ensuring healthy lives and promoting the well-being at all ages is essential to sustainable development” [1,2].

Achieving health requires striving for complete physical and mental health, the latter being “a state in which a person is most fulfilled, can make sense of the surroundings, feel in control, can cope with every day demands, and has purpose in life” [3] (p. 27).

The urban built environment particularly influences social health and wellbeing, especially of the elderly [3]. Worldwide, the total number of people over 60 is set to double by 2050, rising from 1 billion to 2 billion, with 80% living in low- and middle-income countries [4].

According to the World Health Organization (WHO) ‘Healthy Ageing’ is the “process of developing and maintaining the functional ability that enables wellbeing in older age” [5] (p. 28). Healthy ageing represents, therefore, the continuous interaction between people and the environment in which they live [6].

There is growing recognition that the leading causes of disease and death, including heart disease, cancer, cerebrovascular disease, chronic lower respiratory disease and injury, can be exacerbated...
by elements within the built environment which contribute to sedentary lifestyles and unhealthy environments [7,8]. Moreover, climate change is determining a host of mental health challenges, and the public health threats people are experiencing are considered among the most urgent of the 21st century [9]. Thermal stress negatively affects the functioning and health of people. When the temperature is extreme, vulnerable groups (e.g., groups with mental health conditions or with substance abuse problems, the poor, the children, the elderly) have a higher risk of worsened mood or behavioral disorders, violence, aggression or suicide [10]. Elderly people are particularly susceptible and are likely to suffer from moderate heat stress even under prevailing conditions. During periods of heat waves, however, the risks to vulnerable urban residents increase—with increased mortality rates having been recorded for many countries, including France, US, Korea, Russia and the Netherlands [11–14].

Another serious health risk increasingly connected with the ageing population is dementia, currently affecting approximately 5% of the world’s elderly population [15]. Dementia is one of the most expensive diseases to manage, and is the fifth-biggest cause of death in high-income countries [16]. The worldwide figure of people living with dementia more than doubled up from 1990 to 2016, mainly due to increases in population ageing and growth [17].

The connection between the built environment and health has been extensively examined in working-age populations, but we can count on comparatively fewer studies concentrating on the elderly and mentally impaired urbanites [18].

The World Health Organization’s goal of the Global Action Plan on the Public Health Response to Dementia 2017–2025 is to improve the lives and careers of people with dementia and the lives of their relatives, while reducing the impact of dementia on them and on communities and nations [19]. It is considered equally important to understand how to efficiently promote healthy aging and prevent dementia-like neurodegenerative diseases, such as Parkinson’s, Alzheimer’s, and Huntington’s disease [15].

Nowadays, we can rely on many decades of environmental psychology and environmental behavior research examining the mentally restorative potential of exposure to the natural environment, as well as to the natural elements and systems in our urban built environment. With the sociocultural environment influencing the degree of psychological and restorative benefits that we may be genetically predisposed to receive [20].

Urban design can play a primary role in the healthy ageing process, helping adults stay socially active as they age, and thus supporting their general health and wellbeing [20–22]. There is substantial evidence demonstrating that urban design and landscape architecture are powerful tools to improve the human condition and health [23–26]. We can also already count on several bottom-up initiatives, i.e., age-friendly towns, districts and communities—such as Manchester’s “Older People’s Forums”, Hong Kong’s “Elder Academy”, Ottawa’s “Better Strength Better Balance”—which are promoting healthy and active ageing, assisting elderly people to stay autonomous for as long as possible, and providing care and security when required, while respecting the autonomy and dignity of elderly people [5].

International research confirms in principle the need for better knowledge of specific landscape aspects and design strategies, as well as of blue and green features able to promote healthy ageing and mental health and wellbeing in increasingly critical urban scenarios [22,27]. For example, in a recent European project conducted across 17 cities in Austria, Germany, Norway, Poland, Romania and Slovenia, Artmann et al. (2017) [28] reported that more types of age-sensitive facilities should be considered in urban green areas, particularly in support of physical activity for elderly and mentally impaired people [28].

