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Precision medicine and metabolic syndrome

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Review Article

Abstract

Metabolic syndrome (MetS) is one of the most important health issues around the world and a major risk factor for both type 2 diabetes mellitus (T2DM) and cardiovascular diseases. The etiology of MetS is determined by the interaction between genetic and environmental factors. Effective prevention and treatment of MetS notably decreases the risk of its complications such as diabetes, obesity, hypertension, and dyslipidemia. According to recent genome-wide association studies, multiple genes are involved in the incidence and development of MetS. The presence of particular genes which are responsible for obesity and lipid metabolism, affecting insulin sensitivity and blood pressure, as well as genes associated with inflammation, can increase the risk of MetS. These molecular markers, together with clinical data and findings from proteomic, metabolomic, pharmacokinetic, and other methods, would clarify the etiology and pathophysiology of MetS and facilitate the development of personalized approaches to the management of MetS. The application of personalized medicinebased on susceptibility identified genomes would help physicians recommend healthier lifestyles and prescribe medications to improve various aspects of health in patients with MetS. In recent years, personalized medicine by genetic testing has helped physicians determine genetic predisposition to MetS, prevent the disease by behavioral, lifestyle-related, or therapeutic interventions, and detect, diagnose, treat, and manage the disease. Clinically, personalized medicine is providing effective strategies for the prevention and treatment of MetS by reducing the time, cost, and failure rate of pharmaceutical clinical trials. It is also eliminating trial-and-error inefficiencies that inflate health care costs and undermine patient care.

Keywords: Metabolic Syndrome; Personalized Medicine; Genomics; Proteomics; Metabolomics

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Introduction

Metabolic syndrome (MetS) is defined as a cluster of metabolic disorders including obesity, dyslipidemia [high triglycerides (TG) and lower high-density lipoprotein (HDL)], elevated fasting plasma glucose, and elevated blood pressure.[1] Moreover, there is a continuing discussion by scientific societies and healthcare managers in regard to whether obesity or insulin resistance is the underlying feature of MetS.[2] A recent meta-analysis showed that according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition, over one third of Iranian adults have MetS.[3]

Several ways for the prevention and management of MetS have been suggested in many studies such as changes in lifestyle by changing nutritional habits, effective weight control, modified alcohol intake, and increasing physical activity as well as medical treatments.[4,5] In fact, change of lifestyle is sometimes considered as the first line of therapy, yet medical treatment is regarded as the optimal control.[5] Moreover, it is suggested that pharmacological therapy is a critical step in the management of subjects with MetS when lifestyle modifications fail to achieve the therapeutic goals.[6]

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Independent studies have shown that if some of the components of MetS including atherogenic dyslipidemia, elevated blood pressure, elevated fasting glucose, prothrombotic factors, and proinflammatory state[7] can be controlled, then the onset of MetS can be delayed, and needed treatments can be more effective. However, no single best therapy can be deducted for individual components of MetS.[8]

It is to note that MetS has co-associated diseases including obesity, insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease, and non-alcoholic fatty liver disease.[9,10]

Moreover, risk factors predisposing to these diseases are considered risk factors for the others. In terms of the etiology, it is a common understanding that a variety of factors could play roles as the cause for the presence of every component of MetS. These include not only environmental, but genetic factors.[1,11] Therefore, a more beneficial treatment should consider the interconnection among components of MetS as well as the interconnection in MetS with other diseases.

Moreover, early detection and diagnosis of the syndrome is of great importance, allowing for early therapeutic intervention,[12,13] which is ultimately beneficial for patients with MetS who would also need to spend more money than those without MetS, including a 20% increase in cost if they suffered additional components of MetS.[14-16] In recent years, scientists have tried to find a new approach for treatment of disease and have introduced an approach which is named "personalized medicine".

In this review, we aimed to introduce how personalized medicine could help physician to manage MetS by effective changing in behavioral and lifestyle factors or pharmacological therapy based on the genome and omics.

