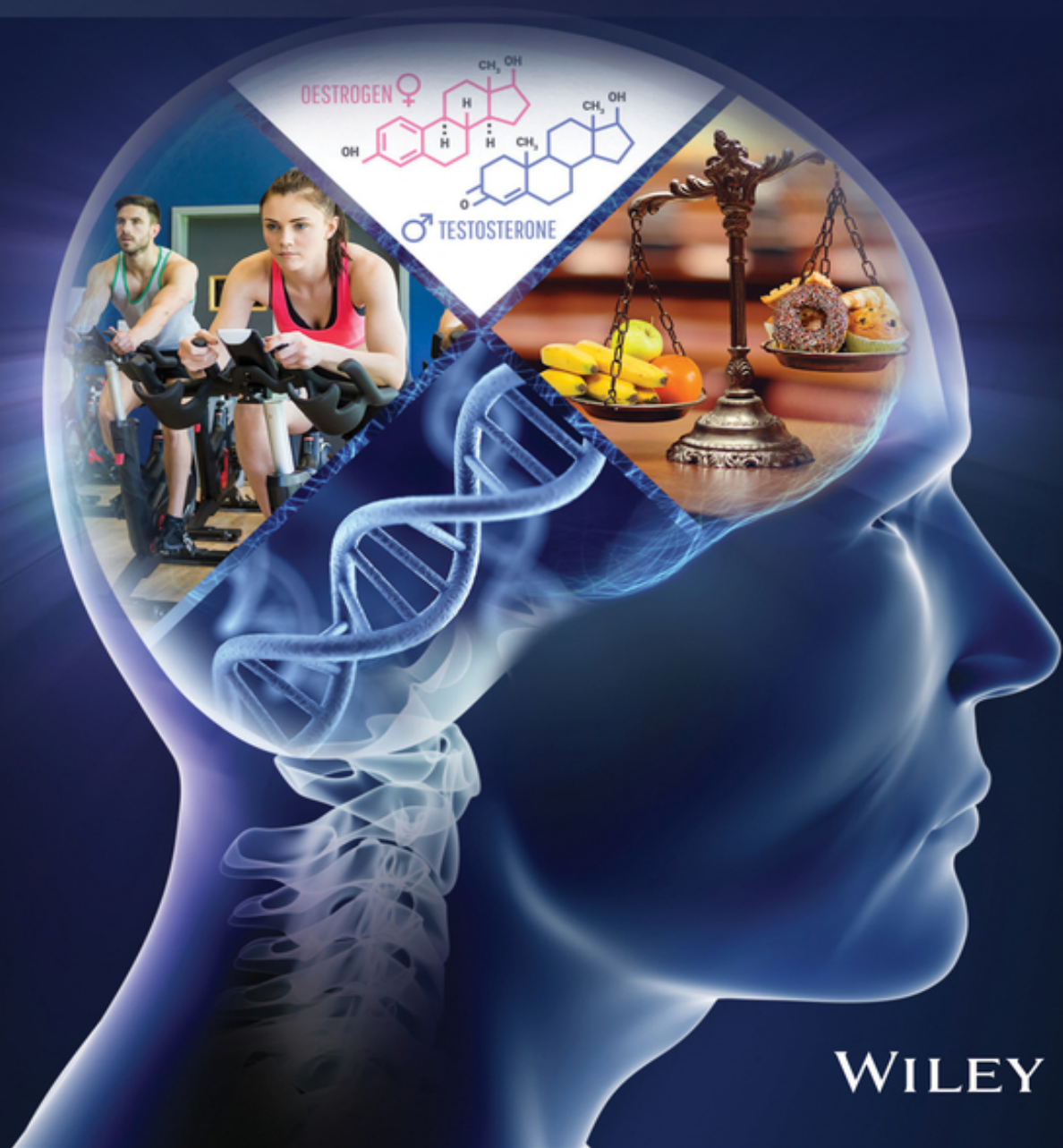


Editors: Ralph N. Martins, Charles S. Brennan
Associate Editors: W.M.A.D. Binosha Fernando,
Margaret A. Brennan, Stephanie J. Fuller

Neurodegeneration and Alzheimer's Disease

The Role of Diabetes, Genetics, Hormones, and Lifestyle



WILEY

Neurodegeneration and Alzheimer's Disease

Neurodegeneration and Alzheimer's Disease

The Role of Diabetes, Genetics, Hormones, and Lifestyle

Edited by

Editors:

Ralph N. Martins

Edith Cowan University
Joondalup
Australia

Macquarie University
Sydney
Australia

Charles S. Brennan

Lincoln University
Christchurch
New Zealand

Associate Editors:

W.M.A.D. Binoshia Fernando

Edith Cowan University
Joondalup
Australia

Margaret A. Brennan

Lincoln University
Christchurch
New Zealand

Stephanie J. Fuller

Edith Cowan University
Joondalup
Australia

WILEY

This edition first published 2019
© 2019 John Wiley & Sons Ltd

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by law. Advice on how to obtain permission to reuse material from this title is available at <http://www.wiley.com/go/permissions>.

The right of Ralph N. Martins, Charles S. Brennan, W.M.A.D. Binosha Fernando, Margaret A. Brennan and Stephanie J. Fuller to be identified as the authors of this editorial material has been asserted in accordance with law.

Registered Office(s)

John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office

The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Limit of Liability/Disclaimer of Warranty

While the publisher and authors have used their best efforts in preparing this work, they make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives, written sales materials or promotional statements for this work. The fact that an organization, website, or product is referred to in this work as a citation and/or potential source of further information does not mean that the publisher and authors endorse the information or services the organization, website, or product may provide or recommendations it may make. This work is sold with the understanding that the publisher is not engaged in rendering professional services. The advice and strategies contained herein may not be suitable for your situation. You should consult with a specialist where appropriate. Further, readers should be aware that websites listed in this work may have changed or disappeared between when this work was written and when it is read. Neither the publisher nor authors shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

Library of Congress Cataloging-in-Publication data has been applied for

ISBN: 9781119356783

Cover Design: Wiley

Cover Images: © Irina Shatilova/Shutterstock, © Henrik5000/iStock.com, © corgarashu/Shutterstock, © Andrey Prokhorov/iStock.com

Set in 10/12pt WarnockPro by SPi Global, Chennai, India

10 9 8 7 6 5 4 3 2 1

Contents

List of Contributors xv

- 1 **Current Understanding of Alzheimer's Disease and Other Neurodegenerative Diseases, and the Potential Role of Diet and Lifestyle in Reducing the Risks of Alzheimer's Disease and Cognitive Decline** 1
Charles S. Brennan, Margaret A. Brennan, W.M.A.D. Binosh Fernando and Ralph N. Martins
 References 7
- 2 **Alzheimer's Disease and Other Neurodegenerative Diseases** 9
Stephanie J. Fuller, Hamid R. Sohrabi, Kathryn G. Goozee, Anoop Sankaranarayanan and Ralph N. Martins
 - 2.1 Introduction 9
 - 2.2 Alzheimer's Disease 9
 - 2.2.1 Pathology 9
 - 2.2.2 Symptoms 10
 - 2.2.3 Incidence 11
 - 2.2.4 Onset and Risk Factors 12
 - 2.2.5 Treatment 12
 - 2.2.6 Potential for AD Prevention 13
 - 2.3 Frontotemporal Lobe Dementia 13
 - 2.3.1 Neuropathology and Causes 14
 - 2.3.2 Treatment 15
 - 2.3.3 Diagnosis and Clinical Overlap with Other Diseases 15
 - 2.4 Vascular Dementia 16
 - 2.4.1 Symptoms and Diagnosis 16
 - 2.4.2 Causes and Risk Factors 16
 - 2.4.3 Prevention and Treatment 17
 - 2.4.4 Dementia with Lewy Bodies 18
 - 2.4.5 Causes 18
 - 2.4.6 Symptoms 18
 - 2.4.7 Diagnosis of DLB 18
 - 2.4.7.1 Clinical Approach to Dementias 19

