発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内外の別
小児再生不良性貧血の治療（口頭）	小島勢二	第 76 回日本血液学会学術集会	2014 年 11 月 2 日	国内
Overview: Genetic analysis of hereditary hematologic disorders.（口頭）	Yoshida, K. and Ogawa, S.	第 76 回日本血液学会学術集会	2014 年 11 月 1 日	国内
Molecular profiling diagnostics of myeloid neoplasms（口頭）	Ogawa, S	IFCC WorldLab	June 26, 2014.	国外
Novel Somatic Mutations in AML and MDS（口頭）	Ogawa, S	XXXV World Congress International Society of Hematology	September 4, 2014.	国外
Molecular profiling of MDS for precision therapy.（口頭）	Ogawa, S	An AACR Special Conference on Hematologic Malignancies,	September 23, 2014.	国外
加齢を反映する遺伝子発現バイオマーカーの探索（ポスター）	畑隼平・中村誠二・松原謙一・的場亮	第 37 回分子生物学会	2014 年 11 月 27 日	国内
疾病中心から患者中心の希少難治性疾患研究を可能とする患者支援団体と専門化集団とのネットワーク構築（第 3 報）（ポスター）	河村理恵・松原洋一・野村文夫・斎藤加代子・高田史男・小杉眞司・玉置知子・櫻井晃洋・関島良樹・涌井敬子・加藤光広・小泉二郎・中村勝哉・香取久之・古庄知己・福嶋義光	第 38 回日本遺伝カウンセリング学会学術集会	2014 年 6 月 27 日	国内
遺伝性甲状腺髄様癌の発症前診断と甲状腺全摘の時期（口頭）	内野 眞也・櫻井晃洋・小杉眞司・MEN コンソーシアム	日本人類遺伝学会第 59 回大会・日本遺伝子診療学会第 21 回大会合同学術集会	2014 年 11 月 22 日	国内
NGS における Incidental Findings の取扱いついて（口頭）	小杉眞司	日本遺伝子診療学会：遺伝子診断・検査技術推進フォーラム	2014 年 12 月 12 日	国内

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内外の別
科学的根拠―ガラパゴス化する日本の遺伝子検査ビジネス （口頭）	小杉眞司	日本総合健診学会第43回大会	2015年 2月20日	国内
わが国における家族性膵癌登録制度立ち上げに向けたJohns Hopkins大学病院研修の報告 （口頭）	鳥嶋雅子・村上裕美・高折恭一・森実千種・谷内田真一・和田慶太・水本雅巳・鈴木雅美・細井寛子・小杉眞司	第20回日本家族性腫学会学術集会	2014年 6月14日	国内
京都大学遺伝カウンセラーコースの遺伝教育への取り組み：京都大学アカデミックデイでの遺伝教室―実践報告― （口頭）	秋山奈々・鳥嶋雅子・柴田有花・和田敬仁・高井響子・福江美咲・土屋実央・中國正祥・村上裕美・三宅秀彦・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月27日	国内
患者・研究支援チャリティーイベントにおける「あったかいでんブース」活動報告 （口頭）	村上裕美・鳥嶋雅子・和田敬仁・三宅秀彦・秋山奈々・高井響子・福江美咲・土屋実央・柴田有花・中國正祥・中川奈保子・佐藤智佳・黄瀬恵美子・SORD・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月27日	国内
日本における無侵襲的出生前遺伝学的検査関連情報の報道～新聞記事内容分析による検討 （口頭）	福江美咲・三宅秀彦・山田重人・高井響子・秋山奈々・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月28日	国内
次世代シークエンサーにおけるIncidental Findingsの取り扱いにか関する検討～遺伝医療専門家を対象とした質問票調査より　倫理問題検討委員会報告 （口頭）	土屋実央・柴田有花・中國正祥・古庄知己・佐々木愛子・玉井真理子・中谷中・野村文夫・四元淳子・黒澤健司・鳥嶋雅子・村上裕美・三宅秀彦・和田敬仁・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月29日	国内
難聴の遺伝学的検査を受検した患者の臨床的検討 （口頭）	中國正祥・岡野高之・谷口美玲・柴田有花・土屋実央・北尻真一郎・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月29日	国内
遺伝子検査ビジネスにおける消費者用注意喚起書改定案の作成及び有効性の検討 （口頭）	柴田有花・村上裕美・鳥嶋雅子・土屋実央・中國正祥・三宅秀彦・和田敬仁・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月29日	国内
日本国内の医学教育における家族歴聴取・家系図記載法の扱い （ポスター）	高井響子・三宅秀彦・和田敬仁・村上裕美・鳥嶋雅子・秋山奈々・福江美咲・小杉眞司	第38回日本遺伝カウンセリング学会学術集会	2014年 6月27～29日	国内

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Kyoto Model of developing a genetics education program in Japan（ポスター）	Akiyama, N., Torishima, M., Wada, T., Kosugi, S.	64th Annual Meeting of the American Society of Human Genetics	October 18-22, 2014.	国外
日本国内における無侵襲的出生前遺伝学的検査関連情報の新聞報道～計量的テキスト分析での検討（口頭）	福江美咲・三宅秀彦・山田重人・秋山奈々・高井響子・小杉眞司	日本人類遺伝学会第59回大会・日本遺伝子診療学会第21回大会合同学術集会	2014年11月20日	国内
高校生を対象としたヒト遺伝に関する授業支援（ポスター）	秋山奈々・片山徹・鳥嶋雅子・和田敬仁・小杉眞司	日本人類遺伝学会第59回大会・日本遺伝子診療学会第21回大会合同学術集会	2014年11月20日	国内
日本国内の医学教科書における家族歴聴取・家系図記載法の扱い（口頭）	高井響子・三宅秀彦・秋山奈々・福江美咲・村上裕美・鳥嶋雅子・和田敬仁・小杉眞司	日本人類遺伝学会第59回大会・日本遺伝子診療学会第21回大会合同学術集会	2014年11月22日	国内
小学生に対するヒト遺伝教育の方法論探索（口頭）	鳥嶋雅子・秋山奈々・平岡弓枝・西尾瞳・高井響子・本田明夏・和田敬仁・小杉眞司	日本人類遺伝学会第59回大会・日本遺伝子診療学会第21回大会合同学術集会	2014年11月22日	国内
研究計画書に記載すべき事項に関する質問紙調査（ポスター）	山中真由美・富田博子・矢野郁・高秀子・中正朱美・山本陽子・安藤直子・岩江荘介・大守伊織・小杉眞司	第35回日本臨床薬理学会学術総会	2014年12月4～6日	国内
新生児聴覚スクリーニングの有効性評価：分析的枠組み（Analytic Framework）に基づく文献的検討（ポスター）	渡辺智子・小杉眞司・沼部博直・中山健夫	第16回日本子ども健康科学会	2014年12月13日	国内
研究計画書に記載すべき事項」のうち何が書きにくいか―医師・コメディカルを対象とした調査（ポスター）	富田博子・山中真由美・矢野郁・高秀子・中正朱美・山本陽子・安藤直子・岩江荘介・大守伊織・小杉眞司	日本臨床試験学会第6回学術集会総会	2015年2月20～21日	国内