Precision Medicine (PM)

The randomized controlled trial (RCT) is the gold standard for determining the best possible treatment, solving the problem of bias present in other study designs. RCTs assure that known and unknown factors affecting individual responses to treatment are present equally in all aspects of the study. Average response rate implies that it is the expected result from treatment, but most patients do not experience the average treatment effect. Age, genetic characteristics, and specific biomarkers are some causes for this variable response.[17,18]

PM, formerly known as personalized medicine, takes individual characteristics and a patient's environmental, lifestyle, genetic, and biomarker factors into account and recommends the optimum treatment for every individual.[19]

It is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. Currently, when prescribed medication is not effective, the patient may switch to a different medication. This trial-and-error approach leads to poorer outcomes for patients, in terms of adverse side effects, drug interaction, and potential disease progression while effective treatment is delayed and patient dissatisfaction.[20,21]

PM has several benefits not only for patients but also for hospitals, health care providers, and health plan sponsors. It enables each patient to receive earlier diagnoses while also lowering costs.[22]

PM in MetS

A very important question is how PM is applicable to the treatment of MetS. Apparently, PM helps us in several ways, such as determining the risk of MetS by assessing related genes that predispose a person to MetS earlier. This knowledge can then be applied to the prevention of MetS by encouraging changes in lifestyle, or awareness of risk factors, such as nutritional habits, the amount of physical activity, as well as personalized application of pharmacological treatment. This information, revealing the primary diagnosis of MetS at the molecular level, allows tailoring outcomes through targeted treatments and reduced side effects, and monitoring efficacy of response to treatment and disease progression.[23,24]

Another approach of PM is to predict, manage, and treat the disease by knowing the individual microbiome composition using novel technology. Recently, we know about crucial role of microbiome in the incidence of obesity, T2DM, non-alcoholic fatty liver disease, and their complications. It seems that the composition, function, and growth dynamics of microbiome has association with metabolite profile and in addition, has diverse effects on the host immune and metabolic systems. Thus, personal differences in microbial-derived products is able to justify how microbiome-based PM could be effective in treating MetS-related diseases.[25]

Today several biomarkers should be considered in PM of MetS. Recently, omics-based biomarkers

are in top of attention for management of different diseases.[26] Omics informally refers to a field of study in biology ending in -omics, such as genomics, proteomics, or metabolomics. Omics aims at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms. The aim of omics studies is finding putative biomarkers that serve as a valuable early diagnostic tool to identify a subset of patients with increased risk to develop MetS.[27]

Nowadays, omics technologies contribute to the process of biomarker development and consist of genomics, which studies the whole genome or a large subset of it (e.g., the exome), transcriptomics, which deals with the full set of transcripts of a cell, tissue, or organism, proteomics, comprising the study of the full set (or a large subset) of proteins present in a cell or tissue type, epigenomics, which investigates the complete set of covalent modifications of deoxyribonucleic acid (DNA) that do not alter the DNA sequence itself but result in changes in gene activity, microbiomics, which concerns itself with the community of microbes and their genes in a patient, metabolomics, which analyses the complete set of low-molecular-weight metabolites (e.g., amino acids, organic acids, lipids, and sugars), and the field studying the exposome, which comprises molecules and events to which a person is exposed to (e.g., drugs, diet, and other environmental factors).[28]

In a first step, omics technologies allow generating vast amounts of data on particular molecules (e.g., DNA, metabolites) in individuals with a specific condition.[28-31] Data are then analyzed to determine whether particular biomarkers are associated with the occurrence of the disease or, perhaps, with a given prognosis, or even with a certain response to a defined therapeutic intervention. Upon identification, biomarkers are validated with other analytical platforms, usually with those that are more likely to be found in a clinical laboratory, such as fluorescence in situ hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR), polymerase chain reaction (PCR), or immunoaffinity-based assays.[26] At the end of several rounds of analytical and clinical validation, biomarkers may be approved to be used in the clinic.

In summary, the aim of PM is transporting the whole genome to the clinic and having a new insight in pharmacogenomics – how genes affect a person's response to particular drug - for managing MetS.