2.5	Parkinson's Disease	19
2.5.1	Onset	22
2.5.2	Causes and Risk Factors	22
2.5.3	Incidence	22
2.5.4	Pathology	22
2.5.5	Treatment	23
2.6	Huntington's Disease	24
2.6.1	Genetics of the Disease	24
2.6.2	Incidence and Prevalence	25
2.6.3	Pathology	25
2.6.4	Treatment	26
2.7	Motor Neuron Diseases	27
2.7.1	Amyotrophic Lateral Sclerosis	27
2.7.2	Spinal Muscular Atrophy	27
2.7.3	Hereditary Spastic Paraplegia	27
2.7.4	Onset of MND and Differential Diagnosis	28
2.7.5	Incidence, Causes, and Risk Factors	28
2.7.6	Pathology	29
2.7.7	Treatment	30
2.8	Prion Diseases	30
2.8.1	Causes	31
2.8.2	Symptoms and Diagnosis	31
2.8.3	Treatment	32
2.8.4	Differential Diagnosis of the Various Types of Dementia	32
2.8.5	DLB Treatment	33
2.9	Summary	33
	References	34

3 Current and Developing Methods for Diagnosing Alzheimer's Disease 43

Stephanie J. Fuller, Nicholas Carrigan, Hamid R. Sohrabi and Ralph N. Martins

3.1	Introduction	43
3.2	Classical Post-Mortem Diagnosis	43
3.2.1	Plaques	44
3.2.2	Neurofibrillary Tangles (NFT)	44
3.2.3	Cerebral Amyloid Angiopathy (CAA)	44
3.2.4	Glial Responses	45
3.2.5	Brain Shrinkage	45
3.2.6	Loss of Synapses and Neurons	45
3.3	Clinical Diagnosis	45
3.3.1	Initial Assessment/Screening Tools	47
3.3.1.1	Mini-Mental State Examination (MMSE)	47
3.3.1.2	Montreal Cognitive Assessment (MoCA)	47
3.3.1.3	Clinical Dementia Rating (CDR)	47
3.3.1.4	Clock Drawing	48
3.3.1.5	Seven-Minute Screen	48
3.3.1.6	Alzheimer's Disease Assessment Scale (ADAS-Cog)	48
3.3.1.7	Psychogeriatric Assessment Scales (PAS)	48

3.3.1.8	Dementia Rating Scale (DRS)	49
3.3.1.9	Mini-Cog	49
3.3.1.10	Rowland Universal Dementia Assessment Scale (RUDAS)	49
3.3.1.11	The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery (nb) and Other Tests	49
3.4	Brain Imaging in the Diagnosis of Alzheimer's Disease and Other Dementias	51
3.4.1	Imaging Tests in AD Diagnosis: Established Tests	51
3.4.1.1	Computed Tomography (CT)	51
3.4.1.2	Electroencephalography (EEG)	51
3.4.1.3	Magnetic Resonance Imaging (MRI), for the Assessment of Morphological Changes, and the Detection of Stroke	52
3.4.1.4	Positron Emission Tomography (PET)	52
3.4.1.5	FDG-PET	52
3.4.2	Imaging Tests in AD Diagnosis: More Recently Developed Tests	52
3.4.2.1	MRI for Measuring Regional Blood Flow	53
3.4.2.2	Single Photon Emission Computed Tomography (SPECT) Scan	54
3.4.2.3	PiB-PET	54
3.4.3	The Rapidly Evolving Diagnostic Criteria	55
3.4.4	CSF Biomarkers of AD	56
3.4.4.1	A β , Tau, and A β PP-Related Biomarkers	56
3.4.4.2	Other Potential CSF Protein Biomarkers	57
3.4.4.3	Potential Lipid Biomarkers in the CSF	58
3.4.5	Blood Biomarkers of AD	60
3.4.5.1	A β Peptides in Plasma	60
3.4.5.2	Other Potential Blood Biomarkers	62
3.4.5.3	Blood Proteins	62
3.4.6	Blood Lipids	64
3.4.7	Metabolites	65
3.4.8	Blood Platelets	66
3.4.9	Genetic Risk Factors	67
3.4.10	The Eye as a Window to the Brain	68
3.4.11	miRNA Tests	69
3.5	Conclusions	71
	References	72
4	The Link Between Diabetes, Glucose Control, and Alzheimer's Disease and Neurodegenerative Diseases	89
	<i>Giuseppe Verdile, Paul E. Fraser and Ralph N. Martins</i>	
4.1	Introduction	89
4.2	The Impact of Type 2 Diabetes on the Brain	90
4.3	Evidence from Cell Culture, Animal, and Clinical Studies	93
4.3.1	CNS Insulin Signalling and Disruptions in AD	93
4.3.2	The Accumulation of A β Is Associated with Impaired Insulin Signalling	94
4.3.3	Insulin Resistance Promotes the Accumulation of A β	95
4.3.4	Impairments in Insulin Signalling Can Induce Hyperphosphorylation of Tau	96
4.3.5	Type 2 Diabetes and Neuroinflammation	96

4.3.6	Oxidative Stress and Mitochondrial Dysfunction in T2D and AD	97
4.3.7	Targeting Type 2 Diabetes to Slow Down Progression/Prevent Neurodegeneration and Cognitive Decline	99
4.4	Conclusions	103
	References	103
5	Diet and Nutrition, and their Influence on Alzheimer's Disease and other Neurodegenerative Diseases	117
	<i>Stephanie R. Rainey-Smith, Rhona Creegan, Stephanie J. Fuller, Michele L. Callisaya and Velandai Srikanth</i>	
5.1	Introduction	117
5.2	Dietary Patterns	118
5.3	Key Macronutrients	119
5.3.1	Dietary Fatty Acids	119
5.3.2	Cholesterol	120
5.3.3	Polyunsaturated Fatty Acids	121
5.3.4	Dietary Carbohydrates	122
5.4	Key Micronutrients	124
5.4.1	Water Soluble Vitamins	125
5.4.1.1	B Vitamins	125
5.4.2	Fat Soluble Vitamins	128
5.4.2.1	Vitamin A (Retinol, Retinal, and Retinoic Acid)	128
5.4.2.2	Vitamin D	129
5.4.2.3	Vitamin E	130
5.4.3	Dietary Minerals	131
5.4.3.1	Selenium	131
5.4.3.2	Manganese	132
5.4.3.3	Zinc, Iron, Copper, and Calcium	132
5.5	Conclusion	134
	References	135
6	Carbohydrate and Protein Metabolism: Influences on Cognition and Alzheimer's Disease	149
	<i>W.M.A.D. Binosh Fernando, Veer B. Gupta, Vijay Jayasena, Charles S. Brennan and Ralph N. Martins</i>	
6.1	Carbohydrates	149
6.1.1	Carbohydrate Digestion	149
6.1.2	Glucose Ingestion and Use	151
6.1.3	Glucose and Insulin, Insulin Resistance, and Type 2 Diabetes (Short Summary)	151
6.1.4	Relative Intake of Carbohydrate and Its Impacts on Neurodegenerative Disease Risk	152
6.1.5	Ketogenic Diets	154
6.1.6	Glucose and Its Effects on Cognition	154
6.1.7	Possible Mechanisms Related to Memory Enhancement with Glucose	157
6.1.7.1	Glucose and the Hippocampus	158
6.1.7.2	Glucose Availability in Brain Cells	158