2．学会誌・雑誌等における論文掲載

掲載した論文 （発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した 時期	国内外 の別
Inverse association between air pressure and rheumatoid arthritis synovitis.	Terao, C., Hashimoto, M., Furu, M., Nakabo, S., Ohmura, K., Nakashima, R., Imura, Y., Yukawa, N., Yoshifuji, H., Matsuda, F., Ito, H., Fujii, T. and Mimori, T.	PLoS One	2014	国外
Caspase-mediated cleavage of phospholipid flippase for apoptotic phosphatidylserine exposure.	Segawa, K., Kurata, S., Yanagihashi, Y., Brummelkamp, T. R., Matsuda, F. and Nagata, S.	Science	2014	国外
A genome-wide association study of serum levels of prostate-specific antigen in the Japanese population.	Terao, C., Terada, N., Matsuo, K., Kawaguchi, T., Yoshimura, K., Hayashi, N., Shimizu, M., Soga, N., Takahashi, M.; Nagahama Cohort Study Group, Kotoura, Y., Yamada, R., Ogawa, O. and Matsuda, F.	J Med Genet	2014	国外
Large-scale East-Asian eQTL mapping reveals novel candidate genes for LD mapping and the genomic landscape of transcriptional effects of sequence variants.	Narahara, M., Higasa, K., Nakamura, S., Tabara, Y., Kawaguchi, T., Ishii, M., Matsubara, K., Matsuda, F. and Yamada, R.	PLoS One	2014	国外
Identification of three novel genetic variations associated with electrocardiographic traits (QRS duration and PR interval) in East Asians.	Hong, K. W., Lim, J. E., Kim, J. W., Tabara, Y., Ueshima, H., Miki, T., Matsuda, F., Cho, Y. S., Kim, Y. and Oh, B.	Hum Mol Genet	2014	国外
An association between anti-nuclear antibody and HLA class II locus and heterogeneous characteristics of staining patterns: The Nagahama Study.	Terao, C., Ohmura, K., Yamada, R., Kawaguchi, T., Shimizu, M., Tabara, Y., Takahashi, M., Setoh, K., Nakayama, T., Kosugi, S., Sekine, A., Matsuda, F. and Mimori, T; on behalf of the Nagahama Study Group.	Arthritis Rheumatol	2014	国外
Association of Serum-Free Fatty Acid Level With Reduced Reflection Pressure Wave Magnitude and Central Blood Pressure: The Nagahama Study.	Tabara, Y., Takahashi, Y., Kawaguchi, T., Setoh, K., Terao, C., Yamada, R., Kosugi, S., Sekine, A., Nakayama, T. and Matsuda, F.; on behalf of the Nagahama Study Group.	Hypertension	2014	国外
Comprehensive molecular diagnosis of a large cohort of Japanese retinitis pigmentosa and Usher syndrome patients by next-generation sequencing.	Oishi, M., Oishi, A., Gotoh, N., Ogino, K., Higasa, K., Iida, K., Makiyama, Y., Morooka, S., Matsuda, F. and Yoshimura, N.	Invest Ophthalmol Vis Sci	2014	国外
Central blood pressure relates more strongly to retinal arteriolar narrowing than brachial blood pressure: the Nagahama Study.	Kumagai, K., Tabara, Y., Yamashiro, K., Miyake, M., Akagi-Kurashige, Y., Oishi, M., Yoshikawa, M., Kimura, Y., Tsujikawa, A., Takahashi, Y., Setoh, K., Kawaguchi, T., Terao, C., Yamada, R., Kosugi, S., Sekine, A., Nakayama, T., Matsuda, F. and Yoshimura, N.	J Hypertens	2015	国外

掲載した論文 （発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した 時期	国内外 の別
A main contribution of DRB1*04:05 among shared epitope and involvement of 57th DRB1 amino acid in association with joint destruction in ACPA(+) RA.	Terao, C., Yano, K., Ikari, K., Furu, M., Yamakawa, N., Yoshida, S., Hashimoto, M., Ito, H., Fujii, T., Ohmura, K., Yurugi, K., Miura, Y., Maekawa, T., Taniguchi, A., Momohara, S., Yamanaka, H., Mimori, T. and Matsuda, F.	Arthritis Rheumatol	2015	国外
Genetics of rheumatoid arthritis contributes to biology and drug discovery.	Okada, Y., Terao, C. (5 th), Yamada, R. (72 nd), Mimori, T.(87 th), Matsuda, F. (93 th), Plenge, R. M. (total 95 collaborators)	Nature	2014	国外
A nationwide study of SLE in Japanese identified subgroups of patients with clear signs patterns and associations between signs and age or sex.	Terao, C., Yamada, R., Mimori, T., Yamamoto, K. and Sumida, T.	Lupus	2014	国外
Wide-field fundus autofluorescence abnormalities and visual function in patients with cone and cone-rod dystrophies.	Oishi M, Oishi A, Ogino K, Makiyama Y, Gotoh, N, Kurimoto, M., Yoshimura, N.	Invest Ophthalmol Vis Sci	2014	国外
The use of next-generation sequencing in molecular diagnosis of neurofibromatosis type 1: A validation study.	Maruoka, R., Takenouchi, T., Torii, C., Shimizu, A., Misu, K., Higasa, K., Matsuda, F., Ota, A., Tanito, K., Kuramochi, A., Arima, Y., Otsuka, F., Yoshida, Y., Moriyama, K., Niimura, M., Saya, H. and Kosaki, K.	Genet Test Mol Biomarkers	2014	国外
A definitive haplotype map of structural variations determined by microarray analysis of duplicated haploid genomes.	Tahira, T., Yahara, K., Kukita, Y., Higasa, K., Kato, K., Wake, N., Hayashi, K.	Genomics Data	2014	国外
Recent advances in Takayasu arteritis.	Terao, C., Yoshifuji, H. and Mimori, T.	Int J Rheum Dis	2014	国外
History of Takayasu arteritis and Dr. Mikito Takayasu.	Terao, C.	Int J Rheum Dis	2014	国外
Effects of smoking and shared epitope on the production of ACPA and RF in a Japanese adult population: The Nagahama Study.	Terao, C., Ohmura, K., Ikari, K., Kawaguchi, T., Takahashi, M., Setoh, K., Nakayama, T., Kosugi, S., Sekine, A., Tabara, Y., Taniguchi, A., Momohara, S., Yamanaka, H., Yamada, R., Matsuda, F., Mimori, T.; on behalf of the Nagahama Study Group.	Arthritis Care Res	2014	国外

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Histological changes of pulmonary arteries treated by balloon pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension.	Kitani, M., Ogawa, A., Sarashina, T., Yamadori, I. and Matsubara, H.	Circ Cardiovasc Interv	2014	国外
Pulomonary microvascular remodeling after ballon pulmonary angioplasty in a patient with chronic thromboembolic pulmonary hypertension.	Ogawa, A., Kitani, M., Mizoguchi, H., Munemasa, M., Matsuo, K., Yamadori, I., Andou, A. and Matsubara, H.	Intern Med	2014	国内
Balloon pulmonary angioplasty: a treatment option for inoperable patients with chronic thromboembolic pulmonary hypertension.	Ogawa, A. and Matsubara, H.	Front Cardiovasc Med	2015	国外
Treatment of idiopathic/hereditary pulmonary arterial hypertension.	Matsubara, H. and Ogawa, A.	J Cardiol	2014	国外
Anti-CCR4 antibody mogamulizumab targets human T-lymphotropic virus type I-infected CD8+ as well as CD4+ T cells to treat associated myelopathy.	Yamauchi, J., Coler-Reilly, A., Sato, T., Araya, N., Yagishita, N., Ando, H., Kunitomo, Y., Takahashi, K., Tanaka, Y., Shibagaki, Y., Nishioka, K., Nakajima, T., Hasegawa, Y., Utsunomiya, A., Kimura, K., Yamano, Y.	J Infect Dis	2015	国外
HLVL-1 induces a Th1-like state in CD4+CCR4+ T cells.	Araya, N., Sato, T., Ando, H., Tomaru, U., Yoshida, M., Coler-Reilly, A., Yagishita, N., Yamauchi, J., Hasegawa, A., Kannagi, M., Hasegawa, Y., Takahashi, K., Kunitomo, Y., Tanaka, Y., Nakajima, T., Nishioka, K., Utsunomiya, A., Jacobson, S. and Yamano, Y.	J Clin Invest	2014	国外
A plasma diagnostic model of human T cell leukemia virus-1 associated myelopathy Running head: Novel severity grade markers for HAM/TS.	Ishihara, M., Araya, N., Sato, T., Saichi, N., Fujii, R., Yamano, Y., Sugano, S. and Ueda, K.	Ann Clin Transl Neurol	in press	国外
Positive feedback loop via astrocytes causes chronic inflammation in human T lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis.	Coler-Reilly, A., Ando, H. and Yamano, Y.	Clin Exp Neuroimmunol	2014	国外
A case of post-transplant adult T-cell leukemia lymphoma presenting myelopathy similar to but distinct from human T-cell leukemia virus type I (HTLV-I)-associated myelopathy.	Kawamata, T., Ohno, N., Sato, K., Kobayashi, M., Jo, N., Yuji, K., Tanosaki, R., Yamano, Y., Tojo, A. and Uchimaru, K.	Springerplus	2014	国外