Genomics

Because MetS is the combination of the effects of more than one risk factor, pinpointing a causative genotype has been difficult. Numerous single nucleotide polymorphisms (SNPs) are associated with the various components of MetS, and several of these SNPs have been shown to modify a person's response to lifestyle interventions.[32] Studies showed that MetS was a polygenetic (under the control of more than one gene) condition. We summarized all SNPs which are related to MetS not components of MetS in the tables 1 and 2.[33-56]

Transcriptomics

The transcriptome is the set of all ribonucleic acid (RNA) molecules produced in one or a population of cells, and their quantity, for a specific developmental stage or physiological condition. Understanding the transcriptome is as essential as recognizing the metabolites discussed previously for interpreting the functional elements of the genome, revealing the molecular constituents of cells and tissues, and also understanding development and disease.[57]

Proteomics

Proteomics complements genomics by focusing on the gene products active in a cell and therefore, delivers information closer to the observed phenotype. Proteomics is the large-scale measurement of the proteome (the protein complement of a cell, organ, or even organism) at a given time and state.[58] The combination of liquid chromatography electrospray ionization-tandem mass spectrometric (LC-ESI-MS/MS) represents the most effective and used approach for the analysis of proteomes.[59,60]

Nowadays, proteomics is able to adapt with many different functions and activities taking advantage of the huge improvement in mass spectrometry (MS) techniques and instrumentations to carefully identify thousands of proteins in a biological sample.[61]

This makes it attractive in molecular medicine, where it is called clinical proteomics, as a powerful tool able to investigate perturbed pathways causing diseases and discover novel unannotated proteins or biomarkers of disease. A proteomic biomarker is defined as "a specific peptide or protein that is associated with a specific condition, such as the onset, manifestation, or progression of a disease or a response to treatment".[62]

Table 1. Single nucleotide polymorphisms (SNPs) associated with metabolic syndrome (MetS)

Chromosome	Locus	Position	SNP	P	OR (95% CI)	Risk allele	Reference
1	AGT	c.620C>T	rs4762	0.0180	1.36 (0.36-5.11)	T	Pollex et al.[34]
	MACF1	c.221-57201C>T	rs1537817	NA	NA	T	Kraja et al.[35]
	KIAA0754	c.9631-7727T>G	rs3768302	NA	NA	G	Kraja et al.[35]
2	LOC646736	g.227068080A>C	rs2943634	NA	NA	C	Kraja et al.[35]
	GCKR	c.1337T>C	rs1260326	NA	NA	C	Kraja et al.[35]
	GRB14	g.165508389C>T	rs10184004	NA	NA	T	Kraja et al.[35]
	COBLL1	g.165513091T>C	rs10195252	NA	NA	C	Kraja et al.[35]
3	PPARG	Haplotype (-681C>G, -689C>T,1431C>T)	-	0.0020	2.37 (1.42-3.95)	GTGC haplotype	Meirhaeghe et al.[36]
	ADIPOQ	c.45T>G	rs2241766	0.0750	1.15 (1.04-1.28)	G	Zhou et al.[37]
		c.214+62G>C	rs1501299	0.0280	1.80 (1.07-3.05)	C	Larifla et al.[39]
	CX3CR1	926C>T (Thr280Met)	NA	0.0087	1.60 (1.13-2.28)	T	Yamada et al.[38]
4	FABP2	c.2445G>A	rs1799883	0.0680	1.59 (0.97-2.62)	A	Larifla et al.[39]
6	AGER	c.268G>A (Gly82Ser)	NA	0.0245	0.50 (0.27-0.91)	A	Yamada et al.[38]
	ESR1	c.453-351A>G	rs9340799	0.0290	1.53 (1.05-2.27)	G	Gallagher et al.[40]
		c.644-9459G>C	rs2431260	0.0050	2.51 (1.31-4.80)	C	
		c.644-4838A>G	rs2175898	0.0060	2.51 (1.30-4.84)	G	
	GCLC	c.-129C>T	NA	0.0266	2.65 (1.18-6.75)	T	Yamada et al.[38]
	SLC26A8	p.Ile636Val	NA	0.0219	0.80 (0.66-0.97)	NA	Yamada et al.[38]
7	IL6	c.-174G>C	rs1800795	0.0070	1.03 (0.87-1.23)	C	Pollex et al.[34]
	MLXIPL	c.400+4023G>T	rs17145750	NA	NA	T	Kraja et al.[35]
	CYP3A4	c.13989A>G(Ile118Val)	NA	0.0145	0.36 (0.15-0.80)	G	Yamada et al.[41]
	CD36	c.975T>G	rs3211938	0.0012	0.61 (0.46-0.82)	G	Love-Gregory et al.[42]
		g.82782C>T	rs13230419	0.0027	1.36 (1.11-1.67)	T	
		c.*1052C>T	rs13246513	0.0037	1.32 (1.09-1.58)	T	
		c.819-443T>A	rs3173804	0.0049	1.29 (1.08-1.54)	A	
		c.*572G>A	rs7755	0.0110	1.35 (1.07-1.69)	A	
		c.121-2440G>T	rs3211850	0.0300	1.40 (1.03-1.90)	T	
	TBL2	c.131-547T>C	rs11974409	NA	NA	C	Kraja et al.[35]
	NOS3	Haplotype 212	NA	0.0020	1.89 (1.24-2.88)	-	Gonzalez-Sanchez et al.[43]
	BAZ1B	c.107+1647T>C	rs7811265	NA	NA	C	Kraja et al.[35]
	BCL7B	c.92+586G>A	rs13233571	NA	NA		Kraja et al.[35]
		c.-30G>A	NA	0.0027	0.73 (0.60-0.90)	A	Yamada et al.[38]
	NOS3 gene	c.775G>A	rs762580019	0.0022	NA	A	Pollex et al.[34]
8	TRIB1	g.126495818C>T	rs10808546		NA	T	Kraja et al.[35]
	C YP11B2	c.-344C>T	NA	0.0200	2.25 (1.38-3.66)	T	Russo et al.[44]