So far, studies mostly revealed only general associations between greater exposure to the natural environment and improved mental health, and this limit has created a much-needed evidence basis on which to address and solve existing boundaries to conclude clear cause and effect. Case studies and critical appraisal of current and on-going projects represent in this respect a sound methodology to acknowledge and progress mental health-sensitive open space design, as well as encouraging awareness and stewardship.
The purpose of this critical essay is to better explore the relationships between Urban Green Blue Infrastructure, mental health and healthy ageing, and to provide useful insights aimed at progressing informed age-sensitive design and planning for the built environment.

2. Urban Green Blue Infrastructure for Healthy Ageing and Mental Health

Green Blue Infrastructure is strongly linked to the concept of ‘Green Infrastructure’ (GI). GI is an approach related to landscape planning and design linked to Nature-based strategies and solutions, such as greenways and ecological networks [29,30]. GI had originally been defined as “a strategically planned network of natural and semi-natural areas, with other environmental features designed and managed to deliver a wide range of ecosystem services” [31], and more recently as “the elements of biodiversity and the organized systems that can be traced back to the Natural Capital, of any urban area, valuable or degraded, including the individual technological devices that rely on biodiversity and are integrated in the built environment, such as green roofs and vegetation walls, permeable paving, rain gardens and other systems for the collection and management of rainwater, which promote, through the provision of ecosystem services, environmental protection, economic feasibility, health and well-being, equity and social inclusion” [32].

GI is present in rural, urban and peri-urban environments, at different scales [31,33]. In urban areas, Urban Green Blue Infrastructure (UGBI) is normally a hybrid infrastructure of green spaces, or blue spaces if aquatic ecosystem are included, and built systems [31,33,34]. Examples of UGBI are urban forests, parks, domestic gardens, green roofs and walls, community orchards, parklets and sidewalk gardens, while blue components are aquatic ecosystems, such as wetlands, rivers, canals, ponds, creeks, etc. (Figure 1).

Figure 1. Urban Green Infrastructure: (a) Green roof in Antwerp, Belgium, (b) green wall in Oxford, UK, (c) urban park in Padua, Italy, (d) urban–park in St. Petersburg, Russia, (e) “green” tramway in Paris, France, (f) community garden in Freiburg, Germany. Urban Blue Infrastructure: (g) Canal in London, UK, (h) canal in Amsterdam, Netherlands, (i) pocket garden with water feature in New York City, USA, (l) canal in Dublin, Ireland, (m) urban wetland in Suining, China, (n) pond in Moscow, Russia. Credits: Alessio Russo (a–e, g, h, l, m) and Maria Beatrice Andreucci (f, i, n).

The mismatch between what human beings need and what urban built environments often fail to provide—exposure to nature—has proven detrimental to mental health [35]. Conversely, other
studies have reported that human exposure to UGBI increase physical activity \cite{36,37}, improve mental health \cite{38-44}, and decrease crime, violence and aggression \cite{45-48}, as well as morbidity in multiple disease categories \cite{49-51}.

UGBI is essential to support the basic ecosystem services on which human survival depends \cite{52}. UGBI regulates water quantity and quality, controls surface runoffs, protects biodiversity, filters pollutants, improves air quality, and is vital to the food chain leveraging on nutrient cycling and pollination \cite{53,54}.

De Keijzer et al.’s research \cite{27} revealed that proximity to natural green and blue areas is associated with a slower decrease in walking speed and grip strength among respondents between the ages of 50 and 74. Wang et al. (2017) \cite{55} studied the contributions of neighboring green space to mortality among Chinese males and females 65 years of age and elderly living in Hong Kong. Results showed that a 10% increase in green space coverage was correlated with a decrease in all-cause mortality \cite{55}.

Lewis and Booth (1994) \cite{56} found that people living in built-up areas with access to gardens and other greenspaces had a lower prevalence of psychiatric morbidity as compared to people in built-up areas with no such access.

Other studies have recently supported the connection of socio-economic and socio-demographic factors in elderly people as possible confounding variables with respect to the relationship between health and UGBI \cite{57}.