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HTLV-1 関連脊髄症 （HAM）	山野嘉久	神経症候群 （第 2 版）	2014	国内
HTLV-1 の神経障害	山野嘉久	内科	2014	国内
HTLV-1 関連脊髄症 （HAM）の分子病態に基づく治療戦略	山野嘉久	細胞	2014	国内
ヒト細胞白血病ウイルス I 型関連脊髄症	山野嘉久	最新医学	2014	国内
HTLV-1 関連脊髄症 （HAM）に対する分子標的治療薬開発の現状と将来	新谷奈津美・山野嘉久	血液内科	2014	国内
希少な慢性進行性の神経難病 HAM における治療有効性評価モデルの探索	山野嘉久	臨床評価	2014	国内
Perfusion in the tissue surrounding pancreatic cancer and the patient's prognosis.	Nishikawa, Y., Tsuji, Y., Isoda, H., Kodama, Y. and Chiba, T.	Biomed Res Int	in press	国外
Progression of autoimmune hepatitis is mediated by IL-18-producing dendritic cells and hepatic CXCL9 expression in mice.	Ikeda, A., Aoki, N., Kido, M., Iwamoto, S., Nishiura, H., Maruoka, R., Chiba, T., and Watanabe N.	Hepatology	2014	国外
Total lesion glycolysis as an IgG4-related disease activity marker.	Nakatsuka, Y., Handa, T., Nakamoto, Y., Nobashi, T., Yoshihuji, H., Tanizawa, K., Ikezoe, K., Sokai, A., Kubo, T., Hirai, T., Chin, K., Togashi, K., Mimori, T. and Mishima, M.	Mod Rheumatol	2014	国外

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Significant association between CYP3A5 polymorphism and blood concentration of tacrolimus in patients with connective tissue diseases.	Tanaka, K., Terao, C., Ohmura, K., Takahashi, M., Nakashima, R., Imura, Y., Yoshifuji, H., Yukawa, N., Usui, T., Fujii, T., Mimori, T. and Matsuda, F.	J Hum Genet	2014	国内
Gastro-asophageal acid reflux mainly occurs on right side of asophagus.	Ishimura, N., Ishihara, S. and Kinoshita, Y.	Gastrointest Endoscopy	2014	国外
Effect of mosapride on esophageal motor activity and esophagogastric junction compliance in healty volunteers.	Fukazawa, K., Furuta, K., Adachi, K., Moritou, Y., Saito, T., Kusunoki, R., Uno, G., Shimura, S., Aimi, M., Ohara, S., Ishihara, S. and Kinoshita, Y.	J Gastroenterol	2014	国外
Role of Regulatory B Cells in Chronic Intestinal Inflammation: Association with Pathogenesis of Crohn's Disease.	Oka, A., Ishihara, S., Mishima, Y., Tada, Y., Kusunoki, R., Fukuba, N., Yuki, T., Kawashima, K., Matsumoto, S. and Kinoshita, Y.	Inflamm Bowel Dis	2014	国外
Prevalence of irritable bowel syndrome-like symptoms in ulcerative colitis patients with clinical and endoscopic evidence of remission: prospective multicenter study.	Fukuba, N., Ishihara, S., Tada, Y., Oshima, N., Moriyama, I., Yuki, T., Kawashima, K., Kushiyama, Y., Fujishiro, H. and Kinoshita, Y.	Scand J Gastroenterol	2014	国外
Reliability of symptoms and endoscopic findings for diagnosis of esophageal eosinophilia in a Japanese population.	Shimura, S., Ishimura, N., Tanimura, T., Yuki, T., Miyake, T., Kushiyama, Y., Sato, S., Fujishiro, H., Ishihara, S., Komatsu, T., Kaneto, E., Izumi, A., Ishikawa, N., Maruyama, R. and Kinoshita, Y.	Digestion	2014	国外
Apoptotic cells ameliorate chronic intestinal inflammation by enhancing regulatory B cell function.	Ansary, Md. Mu., Ishihara, S., Oka, A., Kusunoki, R., Oshima, N., Yuki, T., Kawashima, K., Maegawa, H., Kashiwagi, N. and Kinoshita, Y.	Inflamm Bowel Dis	2014	国外
Relationship between esophageal cardiac glonols and gastro-esophageal reflux disease.	Hanada, K., Adachi, K., Mishiro, T., Tanaka, S., Takahashi, Y., Yoshikawa, K. and Kinoshita, Y.	Internal Medicine	2014	国外
No increase in gastric acid secretion in healthy Japanese over past two decades.	Ishimura, N., Owada, Y., Aimi, M., Oshima, T., Kawada, T., Inoue, K., Mikami, H., Takeuchi, T., Miwa, H., Higuchi, K. and Kinoshita, Y.	J Gastroenterol	2014	国外

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The number and distribution of eosinophils in the adult human gastrointestinal tract: a study and comparison of racial and environmental factors.	Matsushita, T., Maruyama, R., Ishikawa, N., Harada, Y., Araki, A., Chen, D., Tauchi-Nishi, P., Yuki, T. and Kinoshita, Y.	Am J Surg Pathol	2015	国外
Role of milk fat globule-epidermal growth factor 8 in colonic inflammation and carcinogenesis.	Kusunoki, R., Ishihara, S., Tada, Y., Oka, A., Sonoyama, H., Fukuba, N., Oshima, N., Moriyama, I., Yuki, T., Kawashima, K., Md. Mesbah Uddin Ansary, Tajima, Y., Maruyama, R., Nabika, T. and Kinoshita, Y.	J Gastroenterol	2015	国外
Clinical features of eosinophilic esophagitis: Differences between Asian and Western populations.	Ishimura, N., Shimura, S., Jiao, D. J., Mikami, H., Okimoto, E., Uno, G., Aimi, M., Oshima, N., Ishihara, S. and Kinoshita, Y.	J Gastroenterol Hepatol	in press	国外
好酸球性食道炎	木下芳一	日本医事新報	2014	国内
序文	木下芳一	好酸球性消化管疾患診療ガイドライン	2014	国内
好酸球性食道炎・胃腸炎の診断と治療	木下芳一	日本気管食道科学会専門医通信	2014	国内
クローン病に合併した好酸球性食道炎の１例	宮岡洋一・塚野航介・上野さや香・山之内智志・楠　龍策・伊藤聡子・藤代浩史・高下成明・大沼秀行・木下芳一	Gastroenterological Endoscopy	2014	国内
Whole-exome sequence analysis of ataxia telangiectasia-like phenotype.	Hasegawa, S., Imai, K., Yoshida, K., Okuno, Y., Muramatsu, H., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Kojima, S., Ogawa, S., Morio, T., Mizutani, S. and Takagi, M.	J Neurol Sci	2014	国外
Aldehyde dehydrogenase-2 polymorphism contributes to the progression of bone marrow failure in children with idiopathic aplastic anaemia.	Kawashima, N., Narita, A., Wang, X., Xu, Y., Sakaguchi, H., Doisaki, S., Muramatsu, H., Hama, A., Nakanishi, K., Takahashi, Y. and Kojima, S.	Br J Haematol	2014	国外