Table 1. Single nucleotide polymorphisms (SNPs) associated with metabolic syndrome (MetS) (continue)

Chromosome	Locus	Position	SNP	P	OR (95% CI)	Risk allele	Reference
8	LPL	c.1019-533A>C	rs295	< 0.001	NA	C	Kraja et al.[45]
		g.19844222A>G	rs12678919	NA	NA	G	
		c.*371T>C	rs3289	0.0280	NA	C	
		1595C>G(Ser447X)	NA	0.0064	NA	G	
9	ENG	1691C>G (Asp366His)	NA	0.0168	0.71 (0.53-0.94)	G	Yamada et al.[38]
10	TCF7L2	c.382-41435C>G	rs7903146, DG10S478x	0.0080	1.18 (1.04-1.34)	G	Povel et al.[46]
11	UCP2	c.-866G>A	NA	0.0150	2.66 (1.21-5.88)	A	Shen et al.[47]
	C1QTNF5	1014T>A	NA	0.0073	1.47 (1.11-1.97)	A	Yamada et al.[38]
	APOA1	c.-75G>A	NA	0.0108	0.76 (0.62-0.94)	A	Yamada et al.[38]
	APOC3	c.-455T>C	rs2854116	0.0290	NA	C	Hegele et al.[48]
		c.-482C>T	rs2854117		NA	T	
	BUD13	c.237+1741T>A	rs10790162	< 0.0010	NA	A	Kraja et al.[45]
	ZNF259	c.931-336G>A	rs2075290	< 0.0010	NA	A	Kraja et al.[45]
	APOA5	c.-1131T>C	NA	< 0.0001	1.57 (1.29-1.90)	C	Yamada et al.[38]
		c.-3A>G	rs651821	< 0.0001	1.57 (1.32-1.86)	G	Yamada et al.[38]
		c.553G>T	NA	0.0001	1.62 (1.27-2.08)	T	
		c.-620C>T	rs662799	< 0.0010	1.25 (1.14-1.37)	T	
12	GNB3	825C>T	NA	0.0056	NA	T	Hegele et al.[48]
	ZNF664	c.-660-9250A>G	rs12310367	NA	NA	G	Kraja et al.[35]
13	F7	11,496G>A	NA	0.0012	0.61 (0.46-0.83)	A	Yamada et al.[38]
15	LIPC	-250G>A	rs1532085, NA	0.0048*	0.73 (0.59-0.91)	A	Yamada et al.[38]
16	(CETP)	g.56988044C>T	rs173539	< 0.001	NA	T	Kraja et al.[45]
		c.658+186C>A	rs1532624	NA		A	Hegele et al.[49]
	FTO	c.46-23525T>A	rs9939609	0.0360	1.23 (1.01-1.50)	A	Al-Attar et al.[50]
		c.46-43098T>C	rs1421085	0.0060	1.89 (1.20-2.96)	C	Wang et al.[51]
17	PC1	K121Q	NA	< 0.0100	5.50 (1.40-20.90)	NA	Joy et al.[52]
	SREBF1	-36/3G>2G	NA	0.0286	0.23 (0.05-0.77)	delG	Yamada et al.[38]
18	COLEC12	58+38266G>A	rs16944558	< 0.001	1.20 (1.12-1.30)	A	Lin et al.[63]
	GYS1	260A>G (Met416Val)	NA	0.0028	0.70 (0.55-0.88)	G	Yamada et al.[38]
	RSTN	-420C>G	NA	0.0420	NA	G	Yamada et al.[38]
	APOE	4070C>T	NA	0.0145	NA	T	Yamada et al.[38]
	LDLR	2052T>C (Val653Val)	NA	0.0116	0.79 (0.66-0.95)	C	Yamada et al.[41]
		1866C>T(Asn591Asn)		0.0037	0.37 (0.19-0.72)	T	
	TOMM40	c.275-31A>G	rs2075650	NA	NA	G	Kraja et al.[35]
X	HTR2C	c.551-3008C>G	rs1414334	0.0100	NA	G	Joy et al.[52]
		c.-788C>G/A	rs518147	0.0490			

SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval; NA: Not available

Table 2. Single nucleotide polymorphisms (SNPs) associated with metabolic syndrome (MetS) in genome-wide association studies (GWAS)

Chromosome	Locus	Position	SNP	P	OR (95% CI)	Risk allele	Reference
7	CHRM2	c.-124-364A>G	rs2350786	< 0.001	1.21 (1.12-1.31)	A	Jeong et al.[53]
8	NA	g.19990569G>A	rs17410962	< 0.001	1.34 (1.20-1.50)	G	Jeong et al.[53]
	NA	g.19848080G>A	rs17482753	< 0.001	1.34 (1.20-1.51)	G	Jeong et al.[53]
	NA	g.19847690C>A	rs10503669	< 0.001	1.34 (1.20-1.51)	C	Jeong et al.[53]
9	PTPRD	c.-545+30021T>A	rs605257	< 0.001	1.22 (1.12-1.33)	T	Jeong et al.[53]
10	NA	g.36599534C>T	rs1668775	< 0.001	1.24 (1.14-1.36)	T	Jeong et al.[53]
11	NA	g.116617240A>C	rs11216126	< 0.001	1.33 (1.21-1.46)	A	Jeong et al.[53]
	NA	g.116611827A>T	rs180349	< 0.001	1.28 (1.21-1.46)	A	Jeong et al.[53]
	LOC101929011	g.116655605A>C	rs486394	< 0.001	1.32 (1.18-1.47)	C	Jeong et al.[53]
	ZPR1	c.1017+451C>A	rs6589566	< 0.001	1.27 (1.16-1.39)	C	Jeong et al.[53]
	APOA5	c.-3A>G	rs651821	< 0.001	1.30 (1.10-1.49)	C	Zhu et al.[54]
12	ALDH2	c.1369G>A	rs671	< 0.001	0.68 (0.59-0.79)	A	Zhu et al.[54]
18	PMAIP1	g.60083782T>C	rs12957347	< 0.001			Zabaneh and Balding[55]
19	ATF5	c.615C>T	rs61742136	< 0.001	9.37 (3.30-26.80)	T	Haydar et al.[56]

SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval; NA: Not available

Adipose tissue is mainly responsible for the storage of TGs in adipocytes and in signaling information about the amount stored for the regulation of energy intake and expenditure. Adipose tissue has therefore become an interesting organ for studying proteomic patterns related to the MetS. Adachi et al. investigated the adipocyte proteome by combining high-accuracy, high-sensitivity protein identification technology with subcellular fractionation of nuclei, mitochondria, membrane, and cytosol of 3T3-L1 adipocytes.[64]