6.1.7.3	Glucose and the Central Cholinergic System	159
6.1.7.4	ATP-Regulated Potassium (K-ATP) Channels and Brain Control of Glucose Homeostasis	159
6.1.7.5	Effects of High Fructose Diets	160
6.1.7.6	Sucrose	161
6.2	Proteins	161
6.2.1	Protein Metabolism in General	162
6.2.2	Links Between Specific Amino Acids and Brain Function	163
6.2.2.1	Tryptophan	163
6.2.2.2	Tyrosine	164
6.2.3	Clinical Studies of Protein Supplementation	165
6.2.4	Links Between Loss of Protein Function and Neurodegeneration	167
6.2.5	Clearance Mechanisms Associated with Proteinopathies Involved in Neurodegeneration	168
6.2.6	Role of Protein Crosslinking and Inflammation in Neurodegeneration and AD	170
6.3	Conclusion	171
	References	171
7	Fat and Lipid Metabolism and the Involvement of Apolipoprotein E in Alzheimer's Disease	189
	<i>Eugene Hone, Florence Lim and Ian J. Martins</i>	
7.1	Introduction	189
7.2	Alzheimer's Disease	189
7.3	Cholesterol and Lipid Metabolism	190
7.3.1	Cholesterol Synthesis and Metabolism	190
7.3.2	Oxysterols	191
7.3.2.1	Oxysterols in AD	191
7.3.3	Pathways of Dietary (Exogenous) Lipid Homeostasis	192
7.3.4	Pathways of Endogenous Lipid Homeostasis	193
7.3.5	Peripheral Clearance of Lipoproteins and Reverse Cholesterol Transport	195
7.3.5.1	Lipoproteins in the CNS	197
7.4	Apolipoprotein E Alleles and Isoforms	197
7.4.1	ApoE in the Brain	198
7.4.2	Apolipoprotein E and Alzheimer's Disease	198
7.4.2.1	ApoE Binding to A β	199
7.4.2.2	ApoE in the Cellular Clearance of A β	200
7.4.2.3	ApoE and Antioxidant Properties	201
7.4.2.4	ApoE and Tissue Transglutaminase	201
7.4.2.5	Apolipoprotein J (Clusterin, CLU)	202
7.5	LRP-1 in the Brain and Its Role in A β Clearance	203
7.5.1	LDL, HDL, and AD	203
7.5.2	Statins, Cholesterol, and AD	204
7.6	The Role of Lipid Rafts in Neurodegenerative Diseases	205
7.7	Changes to Glycerophospholipids in Alzheimer's Disease	206
7.7.1	Omega-3 and Omega-6 Fatty Acids	207

7.7.1.1	Omega-3 Fatty Acids, Modern Diets, and Health Implications	208
7.8	Sphingolipids	208
7.8.1	Ceramides	208
7.8.2	Sulfatides	209
7.8.3	Gangliosides	209
7.9	Conclusions	210
	References	210
8	Inflammation in Alzheimer's Disease, and Prevention with Antioxidants and Phenolic Compounds – What Are the Most Promising Candidates?	233
	<i>Matthew J. Sharman, Giuseppe Verdile, Shanmugam Kirubakaran and Gerald Münch</i>	
8.1	Introduction	233
8.2	Inflammation and the Immune Response in AD	233
8.2.1	The Role of Microglia and Astrocytes in Chronic Inflammation in AD	233
8.3	Oxidative Stress	236
8.3.1	Advanced Glycation End Products	237
8.3.2	Involvement of the Complement System in AD	238
8.3.3	Involvement of Cytokines and Chemokines in Inflammation	239
8.3.4	Inflammation – Susceptibility to A β Deposition or Aggregation	240
8.3.5	Inflammation Can Influence A β PP Metabolism and A β Clearance Directly	241
8.4	Current Medications for AD	242
8.4.1	Current Medications – Acetylcholinesterase Inhibitors and Memantine	242
8.5	Disease Modification and Treatment Approaches	243
8.5.1	Non-Steroidal Anti-Inflammatory Drugs (NSAID)	243
8.6	Some Anti-inflammatory Foods, Supplements, and Newly Developed Drugs for the Treatment of AD	244
8.6.1	Cinnamon/Cinnamaldehyde	244
8.6.2	(–)Epigallocatechin-3-Gallate (EGCG) and Other Green Tea Polyphenols	245
8.6.3	Curcumin	247
8.6.4	Other Polyphenolic Antioxidants	248
8.6.5	Omega-3 (n-3) Essential Fatty Acids	249
8.6.6	Lipoic Acid	250
8.7	Conclusion	253
	References	253
9	Cognitive Impairments in Alzheimer's Disease and Other Neurodegenerative Diseases	267
	<i>Hamid R. Sohrabi and Michael Weinborn</i>	
9.1	Introduction	267
9.2	Dementia due to Alzheimer's Disease	268
9.2.1	Subjective Cognitive Decline [4] and Mild Cognitive Impairment (MCI)	268

9.2.2	Memory Impairments in AD	271
9.2.2.1	Episodic Memory	271
9.2.2.2	Semantic Memory	272
9.2.2.3	Prospective Memory (PM)	272
9.2.3	Attention and Executive Dysfunction in AD	273
9.2.4	Language	274
9.2.5	Visuospatial Abilities	276
9.2.6	Dementia with Lewy Bodies and Parkinson's Disease with Dementia	276
9.2.7	Vascular Dementia	277
9.2.8	Frontotemporal Dementia	279
9.3	Conclusions	281
	References	282
10	Animal Models of Alzheimer's Disease	291
	<i>Prashant Bharadwaj</i>	
10.1	Introduction	291
10.2	Transgenic Mouse Models	292
10.3	Knock-in AD Mice Models	296
10.4	Non-Transgenic and Other Mammalian Animal Models	297
10.5	Drug Development and Translational Issues	298
10.6	Correlations Between Animal Models of AD and Human AD	300
10.7	Experimental Design and Reporting	301
10.8	The Future of Animal Models in AD	302
	References	303
11	The Products of Fermentation and Their Effects on Metabolism, Alzheimer's Disease, and Other Neurodegenerative Diseases: Role of Short-Chain Fatty Acids (SCFA)	311
	<i>W.M.A.D Binoshia Fernando, Charles S. Brennan and Ralph N. Martins</i>	
11.1	Introduction	311
11.2	Fermentable Substrates and Short-Chain Fatty Acids	312
11.2.1	Colonic Microflora and Fermentation	313
11.2.1.1	Probiotics and Prebiotics	313
11.2.2	Propionic Acid (PPA)	315
11.2.3	Acetic Acid	315
11.2.4	Butyric Acid	315
11.2.5	Short-Chain Fatty Acids and Free Fatty-Acid Receptor Signalling	316
11.2.6	Short-Chain Fatty Acids and Energy Intake	316
11.2.7	Short-Chain Fatty Acids and Energy Expenditure	319
11.2.8	Regulation of Fatty-Acid Metabolism by SCFA	320
11.2.9	Effect of Short-Chain Fatty Acids on Glucose Regulation	320
11.2.10	Regulation of Cholesterol Metabolism by Short-Chain Fatty Acids	321
11.2.11	Regulation of Inflammation by Short-Chain Fatty Acids	322
11.2.12	Short-Chain Fatty Acids and Neuroprotection	324
11.3	Conclusions	325
	References	326