掲載した論文 （発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した 時期	国内外 の別
Peripheral blood lymphocyte telomere length as a predictor of response to immunosuppressive therapy in childhood aplastic anemia.	Sakaguchi, H., Nishio, N., Hama, A., Kawashima, N., Wang, X., Narita, A., Doisaki, S., Xu, Y., Muramatsu, H., Yoshida, N., Takahashi, Y., Kudo, K., Moritake, H., Nakamura, K., Kobayashi, R., Ito, E., Yabe, H., Ohga, S., Ohara, A., Kojima, S.	Haematologica	2014	国外
Loss of function mutations in RPL27 and RPS27 identified by whole-exome sequencing in Diamond-Blackfan anaemia.	Wang, R., Kojima, S. (29 th), Ogawa, S. (32 nd) and Ito, E. (total 33 collaborators)	Br J Haematol	2014	国外
First-line treatment for severe aplastic anemia in children: bone marrow transplantation from a matched family donor vs. immunosuppressive therapy.	Yoshida, N., Kobayashi, R., Yabe, H., Kosaka, Y., Yagasaki, H., Watanabe, K. I., Kudo, K., Morimoto, A., Ohga, S., Muramatsu, H., Takahashi, Y., Kato, K., Suzuki, R., Ohara, A. and Kojima, S.	Haematologica	2014	国外
Recurrent somatic mutations underlie corticotropin-independent Cushing's syndrome.	Sato, Y., Ogawa, S. (23 th) (total 23 collaboratos)	Science	2014	国外
The genomic landscape of nasopharyngeal carcinoma.	Lin, D. C., Meng, X., Hazawa, M., Nagata, Y., Varela, A. M., Xu, L., Sato, Y., Liu, L. Z., Ding, L. W., Sharma, A., Goh, B. C., Lee, S. C, Petersson, B. F., Yu, F. G., Macary, P., Oo, M. Z., Ha, C. S., Yang, H., Ogawa, S., Loh, K. S., Koeffler, H. P.	Nat Genet	2014	国外
Genomic and molecular characterization of esophageal squamous cell carcinoma.	Lin, D. C., Hao, J. J., Nagata, Y., Xu, L., Shang, L., Meng, X., Sato, Y., Okuno, Y., Varela, A. M., Ding, L. W., Garg, M., Liu, L. Z., Yang, H., Yin, D., Shi, Z. Z., Jiang, Y. Y., Gu, W. Y., Gong, T., Zhang, Y., Xu, X., Kalid, O., Shacham, S., Ogawa, S., Wang, M. R. and Koeffler, H. P.	Nat Genet	2014	国外
Acquired initiating mutations in early hematopoietic cells of CLL patients.	Damm, F., Ogawa, S. (25 th), Nguyen-Khac, F. and Bernard, O. A. (total 27 collaborators)	Cancer Discov	2014	国外
Deep sequencing reveals stepwise mutation acquisition in paroxysmal nocturnal hemoglobinuria.	Yoshida, K., Przychodzen, B., Yoshizato, T., Shiraishi, Y., Miyano, S., Ogawa, S., Maciejewski, J. P. and Makishima, H.	J Clin Invest	2014	国外
PRPF8 defects cause missplicing in myeloid malignancies.	Kurtovic-Kozaric, A., Przychodzen, B., Singh, J., Konarska, M. M., Clemente, M. J., Otrock, Z. K., Nakashima, M., His, E. D., Yoshida, K., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Ogawa, S., Boultwood, J., Makishima, H., Maciejewski, J. P. and Padgett, R. A.	Leukemia	2015	国外

掲載した論文 （発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した 時期	国内外 の別
High-resolution genomic copy number profiling of primary intraocular lymphoma by single nucleotide polymorphism microarrays.	Wang, L., Sato-Otsubo, A., Sugita, S., Takase, H., Mochizuki, M., Usui, Y., Goto, H., Koyama, T., Akiyama, H., Miura, O., Ogawa, S. and Arai, A.	Cancer Sci	2014	国外
Biallelic DICER1 mutations in sporadic pleuropulmonary blastoma.	Seki, M., Yoshida, K., Shiraishi, Y., Shimamura, T., Sato, Y., Nishimura, R., Okuno, Y., Chiba, K., Tanaka, H., Kato, K., Kato, M., Hanada, R., Nomura, Y., Park, M. J., Ishida, T., Oka, A., Igarashi, T., Miyano, S., Hayashi, Y., Ogawa, S. and Takita, J.	Cancer Res	2014	国外
Haploinsufficiency of Sf3b1 leads to compromised stem cell function but not to myelodysplasia.	Matsunawa, M., Yamamoto, R., Sanada, M., Sato-Otsubo, A., Shiozawa, Y., Otsu, M., Isono, K., Koseki, H., Nakauchi, H. and Ogawa, S.	Leukemia	2014	国外
Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients.	Kihara, R., Ogawa, S. (32 nd) and Naoe, T. (total 33 collaborators)	Leukemia	2014	国外
Recurrent genetic defects on chromosome 7q in myeloid neoplasms.	Hosono, N., Makishima, H., Jerez, A., Yoshida, K., Przychodzen, B., McMahon, S., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Sanada, M., Gomez-Segui, I., Verma, A. K., McDevitt, M. A., Sekeres, M. A., Ogawa, S. and Maciejewski, J. P.	Leukemia	2014	国外
Detection of the G17V RHOA mutation in angioimmunoblastic T-cell lymphoma and related lymphomas using quantitative allele-specific PCR.	Nakamoto-Matsubara, R., Ogawa, S.(24 th) and Chiba, S. (total 25 collaborators)	PLoS One	2014	国外
Pheochromocytoma as the first manifestation of MEN2A with RET mutation S891A: report of a case.	Hibi, Y., Ohye, T., Ogawa, K., Shimizu, Y., Shibata, M., Kagawa, C., Mizuno, Y., Uchino, S., Kosugi, S., Kurahashi, H. and Iwase, K.	Surg Today	2014	国外
Development and validation of a short scale to measure how social relationships support the continuous and conscious endeavour to lose weight.	Takada, A., Takahashi, Y., Nishimura, S. and Kosugi, S.	J Biosoc Sci	2014	国外
Tooth Loss and Atherosclerosis : The Nagahama Study.	Asai, K., Yamori, M., Yamazaki, T., Yamaguchi, A., Takahashi, K., Sekine, A.,Kosugi, S., Matsuda, F., Nakayama, T., Bessho, K., the Nagahama Study Group.	J Dent Res	2015	国外

掲載した論文 （発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した 時期	国内外 の別
Comprehensive replication of the relationship between myopia-related genes and refractive errors in a large Japanese cohort.	Yoshikawa, M., Yamashiro, K., Miyake, M., Oishi, M., Akagi-Kurashige, Y., Kumagai, K., Nakata, I., Nakanishi, H., Oishi, A., Gotoh, N., Yamada, R., Matsuda, F., Yoshimura, N., Nagahama Study Group.	Invest Ophthalmol Vis Sci	2014	国外
Gastroesophageal reflux disease symptoms and dietary behaviors are significant correlates of short sleep duration in the general population: The Nagahama Study.	Murase, K., Tabara, Y., Takahashi, Y., Muro, S., Yamada, R., Setoh, K., Kawaguchi, T., Kadotani, H., Kosugi, S., Sekine, A., Nakayama, T., Mishima, M., Chiba, T., Chin, K. and Matsuda, F.	Sleep	2014	国外

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Inverse Association between Air Pressure and Rheumatoid Arthritis Synovitis

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Abstract

Rheumatoid arthritis (RA) is a bone destructive autoimmune disease. Many patients with RA recognize fluctuations of their joint synovitis according to changes of air pressure, but the correlations between them have never been addressed in large-scale association studies. To address this point we recruited large-scale assessments of RA activity in a Japanese population, and performed an association analysis. Here, a total of 23,064 assessments of RA activity from 2,131 patients were obtained from the KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance) database. Detailed correlations between air pressure and joint swelling or tenderness were analyzed separately for each of the 326 patients with more than 20 assessments to regulate intra-patient correlations. Association studies were also performed for seven consecutive days to identify the strongest correlations. Standardized multiple linear regression analysis was performed to evaluate independent influences from other meteorological factors. As a result, components of composite measures for RA disease activity revealed suggestive negative associations with air pressure. The 326 patients displayed significant negative mean correlations between air pressure and swellings or the sum of swellings and tenderness ($p = 0.00068$ and 0.00011, respectively). Among the seven consecutive days, the most significant mean negative correlations were observed for air pressure three days before evaluations of RA synovitis ($p = 1.7 \times 10^{-7}$, 0.00027, and 8.3×10^{-8}, for swellings, tenderness and the sum of them, respectively). Standardized multiple linear regression analysis revealed these associations were independent from humidity and temperature. Our findings suggest that air pressure is inversely associated with synovitis in patients with RA.