There are a number of ways that exposure to, and affiliation with, UGBI have shown to support mental health. These include nature’s ability to reduce stress, create positive affective states, and improve cognitive functioning \cite{39,58,59} (Table 1).

Table 1. The health benefits of green and blue infrastructure for elderly people.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower mortality</td>
<td>\cite{55,60,61} c</td>
</tr>
<tr>
<td>Slower decline in walking speed</td>
<td>[27]</td>
</tr>
<tr>
<td>Lower risk of cardiovascular disease</td>
<td>\cite{62,63} **</td>
</tr>
<tr>
<td>Slower cognitive decline</td>
<td>\cite{64} **</td>
</tr>
<tr>
<td>Stress reduction</td>
<td>\cite{65} **</td>
</tr>
<tr>
<td>Decreased inflammation</td>
<td>\cite{66} Θ</td>
</tr>
<tr>
<td>Social connectedness improvement</td>
<td>\cite{66} Θ</td>
</tr>
<tr>
<td>** Passive recreation (e.g., exposure), Θ horticultural therapy, c coverage of green space.</td>
<td></td>
</tr>
</tbody>
</table>

Exposure to the natural environment can take many forms that range from simply viewing images of nature, to actively accessing UGBI, to receiving treatments in institutional settings.

Landscape architects design therapeutic or healing gardens at different scales \cite{67,68}. Healing gardens are outdoor spaces designed to support health and well-being and provide comfort for people suffering from illness \cite{68}.

In countries like the United States and Singapore, some healing gardens focus on the design of sensory stimulation and accommodation of horticultural activities \cite{66,69}. Therapeutic gardens influence the quality of life of aged care residents with dementia \cite{70}.

The beneficial effects of outdoor activities in people with dementia have also been well documented \cite{70,71}. Nature-based walks, as compared to urban walks, have been found to be beneficial to those diagnosed with mental disorders \cite{40}.

At the same time, other studies \cite{72,73} confirm that general mental health improvements may also be attributed to the restoration gained by passive exposure to greenness, independent of exposure gained by actively accessing it for physical activity, and also independent of the mental benefits of the social interaction that can take place in it.

Worldwide, Edible City projects have demonstrated that edible green spaces (e.g., allotment gardens, edible forest gardens, edible urban forests) can improve social cohesion, healthy aging and wellbeing \cite{74–77}. Research in Spain has shown that urban gardens could be promoted as a
nature-based solution in urban planning to facilitate elderly social integration [78]. A study conducted in the UK by Wood et al. 2016 demonstrated that as little as 30 minutes of allotment gardening can produce significant health gains [79].

The experience of visiting allotment gardens positively influences the quality of the elderly participants’ daily lives, including restorative experiences, peacefulness, inspiration, joy, and positive emotion [80].

Although UGBI has been found to be associated with physiological benefits for humans in several studies, it should not be forgotten that increasing biodiversity in the built environment may also support ecosystem disservices, i.e., nuisances and losses produced by ecosystem functions [67,81,82], or even the introduction and survival of vectors or host organisms for infectious pathogens, with the resulting spread of a variety of diseases [67,83]. Ecological, social and technological changes determined by planning and design will affect both what kind of disservices will emerge and how they will be experienced and managed [81].

3. Dementia-Friendly Cities and Biophilic Design for Healthy Communities

Therapeutic design of the built environment is widely recognized as a major aid for people with Alzheimer’s disease [22].

Growing evidence suggests an interrelationship between dementia on one side and lifestyle-related risk factors on the other [84,85]. These risk factors include physical inactivity and obesity, together with unbalanced diets, tobacco use, harmful use of alcohol, diabetes mellitus and mid-life hypertension [86,87]. In addition, other potentially modifiable risk factors are more specific to dementia and include social isolation, low educational attainment, cognitive inactivity and mid-life depression [88,89]. Reducing the level of exposure of elderly populations, and individuals in general, to these potentially modifiable risk factors can strengthen the capacity of urbanites to make healthier choices and follow lifestyle patterns that foster good mental health and wellbeing.