12	Hormonal Expression Associated with Alzheimer's Disease and Neurodegenerative Diseases	335
	<i>Giuseppe Verdile, Anna M. Barron and Ralph N. Martins</i>	
12.1	The Hypothalamic–Pituitary–Gonadal (HPG) Axis	335
12.1.1	Dysregulation of the HPG Axis During Ageing	336
12.2	Roles for Sex Steroids and Gonadotropins in the Neurodegenerative Process in AD	339
12.2.1	Sex Steroids Modulate A β Accumulation	340
12.2.2	Sex Steroids and Oxidative Stress	342
12.2.3	Sex Steroids and Inflammation	344
12.2.4	Testosterone and Diabetes	346
12.2.5	A Role for Gonadotropins in AD Pathogenesis	347
12.3	Hormone-based Therapies	349
12.3.1	The Oestrogens	349
12.3.2	Testosterone Therapy	350
12.3.3	Selective Oestrogen or Androgen Receptor Modulators (SERM or SARM)	352
12.3.4	Gonadotropin-Lowering Agents	354
12.4	Conclusions	355
	References	355
13	The Link Between Exercise and Mediation of Alzheimer's Disease and Neurodegenerative Diseases	371
	<i>Belinda Brown and Tejal M. Shah</i>	
13.1	Introduction	371
13.2	Physical Activity Promotes Health and Well-being	372
13.3	Neuroplasticity	372
13.4	The Link Between Physical Activity and Cognition Across the Human Lifespan	373
13.4.1	Childhood	373
13.4.2	Adulthood and Midlife	374
13.4.3	Older Adults	375
13.5	Physical Activity Reduces the Risk of Dementia and AD	376
13.6	Mechanisms Underlying the Relationship Between Exercise and Brain Health	376
13.6.1	Evidence from Molecular and Cellular Research	377
13.6.2	Neurotrophins	378
13.6.3	Hormonal Pathways	379
13.6.4	Cardiovascular and Metabolic Mechanisms	380
13.6.5	Evidence from Neuroimaging Studies	380
13.7	The Effect of Genetics on the Relationship Between Exercise and Brain Health	381
13.8	Future Directions	382
	References	382

14	Current and Prospective Treatments for Alzheimer's Disease (and Other Neurodegenerative Diseases) 391
	<i>Steve Pedrini, Mike Morici and Ralph N. Martins</i>
14.1	Introduction 391
14.2	Current and Potential Medical Treatments 391
14.2.1	Treatments That Influence Neurotransmission 391
14.2.1.1	Cholinergic System 391
14.2.1.2	Other Neurotransmitters 396
14.2.2	Cholesterol-Lowering Medications 399
14.2.3	Immunotherapy 400
14.2.3.1	Active Immunotherapy (A β) 401
14.2.3.2	Active Immunotherapy (tau) 402
14.2.3.3	Passive Immunotherapy (A β) 402
14.2.3.4	Passive Immunotherapy (tau) 404
14.2.4	Targeting the A β -Producing Pathway 405
14.2.4.1	α -Secretase 406
14.2.4.2	β -Secretase 406
14.2.4.3	γ -Secretase 407
14.2.5	Other Compounds Affecting A β 408
14.2.6	Other Compounds Affecting Tau 410
14.2.7	Inflammatory Targets 411
14.3	Conclusions 412
	References 412
15	The Role of Genetics in Alzheimer's Disease and Parkinson's Disease 443
	<i>Tenielle Porter, Aleksandra K. Gozt, Francis L. Mastaglia and Simon M. Laws</i>
15.1	Introduction 443
15.2	Genetics of Alzheimer's Disease 444
15.3	Autosomal Dominant AD (ADAD) 445
15.3.1	Understanding the Importance of APP and the Presenilins in AD 445
15.4	Amyloid Precursor Protein (APP) 447
15.5	Presenilin 1 (PSEN1) 447
15.6	Presenilin 2 (PSEN2) 448
15.7	Genetic Contributions to Sporadic Late-Onset AD (LOAD) 449
15.8	Cholesterol Metabolism 449
15.8.1	Apolipoprotein E (APOE) 449
15.8.2	Clusterin (CLU) 452
15.8.3	ATP-Binding Cassette Transporter A7 (ABCA7) 453
15.9	Immune Response 454
15.9.1	Complement Receptor 1 (CR1) 454
15.9.2	CD33 (Myeloid Cell Surface Antigen CD33; Sialic Acid-Binding Immunoglobulin-Like Lectin 3) 455
15.9.3	Membrane Spanning 4 Domains, Subfamily A (MS4A) 456
15.9.4	Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) 456

15.9.5	Further Genetic Associations Implicating the Immune Response	457
15.10	Endocytosis	458
15.10.1	Bridging Integrator 1 (<i>BINI</i>)	459
15.10.2	Phosphatidylinositol Binding Clathrin Assembly Lymphoid Myeloid Protein (<i>PICALM</i>)	460
15.10.3	CD2-Associated Protein (<i>CD2AP</i>)	461
15.10.4	Further Genetic Associations Implicating Endocytosis	462
15.10.5	Variants in <i>APP</i> and Genes for APP-Metabolising Proteins	463
15.10.6	Further Mechanisms Implicated Through Genetic Associations	464
15.11	Genetics of Parkinson's Disease	465
15.12	Monogenic forms of PD	466
15.12.1	Autosomal Dominant Forms	466
15.12.1.1	PARK 1 (<i>SNCA</i>)	466
15.12.1.2	PARK 8 (<i>LRRK2</i>)	467
15.12.1.3	PARK 11 (<i>GIGYF2</i>)	468
15.12.1.4	PARK 17 (<i>VPS35</i>)	468
15.12.1.5	PARK 18 (<i>EIF4G1</i>)	468
15.12.2	Autosomal Recessive Forms	469
15.12.2.1	PARK 2 (<i>PRKN</i>)	469
15.12.2.2	PARK 6 (<i>PINK 1</i>)	469
15.12.2.3	PARK 7 (<i>DJ-1</i>)	470
15.12.2.4	PARK 9 (<i>ATP13A2</i>)	470
15.12.2.5	PARK 14 (<i>PLA2G6</i>)	470
15.12.2.6	PARK 15 (<i>FBXO7</i>)	471
15.12.3	Genetic Contributions to Late-Onset Sporadic PD (LOPD)	471
15.12.4	Common Variants in PD Genes	471
15.12.5	Glucocerebrosidase (<i>GBA</i>)	472
15.12.6	Immune-Inflammatory Genes	472
15.12.7	Mitochondrial DNA Variants	473
15.13	Conclusion	473
	References	474

Final Thoughts Regarding Alzheimer's Disease, Diet, and Health 499

Charles S. Brennan, Margaret A. Brennan, W.M.A.D. Binosha Fernando, Stephanie J. Fuller and Ralph N. Martins