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by joint synovitis and resultant joint destruction. Patients with RA present with swellings and tenderness of their joints, especially small joints such as metacarpophalangeal joints and proximal interphalangeal joints. Joint swellings and tenderness are closely related with future joint destruction [1,2] and this is why joint swellings and tenderness are included in the items for composite measures used for evaluation of RA activity [3–6]. Disease activity index (DAS) 28 is the most common composite measure in RA used for evaluation of daily RA activity and is composed of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) as inflammatory parameters, swollen joint count (SJC) and tender joint count (TJC) for the 28 joints with or without visual analogue scale (VAS).

A large number of studies have tried to elucidate basic mechanisms of joint synovitis in RA and revealed the importance of inflammatory cytokines such as TNF-alpha and IL-6 to which biological agents were developed to target [7]. On the contrary, environmental factors which influence joint synovitis are scarcely known. Several studies with a relatively large number of subjects have reported seasonal variations of RA symptoms or joint destruction [8,9], but the relationship is still inconclusive [10–12]. Detailed meteorological differences among various seasons which cause changes in RA symptoms have not been clarified.

Through our daily medical care for patients with RA, we noticed that many patients with RA told us about the fluctuations in their joint symptoms according to changes in air pressure. In particular, many of them recognized worsening of their symptoms when the air pressure decreased such as during a typhoon in the summer. While many rheumatologists have heard of this, there have been no large-scale association studies to date addressing the relationship between air pressure and joint synovitis in RA. Previous studies addressing correlations between RA synovitis and meteorological changes included less than 100 patients with RA and the results were not consistent [10,13–18]. Previously, it was reported that a consistent microenvironment would ease joint symptoms in patients with RA [13]. While one study showed that temperature and humidity were associated with joint pain in 88 patients with RA [15], another study did not find statistically

significant associations between meteorological changes and arthritic symptoms in 70 patients [16]. Another study where researchers observed 18 patients with RA for more than one year did not find significant associations and the authors concluded that this subjective belief in association by RA patients is simply an assumption that people have believed in for thousands of years [19]. However, none of the studies analyzed a large-number of joint assessments and the association is still inconclusive.

Recently, Kyoto University developed a large-scale database named "KURAMA (Kyoto University Rheumatoid Arthritis Management Alliance)" to accumulate detailed clinical information and specimen of patients with RA to uncover the basics of RA [20]. Here, we obtained 23,064 joint assessments for patients with RA from the KURAMA database and analyzed correlations between air pressure and joint synovitis in RA.

Results

Firstly, whether air pressure was correlated with daily disease activity in RA was addressed. DAS28 was selected as evaluation of RA activity for the association study. Table 1 shows the basic characteristics of the DAS28 scores and its components. The mean DAS28 score in the current patient group was 3.28, indicating low to moderate disease activity [21]. 14,999 DAS28 scores with three variables including SJC, TJC and ESR did not show a significant association with air pressure ($p = 0.18$, Table S1). Because DAS is a composite measure for assessing disease activity in RA, other RA composite measures could be associated with air pressure. Correlation analyses between air pressure and SJC, TJC, ESR, patients' VAS (pVAS) and Dr's VAS (dVAS) showed that all elements except for ESR showed suggestive or significant inverse associations with air pressure (Table S1). We also found that the sum of SJC and TJC showed a significant association with air pressure (Table S1). These results suggest that air pressure is associated with RA synovitis across different evaluations and different patients with RA. However, these analyses might be influenced by intra-patient correlations. Considering that significant associations were observed for SJC and the sum of SJC and TJC with air pressure, and that the largest number of data was available for SJC and TJC among the components of composite measures, we adopted SJC, TJC, and the sum of the two counts as best candidates showing associations with meteorological factors to obtain the maximum power for further analyses.

Secondly, correlation between air pressure and RA synovitis in each patient was analyzed to control intra-patient correlations. As the distribution of number of evaluations varied in the patients with RA, we extracted patients with more than 20 evaluations to confirm the correlations between air pressure and joint synovitis across different patients. In total, 12,061 evaluations from 326 patients were used for this analysis. The means of SJC and TJC were comparable with those in the 2,131 patients (Table 1). The overall fluctuations between SJC, TJC, or the combination of the two and air pressure are illustrated in Figure S1. Because we could not find the regular strong tendency of association between air pressure and joint synovitis through the figure, correlation coefficients between air pressure and signs of joint synovitis were calculated for each of the 326 patients. The correlation coefficients in items of synovitis demonstrated normal distributions in each item ($p \geq 0.78$, Shapiro-Wilk test, data not shown), justifying the application of t-test. The mean correlation coefficients across the 326 patients revealed significant negative correlations of air pressure with SJC and the combination of SJC with TJC (mean rho $= -0.0410$ and -0.0455, $p = 0.00068$ and 0.00011, respectively, Table 2). TJC showed a suggestive negative correlation (mean rho $= -0.0306$ and $p = 0.010$, Table 2). Figure 1 illustrates the smallest, largest and median correlation coefficients between air pressure and SJC, TJC or combination of the two among the 326 patients with RA, suggesting that negative mean correlation coefficients of RA synovitis were not brought about by patients demonstrating extreme negative correlation coefficients.

Table 1. Basic characteristics of the subjects in the current study.

Items	Overall	326 patients
Evaluation	23,064	12,061
Patient	2,131	326
Age (mean±SD)	60.7±15.0	62.4±13.6
Female ratio (%)	80.9	82.5
Stage* (mean±SD)	2.63±1.18	2.86±1.16
Class* (mean±SD)	1.92±0.70	1.94±0.70
Disease duration (year, mean±SD)	14.0±11.9	16.1±11.7
Smoking** (%)	33.6	30.8
Biologics*** (%)	19.0	46.6

*Steinbrocker's Stage and Class.
**Current smoker and ex-smoker.
***Patients who have been treated by biological agents between 2005 and 2012.
SD:standard deviation.
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Thirdly, we analyzed which day showed the most significant associations between air pressure and items of joint synovitis, because it was likely that air pressure affected RA joint synovitis by an indirect mechanism taking several days. The air pressure data of six consecutive days before the date of evaluation was obtained and the same analyses using the same data set of the 326 patients were performed to evaluate associations with items of joint synovitis. As a result, the mean correlation coefficients of SJC, TJC, and the sum of SJC and TJC showed a "U-pattern" in the consecutive days (Figure 2A). The strongest associations were found three days before the joint evaluations for the three items ($p = 1.7 \times 10^{-7}$, 0.00027, and 8.3×10^{-8}, for SJC, TJC, and the sum of SJC and TJC, respectively, Figure 2A and 2B). These results strengthened correlations between air pressure and joint synovitis in RA.

Finally, whether these correlations were mainly brought about by other meteorological factors or not was addressed. Data of daily mean temperatures and humidity were obtained from the same period as air pressure. Multiple standardized linear regression analyses were performed to assess independent correlations between joint synovitis and air pressure. As a result, air pressure showed significant associations with joint synovitis in the 21,940 evaluations which were independent from temperature and humidity (beta ≤ -0.0765 and $p \leq 0.0031$, Table 3). The analyses suggested that humidity also negatively influenced RA joint synovitis (Table 3). When multiple standardized linear regression analyses were performed for air pressure three days before the evaluations in each of the 326 patients with more than 20 evaluations of the 28 joints, mean coefficients of air pressure showed significant negative associations with joint synovitis ($p = 0.00023$, 0.036 and 0.0015, for SJC, TJC and the sum of SJC and TJC, respectively, Table 4). The inverse association between humidity and air pressure was also observed in this analysis ($p = 0.0019$, 0.016 and 0.0023, for SJC, TJC and the sum of SJC and TJC, respectively, data not shown).