There is growing consensus that integrated and multiscale nature in the city is protective and can reduce the risk of cognitive decline and dementia: increasing physical activity, preventing and reducing obesity, promoting balanced and healthy diets, discouraging the harmful use of tobacco and alcohol, promoting social engagement, cognitively stimulating activities and learning, as well as preventing and healing depression [85,90].

The biophilic cities concept builds on much of the work of biophilia [91] and biophilic design that have both been experienced more on the building scale [92]. Sets of biophilic design principles have also been generated [93,94] providing reflections and guidance about design qualities and natural conditions people appreciate the most in the urban built environment—biodiversity, light, water, and natural sounds, among others [92,95].

There are numerous case studies of Dementia-Friendly Communities worldwide [96].

As an example, a supportive community specifically for people with dementia has recently been established in Canada [97]. This project, called The Village, includes six single-story cottage-style homes and a community center surrounded by a lush garden [97,98]. The main focus of The Village is to encourage and enable people with dementia to live their lives as they would normally do [97,98]. The development of the Village was influenced by the world’s first dementia village, Hogeweyk, in the Netherlands. Hogeweyk is designed to accommodate 152 people suffering from dementia [99]. The design layout includes 23 houses with a variety of parks and gardens designed by the Dutch landscape architect Niek Roozen [99].

In the UK there are several examples of dementia friendly parks. For example, the oldest Royal Park in Scotland was transformed into a dementia-friendly park in 2018 [100]. The aim of this project was to make green spaces more accessible and inclusive for people with dementia through the provision of additional benches, the installation of a handrail and dementia friendly toilet signage [100]. Another good example is the dementia friendly garden at Springhead Park in Rothwell, Leeds [101]. The garden has been built to support people with dementia and to “demonstrate the principles of
a dementia-friendly garden to inspire families, care home managers and other local authorities to develop their own" [101] (p. 2).

In Oslo, Norway (Figure 2), the horticultural therapy project Loseter Garden of Senses is another example of how bringing fertile soil into our built environment can transform a barren area into a thriving green and dementia-friendly meeting place, where all people can comfortably learn about and experiment with food production.

![Figure 2. Horticultural therapy project Loseter Garden of Senses in Oslo, Norway. Credits: Maria Beatrice Andreucci.](image)

Sprouting Oslo—to which the Loseter project belongs—is an outstanding example of the 2019 Green Capital’s commitment to inclusive urban landscapes.

4. Healing Garden Design and Mental Health Institutional Setting

The psychophysiological or psycho-evolutionary stress recovery theory [58] postulates that our innate connection with the natural environment results in a fairly rapid reduction in stress when viewing natural elements or pleasing natural landscapes. Ulrich’s study into the therapeutic properties of nature views revealed that hospital patients convalescing from surgery had shorter hospital stays, lower intake of narcotic pain drugs, and more favorable evaluations by nurses if their hospital room windows allowed views of trees rather than views of a brick wall [102].

There are few places where the power of landscape architecture is more needed than in institutional settings where patients and relatives react to mental illness.

Along the life course continuum, exposure to the natural environment appears to benefit affective states of older persons in institutional settings with degenerative mental disorders [103,104].

The risk of developing dementia in institutional settings has also been found to be dramatically reduced with exposure to, and affiliation with, nature achieved with regular gardening [105].

In health care settings, a patient’s ability to process information and instruction given by health care providers is critical to enhancing care and health outcomes.

Among those with late stage dementia in nursing homes, natural sounds and pictures have been found to reduce agitation, if not aggression [106,107].

Healing gardens are defined as “green spaces designed to promote and improve health and well-being for people suffering from illness” [68] (p. 43). There has been a growing interest in healing gardens around the world and many of these gardens have been designed in several countries [108].

Design features such as street layouts, building forms, signage and other details influence the orientation and wayfinding abilities of older people with dementia [109].
For example, in Ferrara, Italy, the Garden of Happiness (Figure 3), has been specifically designed for the benefit of almost two hundred elderly patients, their guests and family, as well as the healthcare providers. The space can be set up for community use, and it includes specific design elements that work to maximize accessibility, safety and orientation. The planting design stimulates all senses, while the tree planted areas provide comfort for both informal and spiritual gatherings. The site also provides physical access to a vegetable garden and an orchard suitable for a variety of therapies. There is also equipment and specially-designed furniture, which can also be enjoyed by patients in a wheelchair.