List of Abbreviations 503**Index** 511

List of Contributors

Anna M. Barron

School of Psychiatry and Clinical
Neurosciences
University of Western Australia
Perth, WA, Australia

and

Lee Kong Chian School of Medicine
Nanyang Technological University
Singapore

Prashant Bharadwaj

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

School of Pharmacy and Biomedical
Sciences
Curtin Health and Innovation Research
Institute (CHIRI)
Faculty of Health Sciences
Curtin University
Perth, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Charles S. Brennan

Department of Wine, Food and
Molecular Biosciences
Centre for Food Research and Innovation
Lincoln University
Christchurch, New Zealand

and

School of Food Science
South China University of Technology
Guangzhou, China

and

School of Food Science
Tianjin University of Commerce
Tianjin, China

and

Riddett Institute Palmerston North
New Zealand

Margaret A. Brennan

Department of Wine, Food and
Molecular Biosciences
Centre for Food Research and Innovation
Lincoln University
Christchurch, New Zealand

and

College of Food Science
South China University of Technology
Guangzhou, China

and

School of Food Science
Tianjin University of Commerce
Tianjin, China

Belinda Brown

School of Psychology and Exercise
Science
Murdoch University
Perth, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, Australia

Michele L. Callisaya

Menzies Institute for Medical Research,
University of Tasmania
Hobart, TAS, Australia

and

Peninsula Clinical School
Central Clinical School Monash
University
Melbourne, Vic, Australia

Nicholas Carrigan

Older Adult Mental Health Service
Western Australia Country Health
Service (SouthWest)
Bunbury, WA, Australia

and

School of Medical and Health Sciences
Centre of Excellence for Alzheimer's
Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation Ralph and Patricia Sarich
Neuroscience Research Institute
Nedlands, WA, Australia

Rhona Creegan

Omega Nutrition Health
Perth, WA, Australia

W.M.A.D. Binoshha Fernando

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Paul E. Fraser

Tanz Centre for Research in
Neurodegenerative Diseases
University of Toronto
Canada

Stephanie J. Fuller

School of Medical and Health Sciences
Centre of Excellence for Alzheimer's
Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

Kathryn G. Goozee

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical
Neurosciences
University of Western Australia
Perth, WA, Australia

and

Cooperative Research Centre for
Mental Health
Carlton, Vic, Australia

and

Kara Institute of Neurological Diseases
Sydney, NSW, Australia

and

Anglicare
Sydney, NSW, Australia

Aleksandra K. Gozt

Collaborative Genomic Group
Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

Veer B. Gupta

School of Medicine
Deakin University
Geelong, Vic, Australia

Eugene Hone

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

Vijay Jayasena

School of Science and Health
Western Sydney University
Sydney, NSW, Australia

Shanmugam Kirubakaran

Department of Pharmacology and
Molecular Medicine Research Group
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Simon M. Laws

Collaborative Genomic Group
Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

and

School of Pharmacy and Biomedical
Sciences
Faculty of Health Sciences
Curtin Health Innovation Research
Institute
Curtin University
Bentley, WA, Australia

Florence Lim

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

Ian J. Martins

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

Ralph N. Martins

School of Medical and Health Sciences
Centre of Excellence for Alzheimer's
Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical
Neurosciences
University of Western Australia
Perth, WA, Australia

and

KaRa Institute of Neurological Diseases
Sydney, NSW, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Francis L. Mastaglia

Institute for Immunology and Infectious
Diseases
Murdoch University
Murdoch, WA, Australia

Mike Morici

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

Gerald Münch

Department of Pharmacology and
Molecular Medicine Research Group
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Steve Pedrini

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Tenielle Porter

Collaborative Genomic Group
Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

Stephanie R. Rainey-Smith

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Anoop Sankaranarayanan

Department of Psychiatry
School of Medicine
Western Sydney University
Sydney, NSW, Australia

Tejal M. Shah

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

Matthew J. Sharman

School of Health Sciences
University of Tasmania
Launceston, TAS, Australia

Hamid R. Sohrabi

School of Medical and Health Sciences
Centre of Excellence for Alzheimer's
Disease Research and Care
Edith Cowan University
Joondalup, WA, Australia

and

Department of Biomedical Sciences
Macquarie University
Sydney, NSW, Australia

and

School of Psychiatry and Clinical
Neurosciences
University of Western Australia
Perth, WA, Australia

and

Cooperative Research Centre for Mental
Health
Carlton, Vic, Australia

and

KaRa Institute of Neurological Diseases
Sydney, NSW, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Velandai Srikanth

Department of Medicine, Peninsula
Health
Melbourne, Vic, Australia

and

Peninsula Clinical School, Central
Clinical School
Monash University
Melbourne, Vic, Australia

Giuseppe Verdile

School of Pharmacy and Biomedical
Sciences
Faculty of Health Sciences
Curtin Health Innovation Research
Institute
Curtin University of Technology
Bentley, WA, Australia

and

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences
Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Michael Weinborn

School of Psychology
University of Western Australia
Crawley, WA, Australia

and

Centre of Excellence for Alzheimer's
Disease Research and Care
School of Medical and Health Sciences

Edith Cowan University
Joondalup, WA, Australia

and

Australian Alzheimer's Research
Foundation
Ralph and Patricia Sarich Neuroscience
Research Institute
Nedlands, WA, Australia

Current Understanding of Alzheimer's Disease and Other Neurodegenerative Diseases, and the Potential Role of Diet and Lifestyle in Reducing the Risks of Alzheimer's Disease and Cognitive Decline

Charles S. Brennan^{1,2,3,4}, Margaret A. Brennan^{1,2,4}, W.M.A.D. Binosha Fernando^{5,9} and Ralph N. Martins^{5,6,7,8,9}

¹Department of Wine, Food and Molecular Biosciences, Centre for Food Research and Innovation, Lincoln University, PO Box 85084, Lincoln, Christchurch, New Zealand

²School of Food Science, South China University of Technology, Guangzhou, China

³Riddet Institute, Palmerston North, New Zealand

⁴School of Food Science, Tianjin University of Commerce, Tianjin, China

⁵School of Medical and Health Sciences, Centre of Excellence for Alzheimer's Disease Research and Care, Edith Cowan University, Joondalup, WA, Australia

⁶Department of Biomedical Sciences, Macquarie University, Sydney, NSW, Australia

⁷School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia

⁸KaRa Institute of Neurological Diseases, Sydney, NSW, Australia

⁹Australian Alzheimer's Research Foundation, Ralph and Patricia Sarich Neuroscience Research Institute, Nedlands, WA, Australia

This book is intended to give an up-to-date overview of what is currently known about neurodegenerative diseases, focusing particularly on Alzheimer's disease (AD). Current and developing diagnostic tests are described, and the pathological relationships between AD and other conditions now believed to be risk factors for AD are also described. In particular, we discuss cardiovascular disease, obesity, insulin resistance and type 2 diabetes, focusing on abnormal lipid and sugar metabolism linked to these conditions, and how this is related to AD risk. We provide evidence that improved diet and exercise may reduce AD risk, not just the risk of the other conditions mentioned above. Hopefully this book will provide some food for thought concerning easily adoptable non-pharmacological methods to reduce AD risk, which would need to be adopted at early pre-clinical stages of the disease.