Table 2. Mean correlation coefficients between joint synovitis and air pressure in the 326 patients.

Synovitis	Mean±SD(median)	Mean ρ±SD	P*
SJC	2.07±1.99 (1)	−0.0410±0.210	0.00068
TJC	2.08±2.19 (1)	−0.0306±0.212	0.010
SJC+TJC	4.15±3.70 (2)	−0.0455±0.207	0.00011

*p-values for Student's t-test. SD:standard deviation.
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Discussion

Because environmental effects on RA synovitis are not well established, analysis with convincing results would be beneficial to manage patients with RA properly. This is the first study to address the correlations between air pressure and joint synovitis in RA with a large number of RA patients, and the first to detect significant associations between them. Our results indicate that low air pressure is associated with worsening of joint synovitis. This matches the complaints from RA patients, that they feel worsening of RA synovitis when typhoons come in the summer. Since SJC is an objective element and TJC is a subjective element of patients with RA, significant associations of air pressure with the two cannot be explained by subjective feelings of patients. Previous studies addressing correlations between meteorological effects and joint synovitis did not give consistent results [10,13–19]. The limited number of subjects (not more than 88 patients with RA) is assumed to have caused this inconsistency. In addition, although we found significant associations, the small mean correlation coefficients (ρ: −0.04∼) made the previous studies difficult to detect these small effects. Because RA patients at Kyoto University Hospital frequently told us of the fluctuations in their symptoms in accordance with air pressure, among all the various meteorological

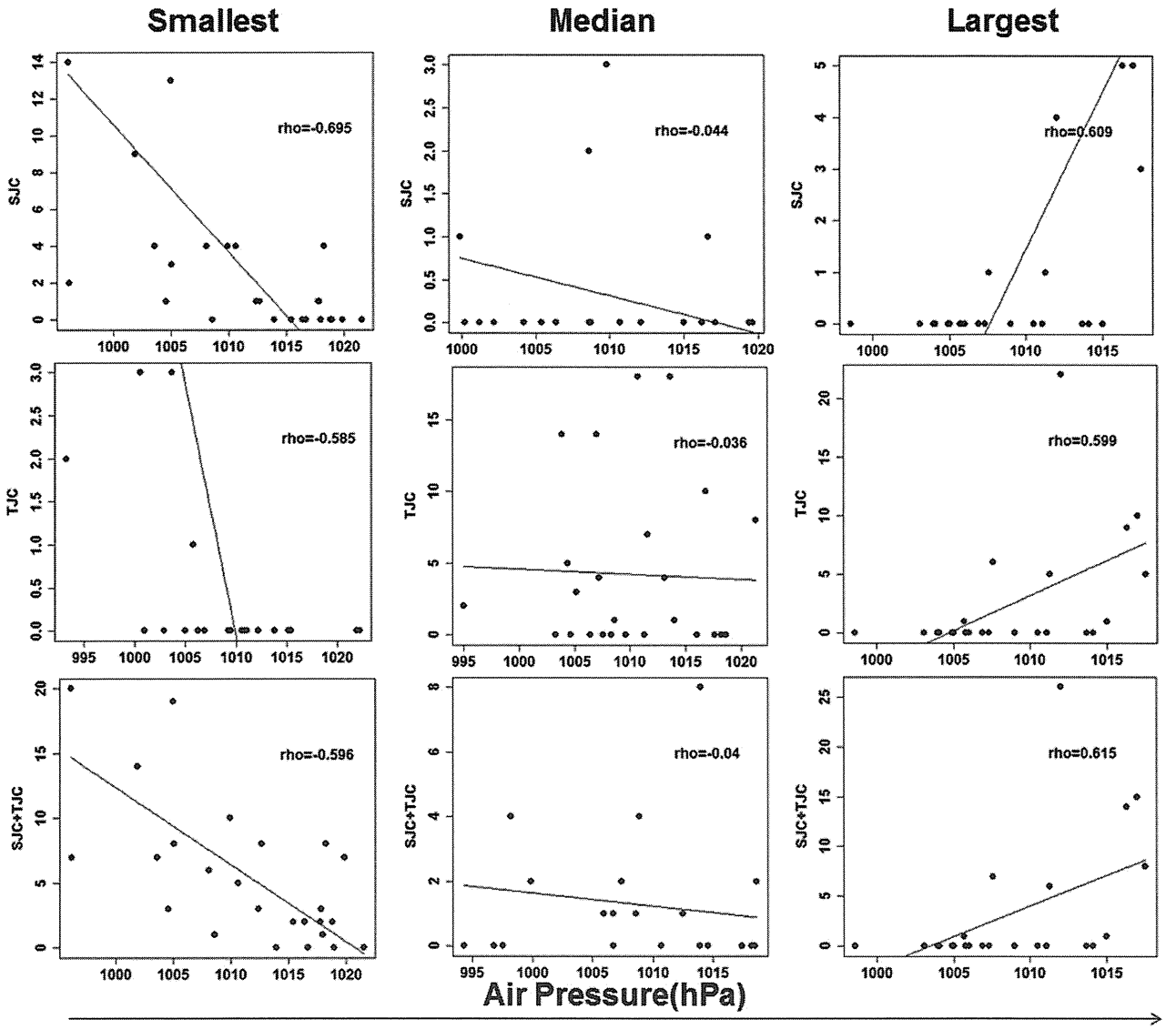

Figure 1. Correlations between joint synovitis and air pressure in RA patients. Correlation plots in patients demonstrating the smallest, median and largest correlation coefficients between joint synovitis and air pressure are illustrated in the left, middle and right panels, respectively.
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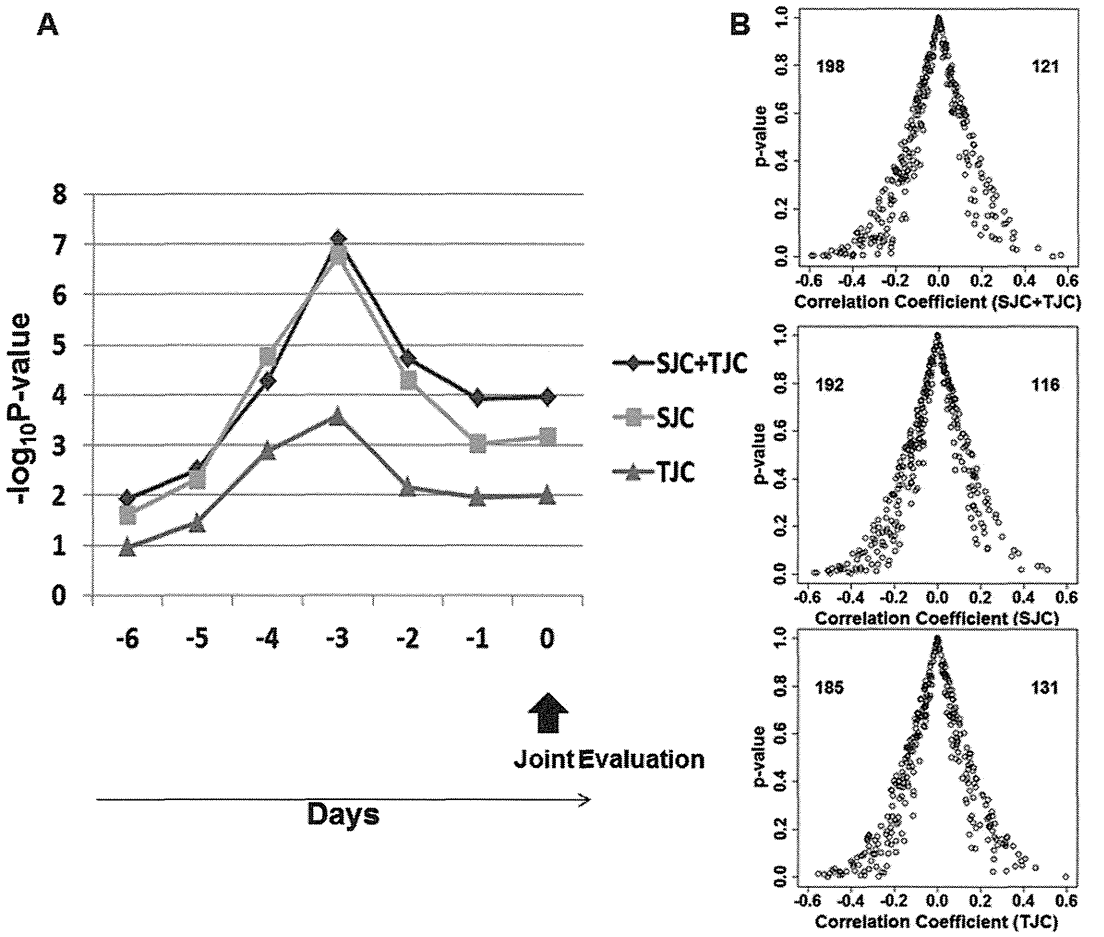