Figure 3. Example of a healing garden in Italy, the Garden of Happiness in Ferrara. Credits: Monica Botta.

On a different scale, in Singapore, there is an ongoing initiative aimed at creating the Therapeutic Gardens Network and Social and Therapeutic Horticulture Programmes, meeting the needs of elderly people, including those affected by dementia [110]. The first, prototype garden was completed in May 2016 by the National Parks Board with design inputs from the Psychological Health Department of the National University of Singapore and the Alzheimer Disease Association. The design principles included: safety, security and privacy, accessibility, physical and emotional comfort, positive distraction, engagement with nature, maintenance and sustainability (Figure 4). It is located within the North Park area in West Singapore. The Therapeutic Garden is located close to a building equipped with comfortable washing areas, toilets, and drinking water sources. It provides deep shade under large tree canopies and comfortable wooden benches (equipped with full support for the back and armrests). The layout is simple and clear without confusing dead ends. The garden is fully accessible for wheelchairs, also through the furniture for horticultural therapy sessions: Planting racks and work benches in which the height and design has been adjusted for both standing participants and those seated in wheelchairs.

Figure 4. Examples of Therapeutic Gardens and Social and Therapeutic Horticulture Programmes in Singapore. Credits: A. Olszewska-Guizzo (a-c) and NParks (d).
Since 2016, three more Therapeutic Gardens have been built in different areas of Singapore, and more are to be implemented in the network, as a response to the ageing population and increasing levels of dementia.

5. Evaluating Design Quality and Potential Benefits of Therapeutic Green and Blue Open Spaces

As the Therapeutic Garden Network in Singapore in expanding, the National Parks Board, through its Research Centre for Urban Greenery and Ecology (CUGE), is keen on collaborating with academics and doctors to test their designs and functions using scientific methods. Several collaborative research studies have been conducted in the Singapore Therapeutic Gardens to evaluate their potential contributions to the elderly and inform the policies for a dementia-friendly urban agenda. For example, a study completed in 2016 assessed the effects of horticultural therapy on the mental health and immune functioning of the 69 elderly participants, using the randomized control-trial design [66]. Recently, the data collection for a follow-up study on the effects of the horticultural therapy on people with dementia has been concluded. Another large cohort study has tested the influence of certain physical activity protocols performed in parks on the health and wellbeing of Singaporeans, including the elderly [111]. Currently, the research on the effects on brain activity of passive exposure to the Therapeutic Gardens’ landscape is being conducted with sample representative of the Singaporean population. This study specifically targets individuals diagnosed with depression, including the elderly [112].

In 2012 the WHO released an assessment tool for the quality of physical attributes and functions of mental healthcare facilities, including homes for elderly people and Alzheimer institutions [113]. However, the “WHO Quality Rights Tool Kit” [113] does not provide any recognition concerning the issue of accessibility of green space to patients of such institutions.

In 2007 Clare Cooper Marcus developed a tool for landscape architects and other designers that evaluates the quality of outdoor space for those with Alzheimer’s disease [114]. The Alzheimer’s Garden Audit Tool (AGAT) includes a checklist divided into seven sections, e.g., moving from Location and Entry to the Garden, to Layout and Pathways, Planting, Seating, Overall Design and Details, to Maintenance and Amenities [114]. This tool has been tested by thirteen participants attending a multi-disciplinary symposium on healing landscapes in Portland in 2005 [114]; however, the tool has not been exposed to psychometric testing and targets environments for advanced dementia [115].

Recently, Paraskevopoulos and Kamperi (2018) have examined the evidence-based design of healing gardens [116]. The study showed that the design of healing gardens must be adapted to the needs of each type of patient [116]. The review of the literature also reported a limited number of evidence-based design strategies and post-occupancy evaluations for the healing of hospital gardens [116].