Diet and health are intrinsically linked, and the effect of dietary intakes on our health has been researched and documented for millennia. The consumption of protein, fat, carbohydrates, vitamins and minerals is required for our physiological function. Certain food-based chemicals – bioactive compounds – yield health benefits beyond their mere chemical constituents, and can modify the biological functionality and health of our cells. These bioactive compounds may help enhance repair of our bodies from injuries, mediate the risk of certain diseases (cancer, coronary heart disease) through altering the physiological functions of our cells and organs. There is strong public awareness in terms of the old adage 'you are what you eat', however the information available to the public ranges from scientifically based research, to traditional dietary remedies, to dangerous fad diets. There is also a plethora of food products that have been designed by the food

industry to provide consumers with foods or supplements designed to combat all sorts of illnesses and disorders.

We have long known that there is a connection between the over-consumption of calories and weight gain, particularly fats and carbohydrates. For example, an excess of refined carbohydrates has been associated with overweight, obesity, type 2 diabetes and a number of metabolic disorders and now also, as described in this book, neurodegenerative diseases such as AD and cerebrovascular disease. However, despite this knowledge, and despite the introduction of numerous public health intervention programmes by governments and medical bodies, the percentage of the population which can be classified as overweight or obese continues to rise. Though there is research evidence that some genetic traits predispose certain people to easier weight gain, leading to obesity, this rise in obesity is believed by most to be mainly a result of increased calorie intake and reduced calorie expenditure.

Recently there has been an increased interest in the role the food industry has played in the production of modern food materials. Researchers and popular writers alike are keen to blame the food industry for today's nutritional problems by suggesting that modern food processing techniques produce what some people call high-calorie, energy-dense, nutrient-poor foods, and it would be foolish to ignore the fact that the food industry has played a part in the situation we find ourselves in. If we are consuming more calories as a population than we were 20 or 50 or 70 years ago, and if many of the foods consumed are highly processed, then this has a double impact on our nutritional status. Combine this with the fact that most of us are becoming more sedentary in our work and social lives, then the balance would be that we will be prone to storing excess calories. As described in this book, overweight and obesity as well as high consumption of refined carbohydrates lead to insulin resistance, type 2 diabetes and cardiovascular disease, which are in epidemic proportions in western countries. There is a train of thought that suggests that this overconsumption of calories is a 'western' problem; however, the situation is manifesting itself to be a global problem, with dramatic increases in Asian countries in recent years (for instance, rapid rises in obesity and diabetes levels in China, Malaysia, Singapore and Taiwan, to name a few).

Fat and lipid metabolism has been studied at length in relation to cardiovascular health, and more recently this topic has become important in AD studies. A few decades ago, all fats were regarded as unhealthy, and a high fat intake, particularly cholesterol, was considered to be the main dietary problem when taking into account the increasing rate of obesity, hypertension and cardiovascular disease in western countries. This led to the food industry generating products that were low in fat. However, to compensate on flavour, these foods often contained higher sugar and salt levels than previously. More recent research indicates that cholesterol is not the main problem, that long-chain saturated fat is a greater problem than cholesterol, and that high sugar intake from carbonated drinks, confectionery and processed foods has only exacerbated the increasing obesity level. Furthermore, lifestyle changes [1] have created a demand for more convenience foods, and foods with a long shelf life. These foods are generally more highly processed than those which were available 30–70 years ago. There is also scientific research which indicates that food processing affects the structure of the protein, fat and carbohydrate components (including sugar in the carbohydrate fraction) in foods. These changes may have led to longer shelf-life, or made the foods more desirable, however many have a high salt or high sugar content,

and may contain undesirable fats such as trans-fatty acids. In addition, our intake of essential fatty acids has changed with the advent of processed foods and other western dietary changes. The intake of essential polyunsaturated fatty acids, in particular the omega-3 and omega-6 fatty acids, has considerable influence on our brain health, levels of inflammation and brain function, yet our intake, and the ratio of omega-6 : omega-3 fatty acids has changed over the millennia. There is evidence that we evolved on a diet with a ratio of omega-6:omega-3 fats of approximately 1:1, yet a western diet has a ratio of approximately 15:1, and omega-6 fatty acids are linked to increased brain inflammation, as discussed in this book.

Several chapters in this book describe how excess refined carbohydrate intake disrupts the metabolic functions of the body. Once these are compromised, the body is subjected to stress. This stress is in the form of chronic inflammation and oxidative stress [2], which then negatively influences cellular functionality, cellular signalling and in the brain – neurological function. These are some of the findings of studies illustrating that obesity and type 2 diabetes are significant risk factors for the development of neurological disorders including AD [3].

Two chapters of the book discuss the various common causes and symptoms of dementia, differential diagnosis, AD diagnostic tests, and current treatments. AD is characterised by gradual cognitive impairment, and the risk of developing this condition increases with age, such that, past the age of 65, the risk doubles every five years. Pathologically, the disease is characterised by the death of neurons in the cerebral cortex, hippocampus and forebrain, which is associated with the formation of extracellular amyloid deposits, intracellular neurofibrillary tangles consisting of hyper-phosphorylated tau protein, as well as inflammation [4]. Although medications are available for the treatment of AD, these medications only serve to reduce the cognitive symptoms of some people with AD and then only for a relatively short period. There are also medications that can reduce other symptoms of Alzheimer's, such as anxiety and sleeplessness, and these are all discussed in this book. However, there are currently no medications that can stop the eventual continuing neurological degeneration and resultant cognitive degeneration of Alzheimer's. As mentioned earlier, one of the main messages of this book is that, if we can manipulate our diet and lifestyle at mid-life, and reduce our risks associated with excess calorie intake, overweight, obesity and type 2 diabetes, we may be able to achieve long-term prevention or delay of the disorder.

We should be concerned about food consumption and obesity. This could be discussed in terms of a change in lifestyle opportunities, or self-esteem or peer perception. The way weight issues contribute to psychological and personal well-being has been studied extensively in the past. More importantly, there is a health cost associated with these issues. Increased weight and obesity have been documented to be associated with a reduction in life expectancy through greater risk factors associated with type 2 diabetes, coronary heart disease, metabolic complications and more recently AD and other neurodegenerative diseases.

Epidemiological studies have investigated the effect of certain diets on longevity and health, particularly the Mediterranean diet and Okinawan diets. Laboratory studies have also investigated the relationship between certain food components and the manipulation of physiological effects either through whole animal studies, or through *in vitro* experiments using cell culture. Many epidemiological and longitudinal studies have illustrated that there is an increased risk for AD and cognitive impairment in

future years, in those individuals exhibiting obesity and diabetes. Several chapters of this book discuss glucose metabolism [5], insulin resistance, carbohydrate metabolism, and how a high intake of refined carbohydrate and sugar can lead to dysregulated brain glucose metabolism, inflammation and oxidative stress, and how all of the above are linked to AD.

Many studies have reported a correlation between diets rich in saturated fatty acids and increased low-density lipoprotein, decreased high-density lipoprotein and what is now regarded as high blood cholesterol levels; this in turn has been associated with the development of neurological impairment through cerebral inflammation, and increased development of A β deposition in the brain. Other studies have indicated that as people age, the content of docosahexaenoic acid (DHA) in the brain decreases. Furthermore, animal studies have shown that DHA supplementation improves cognitive functions through the regulation of cell lipids and A β production. These are some of the findings that support the change from a diet rich in saturated fats to one rich in polyunsaturated fats, particularly the omega-3 fatty acids. Lipids in the diet and how they relate to the risk of AD are discussed in a chapter of this book.