Figure 2. The strongest associations between joint synovitis and air pressure three days before joint evaluations. The 326 patients with more than 20 evaluations were analyzed. A)Associations between air pressure and joint synovitis for the seven consecutive days. Y axis indicates $-\log_{10}$P-value of Student's t-test. X axis indicates days before joint evaluations. B)Volcano plots for distribution of RA patients demonstrating positive or negative associations between joint synovitis and air pressure three days before joint evaluations. X and Y axes indicate Spearman's correlation coefficient and P-value, respectively. Numbers in the panels indicate RA patients showing positive or negative correlation coefficients. Because a part of the patients showed consistent TJC or SJC across all evaluations, the sum of the two numbers in each panel does not make 326.
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factors we focused on air pressure. Another reason we only focused on air pressure was to avoid type I statistical error by performing multiple association studies.

Our data set revealed low to moderate disease activity of RA on average, which reflects the appropriateness of the treatment the patients were receiving at Kyoto Unvesity Hospital. Considering large variation of the synovitis data and large number of joint evaluations, the current data should be enough to detect correlations.

The first analysis addressing correlation between air pressure and DAS28 did not result in a significant association. However, it should be noted that all of the elements of composite measures showed the same negative direction of association with air pressure. These results may suggest common associations between

Table 3. Results of multiple standardized linear regression analysis between air pressure and joint synvoitis.

Synovitis	-	Air pressure (hPa)		Temperature (°C)		Humidity (%)	
	Mean±SD(median)	1009.34±6.42 (1009.25)		16.10±8.77 (16.45)		63.83±9.75 (64)	
	-	Beta	P	Beta	P	Beta	P
SJC	1.96±3.06 (1)	−0.0765	0.0031	−0.0419	0.097	−0.0996	2.8×10^{-6}
TJC	2.12±3.70 (1)	−0.105	0.00082	−0.0535	0.079	−0.0976	0.00015
SJC+TJC	4.08±5.87 (2)	−0.181	0.00027	−0.0954	0.049	−0.197	1.4×10^{-6}

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Table 4. Standardized multiple linear regression analysis for air pressure 3 days before evaluations and synovitis among the 326 patients.

Synovitis	Mean±SD(median)	mean Beta±SD	P*
SJC	2.07±1.99 (1)	−0.126±0.0425	0.00023
TJC	2.08±2.19 (1)	−0.0893±0.0339	0.036
SJC+TJC	4.15±3.70 (2)	−0.215±0.0672	0.0015

*p-values for Student's t-test. SD:standard deviation.
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air pressure and RA joint synovitis instead of limited association between air pressure and a specific element of RA joint synovitis. At the same time, these results may suggest that composite measures composed of multiple elements showing weak association with air pressure are not sensitive enough to detect the influence of air pressure. In addition, because many medical doctors evaluate synovitis of many patients with RA, variations among doctors in each element would be amplified in the composite measure and result in difficulty to detect significant correlations. Considering the strong association between air pressure and sum of SJC and TJC, the fine direction of association between different elements and air pressure should partly overlap but partly differ. PVAS showed the lowest mean correlation coefficient among items of composite measures. This matches our observation that many of the RA patients feel correlation between their symptoms and air pressure. Although the number of data for pVAS is limited, 81 patients with more than 15 data for pVAS revealed a suggestive inverse correlation with air pressure (mean rho = −0.0469, data not shown). Accumulation of more data for each element would detect a significant association between each element and air pressure and a fine direction of association with air pressure in each element.

Because the number of joint assessments differed among patients and it was likely that analyses using all assessments would be influenced by the specific patients with large number of joint assessments, we performed the analyses focusing on the 326 patients with more than 20 assessments to avoid intra-patient correlations. We hypothesized that correlations between air pressure and joint synovitis should be largely different among patients but a large number of patients would result in a significant deviation. We calculated a correlation coefficient in each patient separately. The results supported our hypothesis and showed a significant deviation of the mean correlation coefficient from the null hypothesis. Figure 1 presenting patients with median correlations along with Table S2 indicated that overall distributions of correlations between air pressure and joint synovitis shifted to negative correlations. Considering the size of correlation coefficients, although RA patients show a negative correlation in average between air pressure and joint synovitis, the correlation greatly vary among patients and the correlation should not be generalized.

We found the strongest associations between air pressure and signs of synovitis three days before evaluations. This may indicate that slow mechanisms underlie the correlations or that joint synovitis is prone to unknown factors which reflect past air pressure.

When we classified patients into subgroups based on positivity of disease duration, smoking, Stage, Class and usage of biological agents during the observation period, we did not find significant difference among RA subsets (data not shown). The analysis of confounding factors revealed that the association of air pressure with joint synovitis was not derived from humidity and temperature, which were selected since air pressure, humidity and temperature are representatives of meteorological factors. Although both humidity and temperature showed correlations with air pressure (rho:0.19 and 0.58, between air pressure and humidity or temperature, respectively), their correlations could not explain the association between air pressure and RA synovitis. The analysis also revealed that humidity showed a negative association with joint synovitis that is independent from temperature and air pressure. A previous study reported that a combination of increase in humidity and decrease in air pressure were associated with worsening of joint pain [14]. Their findings matched our results for air pressure, but the association of humidity was opposite to ours. Thus, the association between humidity and joint synovitis is inconclusive and further studies are required. It is notable that mean temperature was not associated with joint synovitis in a multiple standardized linear regression analysis. As increase or decrease of blood flow due to temperature is supposed to influence signs of synovitis in RA, the lack of the association may be explained by rapid influence of finely conditioned temperature in hospitals.

It is difficult to assume the basic mechanisms underlying the correlation between joint synovitis and air pressure. One possible explanation is that air pressure directly presses joint structures in patients with RA. Low air pressure results in reduced outside pressure of joints which allow joints to be swollen more easily. Enlarged space of joints would allow more inflammatory cells to enter joint space and produce inflammatory cytokines. Another explanation is involvement of autonomic nerves to regulate threshold of pain. A Japanese group reported that both decreased air pressure and temperature led to worsening of joint pain in an animal model [22,23]. The group also showed that these correlations in the animal model were mediated by sympathetic nerve, whose excitement and increase of circulating noradrenaline were brought about by decrease of air pressure [24,25]. As the current study did not reveal a strong association between joint tenderness and air pressure, involvement of sympathetic nerve with pain cannot fully explain the current results. Variations of B-cell activity due to meteorological changes could be another possibility. Our previous study reported seasonal variation of IgG in rheumatic diseases [26]. Analysis incorporating altitude of residence for each patient, whose information is not available in the current study, would give a clue for the mechanism underlying the association.