6. Conclusions

While UGBI is supporting mental health, it is simultaneously providing an array of other health benefits, some of which are essential to sustaining life, others to enhancing it. However, it is not solely the volume of co-benefits of GI that pervade life and support health that should be considered, rather the intrinsic design qualities of the open space, favoring maximization and interconnection between these co-benefits [117].

The opportunity of the contact with nature or the use of more biodiverse environments certainly represent an important aspect of healthy ageing and dementia-friendly environments [118]. The case studies presented have identified and highlighted the relevant design qualities and characteristics of dementia-friendly cities, healing gardens, and mental health institutional settings.

The complex dimensions of urban nature cannot be easily synthesized, considering the many interconnected features, and the many variables that come into place at different levels when dealing with associated programs, activities, and other mediators. There are in fact many different ways to experience and interact at different scales with nature in cities. Both physical and visual connections
matter, as the design of the case studies in Italy, UK, Canada, Norway, the Netherlands, and Singapore demonstrates.

Progress in post-occupancy evaluation of therapeutic green and blue open spaces already indicates that elderly people seem to have prevalent preferences for natural, esthetic, and varied landscape design characteristics, with easily accessible and well-maintained infrastructure and amenities.

Notwithstanding the positive findings, the actual benefits of designed garden spaces for people with dementia are still not fully supported by meta-analyses and remain mostly unexplored [119].

The barriers facing people living with dementia in accessing the natural environment particularly need to be investigated further through large scale studies providing both qualitative and quantitative insights [120].

More research is necessary about the negative influence of climate on human health and enjoyment in the open space environment, as scientists at the National University of Singapore have recently highlighted [121].

Context, informed decision making and inclusive governance represent important factors when selecting and implementing integrated, multiscale actions targeting the elderly’s mental health and wellbeing. Financial incentives, public education, applied research and dissemination are to be considered critical for a balanced and sound welfare development.

Author Contributions: All authors were involved in conceptualization and methodology, and contributed to review, visualization and editing. M.B.A. led the writing of the original draft and supervision. A.R. led the literature review. A.O.-G. provided the Singapore case studies. The Ferrara and Oslo case studies have been developed by M.B.A.

Funding: This research received no external funding.

Acknowledgments: The authors thank Monica Botta for providing useful materials and insights regarding the Garden of Happiness in Ferrara.

Conflicts of Interest: The authors declare no conflict of interest.

References


25. Olszewska, A.A.; Bil, J.S. Therapeutic Garden Design for Patients with Neurodegenerative Diseases. *Space Form* 2016, 25, 259–270. [CrossRef]


34. Russo, A.; Escobedo, F.J.; Zerbe, S. Quantifying the local-scale ecosystem services provided by urban treed streetscapes in Bolzano, Italy. *AICS Environ. Sci.* 2016, 3, 58–76. [CrossRef]


49. Maas, J.; Verheij, R.A.; Groenewegen, P.P.; Schellevis, F.G.; Groenewegen, P.P. Morbidity is related to a green living environment. *J. Epidemiol. Community Health* 2009, 63, 967–973. [CrossRef]


68. Erbino, C.; Toccolini, A.; Vagge, I.; Ferrario, P.S. Guidelines for the design of a healing garden for the rehabilitation of psychiatric patients. *J. Agric. Eng.* 2015, 46, 43. [CrossRef]
74. Säumel, I.; Reddy, S.; Wachtel, T. Edible City Solutions—One Step Further to Foster Social Resilience through Enhanced Socio-Cultural Ecosystem Services in Cities. *Sustainability* 2019, 11, 972. [CrossRef]
84. Hachinski, V. Dementia: Paradigm shifting into high gear. *Alzheimer’s Dement.* 2019, 15, 985–994. [CrossRef]
102. Ulrich, R.S. View through a window may influence recovery from surgery. *Science* 1984, 224, 420–421. [CrossRef]


121. Saw, L.E.; Lim, F.K.S.; Carrasco, L.R. The Relationship between Natural Park Usage and Happiness Does Not Hold in a Tropical City-State. *PLoS ONE* 2015, 10, e0133781. [CrossRef] [PubMed]

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).