Mounting scientific data indicates that antioxidants contribute to the neutralisation of oxidative reactions occurring in the body [6], and increased intake of dietary fibre can aid weight control, glucose metabolism and the gut–brain axis. For instance, research has suggested that there is a strong link between the consumption of fruits and vegetables in adults, and the diminishing of the risks associated with the onset of cognitive decline, possibly due to the reduction in incidence or severity of the associated conditions of cardiovascular disease, obesity and type 2 diabetes. However, it is fair to mention that neurodegeneration can arise for a number of reasons which are not solely diet-related (such as genetic predisposition to neurodegenerative diseases, environmental stimuli, hormonal imbalances, stress situations), and interestingly mitochondrial dysfunction, or cell energy impairment, apoptosis, and overproduction of reactive oxygen species is the final common pathogenic mechanism in neurodegenerative diseases [2].

Our own natural antioxidant system, which consists of enzymes as well as biochemical compounds, is crucial in balancing the oxidative stress within our bodies and minimising any damage caused by free radicals [7]. These mechanisms are discussed in this book, as well as changes to this system which have been observed in type 2 diabetes, obesity, ageing and AD.

It is known now that AD develops in the brain for around 20 years before cognitive symptoms emerge. Eventually the cognitive impairment reaches a level where a diagnosis of possible/probable AD is made, using the diagnostic criteria described in detail in a chapter in this book. Again, there is somewhat of a chicken and egg situation regarding dietary imbalances – a bad diet may increase risk of AD and accelerate its development in the brain, then once a person has some level of cognitive impairment, either as self-reported memory loss or as diagnosed, measured mild-cognitive impairment (but not yet clinical AD), there is the risk of withdrawal from normal social life, and the development of depression and anxiety, and these can increase the likelihood of developing dietary problems such as a lower quality of nutrition. In turn this can lead to weight loss, lack of mobility and a further reduction in the quality of life. Intervention studies using rat models as well as clinical studies have indicated that there is a potential to slow the progression of neurological impairment using dietary and lifestyle interventions. This could be in the form of improving the overall diet, promoting

the consumption of bioactive ingredients from certain foods, a reduction in energy consumption, improved mineral uptake and/or maintenance/increased levels of physical activity to improve physiological function and cardiovascular health. The important message here is that if we know a person is in the early preclinical stages of Alzheimer's, there may be sufficient time (at least 10 years) in which preventative treatments or diets can be applied, with the aim of delaying cognitive decline.

Good vitamin and antioxidant [6] intake has been associated with resistance to cognitive decline, and vitamins are discussed in this book, in relation to oxidative stress and AD. For instance folic acid, vitamin B6, and vitamin B12 have been reported to be related to the maintenance of cognitive function [3, 8]. Part of the mechanisms behind this could relate to the fact that these vitamins are physiologically important for the development and repair of neuronal networks, and this may also be associated with the links between vitamins and minerals in cell signalling and development. Individuals who have low levels of vitamin B12 appear to be more prone to the development of neurological impairments. Similarly, it has been suggested that avoiding vitamin C deficiencies can help maintain cognitive function through immunomodulation and protection of neurons [9]. The form in which these vitamins and minerals are ingested is of importance, most likely due to their bioavailability, so that it has been suggested that ingestion of foods rich in antioxidant vitamins (rather than supplements), or combinations of vitamins (such as C and E) may help delay the onset of AD [10], and in fact it has been shown that dietary supplementation using individual vitamins has little effect. Furthermore, studies which investigate the potential use of single refined compounds on neurodegenerative diseases may be hard to translate to normal dietary situations, and it is most likely that a combination of healthy foods is likely to be most effective.

Within this book you will find a variety of tests for determining cognitive impairment, and tests to distinguish between several different types of neurodegenerative conditions, including AD, dementia with Lewy bodies, and fronto-temporal dementia, for example. You will also discover many novel potential methods for the diagnosis of AD. Diagnosis at preclinical stages is the aim now, as the prevention or the slowing of the onset of AD, when the disease is in the very early stages of development, is emerging as the most likely avenue for an effective reduction in AD incidence. Therefore, intervention studies need to be carried out on people with very early stages of AD, preferably well before the onset of symptoms, to determine how dietary change and particular food components may affect the development of AD as well as other neurological disorders. However, a diagnosis of Alzheimer's is clearly not necessary to adopt a healthier diet and lifestyle.

One area of research that has proven of considerable interest in recent years is the antioxidant and medicinal value of plant-based foods, with the aim of providing treatments, including preventative treatments for many conditions. Harnessing these ingredients is not new: traditional European, western or Chinese medicine practices are rich in examples of such uses of common plant species. For instance, Chinese medicinal practices utilise mushroom materials to combat a number of metabolic disorders. This has been a particular research focus of our laboratories. Whilst the consumer in the UK, USA or NZ may be accustomed to 4–5 different types of mushroom species which are commonly available in the supermarkets, there are over 900 different species of mushroom in China. We have shown that mushrooms are a rich source of bioactive compounds such as β -glucans, peptides, chitinous substances, terpenes, sterols and phenolic compounds [11, 12]. In addition, we and

other researchers have illustrated that these bioactive compounds are useful in terms of anti-inflammatory, antioxidant, anti-cancer, anti-virus, anti-microbial, anti-diabetic and immune modulating ingredients, and some have the potential to stimulate axon generation during brain development [11–13]. With respect to AD, the capacity of several medicinal mushroom species to inhibit the enzyme BACE-1 (one of the enzymes required to produce A β amyloid peptide of AD from its precursor, amyloid precursor protein [APP]) was investigated *in vitro*, and it was discovered that extracts of *Auricularia polytricha* (wood ear mushroom) can reduce the activity of the enzyme [14]. When scopolamine-stressed mice were fed mushroom extracts rich in phenolic compounds (for instance from *Inonotus obliquus*), their performance in memory tests improved; whereas in cell culture experiments involving 6-hydroxydopamine-induced stress, a mushroom compound dihydroxybenzalacetone led to protection against neurodegeneration [15, 16].

Chinese tea, green tea, and even black teas have been investigated for the effects of tea phenolic compounds on obesity, oxidative stress, diabetes and neurological functionality [17]. Arguably, tea is the most widely consumed beverage in the world, and tea is a rich source of bioactive ingredients, of which catechins and theanine are the two most studied. These components have been shown to have a neuroprotective effect by inhibiting A β formation through inhibiting fibrillar aggregation, and via inhibition of acetylcholinesterase [18, 19]. Catechins can make up between 12% and 24% of the dry weight of tea leaves, and mainly include epigallocatechin (EGC), epicatechin (EC), catechin, epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG); whereas theanine commonly makes up 1–2% of tea. The process of making tea naturally extracts these compounds into the liquid which we then consume. Both catechins and theanine have been shown to cross the blood–brain barrier and enter brain tissue [17, 20]. The catechins in both green and black tea have been shown to be potent antioxidant compounds. For instance, the antioxidant activity of tea polyphenols has been shown to inhibit the release free radicals and to limit cellular damage [21]. The polyphenol antioxidants in tea are discussed in greater detail in the chapter on inflammation.