We could not conclude whether air pressure directly influences RA synovitis or if it is just a confounding factor of yet-to-be-determined factors with direct effects on RA synovitis. However, our analysis supports the patients' subjective feelings of relationship between air pressure and joint synovitis. Another study addressing correlations between air pressure and joint synvoitis estimated by imaging including ultrasound seems necessary. Further experiments and analyses between air pressure and joint symptoms in humans would clarify the detailed mechanisms. It will be interesting to determine the characteristics of patients who are susceptible to change of air pressure.

Materials and Methods

Ethical statements

The analyses in the current study were performed under policy of data analysis of the KURAMA database approved by Kyoto University Hospital Ethical Committee [20]. Written informed consent to enroll in the database described below was obtained

from most of the patients, but for some patients the information regarding the construction of this database was disclosed instead of obtaining written informed consent. Participants who were informed regarding the construction of the database (instead of obtaining written informed consent) were allowed to withdraw from the study if desired. All data were de-identified and analyzed anonymously. This study was designed in accordance with the Helsinki Declaration.

Data of joint synovotis in patients with RA

A total of 23,064 evaluations of disease activity from 2,131 patients with RA were obtained with the corresponding dates of evaluations from the KURAMA database. The evaluation data contained some or all of the SJC, TJC in the 28 joints, ESR, pVAS and dVAS as well as DAS 28 as a composite measure for RA disease activity. The sum of SJC and TJC was also calculated for each evaluation. 326 patients with more than 20 evaluations of disease activity were extracted for further analysis.

Data of air pressure and other meteorological factors

Data of daily mean air pressure in Kyoto from 2005 to 2012 was obtained from the homepage of Japan Meteological Agency (http://www.jma.go.jp/jma/index.html). Data of daily mean temperature and humidity in Kyoto were also obtained in the same manner.

Statistical analysis

Correlations between mean air pressure on the day of joint evaluation and DAS28, SJC, TJC, ESR, pVAS, dVAS or sum of SJC and TJC were estimated by Spearman's correlation coefficients, using 23,064 evaluations of joint synovitis or evaluations in each of the 326 patients. The mean Spearman's correlation coefficients among the 326 patients with RA were estimated by Student's t-test under the null hypothesis that the mean was zero. Normality of distribution of correlation coefficients in the 326 patients was analyzed by Shapiro-Wilk test. A daily mean air pressure of the six days before the day of joint evaluation was also analyzed for correlations with signs of joint synovitis across the 326 patients with RA. To analyze independent effects of air pressure on joint synovitis from humidity and temperature, multiple standardized linear regression analysis was performed for 23,064 evaluations and each of the 326 patients with more than 20 evaluations. Mean beta values in the multiple standardized linear regression analysis among the 326 patients were assessed by Student's t-test under the null hypothsis that the mean beta values were zero. P-values less than 0.0071 were regarded as significant based on Bonferroni's correction. Data analysis was performed by R software (http://www.r-project.org/) or SPSS (ver 18).

Supporting Information

Figure S1 Fluctuations of air pressure and joint synovitis in the 326 patients. Fluctuations of each item are illustrated between 2005 and 2012. The three figures of SJC, TJC and combination of SJC and TJC are composed of 326 lines presenting fluctuations in the 326 patients.
(TIF)

Table S1 Correlation coefficients of RA joint synovitis in association with air pressure across different evaluations.
(DOC)

Table S2 Detailed information of the 326 RA patients.
(DOC)

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Author Contributions

Conceived and designed the experiments: CT MH FM HI TF TM. Analyzed the data: CT. Contributed reagents/materials/analysis tools: CT MH MF SN KO RN YI NY HY HI TF TM. Wrote the paper: CT MH.

References

1. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, et al. (1999) Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis and Rheumatism 42: 1854–1860.
2. Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, et al. (2006) Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis and Rheumatism 54: 702–710.
3. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, et al. (1990) Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Annals of the Rheumatic Diseases 49: 916–920.
4. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, et al. (1992) Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Annals of the Rheumatic Diseases 51: 177–181.
5. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, et al. (2003) A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 42: 244–257.
6. Aletaha D, Smolen JS (2007) The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best Pract Res Clin Rheumatol 21: 663–675.
7. Furst DE, Keystone EC, Braun J, Breedveld FC, Burmester GR, et al. (2012) Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011. Ann Rheum Dis 71 Suppl 2: i2–45.
8. Iikuni N, Nakajima A, Inoue E, Tanaka E, Okamoto H, et al. (2007) What's in season for rheumatoid arthritis patients? Seasonal fluctuations in disease activity. Rheumatology (Oxford) 46: 846–848.
9. Mouterde G, Lukas C, Logeart I, Flipo RM, Rincheval N, et al. (2011) Predictors of radiographic progression in the ESPOIR cohort: the season of first symptoms may influence the short-term outcome in early arthritis. Ann Rheum Dis 70: 1251–1256.
10. Patberg WR, Rasker JJ (2004) Weather effects in rheumatoid arthritis: from controversy to consensus. A review. J Rheumatol 31: 1327–1334.
11. Hawley DJ, Wolfe F (1994) Effect of light and season on pain and depression in subjects with rheumatic disorders. Pain 59: 227–234.
12. de Rooy DP, Andersson ML, Knevel R, Huizinga TW, Svensson B, et al. (2012) Does the season at symptom onset influence the long-term severity of radiographic joint destruction in rheumatoid arthritis? Ann Rheum Dis 71: 2055–2056.
13. Edstrom G, Lundin G, Wramner T (1948) Investigations into the Effect of Hot, Dry Microclimate on Peripheral Circulation, etc., in Arthritic Patients. Ann Rheum Dis 7: 76–82.
14. Hollander JL (1963) Environment and musculoskeletal diseases. Arch Environ Health 6: 527–536.
15. Patberg WR, Nienhuis RL, Veringa F (1985) Relation between meteorological factors and pain in rheumatoid arthritis in a marine climate. J Rheumatol 12: 711–715.
16. Sibley JT (1985) Weather and arthritis symptoms. J Rheumatol 12: 707–710.
17. Gorin AA, Smyth JM, Weisberg JN, Affleck G, Tennen H, et al. (1999) Rheumatoid arthritis patients show weather sensitivity in daily life, but the relationship is not clinically significant. Pain 81: 173–177.
18. Strusberg I, Mendelberg RC, Serra HA, Strusberg AM (2002) Influence of weather conditions on rheumatic pain. J Rheumatol 29: 335–338.
19. Redelmeier DA, Tversky A (1996) On the belief that arthritis pain is related to the weather. Proc Natl Acad Sci U S A 93: 2895–2896.
20. Terao C, Hashimoto M, Yamamoto K, Murakami K, Ohmura K, et al. (2013) Three groups in the 28 joints for rheumatoid arthritis synovitis–analysis using more than 17,000 assessments in the KURAMA database. PLoS One 8: e59341.
21. van Riel PL, van Gestel AM (2000) Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 59 Suppl 1: i28–31.

22. Sato J, Morimae H, Seino Y, Kobayashi T, Suzuki N, et al. (1999) Lowering barometric pressure aggravates mechanical allodynia and hyperalgesia in a rat model of neuropathic pain. Neurosci Lett 266: 21–24.
23. Sato J, Aoyama M, Yamazaki M, Okumura S, Takahashi K, et al. (2004) Artificially produced meteorological changes aggravate pain in adjuvant-induced arthritic rats. Neurosci Lett 354: 46–49.
24. Jin Y, Sato J, Yamazaki M, Omura S, Funakubo M, et al. (2008) Changes in cardiovascular parameters and plasma norepinephrine level in rats after chronic constriction injury on the sciatic nerve. Pain 135: 221–231.
25. Sato J, Morimae H, Takanari K, Seino Y, Okada T, et al. (2000) Effects of lowering ambient temperature on pain-related behaviors in a rat model of neuropathic pain. Exp Brain Res 133: 442–449.
26. Terao C, Ohmura K, Yamamoto K, Yukawa N, Kawabata D, et al. (2012) Serum IgG levels demonstrate seasonal change in connective tissue diseases: a large-scale, 4-year analysis in Japanese. Mod Rheumatol 22: 426–430.