Approximately, 3300 proteins were identified. Hormones, so-called adipokines, have been identified as secreted by the adipose tissue.[65] Most show a positive correlation between their circulation levels and the amount of adipose tissue mass. Moreover, imbalance in some adipokine levels, probably due to enlarged adipose tissue, have been correlated with obesity, T2DM, and cardiovascular problems.[66] A combination of cleavable isotope-coded affinity tags (cICAT) and label-free quantification showed 317 proteins differentially secreted by 3T3-483L1 adipocytes with or without insulin treatment; 179 proteins were significantly upregulated and 53 were downregulated. Western blot analysis of the reported adipokines like adiponectin or resistin confirmed the quantitative results from MS revealing individualized secreting patterns of these proteins by increasing insulin dose.[67]

The pancreatic beta cell plays a key role in the maintenance of glucose homeostasis primarily by secreting insulin after certain stimuli. As with adipose tissue, proteomic studies using beta cells have focused on cataloguing the proteins for a better understanding of beta cell function. Two-dimensional liquid chromatography/mass spectrometry (2D-LC-MS/MS) analysis of human pancreatic islets revealed 3365 proteins.[68] Major islet proteins (insulin, glucagon, and somatostatin) were detected as well as various beta cell-enriched secretory proteins, ion channels, and transcription factors. Moreover, a wide range of metabolic enzymes and cellular pathway proteins were covered like the integrin signaling cascade, mitogen-activated protein (MAP) kinase, nuclear factor kappa B (NFκβ), and Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway.

Metabolomics

Metabolomics is a systematic analysis of low-molecular-weight biochemical compounds in a biological cell, tissue, organ, or organism, and it has been increasingly applied to discovering biomarkers, identifying perturbed pathways, diagnosing diseases, and measuring the response to treatment.[68] Metabolic profiling can give an instantaneous snapshot of the physiology of the organism and can be seen as the gap between genotype and phenotype.[69]

A study which was done by Wu et al. using liquid chromatography/MS (LC/MS)-based metabolomics methods found that 23 potential biomarkers were mainly related to metabolism; the tricarboxylic acid cycle, galactose metabolism, arachidonic acid metabolism, valine, leucine, and isoleucine degradation, as well as isoleucine biosynthesis were identified in the plasma of patients with MetS. Interestingly, these differential metabolites were mainly associated with lipid metabolism, amino acid metabolism, glucose metabolism, purine metabolism, and other related metabolic pathways.[70]

Future of MetS and PM

Hopefully, future scenario for diagnosing and treating MetS is that a person goes to a clinic, the physician completes the health questioner related to lifestyle habits, then asks the laboratory to determine the genetic-metabolic and proteomic biomarkers. Then, the physician recommends specific and efficient treatment or appropriate nutritional habit or exercise program for the management of each component of MetS, depending on the existing biomarkers. Several barriers can be predicted for applying PM in patients with MetS; the first of all is related to the availability of laboratory techniques and its cost.

Conclusion

PM facilitated through laboratory testing can determine the risk of developing MetS by integrating traditional diagnostic testing into specific risk assessment profiles. For example, if a person's genomic information indicates a higher-than-average risk of developing MetS, that person may choose a lifestyle, or sometimes be prescribed medications, to better regulate the aspects of their health and wellness over which he or she has control. This helps patients to receive more effective treatment with better response and lower side effects and lower cost. In addition, it assists physicians to select certain therapies, improve disease detection, institute earlier disease intervention, and prevent disease progression. One of the most important issues in PM is the cost of genetic and laboratory tests. It is clear that in the

long term, PM could be able to decrease the cost of treatment by avoiding inappropriate treatment.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

MG and IR participated in study conception and design. PN contributed to revising and editing. MG participated in writing/manuscript preparation. LS and AE contributed to searching. SJ agreed with all aspects of the work. All authors approved the final version of manuscript and agreed with all aspects of the work.

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