The consumption of caffeine has also been shown to protect against cognitive impairment. Finnish researchers evaluated data over a number of years relating to a cohort of over 1000 people, and illustrated that the consumption of three cups of coffee a day can delay the progression of AD. These effects have been suggested to be due to the caffeine content of coffee. Research has indicated that the consumption of 300 micrograms of caffeine daily may reduce the risk of AD, slow cognitive impairment and reduce A β levels in the brain and blood [22]. There is also evidence caffeine may inhibit the rate of A β production and hence the formation of toxic A β fibrils which have been linked with neurodegeneration. Caffeine can act as an antioxidant, however coffee is rich in many other antioxidants, and the combination of these may be providing the benefits of coffee.

The study of the genetics of AD has also revealed that particular forms of many genes are linked to increased risk of the disease. The main risk factor gene is apolipoprotein E, for which possession of the e4 allele increases several-fold the risk of developing AD. However, particular forms of many other genes and genetic mutations have been shown to influence Alzheimer's risk, and the study of these other genes is revealing considerable information about the metabolic and biochemical pathways involved in disease pathogenesis, as described in detail in the chapter on genetics.

Another chapter of the book describes the importance of fermentation in our digestive process. Fermentation in our gut produces short-chain fatty acids which have been shown to have a myriad of beneficial effects, including reducing the risk of type 2 diabetes and inflammation. The importance of prebiotics and probiotics in our diet has become a popular topic in health food conversations, yet more clinical research is needed to gain a better understanding of the gut–brain axis and how it influences our health. Having said this, animal studies have provided a huge amount of valuable information concerning AD, especially the studies of AD-model transgenic mice. The major animal models which have been studied over the years are reviewed in one of the book's chapters, including their uses and limitations.

Epidemiological experiments, as well as the *in vivo* and *in vitro* trials conducted on numerous food items, have given rise to a prolific nutraceutical industry endeavouring to provide consumers with a range of supplements to enhance lifestyles and reduce the incidence of many conditions. However, these nutraceuticals should only be regarded as a supplementation to an enhanced lifestyle which includes physical fitness, reduction of stress and healthy eating. The whole issue of diet and human nutrition is a complex relationship of factors which interact to exert effects on physiological function and health. A key message of this book concerns the deficiencies of the western diet, and how overall dietary changes to mimic the Mediterranean diet or Okinawan diet (both linked to health and longevity) are advisable. Such changes are recommended due to the health promoting properties of antioxidants and anti-inflammatory compounds as well as essential fats and vitamins to be found in fresh foods, coupled with reductions in the intake of meat, processed foods, and especially refined carbohydrates. We hope that the chapters of this book explain the background knowledge of AD and some other neurological conditions, and help illustrate the potential new ways in which we can utilise new knowledge that is being obtained in scientific research, to benefit our health and well-being.

References

- 1 Pasinetti, G.M. and Eberstein, J.A. (2008). Metabolic syndrome and the role of dietary lifestyles in alzheimer's disease. *J. Neurochem.* 106: 1503–1514.
- 2 Emerit, J., Edeas, M., and Bricaire, F. (2004). Neurodegenerative diseases and oxidative stress. *Biomed. Pharmacother.* 58: 39–46.
- 3 Cukierman, T., Gerstein, H.C., and Williamson, J.D. (2005). Cognitive decline and dementia in diabetes – systematic overview of prospective observational studies. *Diabetologia* 48: 2460–2469.
- 4 Claeysen, S., Cochet, M., Donneger, R. et al. (2012). Alzheimer culprits: cellular crossroads and interplay. *Cell. Signalling* 24: 1831–1840.
- 5 Shorr, R.I., de Rekeneire, N., Resnick, H.E. et al. (2006). Glycemia and cognitive function in older adults using glucose-lowering drugs. *J. Nutr. Health Aging* 10: 297–301.
- 6 Luchsinger, J.A., Tang, M.X., Shea, S., and Mayeux, R. (2003). Antioxidant vitamin intake and risk of Alzheimer disease. *Arch. Neurol.* 60: 203–208.
- 7 Halliwell, B. (2001). Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. *Drugs Aging* 18: 685–716.

- 8 Clarke, R., Smith, A.D., Jobst, K.A. et al. (1998). Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch. Neurol.* 55: 1449–1455.
- 9 Harrison, F.E. (2012). A critical review of vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease. *J. Alzheimer's Dis. JAD* 29: 711–726.
- 10 Zandi, P.P., Anthony, J.C., Khachaturian, A.S. et al. (2004). Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch. Neurol.* 61: 82–88.
- 11 Xikun, L., BM, A., Luca, S. et al. (2016). How the inclusion of mushroom powder can affect the physicochemical characteristics of pasta. *Int. J. Food Sci. Technol.* 51: 2433–2439.
- 12 Vallee, M., Lu, X., Narciso, J.O. et al. (2017). Physical, predictive glycaemic response and antioxidative properties of black ear mushroom (*Auricularia auricula*) extrudates. *Plant Foods Hum. Nutr.* 72: 301–307.
- 13 Wasser, S.P. (2002). Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl. Microbiol. Biotechnol.* 60: 258–274.
- 14 Bennett, L., Sheean, P., Zabarar, D., and Head, R. (2013). Heat-stable components of wood ear mushroom, *Auricularia polytricha* (higher Basidiomycetes), inhibit in vitro activity of beta secretase (BACE1). *Int. J. Med. Mushrooms* 15: 233–249.
- 15 Giridharan, V.V., Thandavarayan, R.A., and Konishi, T. (2011). Amelioration of scopolamine induced cognitive dysfunction and oxidative stress by *Inonotus obliquus* – a medicinal mushroom. *Food Funct.* 2: 320–327.
- 16 Gunjima, K., Tomiyama, R., Takakura, K. et al. (2014). 3, 4-dihydroxybenzalacetone protects against Parkinson's disease-related neurotoxin 6-OHDA through Akt/Nrf2/glutathione pathway. *J. Cell. Biochem.* 115: 151–160.
- 17 Trevisanato, S.I. and Kim, Y.I. (2000). Tea and health. *Nutr. Rev.* 58: 1–10.
- 18 Grelle, G., Otto, A., Lorenz, M. et al. (2011). Black tea theaflavins inhibit formation of toxic amyloid-beta and alpha-synuclein fibrils. *Biochemistry* 50: 10624–10636.
- 19 Harvey, B.S., Musgrave, I.F., Ohlsson, K.S. et al. (2011). The green tea polyphenol (–)-epigallocatechin-3-gallate inhibits amyloid- β evoked fibril formation and neuronal cell death in vitro. *Food Chem.* 129: 1729–1736.
- 20 Mandel, S.A., Amit, T., Weinreb, O., and Youdim, M.B. (2011). Understanding the broad-spectrum neuroprotective action profile of green tea polyphenols in aging and neurodegenerative diseases. *J. Alzheimers Dis.* 25: 187–208.
- 21 Koh, S.H., Kim, S.H., Kwon, H. et al. (2003). Epigallocatechin gallate protects nerve growth factor differentiated PC12 cells from oxidative-radical-stress-induced apoptosis through its effect on phosphoinositide 3-kinase/Akt and glycogen synthase kinase-3. *Brain Res. Mol. Brain Res.* 118: 72–81.
- 22 Arendash, G.W. and Cao, C. (2010). Caffeine and coffee as therapeutics against Alzheimer's disease. *J. Alzheimers Dis.* 20 (Suppl 1): S117–S126.